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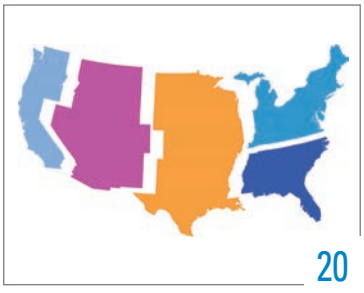
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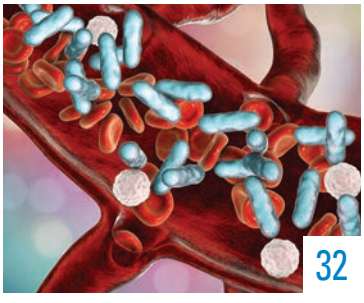
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The value of COVID-19 vaccines

By Linda Wilson
Senior Editor

In February, the Joint Commission announced that its survey standards would now include compliance with federal rules requiring healthcare workers to be vaccinated against COVID-19.

This announcement followed the U.S. Supreme Court's decision in January to uphold the Omnibus COVID-19 Health Care Staff Vaccination Interim Final Rule. Drafted by the Centers for Medicare and Medicaid Services (CMS), the rule requires healthcare facilities to mandate that their employees are vaccinated against COVID-19. Facilities that do not comply face the loss of reimbursement for services provided to Medicare beneficiaries. That is a big stick. As you know, most healthcare organizations would not survive long without government funding.

The flurry of activity around this rule provides an opportunity to consider the merits of COVID-19 vaccination for a few minutes.

When my age group was allowed to be vaccinated, I was one of the first in line at Walgreens. I've been vaccinated and boosted. I dutifully wear my KN95s — or at least a surgical mask. I wash my hands so often that they often look like they belong to one of the alligators living in Florida's ponds and lakes.

Even with my diligence, I came down with a breakthrough case of COVID-19. Other members of my family did as well.

After a few tough days, I started to feel better. I was relieved. I sent a text to a good friend who is the director of nursing services for a county health department. I wanted to let her know about my case. She said, "Can you imagine it if you weren't vaccinated?"

The truth is, the idea is too scary for me to think about. That is why I am suggesting to you that if you haven't been vaccinated, this might be good time to think about your position on the issue, again.

If you decide to do this, consider separating yourself briefly from the rhetoric, social media posts, government activity, and talking heads on television. You might go to a favorite spot by yourself and think about you and your family. Forget about everybody else for a few minutes.

From personal experience, I've concluded that SARS-CoV-2 is not something to mess with. Even with the vaccine, I became infected with the virus. I am thankful that I was vaccinated.

And I'm thankful for all of you, and the hours you spend running tests to diagnose COVID-19, as well as the myriad other diseases common in our society.

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

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Image by Anastasia Gol[illegible] from Pixabay

Fast Facts Pregnant women and COVID-19

Pregnant women with COVID-19 appear to be at greater risk for common pregnancy complications — in addition to health risks from the virus — than pregnant women without COVID-19. The study was conducted by the University of Utah and colleagues in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network.

13,000
pregnant women, from 17 U.S. hospitals, were included in the study.

2,400
pregnant women, infected with SARS-CoV-2, with moderate to severe infection, were more likely to have a cesarean delivery, to deliver preterm, to die around the time of birth, or to experience serious illness from hypertensive disorders of pregnancy, postpartum hemorrhage, or from infection other than SARS-CoV-2.

45.4%
of those women infected with moderate to severe COVID-19 were more likely to deliver by cesarean.

26.9%
of that same infected group were more likely to deliver preterm.

37
weeks, or less, gestation period was identified as the preterm, neonatal outcome for maternal COVID-19 patients with moderate or higher disease severity.

3.5%
of moderate- to severely-infected women show inclination toward having a fetal or newborn death.

Source: National Institutes of Health (NIH) https://www.nih.gov/news-events/news-releases/nih-funded-study-suggests-covid-19-increases-risk-pregnancy-complications

Study identifies how Epstein-Barr virus triggers multiple sclerosis

Scientists have long suspected, but failed to prove, a link between certain viral infections and the development of multiple sclerosis (MS). Now, a study led by Stanford Medicine researchers has proved that the Epstein-Barr virus, a common type of herpes virus, triggers multiple sclerosis by priming the immune system to attack the body's own nervous system, according to a news release from the university.

