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MEDICAL LABORATORY OBSERVER

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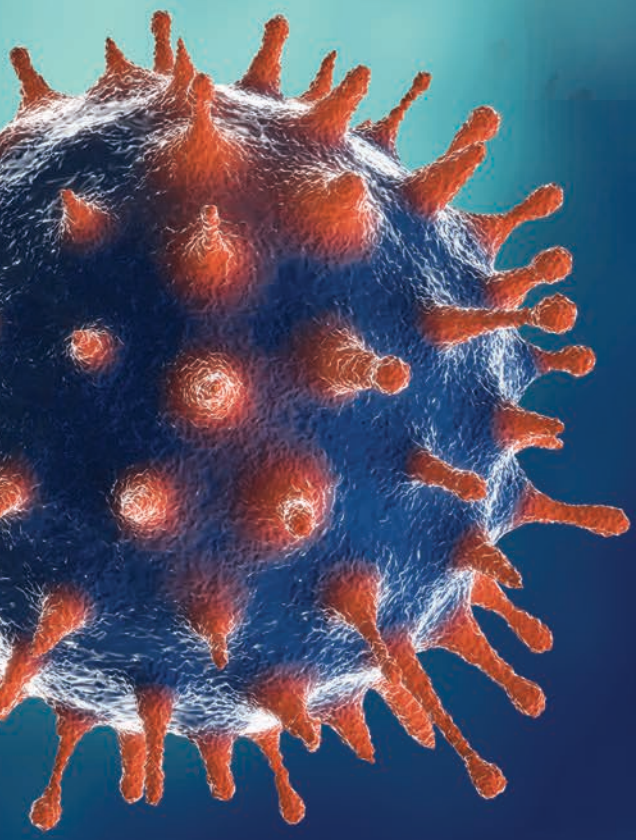

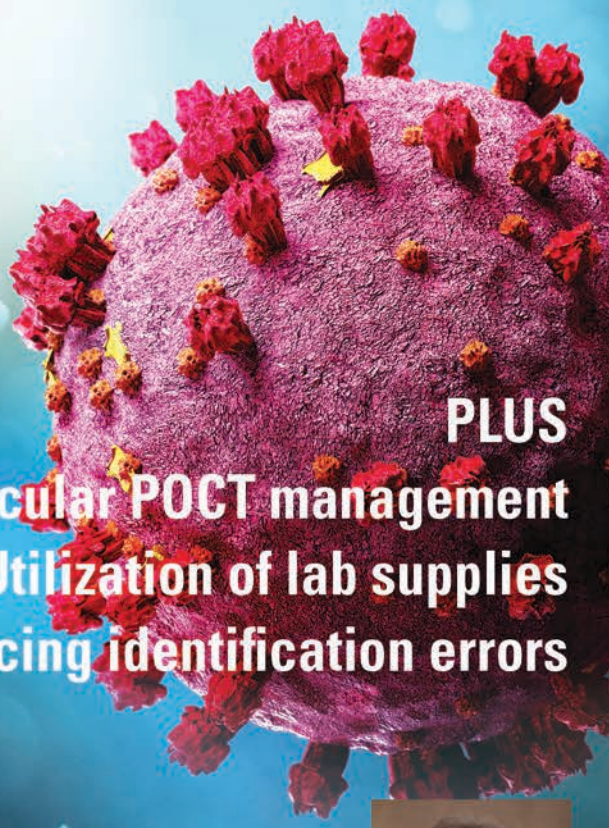

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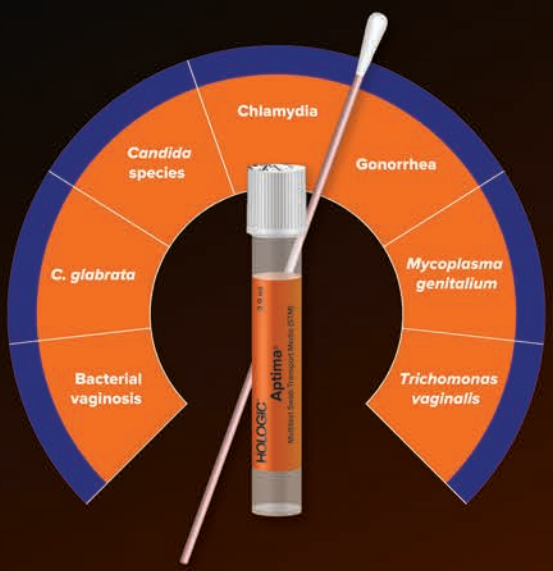

ONE SAMPLE

References: 1. Aptima Combo 2 Assay [package insert] #502446-IFU-PI_012 San Diego, CA; Hologic, Inc., 2021. **2.** Aptima Mycoplasma genitalium assay [package insert] #AW-17946_002, San Diego, CA; Hologic, Inc., 2021, **3.** Aptima CV/TV assay [package insert] #AW-18812, San Diego, CA; Hologic, Inc., 2021. **4.** Aptima BV assay [package insert] #AW-18811, San Diego, CA; Hologic, Inc., 2021.

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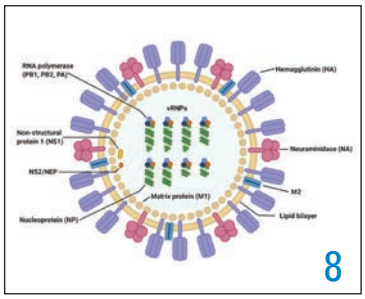

8


20


28


44


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Managing fluctuating COVID-19 testing demand

By Linda Wilson
Senior Editor

As the SARS-CoV-2 Delta variant surges throughout the United States, so has the number of cases and, therefore, the demand for SARS-CoV-2 testing. According to data from the Coronavirus Resource Center at Johns Hopkins University, testing volume was 1,375,959, or 419 per 100,000, with a positivity rate of 11.5% on August 13, 2021.The situation was quite different on June 10, 2021, when the United States conducted 487,395 tests, or 149 per 100,000, with a positivity rate of 4.0%.

Even so, testing volumes are not close to what they were earlier in the pandemic, such as during the 2020 holiday season. For example, the United States conducted 2,031,894 tests on December 24, 2020, according to The COVID Tracking Project, which no longer collects and reports daily data.

Current testing volumes are fueled by both vaccinated and unvaccinated people. The Centers for Disease Control and Prevention (CDC) recommends testing asymptomatic vaccinated people who come in contact with a person with COVID-19.

A recent study published in the CDC's Morbidity and Mortality Weekly Report (MMWR) found that cycle threshold values, which indicate viral load, were similar among specimens from patients who were fully vaccinated and those who were not. The study was based on 469 cases of COVID-19 among Massachusetts residents who had traveled to a town in Barnstable County, MA, where several large public events were held in July. A total of 346 (74%) of those infections occurred in fully vaccinated people.

CDC officials said the results of the study influenced their decision to recommend that fully vaccinated people wear masks indoors in geographic locations with high transmission rates for SARS-CoV-2.

With a rapidly changing situation, labs now are in the position of managing fluctuating demand for SARS-CoV-2 testing, as well as for other infectious diseases, such as flu or respiratory syncytial virus (RSV).

Since the volume of SARS-CoV-2 testing is down overall, compared to the pandemic's peak, labs also are evaluating what to do with the extra capacity for molecular testing on analyzers they purchased earlier in the pandemic.

For example, David T. Pride, MD, PhD, Director of the Molecular Microbiology Laboratory and the Associate Director of the Clinical Microbiology Laboratory at UC San Diego Health, writes about his organization's plan for excess capacity in this issue of *Medical Laboratory Observer (MLO)*. The plan includes expanding the lab's menu to include tests that were sent out to reference labs in the past, such as in sexual health, and preparing for the upcoming respiratory disease season.

I suspect that many of you are implementing similar plans. The editors at *MLO* would love to hear about them, so please reach out.

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

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Fast Facts

Vaccination Effectiveness (VE)

The Centers for Disease Control and Prevention (CDC) reported on the effectiveness of COVID-19 vaccines, based on a combination of agency data and external published studies.

35,000

symptomatic infections per week among 162 million vaccinated Americans

25-fold

reduction in hospitalization and death for vaccinated people

5X

increase from April to May in the percentage of in-hospital deaths among the vaccinated

91%

VE against infection among fully vaccinated

81%

VE against infection for partially vaccinated

40%

lower mean RNA viral load for vaccinated people and shorter duration of viral RNA

85%

effective against the Beta variant for severe illness for vaccinated people in nursing homes

64%

effective against infection and symptomatic disease from Delta variant in Israel (Pfizer-BioNTech)

Higher risk

of reinfection by Delta than Alpha variant if infected more than 6 months ago

More transmissible

than Ebola, Smallpox and the 1918 Spanish flu: the Delta variant

Source: https://covid.cdc.gov/covid-data-tracker/#datatracker-home

Phages are key to emergence of "superbugs" and their treatment

For the first time ever, researchers from the University of Pittsburgh School of Medicine discovered that phages — tiny viruses that attack bacteria — are key to initiating rapid bacterial evolution leading to the emergence of treatment-resistant "superbugs." The findings were published in *Science Advances.*

The researchers showed that, contrary to a dominant theory in the field of evolutionary microbiology, the process of adaptation and diversification in bacterial colonies doesn't start from a homogeneous clonal population. They were shocked to discover that the cause of much of the early adaptation wasn't random point mutations. Instead, they found that phages, which we normally think of as bacterial parasites, are what gave the winning strains the evolutionary advantage early on.

"Essentially, a parasite became a weapon," said senior author Vaughn Cooper, PhD, Professor of Microbiology and Molecular Genetics at Pitt. "What killed off more sensitive bugs gave the advantage to others."

When it comes to bacteria, a careful observer can track evolution in the span of a few days. Because of how quickly bacteria grow, it only takes days for bacterial strains to acquire new traits or develop resistance to antimicrobial drugs.

The new study shows that bacterial and phage evolution often go hand in hand, especially in the early stages of bacterial infection. This is a multilayered process in which phages and bacteria are joined in a chaotic dance, constantly interacting and co-evolving.

When the scientists tracked changes in genetic sequences of six bacterial strains in a skin wound infection in pigs, they found that jumping of phages from one bacterial host to another was rampant — even clones that didn't gain an evolutionary advantage had phages incorporated in their genomes. Most clones had more than one phage integrated in their genetic material — often there were two, three or even four phages in one bug.

Funding for HIV latency research using single cell analysis

The National Institute on Drug Abuse, part of the National Institues of Health (NIH), is funding the Browne lab in the UNC HIV Cure Center for a study on the effects of cannabis use on the reservoir of HIV that is dormant within patients but becomes activated and spreads when antiretroviral medications are ceased. This phenomenon is called HIV latency, and it's considered the main barrier to eradicating the virus that causes AIDS.

UNC HIV Cure Center researcher Ed Browne, PhD, Assistant Professor in the UNC Department of Medicine, is the principal investigator of the $4-million, 5-year research project.

Increasing evidence suggests that drugs of abuse, such as the cannabis (or marijuana), affect the size and nature of the virus reservoir. Cannabis activates the CB2 receptors that are widely expressed on the surface of immune cells, including the CD4 T cells.

"Our hypothesis is that cannabis exposure during HIV infection alters the size, location, and genetic characteristics of the latent HIV reservoir through the activation of CB2-dependent cell signaling in CD4 T cells," Browne said.

The UNC Cure Center research team will use cutting-edge methods from the fields of single cell multiomic analysis to characterize cannabis effects on the latent HIV reservoir.

First, the researchers will capitalize on a primary CD4 T cell model of HIV latency developed in the Browne lab to investigate how CB-induced signaling impacts viral/host gene expression and chromatin structure in latently infected cells.

Second, they will use a newly developed single cell experimental assay to determine the impact of cannabis use on the size and location of the intact HIV reservoir, analyzing samples from a cohort of cannabis-using individuals with HIV.

Third, they will extend their findings to conduct a detailed genomic analysis of the impact of cannabis use on cellular and viral gene expression in people with HIV. Specifically, the researchers will analyze blood cells and CD4 T cells from cannabis-using individuals, using single cell RNA sequencing technologies, and compare what they find to non cannabis-using individuals with HIV. The researchers will identify any cellular and genetic signatures that distinguish cannabis-using people with HIV from non-using HIV-positive individuals.

Johns Hopkins method outperforms previous assessments for risk in cardiac sarcoidosis

Johns Hopkins University scientists have developed a new tool for predicting which patients suffering from a complex inflammatory heart disease are at risk of sudden cardiac arrest. Published in *Science Advances*, their

method is the first to combine models of patients' hearts built from multiple images with the power of machine learning.

"This robust new personalized technology outperformed clinical metrics in forecasting future arrhythmia and could transform the management of cardiac sarcoidosis patients," said senior author Natalia Trayanova, Professor of Biomedical Engineering and Co-Director of the Alliance for Cardiovascular Diagnostic and Treatment Innovation (ADVANCE) at Johns Hopkins.

Doctors don't currently have precise methods for assessing which patients with cardiac sarcoidosis, a condition causing inflammation and scarring that can trigger irregular heartbeats, are likely to have a fatal arrthmia; meaning that some patients don't survive, while others undergo unnecessary, invasive interventions. A recent meta-analysis cited in the study found that roughly only one third of CS patients receive adequate treatment.

Trayanova, who is also a professor at the Johns Hopkins School of Medicine, said,"Some CS patients perish, often in the prime of their life, while others have a defibrillator implanted unnecessarily and often deal with the complications, including infections, device malfunction, and inappropriate shocks, without receiving any real benefit."

In their study, the researchers created digital three-dimensional models of the hearts of 45 CS patients treated at the Johns Hopkins Hospital. To do this, they took the novel approach of combining data from two different kinds of heart scans: contrast-enhanced cardiac MRIs, which detect fibrosis, or scarring, and PET scans, which detect inflammation. The team used computer simulations to apply a series of electrical signals at various locations throughout each of the models and gathered millions of data points measuring each heart's reaction.

The tool significantly outperformed standard clinical metrics for predicting cardiac arrest in CS patients.

Lastly, the team compared their simulations against scans of lesions in the hearts of the patients who had subsequently undergone a procedure to reset their heartbeats, finding that their predictions were consistent with actual outcomes.

Hard working enzyme keeps immune cells in line

Researchers at La Jolla Institute for Immunology (LJI) have shed light on a process in immune cells that may explain why some people develop cardiovascular diseases, according to a news release from the organization.

Their research, published recently in *Genome Biology*, shows the key role that TET enzymes play in keeping immune cells on a healthy track as they mature. The scientists found that other enzymes do play a role in this process — but TET enzymes do the heavy lifting.

TET enzymes control gene expression by triggering a process called demethylation, where a molecule called a methyl group is removed from where it sits in the genetic code. Demethylation is important because it alters how a cell "reads" DNA.

For the study, the researchers investigated how immune cell DNA can be altered by either TET enzymes (a process called passive demethylation) or by a DNA repair enzyme called TDG (active demethylation).

The researchers aimed to uncover which demethylation pathway has a bigger role in determining the gene expression of immune cells.

The researchers started with two immune cell models: CD4 "helper" T cells and monocytes. Both cell types must proliferate and mature into more specific cell types to help fight off pathogens. However, once monocytes are differentiated into macrophages and stimulated with a molecule called LPS, they stop proliferating. By taking a close look at these CD4 helper T cells and macrophages the researchers could better understand proliferating and non-proliferating models.

The proliferation process is very quick, making it a prime time to witness how demethylation occurs and how it affects gene expression. Onodera used CD4 helper T cells to analyze the demethylation process using a cutting-edge computational analysis program developed for this study. This tool gives scientists a look at which regions of DNA within a cell are methylated.

Using a new technique called pyridine borane sequencing, the researchers showed that "active" demethylation — through TDG — is working in immune cells. Onodera says TDG's role is minor: it does the job of removing two molecules generated by TET enzyme activity.

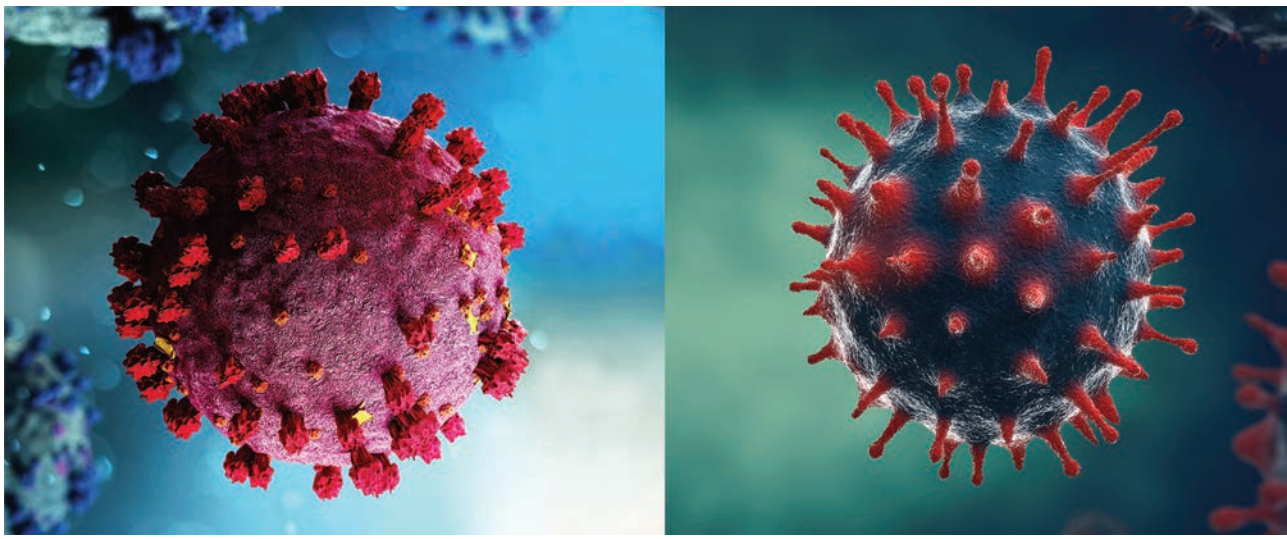
NIH panel proposes standard definition of placental SARS-CoV-2 infection

A panel of experts convened by the National Institutes of Health (NIH) has recommended standardized criteria to define infection of the placenta with SARS-CoV-2, the virus that causes COVID-19. The panel also released a guidance about the best methods to evaluate placental SARS-CoV-2 infections for research and clinical applications.

SARS-CoV-2 infection during pregnancy has been linked to complications that may involve or be reflected in the placenta, including preeclampsia and preterm birth. To date, researchers have used a variety of methods to diagnose SARS-CoV-2 infection of the placenta, making it difficult to compare results from different studies and to establish definitive scientific evidence about the risks of placental infection.

To address these gaps, NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) virtually convened a group of experts in obstetrics, virology, placental pathology, infectious disease, immunology and molecular biology to propose a standardized definition of placental infection. The resulting guidance appears in the *American Journal of Obstetrics and Gynecology*.

The experts recommend preferred techniques to detect SARS-CoV-2 replication, viral transcripts or proteins in placental tissue. Depending on the scientific rigor of the technique used, the likelihood of placental SARS-CoV-2 infection may be classified as definitive, probable, possible or unlikely. The authors encourage investigators to use the most scientifically rigorous technique available in their laboratory or clinic. They also recommend that scientific papers reporting placental SARS-CoV-2 infection describe the location and number of placental tissue samples collected, method of preserving the tissue and detection technique. Finally, they offer guidance for handling, processing and examining placental tissue. The authors anticipate that use of these recommendations will make it easier to compare and interpret results across studies.



Comparing the structure, diagnosis, and prevention of SARS-CoV-2 and influenza

by Sophia Richards, MLS(ASCP); Masih Shokrani, PhD, MT(ASCP)

With COVID-19 being a respiratory disease that has similar symptoms to the influenza virus, and while the two viruses share some similarities, the differences are clinically significant. The severity of both viruses varies from person to person, with some people acting as asymptomatic carriers, and others receiving treatment in the intensive care unit on ventilators. The pandemic taught the scientific and medical communities more about COVID-19 than they knew in late 2019. Everything learned throughout the pandemic has led to the development of reliable laboratory testing and multiple vaccine options for COVID-19.

While COVID-19 is caused by SARS-CoV-2, influenza is a common seasonal illness caused by influenza virus A or B (IAV or IBV). The influenza virus was first isolated in the laboratory in 1932 but has caused pandemics and epidemics every year, which is similar to what we experience with seasonal influenza activity today.[1] One of the most well-known outbreaks of the influenza virus was the 1918 Spanish flu, which was an outbreak of H1N1, or swine flu. The flu epidemic occurs every year in the United States in the fall and winter months. Like COVID-19, symptoms and severity of influenza vary from person to person. Getting a yearly flu vaccine helps reduce the risk of illness from the seasonal influenza virus. In 2017, the World Health Organization (WHO) reported that 650,000 people worldwide die due to flu-related respiratory illness each year. The data from the WHO includes low- to middle-income countries without the same access to preventative and acute medical care as is available in developed countries such as the United States.[2]

A comprehensive analysis of COVID-19 and influenza is necessary to differentiate between these two viruses regarding structure, identification, and vaccine development. Some of the most important similarities and differences are seen in the structure, symptoms, transmission, rate of mutation, laboratory testing, and available vaccinations.

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LEARNING OBJECTIVES

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

1. Describe the structural differences between SARS-CoV-2 and influenza virus A or B (IAV or IBV).
2. Describe how antigenic drift and antigenic shift occur for IAV or IBV and SARS-CoV-2.
3. Describe the types of lab assays available for detecting an infection with SARS-CoV-2 or IAV and IBV, as well as tests used to monitor the health status of patients with COVID-19.
4. Describe the vaccines available to prevent disease from SARS-CoV-2 or IAV and IBV.

Structure

Coronaviruses are characterized as positive single-stranded RNA enveloped viruses (ssRNA).[3] The genome of positive sense ssRNA viruses can be used as messenger RNA (mRNA). This means that the genome does not have to be transcribed as mRNA first. SsRNA viruses are the least complex form of viruses and only contain information that is needed to infect a host cell. This type of virus replicates the nucleocapsid and the genetic material that will be contained in the nucleocapsid at the same time. Due to the ssRNA structure of coronaviruses, they rely greatly on host mechanisms for replication. Replication of the genome happens spontaneously, which does not require energy or adenosine triphosphate (ATP). This differs from DNA or RNA transcription where ATP is required for replication.[4] Coronaviruses range in size from 26 to 32 kb, which makes them the largest single-stranded RNA virus.

Glycoprotein projections on the surface of the virus give the virus a crown-like appearance that is visible using electron microscopy (EM).[3] The basic structures of SARS-CoV-2 and influenza virus are shown in **Figure 1**.

The major proteins that contribute to the structure of coronaviruses are the membrane (M), envelope (E), nucleocapsid (N), spike (S), and hemagglutinin-esterase (HE) protein.[5] The M protein is a structural protein that determines the shape of the envelope and binds to the N protein to strengthen and stabilize the nucleocapsid. The M protein also contributes to the viral envelope with protein E, which has a minor role in the envelope formation of the virus.[6] While the E protein does not form the membrane of the virus, the E protein is an integral protein, forming a lattice with the M protein to form the membrane. The N protein is responsible for binding to the genome of the virus and is seen at the highest abundance in host cells infected with the virus. The S protein creates the hallmark spikes of coronaviruses that can be seen through EM. The S protein is composed of two subunits, the S1 subunit is responsible for receptor binding, and the S2 subunit is responsible for membrane fusion.[7] Hemagglutinin esterase is an enzyme composed of hemagglutinin and acetyl esterase and is believed to play a role in the pathogenicity of coronaviruses.

On the other hand, the influenza virus is a negative ssRNA virus that has glycoproteins that project on the surface of the virion. Since the influenza virus is a negative ssRNA virus, the ssRNA is not transcribed directly because the genetic material is made of the complementary strand of RNA. This means that to replicate, the complementary RNA strand must be transcribed into the template strand first. Influenza A (IAV) and B (IBV) are 12kb in size, which is typical for negative ssRNA viruses. The genome of IAV is made up of eight different segments of negative ssRNA. The main proteins found in IAV are the hemagglutinin (HA) and neuraminidase (NA) proteins, which make up the projections on the surface of the virion. In the envelope of IAV, HA, NA, and the matrix-2 (M2) proteins are integral proteins on the membrane of the virion. An integral protein is essentially locked into the membrane of the virus. HA, NA, and M2 overlay a matrix of the matrix-1 (M1) protein, which encloses the virion core. IBV is similar to influenza A, but the NB and BM2 proteins replace M2. Both HA and NA are responsible for categorizing IAV into subtypes that contribute to the infectivity and mutation rate of the virus that will be discussed in later sections.[8]

One key difference between coronavirus and influenza is the ssRNA that contains the genetic material for each virus. Coronavirus has positive sense ssRNA; whereas, influenza has a negative sense ssRNA. The difference between these two types of genetic material is that the positive sense genome can act as mRNA and be directly translated into proteins by the ribosomes of the virus. On the other hand, negative sense ssRNA in the influenza virus does not have this ability.[3,8] To produce mRNA, the negative sense ssRNA relies on RNA-dependent RNA polymerase to transcribe the RNA strand that codes for mRNA and to make the corresponding proteins.[8] Another difference between COVID-19 and IAV is genome complexity. As mentioned earlier, coronaviruses are the least complex viruses; whereas, IAV has a more complex genome. Genomic size is also a difference between each virus because coronavirus is 32kb; whereas, the influenza virus is 12kb.[3,8]

Rate of viral mutations

Influenza is well known for its predisposition to antigenic drift and antigenic shift. Antigenic drift is the result of point mutations in the amino acid sequence that makes up the antigens HA and NA, which are presented on the viral lipid envelope. Mutations can result in the expression of different HA or NA glycoproteins. Antigenic shift occurs in the virus when there is an abrupt change to the glycoproteins on the surface of IAV. This can occur when IAV infects a species of animal that is not the intended host. H1N1, or "swine flu," is an example of this because the virus was passed from swine to humans. In this scenario, pigs are the intended host, and humans are the accidental host. The H1N1 outbreak was the cause of concern, as the surface antigens HA and NA were different from previous antigens. Due to this, humans that became infected with the H1N1 variant of IAV did not have immunity because their immune systems did not have antibodies for the respective antigens on H1N1.[11]

COVID-19 can also undergo antigenic drift and antigenic shift over time. Two examples of prominent variants are SARS-CoV-2: B.1.1.7, which began in the United Kingdom (UK), and B.1.351, which was discovered in South Africa. Variant B.1.1.7 has a mutation in the receptor-binding domain, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor of the host. The mutation in this variant is at position 501 of the spike protein, where asparagine is replaced with tyrosine. This variant

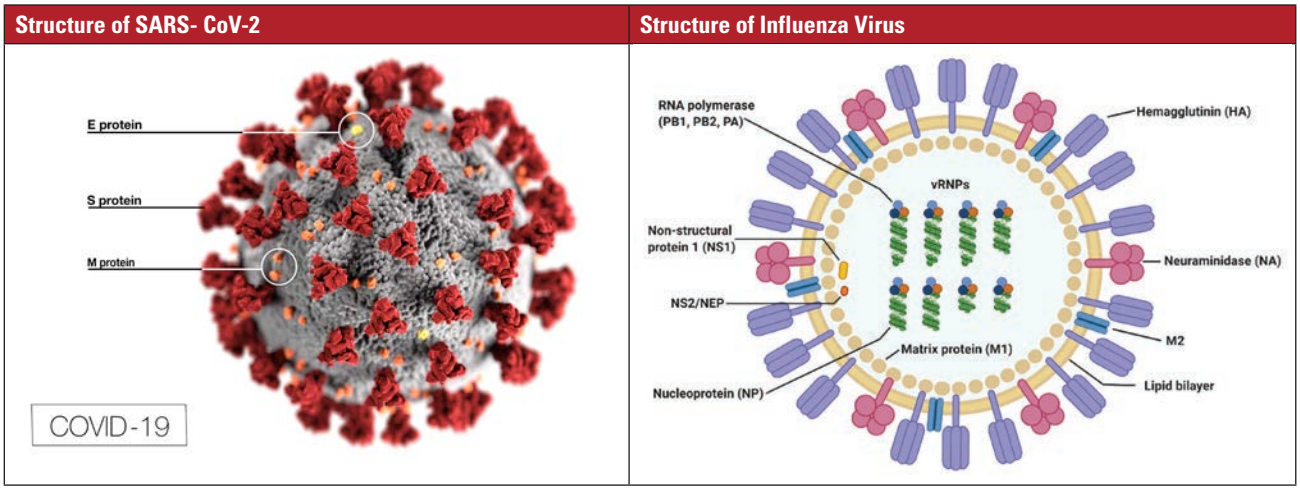

Figure 1: This image displays the structure of SARS-CoV-2 (left) and influenza virus (right). Left photo courtesy CDC. These images are not to scale.[9,10]

has also shown an increase in transmissibility compared to the parent strain.[12] Due to the increase of transmissibility of the B.1.1.7 variant, the virus strain was the most prominent strain in the United Kingdom at one point. The B.1.351 variant has multiple spike protein mutations. Both the B.1.1.7 and B.1.351 variant are more transmissible than the parent strain of COVID-19. The now-dominant Delta variant, or B.1.617.2, which first emerged in India, also is more transmissible.[13]

One mechanism that contributes to the high mutation rate of RNA viruses is RNA polymerase. RNA polymerase is an enzyme responsible for proofreading the RNA of a genome, before the RNA gets translated for replication. Since RNA viruses IAV and COVID-19 lack an effective proofreading functionality to ensure that the genome is being replicated accurately, they lend themselves to high mutation rates and the formation of different strains or variants. In IAV, the mutation rate ranges from 1.5^-3 to 7.2^-5/ bp.[14] This means that, on average, for every 667 to 13,888 base pairs translated, there could be a mutation. While the errors from RNA polymerase contribute to the creation of new variants of existing viruses, RNA polymerase may be a detriment to the survivability of the virus. [14]

Laboratory testing and diagnosis

Infection of COVID-19 or IAV may be first recognized by characteristic symptoms, but the only way to confirm the suspicion of infection is through laboratory testing, combined with a patient's presentation of symptoms. There are two common methods of testing for COVID-19 and IAV: polymerase chain reaction (PCR) and antigen testing. There is also serological testing available to determine if a patient recently had an infection, which is determined by detecting antibodies.

Antigen testing identifies antigens from the virus that are in the host, which can be used to determine if there was a previous infection of COVID-19 or influenza. While molecular testing is used to confirm a COVID-19 diagnosis, other laboratory tests help providers manage patients with severe COVID-19 infections. According to an article published by Justin Jones, PhD, in *Medical Laboratory Observer,* COVID-19 patients show elevated levels of procalcitonin (PCT), Interleukin-6 (IL-6), D-dimer, ferritin, cardiac troponin, and N- terminal pro-B-type natriuretic peptide (NT-proBNP), compared to healthy individuals. [15]

Molecular testing

PCR is a nucleic acid amplification process that detects the presence of a target genetic sequence by making millions of copies of the desired target in a matter of hours in vitro. This methodology uses the same components as in vivo replication, which includes DNA polymerase and a primer sequence. For viral nucleotide sequence detection, reverse transcriptase (RT) is also present to transcribe the RNA into complementary DNA (cDNA) for detection of the target sequence. In vitro RT-PCR replication differs from in vivo replication because in vitro RT-PCR targets a specific nucleotide sequence from the template strand of DNA, rather than duplicating the entire DNA strand.[16] If the target sequence is present in the sample, the reagents used in the testing will fluoresce, indicating a positive result in the RT-PCR method of testing.

According to an article published by the College of American Pathologists (CAP), RT-PCR can detect the presence of 500-5000 copies of viral RNA/mL near 100 percent of the time. However, pre-analytical factors, such as sample collection technique and the viral load at the collection site, affect the sensitivity and specificity of RT- PCR.[17] For example, if most of the viral load is in the lungs, but a nasal swab is collected, then the test may be negative because the viral load is not present at the nasal collection site.

In addition to assays that detect a single virus, some assays detect multiple pathogens. Having an assay that detects more viruses decreases the amount of testing a patient may undergo to receive a diagnosis.[18] Rather than performing a test for influenza, respiratory syncytial virus (RSV), and COVID-19 separately with multiple different patient specimens, some assays require one specimen from the patient and can detect a positive result in less than an hour. A disadvantage of performing this testing is that the reagents are in short supply due to the high demand to detect COVID-19 infection.

A variety of assays and tabletop analyzers were approved for emergency use by the U.S. Food and Drug Administration (FDA) during the pandemic.

Tabletop analyzers use isothermal technology to rapidly replicate the viral RNA. An acidic solution is heated to 132.8 Fahrenheit, which damages the viral envelope of COVID-19, exposing the RNA for replication.

Testing advantages include the fast turnaround time and portability, making it ideal for any decentralized lab location.[19] A disadvantage to this type of test is seen in the high false-negative rate. In a 2020 research study conducted by the Cleveland Clinic, 239 known COVID-19 specimens were tested on a tabletop analyzer, but only 85.2% of the specimens were considered positive. The desired sensitivity of a rapid test is 95%.[20]

The same isothermal nucleic acid technology can be used to replicate and differentiate between IAV and IAB nucleic acids.[19, 20, 21, 22]

Antigen Testing

Antigen testing is another method that can be used to diagnose COVID-19 and influenza infections. Antigen testing is a rapid testing method that detects the presence of viral antigens in the host. This method is not as sensitive or specific as molecular testing. This testing method is a useful tool when screening for COVID-19 or influenza. The high specificity is the ability of the test to determine the absence of an infection. This testing method is cost-effective and only requires a small cartridge, or tabletop analyzer, rather than the large analyzer that was discussed previously. This testing method produces results for COVID-19 influenza A and B in minutes.[23, 24]

One example of antigen testing for detection of the influenza virus is a rapid influenza diagnostic test (RDIT). This testing method detects viral antigens in 10-15 minutes.[25] The tests identify IAV and IBV nucleoprotein antigens present in respiratory specimens.[26]

Serological testing

Serological testing can also be used to detect a COVID-19 infection. Rather than replicating a target genetic sequence in PCR, serological testing detects the presence of antibodies produced as an immune response by a person infected with a virus. Immunoassays for qualitative and quantitative detection of IgG or IgM antibodies to SARS-CoV-2 in serum are available.[27] Serological testing can be used for influenza infections as well; however, the assays are not recommended for clinical diagnosis of IAV or IBV, as the diagnosis cannot be reliably interpreted since testing requires paired acute and convalescent sera collected 2-3 weeks apart for accurate testing.[25] This does not allow for timely or rapid detection of IAV or IBV.[26] Serological

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Manufacturer	Mechanism of Action	Required Doses	Efficacy	Storage Temperature	Approved for Use
Moderna	Modified mRNA in lipid particles is delivered into host cells, allowing expression of SARS-CoV-2 S glycoprotein	A series of 2 0.5mL doses administered 1 month apart	94.1%	-50 to –15C and protected from light 2-8C for 30 days 8-25 for 24 hours	Approved by the FDA for use in the United States under EUA. Approved for CMA by the EMA.
Pfizer-BioNtech (Comirnaty in the UK)	Modified RNA in lipid particles is delivered into host cells, allowing expression of SARS-CoV-2 S glycoprotein	A series of 2 0.3mL doses administered 21 days apart	95.0%	-80 to –60C until expiration -25 to –15C for 2 weeks Protected from light until use	Approved by the FDA for use in the United States under EUA. Approved for CMA by the EMA.
Johnson & Johnson	Recombinant Ad26 expressing the SARS-CoV-2 S glycoprotein	A single 0.5mL dose	66.3%	3 months at 2-8C 2 years at -20C	Approved by the FDA for use in the United States under EUA.
Vaxzevria (previously AstraZeneca)	Recombinant ChAdOx1 vector encoded with S glycoprotein of SARS-CoV-2	A series of 2 0.5mL doses administered 4-12 weeks apart.	62.6% in individuals who received both doses	Unopened 6-month shelf life when stored at 2-8C Opened 48hours at 2-8C Or 6 hours at 30C	Approved by the EMA for use in the European Union. Not approved for use in the United States.
Novavax**	Prefusion spike protein encoded with SARS-CoV-2 using recombinant nanoparticle technology and a saponin based adjuvant	A series of 2 doses administered 21 days apart	89.3%	2-8C for an estimated minimum of 6 months	Currently in Phase 3 trial in US, UK, and Mexico.