The study, published in *Nature,* shows that approximately 20% to 25% of patients with multiple sclerosis have antibodies in their blood that bind tightly to both a protein from the Epstein-Barr virus, called EBNA1, and a protein made in the brain and spinal cord, the glial cell adhesion molecule, or GlialCAM.

"Part of the EBV protein mimics your own host protein — in this case, GlialCAM, found in the insulating sheath on nerves," said William Robinson, MD, PhD, Professor of Immunology and Rheumatology at Stanford. "This means that when the immune system attacks EBV to clear the virus, it also ends up targeting GlialCAM in the myelin."

Myelin forms the protective coating around nerve cells, and when it's damaged, electrical impulses can no longer jump efficiently from one nerve to the next, resulting in the numbness, muscle weakness, and severe fatigue of multiple sclerosis.

Previous research has shown that multiple sclerosis patients have increased antibodies to a variety of common viruses, including measles, mumps, varicella-zoster, and Epstein-Barr virus. In fact, more than 99% of MS patients have EBV antibodies in their blood, indicating a prior infection, compared with 94% of healthy individuals. But despite this epidemiologic correlation, scientists have struggled to prove a causal connection.

To find this mechanistic link, the researchers started by examining the antibodies produced by immune cells in the blood and spinal fluid of nine MS patients. Unlike in healthy individuals, the immune cells of MS patients' traffic to the brain and spinal cord, where they produce large amounts of a few types of antibodies. Patterns of these antibody proteins, called oligoclonal bands, are found during analysis of the spinal fluid and are part of the diagnostic criteria for MS.

"So, the first thing we did was analyze the antibodies from the oligoclonal bands and showed that they come from B cells in the spinal fluid," Robinson said.

B cells are a type of white blood cell made in the bone marrow, and the technology to sequence these cells individually was developed by the Robinson lab about eight years ago.

The discovery of how EBV triggers multiple sclerosis could also have ramifications for research into other autoimmune diseases, such as lupus and rheumatoid arthritis, which, like MS, have been significantly associated with EBV infection in epidemiologic studies.

Method to detect toxic brain cells could be a step to a new Alzheimer's treatment

Emerging evidence suggests it may be possible to treat Alzheimer's disease by targeting therapy at senescent cells in the brain.

A team from The University of Texas Health Science Center at San Antonio and Wake Forest School of Medicine reported in the journal, *Nature Aging,* a method, based on computational analysis, to objectively identify and quantify these toxic cells. In addition to having value in monitoring the effectiveness of senescent cell therapy, this method could prove to be a highly effective diagnostic tool in detecting Alzheimer's.

If a cell is old, stressed, or damaged by insults such as radiation, it may enter a state in which it can no longer divide or function properly. This is senescence. These cells cannot properly repair themselves and don't die off when they should. They have been called "zombie cells" for this reason. Instead, senescent cells function abnormally and release substances that kill surrounding healthy cells and cause inflammation. Over time, they continue to build up in tissues throughout the body, contributing to the aging process, cognitive decline, and cancer.

Having a signature for senescence will be important clinically for baseline measurements at the time patients are first seen by a neurologist and then to track the impact of medication. Identifying populations of senescent cells is also important to understand how and why cells become senescent.

Using statistical analyses, the research team was able to evaluate large amounts of data. In total, they profiled tens of thousands of cells from the postmortem brains of people who had died with Alzheimer's disease. The researchers looked for the presence of senescent cells and then their quantity and types.

The team found that approximately 2% of the brain cells were senescent. The researchers also identified the type of cell and the characteristic features. The study findings indicated

that the senescent cells were mostly neurons, which are central nervous system cells in the brain that are lost in Alzheimer's disease.