Table 1: Comparison of Vaccinations for COVID-19 [35, 36, 37, 38, 39, 40]
**Not currently authorized for use in the US or EU. The most recent available data was used.

testing is relevant to the public health field and is a valuable screening method.[26, 28]

Correlated lab findings

While diagnostic testing is necessary to accurately diagnose COVID-19, other laboratory tests help providers monitor patients with COVID-19. Among these tests are Interleukin- 6 (IL-6), D-dimer, Ferritin, Procalcitonin (PCT), and NT- proB- type Natriuretic Peptide (NT-proBNP).[15]

IL-6 is a predictor of hyper-inflammation and respiratory failure in COVID-19 patients.[15] In a meta-analysis conducted in 2020, the"mean IL-6 levels were more than three times higher in patients with complicated COVID-19 compared with those with noncomplicated disease."[29]The increase in IL-6 is related to the"cytokine storm"that occurs in patients with severe COVID-19. The damaging immune response that cytokines promote can lead to acute respiratory distress syndrome.[15] Therefore, an increased IL-6 is a predictor for a negative outcome for a patient with COVID-19, such as the need for a respirator.

D-dimer is another laboratory test that can be useful in managing patients with COVID-19. D-dimer measures degradation products from fibrinolysis after clot formation. In COVID-19 patients, D-dimer levels were reported to be elevated in severe cases. A 2020 study conducted by Berger et al. concluded that considering variables such as hypertension, sex, age, and weight, patients with an elevated D-dimer have an increased association with COVID-19 infection.[30] Another study found that of the 540 COVID-19 patients that were hospitalized, 69.4% of those COVID-19 patients had elevated D-dimer levels.[15]

Ferritin is an intracellular blood protein that contains iron and can be measured to determine the amount of iron that is stored in the body. Ferritin levels may aid COVID-19 diagnosis because patients with severe COVID-19 infection show an increase in ferritin levels of hyperferritinemia. Hyperferratinemia among COVID-19 patients is associated with the cytokine storm that takes place during infection. The cytokine storm increases the amount of pro-inflammatory cytokines. The production of these pro-inflammatory cytokines increases inflammation in the body. When inflammation increases, ferritin levels can indicate the degree of inflammation in a patient.

In a study by Gomez-Pastora et al., ferritin levels of patients in Wuhan, China, with non-severe and severe infection were analyzed. The findings for the study showed that patients with a non-severe infection had normal ferritin levels; whereas, patients with a severe infection that survived had ferritin levels >800 ug/L (reference range is 30-400 ug/L). Those that did not survive the infection had ferritin levels that reached 1400ug/L.[31]

PCT is the precursor of the hormone calcitonin (CT). In bouts of systemic inflammation, PCT is broken down, resulting in elevated PCT in the serum. For elevation of PCT, there must be severe inflammatory stimuli present. An increased PCT is associated with a 5-fold increase in the risk of severe COVID-19 infection.[32] A 2020 retrospective cohort study was done with 95 patients with confirmed COVID-19 infections in Union Hospital of Tongji Medical College in Wuhan, China. Of the patients that were studied, 62 had a moderate infection, 21 had a severe infection, and 12 patients were in critical condition. Six of the critical patients died due to COVID-19 infection. In the study, the mean values of PCT were determined for the varying disease severity. In the moderate infection group, the PCT measured 0.05 ± 0.05ng/mL (reference range: <0.15ng/mL). In the severe group, the PCT was 0.23 ± 0.26ng/mL. Lastly, the critical group PCT levels were 0.44 ± 0.55ng/mL.[32] The retrospective study was able to correlate the severity of COVID-19 infection with increased PCT levels. The findings of the study detailed that the higher the PCT values in patients with COVID-19 infection, the more likely the patient will have a more severe disease state.

NT-proBNP is a nonactivated pro-hormone that is released in response to changes of pressure inside of the heart and secreted

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Virus	Type of vaccination	Mechanism of Action	Brand Name	Efficacy	Considerations
SARS-CoV-2	Protein Subunit	Prefusion spike protein encoded with SARS-CoV-2	Novavax*	90.4%	Currently in Phase 3 trial in US, UK, and Mexico. Not approved for use by the FDA.
	Viral Vector	A harmless, recombinant vector is encoded with S glycoprotein of SARS-CoV-2	Vaxzevria (Formerly AstraZeneca	62.6%	Approved by the FDA for use in the United States under EUA.
			Johnson & Johnson/Janssen	66.3%	
	Nucleic Acid	Modified RNA in lipid particles is delivered into host cells, allowing expression of SARS-CoV-2 S glycoprotein	Moderna	94.1%	Approved by the FDA for use in the United States under EUA. Approved for CMA by the EMA.
			Pfizer- BioNtech	95.0%	
Influenza	Inactivated	Inactivated (dead) form of the virus is used	Afluria	60%	Intended for ages 6 months and up.
			Fluarix	66.9%	
	Live Attenuated	Attenuated (weakened) form of the virus is used	FluMist	44.5%	An intranasal spray intended for ages 2-49.

Table 2: Vaccinations for SARS-CoV-2 and Influenza Virus [35, 36, 37, 38, 39, 40, 41, 42, 43]

when there is an increase in myocardial wall stress.[33] An increase in NT-proBNP is typically associated with heart failure but is also seen in patients with COVID-19. A 2020 retrospective study conducted by Gao Lei and Jiang Dan et al. evaluated the value of NT-proBNP in patient prognosis. In the study, lab data of 102 patients with severe COVID-19 infection at Hubei General Hospital in Wuhan, China, was used in an analysis of NT-proBNP. In the study, a NT-proBNP level of 88.64pg/mL (reference range: 0-74 years of age is 125pg/mL) was the cutoff level to predict in-hospital death in patients with COVID-19 infection. The cutoff value of 88.64pg/mL had 100% sensitivity and 66% specificity. Patients with NT-proBNP levels >88.64pg/mL were also found to have a higher risk of death than patients with a NT-proBNP <88.64pg/mL.[34] The retrospective study concluded that the levels of NT-proBNP may be able to determine the risk factor of in-house death for patients with severe COVID-19 infection.

Vaccines

Many COVID-19 vaccination options are under clinical trials or approved for emergency use by the FDA. **Table 1** shows some of the vaccination options for COVID-19 around the world. In **Table 1**, the mechanism of action, dosage, efficacy, storage temperature, and approval status are discussed. The efficacy is the ability of the vaccinations to reduce the risk of contracting the targeted virus. The higher the efficacy of the vaccination, the lower the risk is of contracting the intended virus. **Table 2** discusses the most effective COVID-19 and influenza vaccinations currently available.

Viral mutations and vaccinations

It is necessary to understand the structure of SARS-CoV-2 and influenza, due to the challenges created by mutations for vaccination development. Regarding the influenza virus, antigenic drift and antigenic shift are the main challenges associated with vaccination efficacy. The main challenge of SARS-CoV-2 is the emergence of variant strains. The influenza virus undergoes mechanisms called antigenic drift and antigenic shift, which allow the H and N glycoproteins on the surface of influenza to change their expression. When the H and N glycoprotein change due to amino acid substitution or mutation, there is the potential for a new strain of the influenza virus. An example of this is H5N1, or bird flu, which has the H5 glycoprotein expressed, changing the glycoprotein's properties. In the example above, the H protein in H5N1 would function differently than H1N1 or swine flu.

Antigenic drift and antigenic shift are challenges for vaccination development. As a result, the WHO makes its recommendations for the influenza strain predicted to be the most prevalent six to eight months before the influenza season. The six- to eight-month window is necessary for vaccine development, manufacturing, and distribution.[44] However, by the influenza season, antigenic shift or antigenic drift can occur, making the manufactured vaccination ineffective against the virus. In **Table 2**, the vaccine efficacy for influenza virus ranges from 44-66%. The changes H and N undergo due to antigenic drift and shift explain the range of vaccine efficacy.

The target for vaccine development for SARS-CoV-2 is the Spike glycoprotein on the surface of the virus. In **Table 2**, the vaccine efficacy for SARS-CoV-2 ranges from 62-95%. The prevalent SARS-CoV-2 variants have Spike glycoprotein mutations. When mutations of the target protein occur, the vaccinations undergo further clinical trials to ensure that the vaccine will be effective against new variants. There are multiple SARS-CoV-2 variants of concern, such as the B.1.351 (Beta), B.1.617 (Delta), and P.1.1 (Gamma) variants.[45] A variant of concern can have more severe infection, reduced vaccine effectiveness, or increased transmissibility. The B.1.6.17.2, or Delta variant, is now the most concerning variant of SARS-CoV-2.[45]

Conclusion

There are many challenges posed by SARS-CoV-2 and the influenza virus regarding diagnosis and prevention. The structure, symptoms, transmission, and rate of mutation of these viruses contribute to these challenges. The spike glycoprotein is the target of vaccination development of SARS-CoV-2. Hemagglutinin and Neuraminidase are the targets for vaccination development of IAV and IBV. Both COVID-19 and influenza have some similar symptoms, such as cough, fever, fatigue, and sore throat; however, the hallmark symptom of COVID-19 is shortness of breath. Both viruses can be transmitted through

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respiratory droplets, or aerosols, and have varying times of survivability on surfaces, including doorknobs and counters. The lack of proofreading associated with RNA polymerase lends itself to mutations, which can create variants of influenza and COVID-19.

Variants of influenza have a differing expression of H and N glycoproteins. An example of this is H1N1 or swine flu. The only way to confirm a diagnosis of COVID-19 or influenza is confirmatory laboratory testing, which should be considered in conjunction with the presenting symptoms to diagnose COVID-19 and influenza.

Molecular testing is the most sensitive and specific method to confirm COVID-19 and influenza infection. Serological testing is used to detect a previous infection of COVID-19 because serological testing detects the presence of antibodies that are produced by the host as a response to infection. Serological testing is not recommended to detect recent influenza infection because serological testing cannot be reliably interpreted due to the rapid mutation rate of influenza. Antigen testing is a rapid method that can determine the presence of COVID-19 or Influenza infection, but antigen testing is less sensitive and specific than the molecular method of RT-PCR.

Currently, in the United States, three vaccines are offered to the public, Moderna, Pfizer-BioNtech, and Johnson & Johnson / Janssen. Moderna and Pfizer are both two-dose mRNA vaccines; whereas, Johnson & Johnson's Janssen vaccine is a single dose viral vector vaccination.

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Comparing the structure, diagnosis, and prevention of SARS-CoV-2 and influenza

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1. **Influenza is a common seasonal illness caused by _____.**
   - A. SARS-CoV-2
   - B. licking a doorknob
   - C. IAV or IBV
   - D. genetic factors

2. **The influenza virus was first isolated in the laboratory in _____.**
   - A. 1925
   - B. 1853
   - C. 1969
   - D. 1932

3. **One of the most well-known outbreaks of the influenza virus was the 1918 Spanish flu, which was an outbreak of _____.**
   - A. SARS-CoV-2
   - B. H1N1
   - C. MERSA
   - D. Monkeypox

4. **In 2017, the World Health Organization (WHO) reported that _____ people worldwide die due to flu-related respiratory illness each year.**
   - A. 650,000
   - B. 250,000
   - C. 3 million
   - D. 80,000

5. **_____ are characterized as positive single-stranded RNA enveloped viruses (ssRNA).**
   - A. Flu viruses
   - B. H1N1 viruses
   - C. Swine flu viruses
   - D. Coronaviruses

6. **The genome of positive sense _____ can be used as messenger RNA (mRNA).**
   - A. fear
   - B. ssRNA viruses
   - C. DNA
   - D. assays

7. **_____ are the least complex form of viruses and only contain information that is needed to infect a host cell.**
   - A. Nucleotides
   - B. Bacteria
   - C. Amoeba
   - D. SsRNA viruses

8. **SsRNA viruses replicate the _____ and the genetic material that will be contained in it.**
   - A. nucleolus
   - B. nucleocapsid
   - C. body's DNA
   - D. host

9. **In DNA or RNA transcription, _____ is required for replication.**
   - A. ATP
   - B. IAV
   - C. H1N1
   - D. mitochondria

10. **Coronaviruses range in size from 26 to 32 kb, which makes them the _____ single-stranded RNA virus.**
    - A. smallest
    - B. most prominent
    - C. largest
    - D. carrier of

11. **_____ projections on the surface of the coronavirus give the virus a crown-like appearance that is visible using electron microscopy (EM).**
    - A. Nucleotide
    - B. SsRNA
    - C. Flagella
    - D. Glycoprotein

12. **The major _____ that contribute to the structure of coronaviruses are the membrane (M), envelope (E), nucleocapsid (N), spike (S), and hemagglutinin- esterase (HE).**
    - A. amino acids
    - B. proteins
    - C. structures
    - D. carbohydrates

13. **The _____ protein is a structural protein that determines the shape of the envelope.**
    - A. S
    - B. N
    - C. E
    - D. M

14. **The _____ protein is an integral protein forming a lattice with the M protein to form the membrane.**
    - A. S
    - B. N
    - C. E
    - D. D

15. **The _____ protein is responsible for binding to the genome of the virus and is seen at the highest abundance in host cells infected with the virus.**
    - A. S
    - B. N
    - C. E
    - D. M

16. **The _____ protein creates the hallmark spikes of coronaviruses that can be seen through EM.**
    - A. S
    - B. N
    - C. E
    - D. M

17. **Positive sense genome can act as mRNA and be directly translated into proteins by the _____ of the virus.**
    - A. ribosomes
    - B. nucleocapsid
    - C. mitochondria
    - D. mRNA

18. **_____ occurs in the virus when there is an abrupt change to the glycoproteins on the surface of IAV.**
    - A. Antigenic drift
    - B. Glucose binding
    - C. Receptor binding
    - D. Antigenic shift

19. **_____ is an enzyme responsible for proofreading the RNA of a genome before the RNA gets translated for replication.**
    - A. Maltase
    - B. Trypsin
    - C. RNA polymerase
    - D. Amylase

20. **_____ patients show increased results for procalcitonin (PCT), Interleukin-6 (IL-6), D-dimer, ferritin, cardiac troponin, and N- terminal pro-B-type natriuretic peptide (NT-proBNP) compared to healthy individuals.**
    - A. Influenza
    - B. C. diff
    - C. COVID-19
    - D. H1N1

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The value of molecular POCT for managing infectious diseases

By Kim Futrell, MT(ASCP), MSHI

Point-of-care testing (POCT) technology continues to advance at a fast pace, making it easier to shrink complex testing platforms into point-of-care (POC) devices. Though not without its challenges, testing at a molecular level far surpasses the accuracy of other POCT methodologies. Molecular POCT devices allow quick, easy-to-use testing in near-patient scenarios where a rapid diagnosis can be the difference between treating one patient and treating a multitude of patients who become infected because the initial diagnosis is delayed.

Molecular testing is a broad term that refers to the detection and/or quantification of specific DNA or RNA sequences in a specimen. Molecular tests are used to detect microorganisms, look for genetic mutations associated with certain diseases and cancers, perform paternity tests, and much more. Highly complex molecular testing is performed in molecular or microbiology specialty laboratories by trained laboratory professionals.

Basic principle of molecular testing

The starting principle behind molecular testing involves multiplying (or amplifying) the amount of DNA or RNA within a specimen by thousands to millions of times prior to analyzing. DNA is amplified using cycling methods, such as polymerase chain reaction (PCR) or isothermal amplification. This means that samples with only a few hundred infectious particles can be amplified billions of times, which increases the likelihood of detection and potentially compensating for suboptimal sample collection.

The amplification of DNA/nucleic acids is achieved using naturally occurring enzymes (proteins). DNA polymerase is one of the key enzymes used in this process, which is the basis for the PCR methodology. Other enzymes can be used for amplification, and these are typically grouped under the generic label of isothermal nucleic acid amplification tests (INAAT). The amplification step makes molecular testing methodologies more sensitive than immunological assays, as each cycle of amplification doubles the amount of DNA in the sample. PCR testing involves amplification achieved through temperature cycling, while isothermal amplification assays use a constant reaction temperature for the amplification that results in a shorter run time than PCR.

PCR versus isothermal

PCR assays use fluorescence to detect the amount of amplified DNA in real time. With each cycle of PCR, more dye molecules are released, so the fluorescence increases proportionally to the amount of target amplicon. In real-time PCR, the amount of target DNA present in the sample typically determines the number of PCR cycles necessary. This number is called the cycle threshold or Ct value.[1] Subsequently, Ct levels are inversely proportional to the amount of target nucleic acid in a sample.

Meanwhile, there are a multitude of types of isothermal molecular technologies, including:

- Helicase-dependent amplification (HDA)
- Loop-mediated isothermal amplification (LAMP)
- Nicking enzyme amplification reaction (NEAR)
- Reverse transcription recombinase polymerase amplification (RT-RPA)
- Rolling circle amplification (RCA)
- Transcript-mediated amplification (TMA)

Although these methods vary, they have some commonali-

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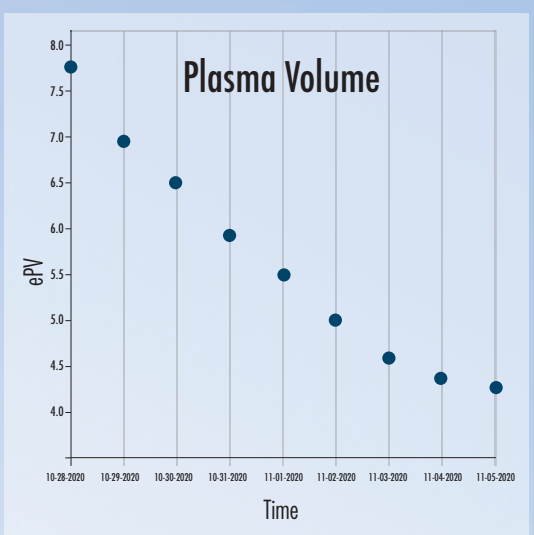

Prime Plus screen showing ePV values

Plasma volume status is vital in testing critically ill patients but is extremely difficult and costly to obtain, particularly as a POC test. Plasma volume assessment affects almost every aspect of a patient's care, including giving IV fluids, diuresing, starting vasopressors, initiating renal replacement therapy, deciding on transfusion requirements and intubation and extubation.[1,2]

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Advantages of Molecular POCT for Infectious Disease

ties. For example, because the nucleic acid strands are not amplified with heat, isothermal methods use an alternative method for primer binding and amplification reaction — a polymerase with strand-displacement activity. The polymerase is also used to separate the strand that is still annealed to the target gene sequence.

Isothermal nucleic acid amplification, used in many molecular diagnostic platforms (and in POCT), speeds the testing process by eliminating the need for thermal cycling. For example, LAMP uses strand-displacing DNA polymerase and primers to amplify specific DNA sequences.[2] RT-RPA uses recombinase, single strand binding protein, DNA polymerase, and reverse transcriptase to amplify the RNA target. For each of these methodologies, the output is interpreted via fluorescent or colorimetric reporters and lateral flow strip platforms to achieve decipherable test results.

The high level of reliability and accuracy that molecular testing techniques offer typically comes with a longer turnaround time (TAT), which is attributed to batch testing, complex multistep testing, and predetermined testing schedules. PCR methodologies, considered the gold standard for RNA virus detection, can take up to four hours for results and require expensive thermal cyclers.[2] In addition, traditional molecular diagnostic methodologies require sophisticated infrastructure, expensive reagents, stable electrical power, and highly skilled staff.

Traditional (non-molecular) POCT

Generally speaking, POCT allows for rapid diagnosis and subsequent timely treatment. Rapid, easy-to-administer POCT has long been used to detect infectious disease antigens or antibodies, such as influenza, mononucleosis, and group A streptococcus (GAS). However, despite offering a quick TAT, many of these assays come with a less than ideal sensitivity and specificity trade-off. Conventional, non-molecular POCT can have suboptimal limits of detection, resulting in false negatives for samples with low viral or bacterial load. Because of this lower sensitivity, these tests typically require a confirmatory test to rule out false negatives. This scenario sets the stage for the rapid TAT combined with higher sensitivity that molecular POCT methodologies offer.

Molecular POCT is much faster than lab-based molecular tests and more accurate than existing non-molecular POCT. The precision and accuracy of molecular POCT gives clinics or other ambulatory care centers the ability to deliver a standard of care equivalent to a tertiary care center.[3]

Infectious disease testing

During the last three decades, more than 30 new infectious diseases have been identified, making it imperative to have a reliable method to identify the responsible pathogens.[4] Access to sensitive and rapid infectious disease assays is essential for accurate diagnosis, effective treatment, and timely infection control. Although antigen-based POC tests offer a quick TAT, the testing has a relatively low sensitivity and specificity (compared to culture) and can be difficult to interpret, potentially leading to erroneous results. As such, the recommendation is to reflex negative results to a confirmatory molecular method.

Group A Streptococcus (GAS)

Annually, there are approximately 11 million pediatric care visits for pharyngitis, of which GAS — the type of pharyngitis that requires treatment — accounts for 15-30%.[5] Traditional culture methods offer a TAT of 24 to 48 hours, causing a significant delay in definitive diagnosis. A rapid, accurate diagnosis for GAS pharyngitis is vital to decreasing transmission and avoiding more serious complications like acute rheumatic fever.

With rapid antigen POCT and its requisite confirmatory testing, an empiric therapy may be employed which can contribute to the unnecessary use of antibiotics. Due to this testing conundrum, unfortunately, antibiotics are prescribed for approximately 60% of all pharyngitis cases, in spite of only 15-30% of pharyngitis cases actually being caused by GAS.[5] In contrast to traditional POCT, molecular POCT for GAS provides more reliable and accurate results that enable faster diagnosis, treatment and eliminate the delay and cost for confirmatory testing.

Influenza

Another respiratory illness that greatly benefits from rapid and highly accurate molecular POCT is Influenza. According to the estimates from the Centers for Disease Control and Prevention (CDC), there were approximately 490,600 hospitalizations and 34,200 deaths attributed to influenza during the 2018–2019

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season. Specific to pediatrics, there were more than 46,000 hospitalizations and 136 deaths.[6]

To achieve best patient care, influenza requires a rapid, highly accurate diagnostic test, so an antiviral treatment can be administered within 48 hours of symptoms. Antigen-based POCT for influenza is frequently used in outpatient settings but is significantly less sensitive compared to molecular methods. The rapid TAT and accuracy of molecular influenza testing allows antivirals to be administered in a timely manner, subsequently preventing unnecessary hospitalizations and antibiotic prescriptions.[3]

Molecular POCT for COVID-19

Response to the COVID-19 pandemic has also been challenged by delays associated with centralized laboratory PCR testing. In hospitals, these delays lead to poor patient flow and nosocomial transmission. To fulfil the demand for rapid diagnoses during disease outbreaks, the healthcare industry needs POCT that is affordable, fast, and deployable in the field.[2] The rapid, accurate test results that molecular POCT methodologies offer are extremely beneficial in a public health crisis, such as a pandemic. Molecular POCT is associated with faster results, improvements in infection control measures, and better patient flow, as compared with centralized laboratory PCR testing.[7] For public health emergencies, molecular POCT can be used to achieve accurate, economical diagnoses, promoting early detection and mitigation to better control an infectious disease outbreak. A rapid, accurate, cost-effective device benefits individual patients and the public by reducing transportation needs, lowering the spread of infection, and reducing the cost of testing.

Laboratory staff shortages

Another factor driving the demand for molecular POCT is the scarcity of skilled laboratory professionals available to perform traditional molecular testing. Laboratory professionals have faced a workforce shortage for many years, with the competition to hire qualified technologists more challenging than ever. The Bureau of Labor Statistics estimates that an additional 35,100 jobs will be needed between 2018 and 2028, which does not include job openings due to retiring workers.[8]

The development and implementation of point of care molecular testing, many of which are CLIA-waived and subsequently easy to use, allows testing to take place near patients in clinics, EDs, pharmacies, etc. — testing that previously could only be accomplished with specialized staff.

Antibiotic stewardship

In addition, the use of more sensitive and specific molecular tests at the POC promotes more appropriate use of antibiotics and improves overall infection control. Antimicrobial resistance is an ongoing major public health issue. Our healthcare system is tasked with improving stewardship of antibiotics; meaning, swift administration of the appropriate antibiotic within an effective time frame and ensuring that antibiotics are not prescribed for illnesses that do not require them. However, effective antibiotic stewardship is complicated by the fact that initial antibiotic use is often empiric because the provider does not have definitive results that identify the pathogen for two to three days post empiric prescription.[9] The consensus among experts is that antibiotic stewardship can be improved by implementing POCT diagnostics to rapidly identify bacterial pathogens.[9] For example, POCT for pharyngitis has become widely available in pharmacies and is considered an effective part of the strategy to contain antibiotic resistance and contribute to antimicrobial stewardship.[10] Successful implementation of rapid POCT has the potential to help prevent the spread of infectious diseases and impede antimicrobial resistance.[11]

Access to sensitive and rapid infectious disease assays is essential for accurate diagnosis, effective treatment, and timely infection control. Innovations in molecular POCT are allowing molecular testing to expand from specialty molecular diagnostics laboratories into clinical laboratories, clinics, and any testing location near the patient's side. The rapid TAT of POCT combined with the superior sensitivity and specificity of molecular methodologies affords the best scenario for diagnosis and containment of contagious infectious diseases. For public health emergencies, molecular POCT can be used to achieve accurate, economical diagnoses, promoting early detection and mitigation to better control an infectious disease outbreak.

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Not all HPV genotypes pose same risk for disease

By Molly Broache, MSN

Cervical cancer kills more than 300,000 women annually. Global data from 2018 indicated that cervical cancer is the fourth most common female cancer, claiming an estimated 270,000 lives annually.[1] It is well established that high-risk human papillomavirus (HPV) is the cause of almost all (99%) cervical pre-cancers worldwide.[2]

HPV is the most prevalent sexually transmitted infection in the United States. The virus currently affects 79 million Americans and is most commonly spread through vaginal or anal sex.[3]

Effective strategies for cervical cancer screening are available. A cytology-based test, the Pap smear, detects abnormal cells in the cervix, while HPV tests detect the presence of high-risk HPV genotypes in cervical cells. The American College of Obstetricians and Gynecologists (ACOG) endorses the U.S. Preventive Services Task Force (USPSTF) recommendations for cervical cancer screening. In women 30-65 years old, the USPSTF recommends the use of cytology-based testing every three years, primary high-risk HPV testing every five years with an assay approved by the U.S. Food and Drug Administration (FDA), or co-testing (high-risk HPV testing and cytology) every five years.[4]

There are more than 100 different genotypes of HPV. The low-risk types can cause genital warts, but the high-risk types can progress to cervical pre-cancer and cancer, with some of the high-risk types more likely to progress to cervical cancer than others.[5] As the population vaccinated against HPV increases, decreases in HPV 16 and 18 can be seen,[6,7] making it crucial to identify the other high-risk HPV types.

There are 14 genotypes that are considered high-risk and can lead to the development of cervical cancer and its precursor lesions: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.[8] The prevalence of high-risk HPV genotypes varies in cervical cancer cases. Of the 14 high-risk HPV genotypes, 16,18, and 45 cause 77% of cervical cancers worldwide. HPV types 16, 18, 45, 33, 58, 52 and 31 contribute to 90% of all cervical cancer. HPV types 51, 35, 39, 68, 56, 59, and 66, contribute to less than 9% of all cervical cancer.[9]

In a large clinical trial of a currently FDA-approved HPV assay with extended genotyping, the occurrence of cervical disease in 33,858 women 21 years and older was tracked during routine cervical cancer screening. High-risk HPV was detected in 15% of the cases.[10]

Researchers compared prevalence of HPV genotypes in samples with a negative histology result with those with severe disease, which is defined as cervical intraepithelial neoplasia disease of 3 or worse (CIN3+). Based on those parameters, 16, 18, and 31 were the most prevalent genotypes in cases of CIN3+.[10]

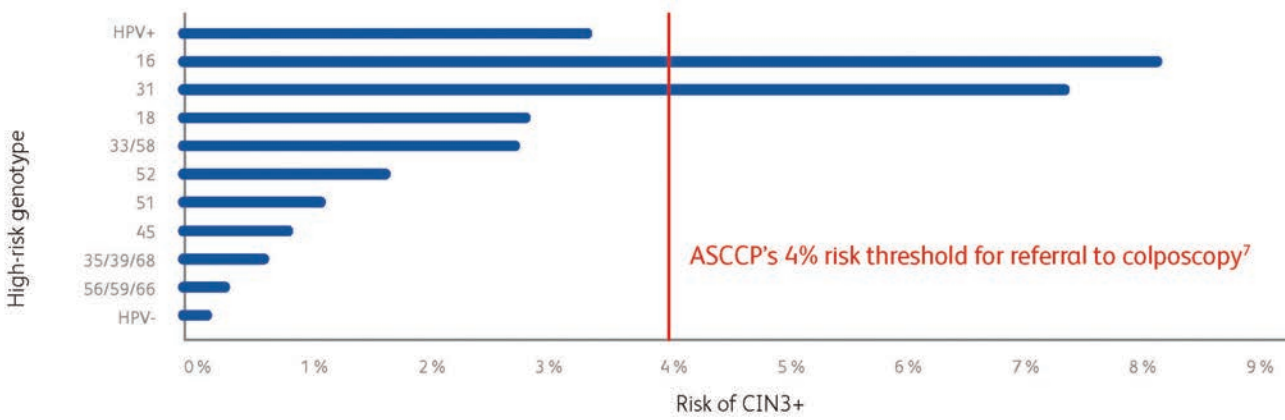
HPV assays

Because not all high-risk HPV types pose the same risk for cervical pre-cancer and cancer, HPV assays often report out information regarding individual HPV genotypes. Some HPV assays offer partial genotyping, reporting HPV 16 and 18 or 18/45 separately, and the remaining high-risk HPV genotypes in a pooled report. HPV assays with extended genotyping detect at least five individual high-risk HPV genotypes, such as HPV 16, 18, 31, 51 and 52.[11]

Reporting some high-risk HPV genotypes in a pooled report may mask the true risk of (CIN3+), particularly for HPV 31, which poses a similar risk for cervical pre-cancer and cancer, as compared to HPV 18. That is why pooled reporting of high-risk genotypes, such as 31, can lead to a one-year follow-up recommendation instead of an immediate colposcopy referral.[12,13,14]

Knowing the HPV genotype of an infection is critical in assessing patient risk. As seen in **Figure 1**, the risk of CIN3+ in HPV positive women over 25 years old with normal cytology varies, depending on which genotypes are detected in a patient's specimen.[14]

Risk of CIN3+ by HPV type in women ≥ 25 years with normal cytology



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The goal of cervical cancer screening is to detect pre-cancer, before it develops into cancer. HPV tests that offer extended genotyping provide a more personalized assessment of an individual's risk for developing cervical pre-cancer and cancer.

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A nonconforming event program reduces misidentification errors

Joanne P. Christopher, MA, ELS

Researchers estimate that more than 160,000 adverse patient events occur each year in the United States as a result of errors in identifying patient specimens used in laboratory testing.[1]

Regulatory and accreditation organizations require policies, processes, and procedures to ensure correct patient and specimen identification, but errors occur frequently. The potential for significant harm exists from test results reported on the wrong patient, not only to misidentified patients, but also to patients whose healthcare decisions are based upon test results from misidentified specimens. The risk of harm in both scenarios is high, and laboratories must establish stringent policies for identification errors. Of all pre-examination processes, improperly identifying patients and incorrectly labeling diagnostic specimens have the most potential to result in catastrophic consequences.[2] Potential harm to the patient from the lack of standardization in identification procedures in healthcare include misdiagnosis, incorrect treatment, failure to treat an existing condition, unnecessary surgery, injury, disability, and death.[3,1]

Patient and specimen misidentification errors

Misidentification can present in the laboratory in a variety of ways, including:[2]

- A specimen is received unlabeled.
- A specimen is incompletely labeled.
- An examination request is received with incomplete or incorrect patient ID information.
- The patient ID information from the specimen and examination requests do not match.
- The specimen and examination request match, but the specimen was collected from the wrong patient.

The patient identification process

Accurate patient identification is necessary at all points where the patient interacts with the healthcare system. While healthcare professionals recognize the full name and date of birth as two possible identifiers, neither name nor date of birth alone can identify a single unique patient.