Study examines treatment options for patients with high-risk prostate cancer

An international study consisting of a consortium of 16 research centers in collaboration with two international cooperative trial groups found that patients receiving high-dose external beam radiation therapy alone may benefit from androgen deprivation therapy (ADT) lasting longer than 18 months, while those with external beam radiation therapy and a brachytherapy boost — the implantation of radioactive seeds to deliver a higher total dose to the prostate — may be optimally managed with 18 months of ADT or possibly less, according to a news release from UCLA, which was involved in the study.

The researchers analyzed individual patient data from three cohorts of patients: a retrospective cohort of patients from 16 cancer treatment referral centers between 2000 and 2014 who received either high-dose external beam radiotherapy or external beam radiotherapy with a brachytherapy boost; a cohort of patients enrolled in a randomized phase 3 trial that included patients from 23 treatment centers in Australia and New Zealand; and a cohort of patients enrolled in a randomized phase 3 trial conducted across 10 treatment centers in Spain.

In the retrospective cohort — looking at ADT durations of less than six months, six to 18 months, and greater than 18 months — a significant interaction was seen between treatment type and ADT duration. A duration of 18 months or more was associated with improved outcomes, relative to shorter durations, for patients receiving high-dose external beam radiation therapy without a brachytherapy boost.

In contrast, among patients receiving radiation therapy and brachytherapy, an ADT duration of at least six months but less than 18 months was associated with improved metastasis-free survival and overall survival, compared to receipt of less than six months of ADT. But there appeared to be no improvement in metastasis-free survival for those receiving both forms of radiation therapy and more than 18 months of ADT.

With further analysis, the researchers determined that for patients receiving radiation therapy without brachytherapy, the optimal ADT duration was 26.3 months; for those treated with radiation therapy and a brachytherapy boost, the minimum threshold was 12 months.

Their hypotheses, drawn from the retrospective study, appeared to be supported by effects observed in the randomized clinical trials

Newly developed inhaled vaccine delivers broad protection against SARS-CoV-2, variants of concern

Scientists at McMaster University have developed an inhaled form of COVID vaccine and confirmed it can provide broad, long-lasting protection against the original strain of SARS-CoV-2 and variants of concern.

The research, recently published in the journal, *Cell*, reveals the immune mechanisms and significant benefits of vaccines being delivered directly into the respiratory tract, rather than by traditional injection. The laboratory and the researchers are part of McMaster's Global Nexus for Pandemics and Biological Threats.

Because inhaled vaccines target the lungs and upper airways where respiratory viruses first enter the body, they are far more effective at inducing a protective immune response, the researchers report.

The reported preclinical study, which was conducted on animal models, has provided the critical proof of concept to enable a Phase 1 clinical trial that is currently under way to evaluate inhaled aerosol vaccines in healthy adults who had already received two doses of a COVID mRNA vaccine.

The tested COVID vaccine strategy was built upon a robust tuberculosis vaccine research program established by Zhou Xing, a co-lead author of the new study and a professor at the McMaster Immunology Research Centre and Department of Medicine.

"What we've discovered from many years' research is that the vaccine delivered into the lung induces all-around protective respiratory mucosal immunity, a property that the injected vaccine is lacking," Xing says.

Currently authorized COVID vaccines are all injected.

"We wanted, first and foremost, to design a vaccine that would work well against any variant," explains the study's co-lead author Matthew Miller, Associate Professor at McMaster's Michael G. DeGroote Institute for Infectious Disease Research.

The McMaster COVID vaccine represents one of only a handful developed in Canada. The urgent work is a critical mission of Canada's Global Nexus for Pandemics and Biological Threats, which is based at McMaster.

Researchers compared two types of adenovirus platforms for the vaccine. The viruses serve as vectors that can deliver vaccine directly to the lungs without causing illness themselves.

"We can remain ahead of the virus with our vaccine strategy," says Miller. "Current vaccines are limited because they will need to be updated and will always be chasing the virus."

Both types of the new McMaster vaccine are effective against highly transmissible variants because they are designed to target three parts of the virus, including two that are highly conserved among coronaviruses and do not mutate as quickly as spike. All COVID vaccines currently approved in Canada target only the spike protein, which has shown a remarkable ability to mutate.

"This vaccine might also provide pre-emptive protection against a future pandemic, and that's really important because as we've seen during this pandemic — and as we saw in 2009 with the swine flu — even when we are able to rapidly make a vaccine for a pandemic virus, it's already way too late. Millions of people died, even though we were able to make a vaccine in record time," says Miller.

"We have revealed in our report that, besides neutralizing antibodies and T cell immunity, the vaccine delivered into the lungs stimulates a unique form of immunity known as trained innate immunity, which is able to provide very broad protection against many lung pathogens besides SARS-CoV-2," Xing adds.

In additional to being needle and pain-free, an inhaled vaccine is so efficient at targeting the lungs and upper airways that it can achieve maximum protection with a small fraction of the dose of current vaccines — possibly as little as 1 per cent — meaning a single batch of vaccine could go 100 times farther, the researchers say .

The long-term health consequences of COVID-19

By Harvey W. Kaufman, MD, and William A. Meyer III, PhD

After the initial onslaught, viral infections can be associated with long-term adverse consequences. This can result from direct damage from the primary infection, a persistent infection, or from downstream effects of the immune response to the initial infection. Disease occurring post-initial viral infection ranges in severity. At its most extreme, this can include some types of cancer, for example, following infection by Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), and human papillomavirus (HPV).

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LEARNING OBJECTIVES

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

1. Describe the definition and range of clinical symptoms associated with Long COVID
2. Describe the organ damage that occurs from COVID-19 and how this leads to ongoing medical issues
3. Describe the case definitions and symptoms associated with multisystem inflammatory syndrome (MIS)
4. Discuss hypotheses about why Long COVID occurs

On the other end of the disease severity scale, many infections are initially asymptomatic and self-limiting. This includes a mild clinical case of severe acute respiratory coronavirus 2 (SARS-CoV-2) that causes novel coronavirus disease 2019 (COVID-19). However, even when viral infections are asymptomatic, some people develop serious post-viral sequelae. Examples include infections associated with post-viral, developmental deficits following congenital viral infections, asthma following respiratory viral infections, immune suppression due to measles virus, and multisystem inflammatory syndrome (MIS) associated with SARS-CoV-2 infection.

We remain in a worldwide pandemic today with more than 400 million confirmed COVID-19 cases and more than five million deaths; consequently, interest is high in understanding the long-term effects of COVID-19. The attention given to these long-term COVID-19 sequelae is personal for many people. Others feel the impact on their communities and healthcare resources. Long-term COVID-19 also can be a disability: as of July 2021, Long COVID can be considered a disability under the Americans with Disabilities Act (ADA).

The term "Long COVID" seems to have stuck as the primary designation of extended symptomatology post primary infection with SARS-CoV-2. "#LongCovid" was first used by Elisa Perego, from Lombardy, Italy.[1] This condition has also been referred to as post-COVID, long-haul COVID, post-acute COVID-19, long-term effects of COVID, or chronic COVID. The more technical term for this condition is "post-acute sequelae of SARS-CoV-2 infection" or "PASC."

Nova Biomedical's Educational Webinar Series Presents:

Estimated Plasma Volume (ePV) in Critical Care

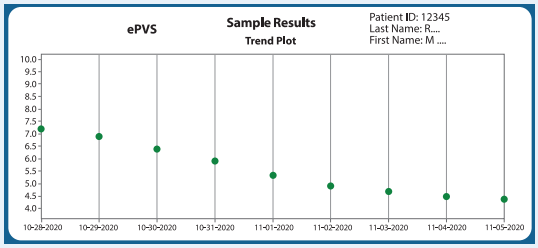
New studies have reinforced the clinical importance of ePV as a diagnostic and prognostic tool in many clinical settings, particularly critical care. The ePV can be calculated using several formulas, mostly based on hemoglobin and hematocrit and sometimes body weight. It has been shown to provide useful prognostic information in patients with heart failure, myocardial infarction, renal failure, and recently acute respiratory distress syndrome (ARDS). Additionally, it has been associated with all-cause mortality and mortality from cancer in large cohort studies. This webinar will review the epidemiology, predictive power and potential clinical uses of ePV, especially in critically ill patients. We will discuss the origin of PV measurement, other techniques for PV measurement, and explore the pathophysiology of how PV can affect various disease processes, with special focus on ARDS and acute illnesses.