Most healthcare systems have created a code, the patient-specific identifier, which is used to link the uniquely identifiable patient to his or her medical record. Confirmation of the patient's identity using photo identification or another acceptable demographic indicator is also recommended.[2] In addition, all inpatients must have ID bands affixed to their person, unless exempted by facility policy (eg, residents in long-term care facilities, patients in psychiatric wards). If any discrepancies are identified, specimens should not be collected, until all inconsistencies are resolved. Any discrepancy, however minor, must be reported to the responsible caregiver as determined by facility policy.[5]

Healthcare professionals must ensure that the specimen is collected from the individual designated on the examination request and/or labels. Examples of high-risk situations that put patients at risk of being misidentified include: [2]

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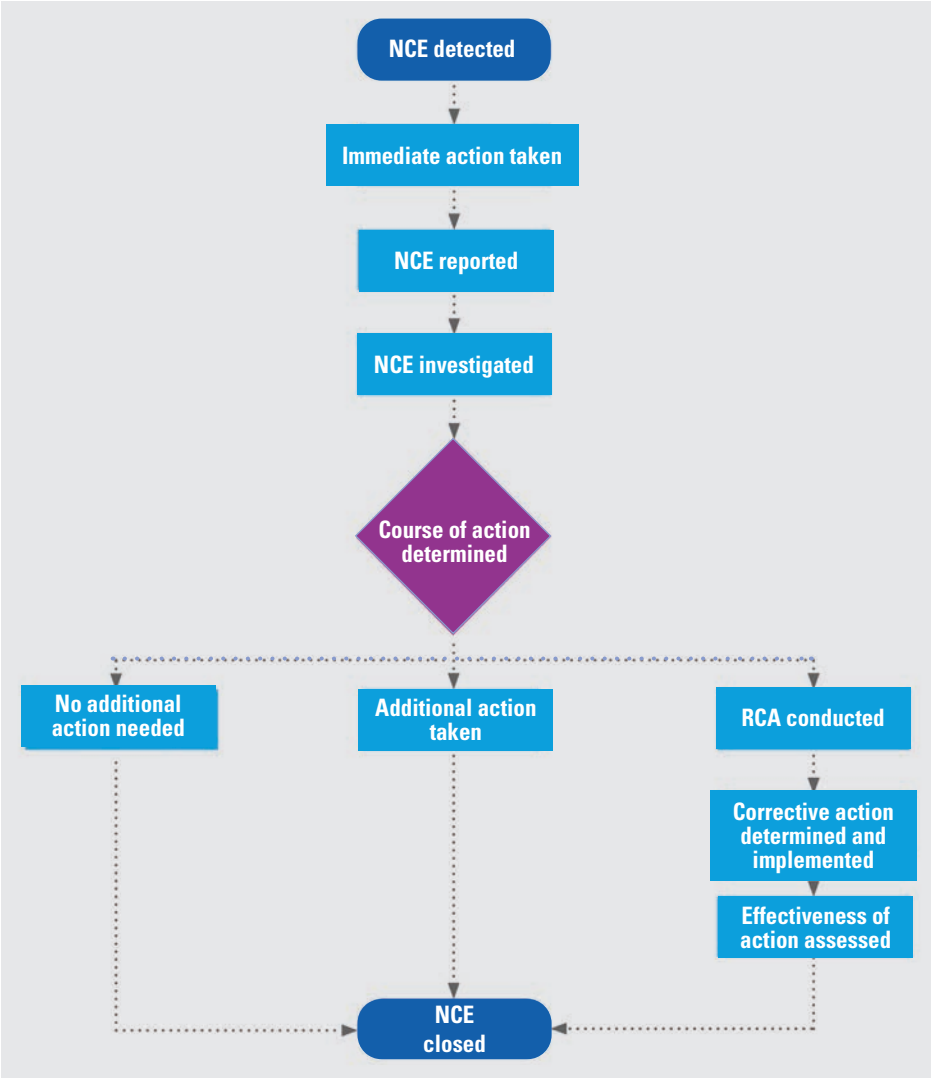

Figure 1. Reprinted with permission from Clinical and Laboratory Standards Institute.[7]

- Siblings or twins
- Newborns
- Common names
- Look-alike or sound-alike names
- Multiple patients in the same room

The five main elements of every patient specimen label include: (1) patient name, (2) a unique patient identifier, (3) date of birth, (4) specimen collection time and date, and (5) a designated space for the collector's identification (initials, signature, code).[4] Specimen collection containers must be labeled immediately after collection, in the patient's presence, by the healthcare professional who collected the specimen, unless the specimen is self-collected. When circumstances result in a specimen being labeled by someone other than the healthcare professional, the person labeling the specimen must witness the collection and that the patient was identified properly.[2]

Patients must confirm to the best of their knowledge that the identifiers on the labeled specimen(s) are correct. For patients without ID bands who are unable to participate in the confirmation process, specimen identifiers must be confirmed by a caregiver, relative, or friend. After labeling, all information, including specimen site, date, and/or time of collection (if relevant), must be verified to match exactly while still in the presence of the patient.

It is the responsibility of the healthcare professional to compare the information: [2]

- As verbally stated by the patient when initially identified
- On the facility ID band (if required to be worn by the patient)
- On each labeled specimen
- On the examination request if present at the time of collection

Any unused labels or labeled collection containers must be appropriately discarded to prevent their accidental use with specimens belonging to other patients.

It is important that laboratories have policies and procedures in place regarding the handling of specimen containers that arrive without labels, or when there is a mismatch between the labeled specimen container and accompanying paper requisition slip or other documentation.[4]

Implementing a system to reduce errors

The implementation of a quality management system (QMS) is a requirement for passing and/or maintaining laboratory accreditation in the U.S. under regulations supporting the Clinical Laboratory Improvement Amendments (CLIA). In addition to following the regulatory requirements and strategies discussed above, implementing and maintaining a QMS that includes a nonconforming event-management program can help reduce errors related to patient and specimen identification.

A QMS can be described as a set of essential building blocks needed for a laboratory's work operations to fulfill stated quality objectives. A QMS manages the interacting processes and resources needed to provide value and realize results for laboratory customers and users.[6]

The foundation of a QMS provides a platform for continual improvement. When a laboratory implements a QMS, the following outcomes are greatly enhanced: [6]

- Ability to reduce or eliminate error by managing risk
- Likelihood of meeting customer expectations
- Effective and efficient operations
- Sustainable attainment of quality objectives
- Improved potential for successful regulatory and accreditation assessments

Nonconforming events management program

One of the essential building blocks of a QMS is a nonconforming events management (NCE) program. The NCE management program is based on principles of quality management, risk management, and patient safety. The purpose of a program to manage NCEs is to identify and characterize problem-prone processes in a laboratory's path of workflow, such as specimen and patient misidentification, and within

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the supporting processes of the QMS, so continual improvement initiatives can be prioritized, resources allocated, and improvements implemented.[7]

Simply reporting NCEs, though, does not solve underlying problems. Analysis is essential to understanding which processes have the most important problems, so the problems can be prioritized for resolution. Interventions are essential to remove the root causes of the problems to reduce or eliminate recurrence.[7]

When the NCE is identified as high risk, having high severity and a moderate or high probability of recurring or a moderate severity and high probability of recurring, it is necessary to identify the root cause of the NCE and implement corrective action to eliminate the root cause. Root cause analysis is a systematic detailed process for identifying causal factors that resulted in the NCE. When the root cause is eliminated, the NCE will not recur.[7] **Figure 1** illustrates the series of activities, including key decision-making steps, that can occur from detection of the NCE, until the case is closed.

Conclusion

Of all pre-examination processes, improperly identifying patients and incorrectly labeling diagnostic specimens have the most potential to result in catastrophic consequences to patients.[2] The best way to improve all laboratory processes, including patient and specimen identification, is by implementing and maintaining an effective QMS in the laboratory. One component of a QMS that can be particularly helpful to preventing patient and specimen misidentification is an effective NCE management program.

Note: Throughout this article, the use of the word "must" indicates a regulatory requirement for the laboratory.

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What to do with expanded molecular testing capacity in a post-pandemic world

David T. Pride, MD, PhD

If ever there were a stress test designed just to assess a clinical lab's agility, flexibility and performance, the COVID-19 pandemic would meet the specifications perfectly. Onboarding new diagnostic platforms and tests with little notice, managing unpredictable and rapidly escalating test volumes, meeting demands for quick turnaround time, and coping with fluctuating supply chains are just a few fundamental challenges imposed by SARS-CoV-2 testing. Forced to operate as reference labs for COVID-19 testing, many hospital-based labs spent most of 2020 ramping up their molecular testing capacity to meet demand. As the pandemic enters a new phase and COVID-19 testing needs decline dramatically, those same labs now face a new challenge: deciding what to do with the expanded testing capacity. Do they get rid of some platforms or repurpose them? And what criteria should they use to make these decisions?

From zero to 4,500 tests a day

Our molecular diagnostics lab, part of UC San Diego Health's full-service microbiology lab, underwent a significant structural change during the COVID-19 pandemic. As one of the earliest labs in the U.S. to start SARS-CoV-2 testing, we had an initial volume of 20 samples a day, which escalated rapidly to meet the demands not only of our own hospital and all first responders in San Diego, but also as a reference lab for other hospitals in San Diego and, importantly, all testing for transplant patients. Very quickly, we evolved a dual strategy: (a) to diversify our testing platforms and (b) to separate SARS-CoV-2 testing from other molecular lab operations by setting up a new lab. This strategy helped us manage a peak volume of 4,500 to 6,000 SARS-CoV-2 tests per day.

We implemented SARS-CoV-2 testing using real-time PCR on seven platforms from six different manufacturers, five of which were new acquisitions during the pandemic. This meant bringing one new SARS-CoV-2 test online a week, every week, until COVID-19 testing on all platforms went live. This planned diversification of platforms and manufacturers was driven in part by the somewhat limited availability of instruments and reagents, and, in part, by our own preference not to become overly dependent on one vendor during a time of unpredictable supply chains. In parallel with acquiring multiple platforms, we set up a separate facility dedicated to SARS-CoV-2 testing that is physically and operationally distinct from our molecular lab. We were fortunate to have an unused, newly constructed lab in a separate wing of our building — ready to start operation once power was connected and internet access was online.

Right from the start, we chose real-time PCR testing rather than antigen assays, even though both types of assays are available with emergency use authorization (EUA) from the U.S Food and Drug Administration (FDA). A comparative study in our lab showed that antigen-based assays may be insufficient to diagnose SARS-CoV-2 infection when lower levels of the virus are shed.[1]

Pooled testing for asymptomatic individuals was also integral to our testing strategy. (Specimens from symptomatic

UC San Diego Health, La Jolla, CA At-A-Glance

- Number of hospitals: 3
- Number of outpatient facilities: 35
- Number of lab employees in clinical and molecular microbiology: 65, including 15 people assigned to SARS-CoV-2 testing
- Annual volume of lab tests: 300,000-420,000 per year (peak 85,000/month during height of pandemic)
- Current range of daily volume for SARS-CoV-2 tests: About 1,000 per day (peak about 4,500 per day)

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individuals were tested individually.) About a third to half of testing was done on pooled specimens. Separately, a point-of-care PCR test with a 15-minute turnaround time was also implemented. All told, our lab had completed close to 1 million SARS-CoV-2 tests by the end of June 2021.

Leveraging expanded lab capacity

With increased vaccination and slowing infection rates, the pandemic entered a new phase and the need for SARS-CoV-2 testing decreased. Like many labs that have built up capacity during the pandemic, our lab now looks toward leveraging our expanded capacity to enhance our services. We kept three goals in mind as we reviewed the platforms we have on hand to make decisions on how best to deploy them in the post-pandemic environment.

First and foremost is improving patient care and, thus, physician and patient satisfaction. Faster turnaround time is key to meeting this goal. Secondly, we saw the opportunity to maximize productivity through automation, and that means assessing each platform on its ability to reduce hands-on labor — for example, through pre-analytics automation capabilities. A third consideration is the menu.

Operationally, a broad menu enables us to streamline workflow and achieve greater efficiency. A broad menu also allows us to offer more choices of tests to our clinicians and, importantly, to reduce the number of tests we send out to other labs. Reducing send-outs decreases turnaround time and gets results in clinicians' hands sooner. It also helps increase revenue and reduce costs. Along those lines, having a utility channel on our instrument platform gives us the ability to run lab developed tests (LDTs) more efficiently (i.e., on a fully automated, high-throughput system) and even more flexibility to support our clinicians.

These goals readily translate into criteria for weighing the relative strengths and weaknesses of each platform: menu, level of automation, and cost. A broad menu enables us to meet diverse testing needs on the same platform, streamlining the workflow and increasing lab efficiency and productivity. A higher level of automation (including pre-analytics) and higher throughput are key to improving workflow and freeing up highly trained, specialized molecular staff. As always, cost is a consideration, with financial performance being a key metric of a lab's success.

U.C. San Diego Health opened a separate lab to process COVID-19 tests.

During the pandemic, our prior experience with a fully automated, real-time PCR system was one reason behind our decision to bring a second, even higher-throughput system online. Post-pandemic, we dedicated one of the two systems to an expanded sexual health menu, including TV/MG (Trichomonas vaginalis and Mycoplasma genitalium), previously a send-out, and infectious disease testing (e.g., HIV-1/HIV-2 qualitative). The same system also handles transplant viral load testing. EBV (Epstein-Barr virus) and BKV (BK polyomavirus), previously only available as LDTs from our lab or as send-outs, will be run using FDA-cleared tests on our automated system, improving turnaround time. A second automated system is now dedicated to SARS-CoV-2 and influenza A/B testing, as well as a respiratory panel, in readiness for the upcoming respiratory season. A third older, lower-throughput and partially automated model of the same platform will be used as a backup.

The fourth platform, a real-time PCR system, with liquid handler added during the pandemic to meet testing demand, will be dedicated to research use in our human genetics lab and as part of our microbiome initiative. A fifth automated, real-time PCR system served us well for SARS-CoV-2 testing but will no longer be needed, primarily due to its limited menu, and will be set aside as a reserve system for future use. A sixth platform remains in use for SARS-CoV-2 testing, until all reagents are depleted. We discontinued the seventh platform when testing demand began to drop.

Conclusion

As we emerge from the pandemic, our added capacity opens the door to improved patient care, greater physician satisfaction, and more revenue opportunity as we leverage our fully automated systems to offer more tests at faster turnaround time and more streamlined lab operations. Looking ahead, pandemic preparedness will always be within our line of sight. Our experience and our expanded capacity are foundations for an effective response.

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Covering a broad range of ancestries with genetic testing

By Gary J. Latham, PhD

Clinical laboratories have never been more important in the medical decision-making process. From novel therapies that can only be prescribed to patients with certain genetic variants to increasing interest in family planning based on actionable clinical data, the demand for accurate and reliable genetic tests continues to grow.

But the development of such genetic tests has been limited by several factors. The content for many tests is shaped by genomic databases populated almost entirely by information from people of European descent. For example, a 2009 evaluation revealed that 96% of 1.7 million genome-wide association study samples were of European ancestry; over the next 7 years, the number of samples grew more than 20-fold, yet the proportion from African and Hispanic or Latin American ancestry increased by just 2.5% and 0.5%, respectively.[1-2] Inconclusive or erroneous results are far more common when tests designed using data from one ancestry are applied to others. Technological shortcomings have also made it difficult to access clinically important information, such as the ability to phase variants to determine whether a patient has a copy of a certain variant on both alleles or two copies on one allele. In addition, standard sequencing technologies cannot represent complex disease-causing structural variants accurately.

As more healthcare decisions are guided by data produced by clinical lab experts, it is essential to overcome these issues to ensure that all patients and their physicians have access to the most relevant and accurate information. Thanks to a combination of increasingly diverse genomic data and technical advances, clinical labs have more opportunity than ever to improve the quality and applicability of the tests they offer.

Two examples illustrate these advances nicely: spinal muscular atrophy (SMA) and cystic fibrosis (CF), the only two genetic diseases for which universal carrier screening is currently recommended regardless of a parent's ethnicity. Ultimately, these examples provide a framework for how thousands of other molecular tests might be improved for use in a broader population of carriers and patients. This is especially important for public health, since more than 70% of the roughly 7,000 rare diseases have a genetic basis and collectively, nearly 1 in 10 people in the US are affected by a rare disorder.

Spinal muscular atrophy

SMA is a rare and debilitating disease of the central nervous system and a leading cause of infant death. The introduction of life-saving therapies within the last five years has transformed not only the prognosis for patients but also the utility of genetic testing for carrier screening and diagnosis.

Detecting pathogenic variants that cause SMA is technically challenging. There are copy number changes, single nucleotide variants, and insertion-deletion variants than can identify patients with SMA, as well as couples at risk for passing on the disease through recessive inheritance. Conventional genetic testing technologies often fail to detect the full spectrum of variant types.

Another complicating factor in SMA screening is identifying so-called silent carriers. Typically, carrier screening tests for SMA do a simple count of the number of SMN1 genes in an individual. People with the disease have no copies, whereas carriers typically have one copy, leaving one allele without any copies. However, as scientists developed tools that could ac-

curately phase genes into maternal and paternal haplotypes, they discovered that some people have two copies of the SMN1 gene on the same allele, and no copies on the other allele. While a standard carrier screen would tally the two copies and find the individual at no risk for passing on the disease, in reality, that person is just as much a carrier as someone with only one copy of the SMN1 gene.

The inability to phase variants meant that clinical labs had been missing silent carriers for years, and unfortunately, giving them inaccurate risk information for having an affected child. Even worse, this problem has not been evenly distributed. The silent carrier genotype is several times more common among people of African ancestry than other groups, such as those with European heritage.

In addition, SMA tests can be difficult to perform by the lab. The most commonly used approach, based on MLPA technology, takes days to generate results. It can also lack consistency across labs when distinguishing between copy numbers for genes associated with SMA.[3]

Recent improvements have made SMA testing faster, more accurate, and more representative for patients of all ancestries. By incorporating technology that can detect not only gene copy number but also silent carrier-linked gene duplication events, screening for SMA can now be performed at higher throughput with results that better capture the full range of pathogenic variants in all populations.[4] These newer tests can be run with blood samples or buccal swabs, which also expands their accessibility and utility, particularly for carrier screening.

Cystic fibrosis

Another example comes from CF, a serious autosomal recessive genetic disorder that affects several organs and leads to frequent lung infections and difficulty breathing. Like SMA testing, CF screening is needed both to diagnose patients with the condition and to identify carrier couples at risk of transmitting the disease to their kids.

CF testing has been around for more than two decades, and knowledge of CF-causing mutations in the CFTR gene has relied heavily on the CFTR2 database. This database is the gold standard for linking genotype with phenotype in CF, with data from nearly 90,000 patients and more than 350 pathogenic variants. Like so many genetic databases, CFTR2 has been populated with information collected almost entirely from one ancestral group — 95% of patients represented are generally of European descent.