Primary Presenter

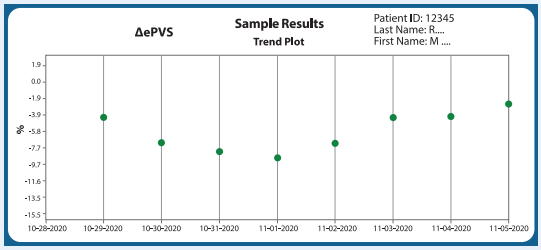
Thomas Metkus, MD
Divisions of Cardiology and Cardiac Surgery, Departments of Medicine and Surgery
Johns Hopkins University School of Medicine, Baltimore, MD

Measuring ePV in Critical Care

There is growing recognition that PV is an important parameter to determine in various disease processes. Nova Biomedical offers a blood gas analyzer that can calculate and trend ePV and ΔPV at the point-of-care as part of a comprehensive blood gas/critical care profile. Since ePV requires both measured hemoglobin and hematocrit, Nova's blood gas analyzer is uniquely qualified to give an accurate calculation of ePV. This portion of the webinar will review this technology and reinforce the clinical importance of ePV as part of the blood gas critical care profile.



Prime Plus trend screen showing absoute values (ePVS)



Prime Plus trend screen showing percent change (ΔePVS)

Presenter

Dennis Begos, MD, FACS, FACRS
Medical Director
Medical and Scientific Affairs
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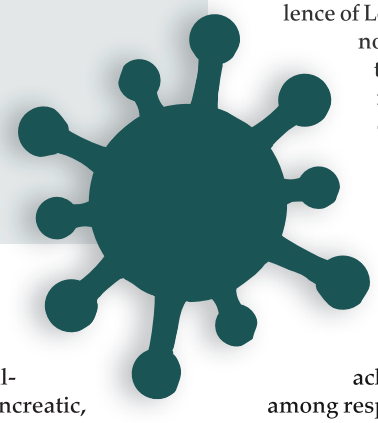
Common Symptoms Associated with Long COVID

- Fatigue
- Shortness of breath or difficulty breathing
- Cough
- Joint pain
- Chest pain
- Memory, concentration, or sleep problems
- Brain fog (not a medical term but describes when thinking is sluggish, fuzzy, and not sharp)
- Muscle pain or headache
- Fast or pounding heartbeat
- Loss of smell or taste
- Depression or anxiety
- Fever
- Dizziness when you stand
- Worsened symptoms after physical or mental exertion activities

Table 1.



Long COVID complications

Long COVID complications may arise in a wide variety of organ systems including pulmonary, cardiovascular, hematological, pancreatic, dermatological, neurological, and psychological, to list just a few. (For expanded information on this topic there are excellent reviews and resources available.[2,3,4]) This persistence of symptoms — or the development of new symptoms — over many weeks and months post SARS-CoV-2 infection is consistent with a slow recovery and is generally considered to be Long COVID. Thus, Long COVID is defined as having a wide range of new, returning, ongoing health problems that are experienced a minimum of four weeks after initial COVID-19 infection, including initially asymptomatic people **(Table 1)**.[5,6,7]

The minimum four-week time period for prolonged symptom expression as a requirement for a Long COVID diagnosis is not based on scientific analysis but seems to fit with general clinical observations. Long COVID symptoms vary in severity and duration and can change over time. Many weeks after a COVID-19 infection, people may still feel tired or achy in a similar fashion that some experience following the flu. In one study, COVID-19-associated cough persisted for an average of 19 days. In approximately 5% of patients, a cough lasted for four weeks or longer.[8] Just as there are many causes of cough that can be due to COVID-19 or other reasons, symptoms of anxiety, depression, and mood changes also have many causes.