Conventional screening tests for CF are targeted panels made up of the variants reported most frequently in these repositories, making them excellent at capturing risk among people of European ancestry. For other populations, though, conventional CF screening can miss the most important variants. An analysis of CF screening in non-European populations found that people of Hispanic, African, or Asian ancestry were more likely to get negative results from typical tests. The same study also identified several novel variants in those populations that appear to be associated with CF carrier status.[5]

For clinical laboratories serving diverse patient populations, the standard CF screening is a suboptimal approach. Fortunately, the availability of new information — rather than development of novel technologies — has significantly improved this situation.

One study compared standard screening to a sequencing-based approach in which researchers sequenced all coding bases in the CFTR gene.[6] The population studied was not only large, with more than 115,000 individuals, but also representative of the diverse U.S. demographic. Caucasians made up just over half of the cohort, and groups of African, Latin American, or Asian descent made up at least 10% each. With such a heterogeneous cohort, the scientists reported more than 200 variants that were pathogenic or likely pathogenic across various ancestral groups, including many that were underrepresented in CFTR2.

By incorporating the most common variants for each ancestry from this study, the global gnomAD (Genome Aggregation Database) repository,[7] and other representative sources, it is now possible to redesign or update CF tests, so results are relevant for much more diverse patient populations. This will improve screening accuracy and expand the benefits of actionable information to more people.

Conclusion

The examples of CF and SMA demonstrate that conventional genetic tests run in clinical labs can be significantly improved using technologies that are already available. In both cases, the incorporation of more robust data — especially data from studies that better represent the target testing population — is essential for generating more reliable and relevant results for all individuals. With the increasing availability of large-scale sequencing studies from worldwide populations and the advent of powerful long-read sequencing methods that can untangle challenging DNA sequences and variants involved in established and emerging diseases, we should rethink how genetic tests are designed and used. We are now armed with the right resources to ensure that molecular tests are thoughtfully designed for people of all ancestries. In some cases, more representative data will be enough to expand the value of testing. In others, the adoption of more informative technologies — such as those that make it possible to phase variants or resolve complex sequences — may be needed. As studies uncover more pathogenic variants in more populations, those newer technologies can scale to a plethora of genetic tests and should represent a useful investment for clinical labs.

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How NGS panel advancements help us find and fight colorectal cancer

By John Townes, BSc, OGT

Colorectal carcinoma (CRC) is not only the fifth most deadly cancer but also one of the most commonly diagnosed cancers worldwide.[1] Therefore, it is imperative that we develop better methods to diagnose and treat CRC. Next generation sequencing (NGS) technologies have been advancing the use of genomic sequencing for clinical applications, including the simultaneous study of mutations in high-penetrance colorectal cancer genes.

NGS panels — also referred to as targeted gene sequencing panels — offer practical diagnostic tools that help inform personalized treatment. For example, while monoclonal antibodies (such as cetuximab and panitumumab) can block tumor progression by targeting the epidermal growth factor receptor (EGFR), there are some tumors with specific mutations that do not respond to these therapies.[2] By focusing on the select set of genes or gene regions carrying these mutations, NGS panels offer a rapid way to identify whether a patient will respond to treatment.

Although NGS panels are now in routine use for a wide range of research and clinical applications, there remains significant hurdles — including how to handle challenging formalin-fixed paraffin-embedded (FFPE) samples, GC-rich target regions, and tandem repeats. However, recent advances in workflow design are enhancing the coverage, uniformity, accuracy, and sensitivity of colorectal cancer NGS panels.

Dealing with difficult samples

One of the most common sources of materials for NGS CRC panels is FFPE tissues from biopsies or resected tumors. While these tissues are readily available and can be stored at room temperature for long periods of time, the process is known to affect the quality of the DNA. Both fragmentation and chemical modification to the DNA nucleotides in FFPE samples can lead to significant challenges in downstream data interpretation.

The use of an upstream FFPE repair step — which can remove a broad-range of damage including nicks, gaps, oxidized bases, and cytosine to uracil deamination — has been shown to significantly improve sequencing performance (**Figure 1**). Additionally, the choice of target enrichment strategy can impact how well an assay performs.

Which enrichment strategy?

Target enrichment is one of the most important pre-sequencing steps of NGS colorectal cancer panels. The two most used target enrichment strategies are PCR-based (amplicon) and hybridization-based assays. Selecting the right target enrichment strategy is critical, since it will influence the outcome of sequencing results — and ultimately, research conclusions and clinical decisions. For example, PCR-based enrichment is known to be particularly susceptible to contaminants found in FFPE materials, while hybridization-based assays are typically more robust.

Challenging target regions

Researchers often find themselves trying to work with difficult sequences. For example, TP53 has been identified as a mutated cancer gene, including in CRC. However, sequencing is frequently confounded by the GC-rich content of the exons (5-8) where TP53 point mutations typically occur. Moreover, non-uniform, incomplete, and non-specific amplification caused by varied GC content is a common problem associated with PCR-based target enrichment. Careful design of hybridization baits has led to efficient capture, resulting in much more uniform coverage than amplicon assays (**Figure 2**). The ability to use longer probes also lends itself to tolerance of sequence variation, such that all alleles can be captured equally.

Other challenging target regions include those containing internal tandem repeats. However, by designing additional hybridization probes — both upstream and downstream of the repetitive region — sequences around the repeat areas can be captured. Additionally, the potential use of longer probes in hybridization-based enrichment assays can read through short (up to 100 bp) repetitive regions.

Getting rid of the noise

As NGS panels transition into routine clinical diagnostics, reducing false negatives and false positives — the 'noise' — is critical. For example, if a patient is given a false negative/positive result, they may be considered for a treatment that will ultimately be ineffective.

While poor coverage of the target site represents the primary cause of false negatives, improving uniformity of enrichment by well-designed hybridization assays can reduce their incidence. On the other hand, the most common cause of false positives are artefacts introduced during PCR. Since artefacts will be amplified exponentially in line with increasing PCR cycles, the much lower number of cycles required for hybridization assays are favorable.

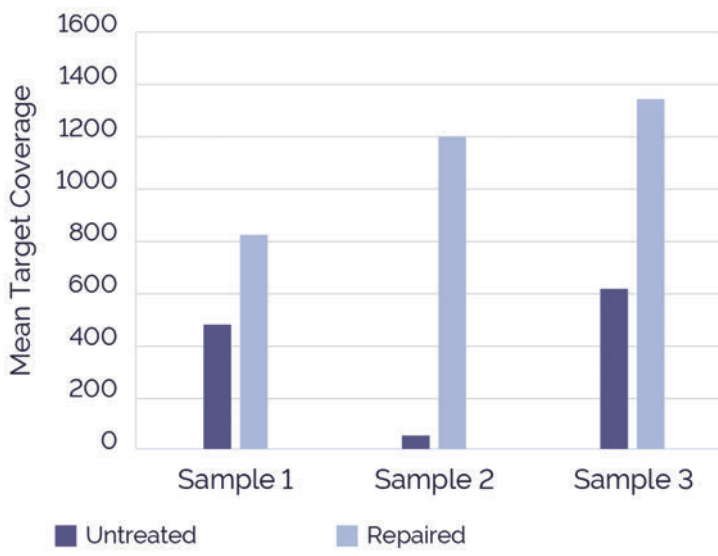

Figure 1. Mean target coverage of ovarian and colon cancer samples increases when FFPE is repaired.
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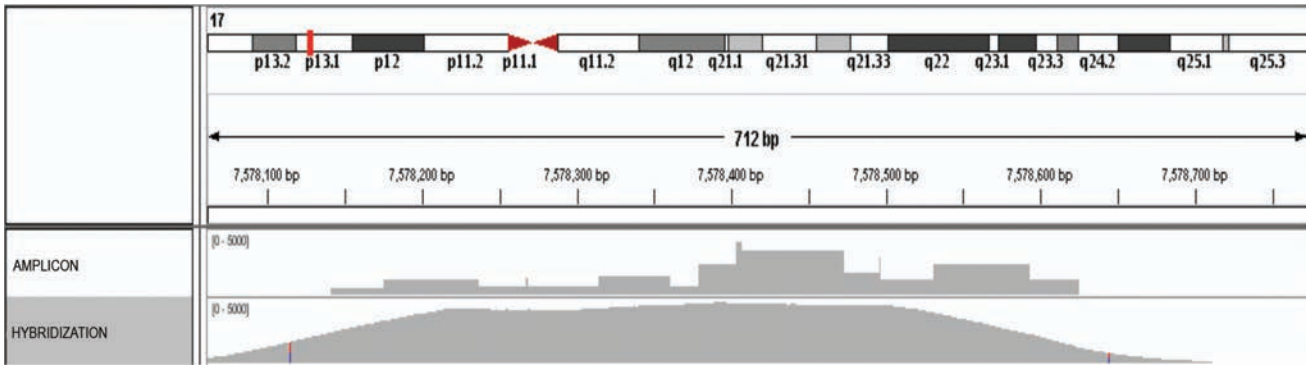

Figure 2. Comparison of coverage results produced by either amplicon or hybridization-based target enrichment of the GC-rich exons 4 and 5 of the TP53 gene. Hybridization-based enrichment produced more uniform coverage of challenging GC-rich targets.
Image courtesy of OGT.

These minimal PCR cycles needed for hybridization assays translate as reduced 'noise' and, in turn, higher detection sensitivity of low frequency variants. Indeed, one study compared commercially available kits for the detection of 24 mutations associated with cancer, and the hybridization-based assay showed the highest sensitivity, able to detect all known variants (100% sensitivity) as well as two novel mutations.[3] The more comprehensive profiling for all variant types, both novel and known, lends itself to both research and clinical applications.

It is time for PCR to shine – or is it?

One of the major benefits of PCR-based amplification is its more streamlined library preparation, compared to hybridization-based strategies. However, changes in hybridization-based workflow design, such as combining the end-repair and adaptor ligation steps, mean that it is now possible to load more samples onto a sequencer within a single day.

PCR-based amplification typically requires significantly less DNA input than hybridization assays. However, recent design advances to hybridization mean that some now need considerably less starting material (**Figure 3**). Moreover, while smaller starting concentrations might sound desirable, it is important to consider the effect on sequencing results.

Small amounts of input DNA mean less template DNA is available, and less template DNA can lead to high duplication rates. With hybridization assays, duplicates can be removed swiftly during the bioinformatics process. This is not a possibility with amplicon data without the use of molecular barcodes, resulting in skewed data due to the over-amplification of a small number of fragments.

The outlook - from research to clinic

Multiplex NGS panels are set to change diagnostics, prognosis, and treatment options for colorectal cancer patients, affording the ability to effectively screen patients for numerous mutations simultaneously. Moreover, as we see a rapid improvement in NGS technology, it is likely that there will be a significant reduction in sequencing cost and the ability to test specimens from many patients on the same assay, making the jump from research lab to clinical lab much more manageable.

Importantly, we must also consider how changes in workflow design can significantly affect sequencing outcomes, particularly during target enrichment. While choice of target-enrichment strategy is fundamentally dependent on goals and resources, hybridization-based assays offer more confidence in calling all variants, with less noise. This will ultimately impact both research and clinical outcomes.

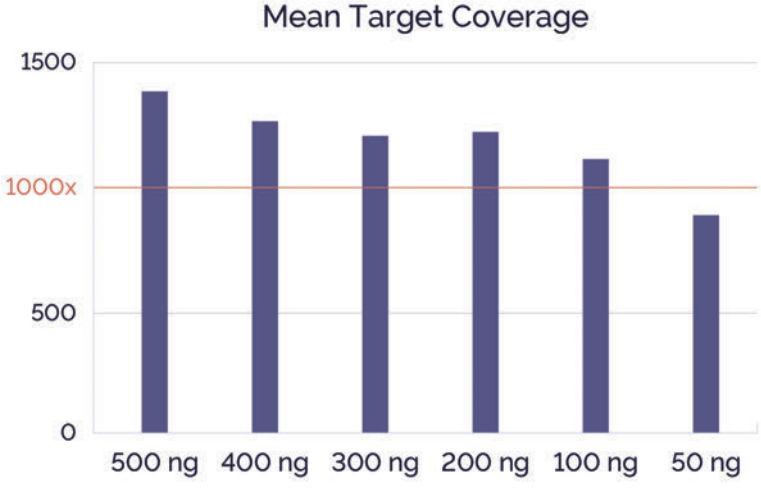

Figure 3. Well-designed hybridization-based target enrichment can significantly reduce the required input quantity of DNA without compromising the mean target coverage.
Image courtesy of OGT.

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Creative conservation of lab supplies reduces waste

By Marisa L. Williams

Supplies are precious commodities in the lab, and during the COVID-19 pandemic, conservation has become key, inspiring some labs to come up with creative ways to conserve their supplies. Taking the time to do things right — not rushing, which often leads to errors, can be the first step to preventing waste. Be aware of ordering. Fight the urge to overorder, as expired products are still a waste, and forecast anticipated supply use, taking the big picture into consideration when ordering.

Preventing common mistakes

During supply shortages, labs must try to conserve their supplies as much as possible. Preventing waste is one of the easiest proactive steps labs can take to ensure their supplies are there when needed, and taking a few steps extra to be proactive ahead of time can help with these efforts.

Take the time to do things right, as rushing can be costly. Open vacuum seals slowly, ensure pipettes are over a tube before releasing, spin the centrifuge at the right speed, fill tubes to the proper level, take time to follow protocol, and simply be aware of surroundings to prevent bumping into things or getting a lab coat caught brushing past something.

Prioritizing supply use for conservation

"The main thing we've done is evaluate the different usages," explained Susan Geddes, Lab Supervisor for ProMedica Bay Park in Oregon, OH. "Sodium citrate tube issues have impacted the entire country. It used to be part of pre-draw in the ER, blue in addition to lavender; we've eliminated that. We have to have orders, before any of the blue tubes will be drawn. That has prolonged our supply."

The lab prioritizes supply use for those with greatest need, Geddes shared, "There's a shortage of the 1.8 draws and other blues. We've been reserving them for our tertiary care center and our children's hospital where they really need the lower draw."

They had to use alternative types of needles, as needles have also been a supply issue. "There's been a lot of waiting, so we've been evaluating. The shortage occurred primarily when across the nation, vaccination clinics started popping up. The one-inch blood draw was being used for vaccines, so there were none available. We've had to work with one and half inch, which is a bit longer, and it's easier to go through veins. There was a bit of a learning curve adapting, but that has been lightening up a little bit. One-inch needles are coming back in now, but that's been ongoing over a year."

Susan Geddes

They looked at four different manufacturers, but nobody had one-inch needles for blood draw readily available, inspiring the changeover to the longer needles for blood draws. "There were some not marketed for blood draw. Not many needles are researched for blood draw; there's more for injection."

Creating a tracking system for supply use

To ensure supply, part of their strategy involved finding a couple of different distributors and developing a good process to keep needles in stock. They manually created their own tracking

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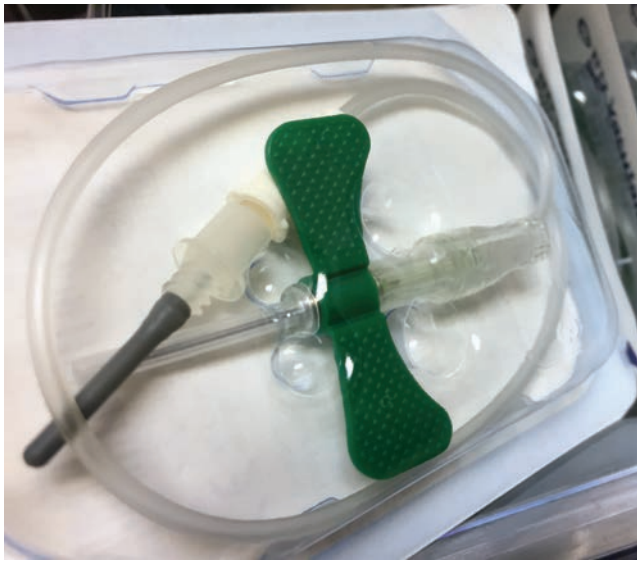

Photo by Marisa L. Williams

system within their seven-hospital system, showing the use in each lab location and overall totals.

Geddes is not only a lab supervisor at the regional hospital, but a system quality team member. The quality team meets to create daily backorder lists, communicating directly with each other and materials management to prepare for stock shortages, alerting all sites to any potential delays. "There's a lot less of people not knowing, so this helps prepare staff for any changes coming. That's also connected us a little closer to the distributor as well."

Monitoring how many days' worth of supply the lab has on hand, team members track the expiration dates, making sure they can easily use the stock before expiration. Additionally, they monitor test volumes for utilization purposes. A test utilization committee looks at test appropriateness, volumes and includes staff member input if anyone suspects overuse of supplies. Claims are researched on a case-by-case basis.

"If someone is overusing a certain supply, we try to educate the employee to clarify the appropriate way to do things. There's some variation with training at different places they've worked. Just a little reminder seems to have definitely decreased waste," Geddes noted.

Paying attention to supply use within the lab can reveal usage issues.

Before the pandemic, Geddes noticed a high use of butterflies in her lab. "Butterflies are variable by site, but here at my site, we moved the location of them into the main office. There's still open access, but just the fact they're not in the supply room, we decreased (usage): instead of a box a week, it's down to a box every two months. There's no formal sign out or limit, but just that notion of going to a different spot seems to definitely help."

Even when a forecasting system is created, there can be unforeseen circumstances and opportunities for improvement, Geddes said, "When we forecast out, we base it on standard receiving, but there's been times where it suddenly took a couple extra weeks. On the reagent side, we had issues. A kit will expire sooner than expected, and we noticed we did not have a separate area to track expiration dates. So, we improved our process for that and for products with short outdates."

Green measures for supply use

Even before the pandemic, ProMedica had transitioned to using washable lab coats and other green measures.