Unfortunately, the COVID-19 pandemic has also created and heightened social isolation that leads more people to have anxiety, depression, and mood changes — although it is important to recognize that these ailments do occur in the absence of a pandemic. Thus, connecting new, returning, or ongoing health problems with a prior COVID-19 episode is imprecise, especially at the individual patient level. For example, when evaluating the reasons for another common clinical event, a heart attack occurring while watching a sporting event, the cause could be related or unrelated to the excitement of watching the sporting event itself. In this instance, the underlying heart disease may have been a "ticking time bomb" that exploded during the sporting event. Accordingly, relating new symptoms to Long COVID-19 can be challenging, given the underlying health risks and conditions of any individual person.

Researchers at University of Michigan, led by Jeffrey Myers, MD, Professor of Diagnostic Pathology, examined chest X-rays and lung biopsies from patients who had COVID-19 and persistent respiratory symptoms. They found evidence of preexisting chronic lung disease in many patients, suggesting that COVID-19 exacerbated underlying lung disease that likely contributed to the development of Long COVID respiratory symptoms.[9]

Thus, for some people with Long COVID, the role of pre-existing, diagnosed or undiagnosed, underlying health issues (like the ticking time bomb predating a heart attack in the example above) may be an important contributory factor. Additionally, some studies show minimal differences between the prevalence of Long COVID symptoms between hospitalized and non-hospitalized COVID-19 patients, suggesting that, in some cases, the severity of COVID-19 is not the driving force behind the subsequent development Long COVID.[10]

An online Long COVID support group, Survivor Corps, solicited input from 5,163 group members. Participants listed, on average, 21 symptoms. The most common symptoms were fatigue (79%), headache (55%), shortness of breath (55%), difficulty concentrating (54%), cough (49%), changed sense of taste (45%), diarrhea (44%), and muscle or body aches (44%). The timing of symptom onset varied among respondents and was best described as happening in waves.[11]

Researchers at Mass General Brigham extracted 328,879 clinical notes from 26,117 COVID-19 positive patients in their post-acute infection period (days 51–110).[12] Of 355 recorded symptoms, the most common were pain (43%), anxiety (26%), depression (24%), fatigue (23%), joint pain (21%), shortness of breath (21%), headache (20%), nausea and/or vomiting (20%), myalgia (19%), and gastroesophageal reflux (19%). Differences among studies reflect differences in the population studied, methodology, and SARS-CoV-2 variants.

An important feature of SARS-CoV-2 infection is that the virus doesn't infect just the respiratory tract (nasal passage, throat, bronchus, and lungs). SARS-CoV-2 can also damage many other organs, including the heart, pancreas, kidneys, and brain. This is because the cell receptor for SARS-CoV-2's entry is the angiotensin-converting enzyme 2 (ACE2) that is expressed on most types of cells throughout the body.

Direct organ damage, resulting from acute viral infection, may lead to health complications that remain after the acute COVID-19 respiratory illness is clinically resolved **(Table 2)**. In some people, lasting effects may include breathing problems, heart complications, chronic kidney impairment, diabetes development, stroke, and neurological damage. For example, in a study of more than 500,000 patient records, researchers found among patients older than18 years of age a significant increase in new diabetes diagnoses of those with COVID-19 compared to patients without COVID-19 during the pandemic period, or among those with acute respiratory infections during the pre-pandemic period.[13] The researchers suggest the development of diabetes results from a direct effect of SARS-CoV-2 on pancreatic cells. Thus, long term unfavorable effects of COVID-19 may result from direct infection of multiple organs. Additionally, a

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MIS-C Case Definition from the CDC

Multisystem Inflammatory Syndrome-Child (MIS-C) Case Definition.[25] A person younger than 21 years of age presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND

- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

**Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LD), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin.

Additional comments:

- Some people may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

Figure 1

direct adverse effect on one organ, e.g., pancreas or brain, can ultimately harm other organ systems.

One of the most serious of the Long COVID effects is multisystem inflammatory syndrome (MIS), described by Bruno Larida in the January edition of *Medical Laboratory Observer*.[14] Fortunately, to date, MIS is rare and only occasionally lethal. This medical condition is associated with inflammation in multiple body organs including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal tract. In affected children, the peak of MIS is approximately one month after onset of COVID-19, with more than 6,400 children reportedly affected and among these, 55 deaths, according to the Centers for Disease Control and Prevention (CDC). **Figure 1** provides a case definition of multisystem inflammatory disease for children (MIS-C). Adult cases have been reported, as well, and a separate list of criteria apply.