In 1990, Congress passed the Pollution Prevention Act (PPA) with management approaches to minimize waste and preference for those providing the greatest environmental protection. The American Chemical Society[1] cautions not to overorder hazardous materials to minimize any risk and reduce the cost of hazardous waste disposal. Labs may substitute some hazardous materials when less or nonhazardous materials are available, such as using less hazardous glass cleaning chemicals, extraction solvents and reagents.[1]

Proactively conserving reagents

Proactive steps to conserve reagents can include something as simple as taking time to make sure the right reagent is used and dissolved properly to help prevent errors and waste. Simply holding a sample up to a light to make sure reagent particles are dissolved is an easy waste prevention measure.

During the pandemic, some reagents have been in short supply, and unfortunately, facilities have run low in some products, and ProMedica is one of those facilities. "In those cases where we temporarily don't perform those tests, they are offered as a send out to a reference lab. We do have a couple right now that we're just not offering because we do not have the collection containers. Those have specific requirements for one tube type and cannot validate another tube type," Geddes added.

Krishna Kannan

Krishna Kannan, Director of Research and Development at Codex DNA, said automated systems can help prevent waste by eliminating manual processes that are prone to errors. "An automated solution of mRNA synthesis obviates the need for manual pipetting and handling steps that could introduce errors and RNA-destroying RNases. A closed production system is ideal for generating labile molecules like mRNA."

Kannan spoke of the advantages that technology has created, noting how companies used reagents and automated capping technology in the development the mRNA COVID-19 vaccines to generate highly functional mRNA molecules.

Providing not only higher amounts of mRNA per volume of an IVT reaction, but also a much higher fraction of the functional mRNA molecules, this enables automated solutions for mRNA production with higher throughput capability, generating higher yields of mostly functional mRNA molecules that can be used for downstream applications.

Of course, even with automated systems, there can still be errors. Make sure your equipment is hooked up properly. This sounds like an obvious one, but cords plugged into the wrong area, or not plugged in at all, can waste time and samples. Ensure cords are tucked away neatly, so they do not create a tripping hazard in the lab.

Make sure things are labeled properly, as being in a hurry, it is easy to forget a patient identifier, and if a sample is being sent out, that sample might not get processed due to a simple mistake.

Always make sure not to confuse which sample is which. Double check orders before placing them to make sure there are no errors and the right products are listed, as order mistakes cost time and money, especially during times of shortages.

Forecasting supply delays

Beyond unforeseen events, it is important to track the volume of products being used and ordered in the world, as these trends may impact an individual lab's supplies, signaling it may be worth looking into the future availability of a certain

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product. After analyzing the global use of medical supplies,[2,3,4,5] Shambhu Nath Jha, Client Research Partner at Fact.MR, discussed how supply use impacts laboratories across the globe, sharing a report that discussed how the urge to lessen the use of fossil fuels may be inspiring more bioplastic textiles, which are made from renewable sources like sugarcane, corn starch or wood chips.


Shambhu Nath Jha

Since the COVID-19 restrictions prevent medical devices from being shared with too many people, this has resulted in an increase in demand for portable healthcare equipment.

Amidst the pandemic, demand for laboratory supplies surged, along with the urgency for more complex testing with molecular diagnostics, driving laboratory automation into popularity. More labs are turning to Next Generation Sequencing (NGS) for advanced oncology diagnostics, and the launch of a recent cell painting kit for imaging with microplates expands reagent portfolios. As researchers develop new therapeutics, this demand does not seem to be slowing, Nath Jha explained.

The future of the laboratory supplies market appears to strong, as Nath Jha said the global laboratory equipment and supplies market is vast and is anticipated to generate revenue worth more than $30 billion, with 1.8 times higher spending on lab equipment in 2021 in comparison to pre-COVID years. "The interesting thing about this so far dormant sector is its growth. Across all potential market, we project the growth to remain over 6%, which is enough for catch the eyes of all big players in this business."

A variety of medical equipment has been in demand, especially with the pandemic inspiring new lab testing, increased diagnostics, and resulting in shortages. Specifically, Nath Jha mentioned, "Legacy equipment, such as incubators, centrifuges, and laminar air flow, will continue to gain in replacement sales category. However, lab air filtration systems have witnessed the new dawn, as most of the big laboratories that did not have this system installed are going for it."

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Laboratory medicine training for rural family physicians

By Daniel M. Avery, Jr, MD, and Charles E. Geno, MD

Clinical laboratory directors may be pathologists, other specialty physicians or doctoral level scientists with laboratory training, such as in clinical chemistry. In small, rural hospitals, a pathologist may serve as laboratory director, but not be present, except on occasions when he or she is needed, such as for a meeting. However, this may also be a role for a local family physician or other non-pathologist physician trained in laboratory medicine, particularly in rural communities without a pathologist.

While there are no laboratory medicine fellowships for family physicians, we obtained the requirements for training a non-pathologist physician to be a laboratory director from the Alabama Department of Public Health (ADPH).

We then created a training program and now have a family physician serving as lab director. A local hospital or clinic and community physicians may also benefit from having a trained local family-medicine physician serve as the laboratory director, and there may be a role for a fellowship in laboratory medicine for family physicians.

What is laboratory medicine?

Laboratory medicine is the area of medicine dealing with laboratory analysis of blood, urine, and other specimens to provide important information about a patient. This assists physicians in determining diagnoses and how to care for sick patients. Laboratory medicine is taught in medical school and most residency and fellowship programs, and it is an essential element of patient healthcare, as 60-70% of healthcare decisions depend on laboratory analyses.[1] Medical practice and patient care depend on accurate, timely and quality laboratory results.[2] Clinical laboratory directors validate accurate laboratory results and ensure quality, and they are also the liaison between the clinical laboratory and healthcare providers.[2]

Charles E. Geno, MD, a family physician, is a lab director.

Clinical laboratory directors

Clinical laboratory directors may be pathologists, other specialty physicians with training in laboratory medicine or non-physician doctoral-level scientists with training in specific laboratory areas, such as clinical chemistry.[2, 3] Pathologists are residency trained in clinical and anatomical pathology. Over time, there has been a decrease in the number of pathologists, especially clinical pathologists, resulting in a decrease in the number who serve as laboratory medical directors.[2] In smaller hospitals, especially in rural areas, a pathologist may serve as the clinical laboratory director but not be present in the laboratory except on certain days by request (i.e. for frozen sections) and for staff and executive committee meetings. They are usually available by phone for questions or problems when needed.

The Clinical Laboratory Improvement Amendments (CLIA) state that the clinical laboratory director may be a licensed doctor of medicine, osteopathy or podiatry with one year of laboratory training during a hematology or hematology/oncology fellowship or two years of experience directing or supervising high complexity testing.[2, 4] Clinical laboratory directors may also be non-physician doctoral-level scientists with post-doctoral fellowships in clinical chemistry,[2, 3] clinical immunology,[2] clinical microbiology[2, 5] or clinical genetics.[2, 6]

The clinical laboratory director at the College of Community Health Sciences (CCHS) University Medical Center supervises high complexity testing, certifies urine drug screens as the medical review officer, oversees medical functions of the laboratory, certifies proficiency testing, and validates outside-ordered laboratory tests. The director also teaches laboratory medicine to medical students, residents and fellows, serving as a liaison between the laboratory and faculty members and staff physicians. The CCHS laboratory is a high complexity laboratory because of its hematology and microbiology service. The laboratory serves the medical school practices, University Medical Centers in Tuscaloosa and Northport, the University of Alabama Student Health Center and several outlying practices and private physicians.

The lab provides full-service laboratory medicine and clinical pathology, including phlebotomy, urinalysis, hematology, chemistry, microbiology, toxicology, and special chemistry. The lab does not provide anatomical pathology, cytology, bone marrow, or blood bank services. CLIA recommendations for training a non-pathologist to be the laboratory director are outlined below. Training involves 3-4 hours a day in the lab over two years, which could conceivably evolve into a laboratory medicine fellowship for physicians in rural areas where there are no locally available pathologists.

Fellowships for family medicine physicians

Fellowships are usually clinical training beyond residency. Family medicine fellowships at the College of Community Health Sciences (CCHS) at the University of Alabama date back to 1984 with the formation of the Family Medicine/Obstetrics Fellowship. CCHS also has fellowships in emergency medicine, hospital medicine, behavioral health, geriatrics, and sports medicine. The American Academy of Family Physicians (AAFP) website lists 17 different types of fellowships for family physicians.[7] The only fellowships for family medicine approved by the Accreditation Council for Graduated Medical Education (ACGME) are sports medicine, geriatrics, addiction medicine, clinical informatics, and hospice and palliative care.[8]

Most laboratory medicine fellowships are designed for pathologists or doctoral-level scientists with training in specialized areas, such as clinical chemistry.[2, 3] To the authors'

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knowledge, there are no laboratory medicine fellowships for family physicians.

Clinical laboratory director training

To train a non-pathologist physician to be a CLIA laboratory director, CCHS sought direction from the CLIA laboratory unit director and the licensure and certification supervisor at the Alabama Department of Public Health (ADPH). CCHS also referred to the Electronic Code of Federal Regulations (e-CFR), current as of Nov. 1, 2018,[4] which lists the requirements for a laboratory director at laboratories performing high complexity testing.

There are numerous key requirements, according to these sources. The laboratory director must be qualified to manage and direct laboratory personnel and oversee the performance of high complexity tests, as well as be eligible to be an operator of a laboratory within the requirements, such as possessing a current license as a laboratory director issued by the state in which the laboratory is located, if such licensing is required.

The laboratory director also must be a doctor of medicine or doctor of osteopathy licensed to practice medicine or osteopathy in the state in which the laboratory is located, as well as be certified in anatomic or clinical pathology, or both, from the American Board of Pathology or the American Osteopathic Board of Pathology (or possess qualifications that are equivalent to those required for such certification).

Additionally, the lab director should have at least one year of laboratory training during an internal medicine residency or hematology/oncology fellowship. Alternatively, the lab director could have at least two years of experience directing or supervising high complexity testing,[3] or hold an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution and be certified and continue to be certified by a board with approval from the Department of Health and Human Services (HHS).[4]

According to ADPH, the training experience must be clinical in nature, with the laboratory director-in-training personally examining and performing tests on laboratory specimens, in contrast to ordering, interpreting, and applying test results to the care of patients.[4] This is evidenced by laboratory worksheets, training checklists, exams, and competency evaluations over the two-year period. He or she must demonstrate supervisory skills, such as signing policies and procedures, or reviewing quality assurance and quality control, with oversight from the current laboratory director, which must be documented. Test performance must be supervised by the general laboratory supervisor. The trainee must also have periodic oversight and review from a supervisor, including signed documentation.[9]

The director-in-training is expected to learn to perform the tests ordered in the UMC laboratory and demonstrate proficiency. For example, the microbiology education and proficiency test includes specimen collection, gram stain, media selection, inoculation and isolation techniques, and culture incubation.

There are also lectures for the director trainee in (1) preparation for the biennial laboratory recertification survey, (2) statement of deficiencies and plan of corrective action, (3) proficiency testing, (4) alcohol testing, and (5) review of procedure manuals. The responsibilities of the clinical laboratory director include consultations, verification and certification of results, interactions with patients/physicians/administration, quality assurance, education of residents and medical students, standards of performance, safety, monitoring and correlation of laboratory data and ethical concerns.[10]

The benefits of having a non-pathologist in-house physician serving as the laboratory director at CCHS are:

1. CLIA certified laboratory director
2. Senior level practicing physician
3. In-house practicing physician present every day
4. Physician with a breadth of knowledge of codes for ordering and billing
5. Liaison with administration, most of whom are not physicians
6. Liaison between laboratory and medical school, student health center and community physicians
7. Laboratory medicine physician teaching medical students, residents, and fellows
8. Physician to interpret laboratory results
9. Verification of outside-ordered laboratory results, especially life-threatening values
10. Public relations for the laboratory
11. An interface between clinical medicine and laboratory medicine
12. Medical review officer certification of drug screen and blood alcohol results
13. Cost savings to the physician foundation

In summary, this postgraduate training may be useful to other rural communities as a laboratory medicine fellowship for family physicians. There is a shortage of pathologists, and at the same time, the likelihood of having a pathologist full-time in a small, rural hospital laboratory is very small. It may be beneficial to both the hospital/clinic and the practitioners to have a local physician serve as the CLIA laboratory director of their high complexity laboratory.[4]

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Daniel M. Avery, Jr, MD, is the former Medical Laboratory Director and Medical Review Officer at University Medical Center at The **University of Alabama**. He is a Professor Emeritus of Community Medicine and Population Health and Obstetrics and Gynecology. He is also the Medical Director for the Institute of Rural Health Research.

Charles E. Geno, MD, completed training for family physicians on becoming a lab director and has been approved by the Alabama Department of Public Health to be the Laboratory Medical Director at the **University of Alabama** College of Community Health Sciences and University Medical Center Laboratory in Tuscaloosa, AL.

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LumiraDx receives EUA for COVID-19 antibody test

LumiraDx has received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for its SARS-CoV-2 Ab test.

The test, which returns results in 11 minutes, utilizes a combination RBD and S1 spike SARS CoV-2 antigen for the detection of total antibody (Ab) elicited in response to recent or prior SARS-CoV-2 infection. The LumiraDx SARS-CoV-2 Ab test has been commercially available in Europe since achieving CE mark in September of 2020. The test demonstrated 100% sensitivity and 100% specificity for detection of IgM and IgG antibodies against SARS-CoV-2 in serum and plasma samples. (Photo Courtesy of LumiraDx.)

Software facilitates at-home specimen collection

LigoLab Information System announced that its TestDirectly patient engagement platform now includes electronic processes for at-home specimen collection. The services supported by TestDirectly include online ordering of a test kit, shipping of the test kit to the patient's home, the laboratory's receipt of the patient's specimen after collection, processing of the specimen, automated delivery of the test result back to the patient, and videoconferencing and scheduling of consultations if needed. (Photo courtesy of LigoLab.)

Bio-Rad launches controls for SARS-CoV-2 variants

Bio-Rad Laboratories has launched the SARS-CoV-2 S Gene Alpha, Beta, Gamma and Epsilon Variant Controls as part of its Exact Diagnostics line of molecular quality control products for research testing.

These Exact Diagnostics SARS-CoV-2 S Gene Variant Controls are intended to be validated as independent external run controls and used for research testing with molecular assays targeting mutations in the Spike (S) gene. The products are to be used with assays detecting SARS-CoV-2 variant RNA and to be processed in the same manner as patient specimens to monitor all the steps of molecular assays.

This line of variant controls consist of synthetic RNA transcripts of the respective variant SARS-CoV-2 S genes in a matrix simulating transport media. Because the products also contain human genomic DNA (human gDNA; which includes the human RNase P) for internal control needs, they also enable laboratories to monitor the entire process of a molecular assay, including extraction (optional), amplification, and detection.
(Photo courtesy of Bio-Rad.)

FDA issues EUA for BD sodium-citrate blood-specimen collection tubes

The U.S. Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) to Becton, Dickinson and Company (BD) for its BD Vacutainer Plus Citrate Plasma Tubes.These are sodium-citrate blood-specimen collection tubes used to collect, transport, and store blood samples for coagulation testing.

The FDA said the tubes authorized under the EUA are for use in coagulation testing, performed by authorized laboratories, to aid in the identification and treatment of coagulopathy in patients, including patients with known or suspected COVID-19. (Photo courtesy of BD.)

Ortho Quantitative COVID-19 IgG antibody test receives FDA EUA

The U.S. Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) to Ortho Clinical Diagnostics for the company's VITROS Anti-SARS-CoV-2 IgG Quantitative Test.

Ortho said its new quantitative COVID-19 IgG antibody test targets the S1 spike protein and is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2. The new test has 100% specificity and 91.9% sensitivity at greater than 15 days after symptom onset. Ortho also offers a total antibody test to the nucleocapsid protein.
(Photo courtesy of Ortho Clinical Diagnostics.)

Labcorp to offer Qiagen test for non-small cell lung cancer

Labcorp announced the availability of therascreen KRAS PCR Mutation Analysis, a companion diagnostic to identify patients with non-small cell lung cancer (NSCLC) who are eligible for treatment with LUMAKRAS (sotorasib), a new treatment option developed by Amgen.

The therapy and the use of the test, which was developed by Qiagen as a companion diagnostic, received approval from the U.S. Food and Drug Administration (FDA) in late May 2021. The therascreen KRAS PCR Mutation Analysis allows labs, such as Labcorp, to determine if patients carry a specific mutation in the KRAS gene. (Photo courtesy of Qiagen.)

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Mass spectrometry allows up to one million times resolution

By Marisa L. Williams

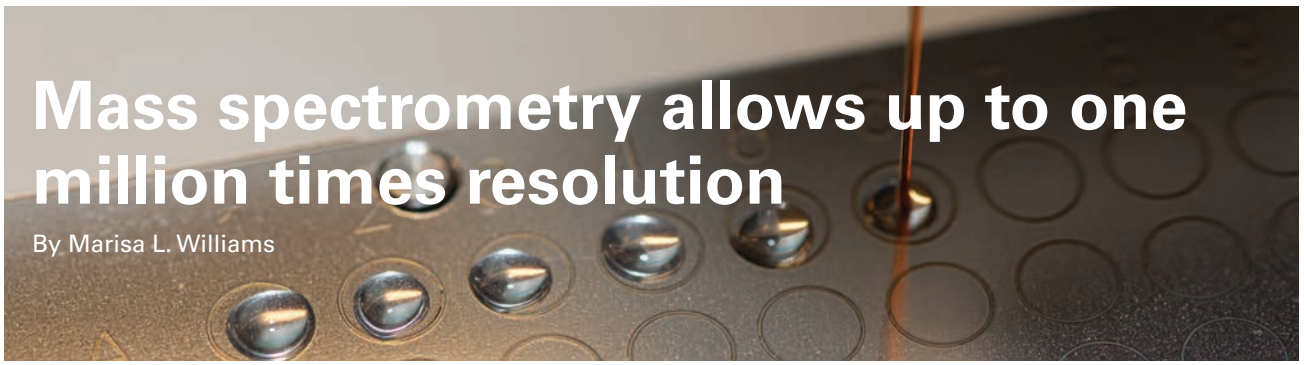

Photo by Mass Spectrometry at Dreamstime.com

Mass spectrometry can help identify what things are made of, being able to identify small molecules metabolized in the body, which helps researchers with everything from drug metabolization to how foods break down within the body and more. The silver lining of the COVID-19 pandemic was that it opened more avenues of research, shining a new spotlight onto mass spectrometry, which combines concepts from physics and chemistry to advance the medical field.

Mitch Kennedy, President of Chromatography and Mass Spectrometry at Thermo Fisher Scientific, hosted a webinar about mass spectrometry advances,[1] explaining the latest advances in mass spectrometry are not only in the healthcare field, but also in food, environmental, water testing, and testing the contamination in lithium ion batteries. These open vast new areas of research, including how carbohydrates break down in food, enhancing diet and nutrition.

Mass spectrometry allows up to one million times resolution, revealing complex molecular structures. Kennedy mentioned when a drug is manufactured, the U.S. Food and Drug Administration (FDA) requires manufacturers to identify the primary and secondary metabolites, the pieces the body metabolizes from the product, which mass spectrometry can identify.

From metabolites to lipids, this helps find molecules in the body, as mass spectrometry deconvolutes to see what is present. First used to measure the mass of atoms, it proved the existence of isotopes, which inspired atomic structure. Mass spec can identify the differences between cold, flu, COVID-19, and tuberculosis, and it shows the cells for global profiling. When used for single cell proteomics, heterogeneity, scarcity, novel cell types and cell state transitions are seen. In spatialomics, lab professionals can measure cell to cell variation, cellular and tissue heterogeneity and connectivity.[1]

Microbial identification has been advanced by mass spec, according to the American Chemical Society. Systems can identify more than 400 bacteria and yeast species for bacterial identification, with accuracy rivaling nucleic acid sequencing.[3] Liquid chromatography with tandem mass spectrometry (LC-MS/MS), which combines the separating power of liquid chromatography with the mass analysis of triple quadruple mass spectrometry, advanced dried blood spot analysis and metabolism information, screening for more than 50 metabolic disorders with one rapid test, advancing newborn screenings.[3]

The specs of mass spec

Direct Analysis in Real Time Mass Spectrometry (DART MS) is an ambient ionization technique on a gas-phase ionization mechanism, usually helium or nitrogen, initiating reactions, which can generate positive or negative ions, predominantly even-electron species, such as the technology used by IonSense. This can analyze analytes in their native form, including many that don't ionize well in other methods, allowing it to be applied to compounds that have been deposited, or are being desorbed into the atmosphere, without the use of chemical solvents.

The ease of automated models for the labs can increase workflow efficiency, adding analytical intelligence to maximize laboratory outputs. Some models, such as Shimadzu's LCMS-8060NX triple quadrupole liquid chromatograph mass spectrometer, uses ion focused lenses and integrates electrospray, so neutral particles are expelled to reduce noise and provide stability. Heat assists with desolvation, and ions are swept from the collision cell. On this model, the ESI spray needle and the inlet desolvation line (DL) can be changed without breaking the vacuum.

Excellims GA2200 is an alternative high speed screening high performance ion mobility spectrometer (HPIMS), which operates like a mass spectrometer using an electrospray ionization source that exceeds portable mass spectrometers. It can be used at the point of need, as it works without a vacuum pump and has no need for large quantities of solvents, with rapid results in 10-120 seconds.

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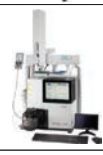
Brand		Model	Lab volume	Size	Weight	Ionziation source	Throughput
Agena Bioscience		MassARRAY System with CPM 96	Low to medium	37 x 43 x 27 in	295 lb	Laser	1-1000s per day
Agena Bioscience		MassARRAY System with CPM 384	High-volume labs	37 x 43 x 27 in	295 lb	Laser	1-1000s per day
Agilent		6495C Triple Quadrupole LC/MS	Low to high	47.5 x 77.3 x 91.5 cm	271 lb	ESI, AJS, APCI, MMI, NanoESI	Scan speed: 17000 Da/s
Agilent		Ultivo Triple Quadrupole LC/MS	Low to high	32 x 88 x 39.5 cm	130 lb	ESI, AJS, APCI	Scan speed: 15000 Da/s
Excellims		GA2200, high speed screening HPIMS, a MS alternative	Low to high	45 x 66 x 46 cm	52.9 lb	Electrospray or corona discharge (DBD)	10-120 seconds/ sample
Excellims		MC3100, HPIMS-MS, a 2D chemical identification tool	Low to high	43 x 71 x 43 cm	77.2 lb	Electrospray or corona discharge (DBD)	10-120 seconds/ sample
Excellims-Thermo Fisher Scientific		MA3100-Orbitrap, high resolution ion-mobility-mass spec	Low to high	Analyzer 49.5 x 18 x 17 cm; tower 43.9 x 21.3 x 34.6 cm	Analyzer 22 lb; tower 37.5 lb	Electrospray or corona discharge (DBD)	10-120 seconds/ sample
IonSense		DART OS	Low to high	Controler: 5.5 x 12 x 10 in; Source: 4.25 x 4 x 11 in		Ambient Ionization	1 sample at time
IonSense		DART MS JumpShot	Low to high	Controler: 5.5 x 12 x 10 in; Source: 4.25 x 4 x 11 in		Ambient Ionization	Automation for medium throughput
IonSense		DART MS JumpShot HTS	Low to high	Controler: 5.5 x 12 x 10 in; Source: 4.25 x 4 x 11 in		Ambient Ionization	384 samples in less than 25 minutes
Shimadzu		LCMS-8060NX	High-volume labs	1,180 × 540 × 610 mm	308.6 lb	ESI (standard); Micro-ESI and APCI optional	Depends on complexity of test
Thermo Fisher Scientific		FAIMS Pro Duo interface	Low to high	Controler: 19 × 12.5 × 2.5 in; RF coil: 10 × 13 × 19 in	Controller: 8.2 lb; RF coil 7.7 lb	Low- or standar-flow ionization	Depends on complexity of test
Thermo Fisher Scientific		Orbitrap IQ-X Tribrid Mass Spectrometer	Low to medium	50 × 30.2 × 27.7 in	700 lb	Electrospray ionization (ESI)	Gradient length 5 - 60 mins/test
Waters Corporation		Waters SARS CoV-2 LC-MS Kit (RUO)	Medium to high	70.7 x 61 x 99.5 cm		ESI (standard) APCI or APPI (optional).	Less than 2 minutes/sample
Waters Corporation		RenataDX Screening System	Medium to high	770 x 1440 x 930 mm	319.7 lb	Electrospray Ionization (ESI)	384 samples in less than 12.5 hours

Combining IMS and MS, the MC3100 HPIMS-MS is a 2D, portable chemical identification tool used for drug screening and more. Compact with benchtop performance, it integrates atmospheric pressure IMS with a linear ion trap MS, enabling chemical separation and identification based on ion mobility, then the same sample can be used in the MS for m/z identification in the field portable instrument.

Another compact design is the Agilent Ultivo liquid chromatography quadrupole mass spectrometer, which is stackable and smaller than the average triple quadrupole for liquid chromatography (LC/TQ) with the same power. Agilent's VacShield offers ventless ion injector maintenance. This same VacShield, which reduces downtime with quick maintenance without breaking vacuum, is offered in Agilent's larger 6495C Triple Quadrupole LC/MS with hexabore capillary and iFunnel Technology to reduce noise.

Excellims and Thermo Fisher Scientific combine forces with the MA3100 Orbitrap, an ion mobility pre-separator for mass spectrometers, which enhances versatility and more targeted analysis of gas phase ions, a process not always available by mass spectrometry alone. This is exchangeable with other ionization sources, providing add-on molecules to the ionization sources of the MS, enabling orthogonal separation, and it cleans up the ion beam for MS. So far, it is the only way to obtain "collision cross section" information for Thermo Fisher Scientific's MS systems.

The Thermo Fisher Scientific Orbitrap IQ-X Tribrid mass spectrometer combines these technologies, and the Met-IQ workflow leverages Real-Time Library Search with MS spectral matching, with optional extras that include an Ultraviolet Photodissociation (UVPD) for lipid double-bond localization, site specific glucuronidation and fragmentation, as well as the 1,000,000 (1M) resolution option. The Thermo Fisher Scientific FAIMS Pro Duo interface extends differential ion mobility to proteomics, plasma profiling, and small-molecule quantification. Covering a wide range of chromatographic flow rates on different compound types, it overcomes matrix interferences by orthogonal selectivity leveraging gas-phase fractionation, enhancing signal-to-noise ratios. Integrating with liquid chromatography provides identification of proteins, peptides, oligonucleotides, and small molecules.

Waters RenataDX Screening System uses flow injection for high-throughput dried blood spot analysis. Accommodating samples in microtiter, deep-well plates or vials, both laboratory developed tests

(LDT) and commercial reagent kits can be used. The RenataDX can receive barcode scanning information, and high-volume labs can add three extra trays to the standard 12-plate configuration. Expanding research opportunities, Waters SARS-CoV-2 LC-MS kit is for research use only (RUO) with an orthogonal analytical method to detect and quantify nucleocapsid peptides showing a lower limit quantitation of 3amol/µL.

The MassARRAY System by Agena Bioscience enables applications with off-the-shelf panels for pharmacogenetics, liquid biopsy, tumor profiling, sample identification, SARS-CoV-2 and variants, hereditary genetics, bone marrow engraftment chimerism, and blood typing. It supports rapid custom panel creation and can identify variant allele frequencies as low as 0.1%, while eliminating the need for fluorescent markets.

For genetic analysis, after extraction, nucleic acid is amplified and added to the MassARRAY for target sequence detection and data analysis. This process allows the identification of SNPs, insertions, deletions, translocations, copy number variation, and methylation markers. The reporting software delivers result reports without complex bioinformatics.

To help decipher results, ASCENT, from Indigo BioAutomation, is a software service that accelerates the release of high-quality both liquid and gas chromatography MS results. Although assays are built and validated on clean and well resolved peaks, sometimes the samples aren't clean. Whether samples are near the baseline, suffer co-elution, or have lost sensitivity and specificity expected, ASCENT starts from an adaptive per-peak smoothing algorithm to minimize the amount of peak distortion, applying machine-learning techniques to distinguish the true peak signal within the chromatographic trace. The rules engine is customizable to the laboratory SOP, and there is high visibility into the audit trail, with cross-batch rules and cross-batch reporting built in.

With these new avenues of analysis, the possibilities for discovery are endless. It will be exciting to see what laboratorians research next, as ground-breaking technologies continue to develop in the field.

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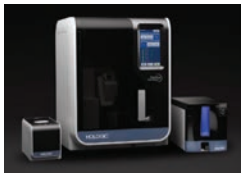

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LABORATORY INNOVATOR

Expanding molecular testing

By Marisa L. Williams

Harold Vore, Jr., BS, MS, Director of Laboratory Services at **Sarasota Memorial Hospital (SMH)**, was previously the Director of Laboratory Services at Owensboro Health and Laboratory Director at Daviess Community Hospital.

What was it like when the first patient from the Suncoast region tested positive for Covid-19?

At the time of the Covid-19 onset in February and March of 2020, we were eagerly awaiting the shipment of a new automation system for our microbiology department. Most of the instrumentation was being manufactured in northern Italy. That region of the world was one of the first areas, outside of China, to confront widespread SARS-CoV-2 infection rates. We thought the shipment of our specimen processing and culture incubation system would be delayed, but it arrived on time in July 2020. In addition to automation, we also converted to a new bacterial identification and sensitivity system and added MALDI-TOF mass spectrometry. Had we been able to predict the impact of the novel coronavirus on our microbiology department, we would have chosen another year to transform our bacteriology systems. As it turned out, the staff embraced the new technology, and the transition was very smooth.

What adjustments were made to the lab during the COVID-19 pandemic?

Our first priority was patient and staff safety. Early on, we were unsure how infectious the SARS2 virus would become. We knew several laboratory workers throughout the world had become infected and died during the original SARS1 outbreak of 2003. We made sure to process all respiratory specimens in BSL cabinets and constantly reviewed guidelines. We were especially concerned with aerosol production, even in blood specimens. Fortunately, it was determined early in the pandemic that the SARS2 virus was not transmitted via blood sources. It became evident the greatest risk for SARS2 transmission was human-to-human, and our normal universal precautions for specimen processing were adequate.

With the six new molecular platforms that were purchased for COVID-19, now that the pandemic numbers are not as high as before, will those be put to a new use?

We made a decision to utilize only NAAT methods for our hospital system. We already had partnerships, but testing supplies for SARS-CoV-2 were not available until April. After April 2020, all vendors were limiting shipments due to supply and demand. We ordered a high-throughput analyzer in early May, and waited until late September to receive the instrument, again with limited supplies from the vendor. The challenges we faced with testing instruments and supplies were the same challenges felt in hospitals throughout the United States. There was not enough testing capacity, so we partnered with our public health system, neighboring hospitals, reference laboratories, and vendors to incrementally increase our test capacity over time.

Fortunately, the instruments we purchased have clinical utility in a post-pandemic world. We will continue using the instruments for various PCR tests and plan to offer additional viral load testing on the high-throughput analyzer, which is an expansion of our test menu.

With the new oncology unit, what tests will be done in-house, and will any be sent out?

SMH will be adding a flow cytometry laboratory to the new facility to increase and enhance the range of diagnostics and personalized cancer treatments we provide to our patients. We maintain connections with many large cancer centers in the nation, and based on the type of cancer and tissue in question, will partner with them when more specific testing is needed.

We are working with our pathology team to expand diagnostics and facilitate the profiling and identification of patients who are candidates for personalized medicine and targeted immunotherapy.

What is the most exciting new technology being used in the laboratory?

SMH Laboratory has always relied on automation to allow growth, maintain efficiency, and improve safety through standardization. We are one of the most automated laboratories in the country with our single automation line in the core laboratory and a full specimen processing and culture incubation system in microbiology. While we have added new technologies for NAAT, MALDI-TOF, and FISH, automation and the accompanying information technologies represent a nearly limitless area of advancement for laboratories.

Were there any supply challenges to overcome during the pandemic, and if so, were there any creative solutions worth mentioning?

Like many, we had shortages of swabs and viral media early on. We found ways to split the media and create two for one. Running out of a needed supply or reagent was a daily event for all laboratories.

Our partnerships were an important resource and source of pride. Our local/state health department helped tremendously, and our partners at a reference laboratory were helpful in times of need. A large hospital in Tampa was quite helpful, and we were helpful to others in return. We ultimately overcame the challenges by working together across public and private sectors.

Anything else you would like to add?

The medical laboratory profession is a challenging and rewarding field for those with a sincere interest in the sciences. Approximately 70% of clinical decisions are based on laboratory test results. Laboratory professionals delivering accurate, prompt and reliable results are vital members of the healthcare team. Although most of our work is done outside of public view, laboratory professionals contribute a great deal to the safety and high-quality care of patients, and that has been especially true during this pandemic.

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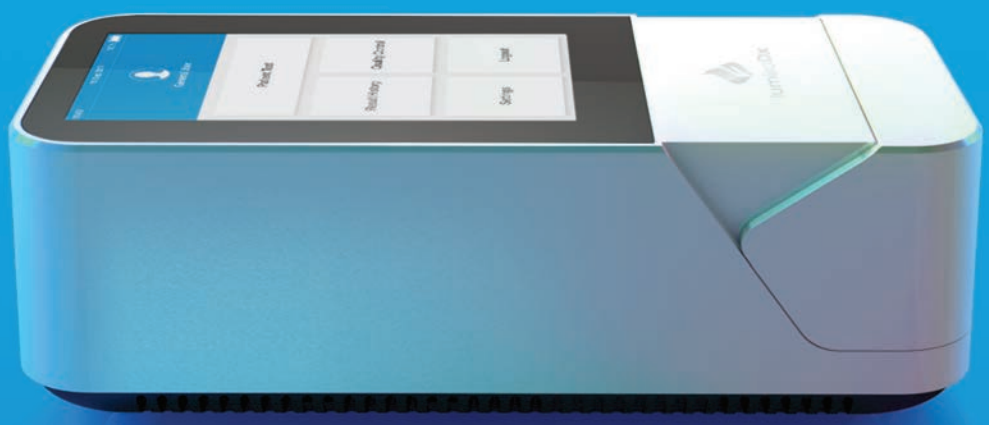

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HS Troponin	HbA1c	SARS-CoV-2 & RSV	SARS-CoV-2 & Flu A/B	Strep A	INR	D-Dimer	SARS-CoV-2		
In development	In development	In development	In development	In development	CE Mark	CE Mark	CE Mark	FDA EUA*	FDA EUA*

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*The LumiraDx SARS-CoV-2 Ag test and the LumiraDx SARS-CoV-2 Ab test have not been cleared or approved by FDA. The LumiraDx SARS-CoV-2 Ag test has been authorized by FDA under an EUA only for the detection of SARS-CoV-2 nucleocapsid protein. The LumiraDx SARS-CoV-2 Ab test has been authorized by FDA under an EUA only for detecting the presence of total antibodies to SARS-CoV-2. They have not been authorized for use to detect any other viruses or pathogens. The tests are authorized in the United States for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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SPOTLIGHT ON THE LAB

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