The expected duration of Long COVID is hard to pin down because of varying methods used to collect data, different time periods of evaluation, different variants, and different affected populations studied. For example, at six months after COVID-19 diagnoses, an online study found 76% of patients were affected with Long COVID, while a study from China found 33% affected with Long COVID symptoms.[15,16] In a different population, the UK Office for National Statistics (ONS) estimated 22% of COVID-19 patients had post-infection symptoms at five weeks and 10% at twelve weeks.[17] Persistent loss of taste or smell can affect diet, appetite, and weight. Difficulty sleeping may impact ability to perform home chores, work, and general wellbeing. Regardless of the method, these reports suggest that Long COVID is relatively common and may have a serious negative impact on an affected individual's personal health and on our healthcare system. In summary, further studies are needed to provide ongoing epidemiological tracking of Long COVID.

Long COVID can develop after either a SARS-CoV-2 infection or after a breakthrough infection following vaccination. Of several such studies, the largest and most representative is a study of 1.2 million British adults who had received, at least, one vaccine dose between December 2020 and July 2021. The researchers found approximately 5% of those with breakthrough COVID-19 infections reported Long COVID symptoms, compared with 11% of unvaccinated control group who had COVID-19.[18]

On the other hand, some patients with Long COVID appear to improve after vaccination.[19] A Survivors Corps survey found that 42% of people with Long COVID reported improvement after vaccination. Another patient advocacy group, LongCovidSOS, found 58% of COVID-19 patients reported improvement of symptoms after vaccination.[20] A third study found that 22% of patients with Long COVID improved after vaccination, but 31% of them did not improve. [21]

One theory is that vaccination stimulates the immune system to target remnant viral particles; another is that some patients with Long COVID have an autoimmune response and that vaccination induces certain types of cytokines that can positively impact these autoreactive cells.

Table 2: COVID-19 Impact by Organ System, Common Symptoms, and Laboratory Tests

Organ/Tissue	Symptoms	Laboratory Test Effects
Heart	Chest pain	
	Myocarditis	CK-MB and Troponin, increased
	Palpitations	
Lungs	Shortness of breath	
	Cough	
	Chest pain	
Pancreas	Pancreatitis	Amylase and Lipase, increased
Kidneys	Acute Kidney Injury	Creatinine, increased
Gastrointestinal	Nausea	Electrolyte disturbance
	Vomiting	
Blood Vessels	Inflammation	Coagulopathies
		Fibrinogen, increased
Liver	Inflammation	AST and ALT, increased
Spleen	Atrophy of lymphoid follicles	Lymphocytes, decreased
Brain	"Brain fog"	
	Fatigue	
	Sleep disturbances	
	Anxiety and depression	

Adapted in part from Crook H, Raza S, Nowell J, Young M, Edison P. Long Covid – mechanisms, risk factors, and management. BMJ. 374:n1648 doi:10.1136/bmj.n1648.[2]

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Why does Long COVID occur?

The exact mechanism(s) responsible for Long COVID complications remain unidentified. Several theories have been suggested — and any combination of these, or perhaps as-yet unidentified hypotheses, could be responsible for the development of Long COVID.[22] The theories include:

1. Direct organ damage due to the primary SARS-CoV-2 infection of cells. As the ACE2 receptor on host cells that allow for SARS-CoV-2 infection is found throughout the body — including respiratory goblet cells, other epithelial and endothelial cells, gastrointestinal epithelial cells, pancreatic beta cells, and renal podocytes — the possibility exists that direct organ injury may be responsible for a portion of Long COVID cases.
2. Persistent reservoirs of SARS-CoV-2. Some studies have found remnant viral RNA in tissues. One study described a SARS-CoV-2 CD8 T-cell response of increased magnitude and breadth that was associated with prolonged SARS-CoV-2 PCR-positivity that extended over three months following the patient's initial infection.[23]
3. "Viral ghosts" or viral remnants that persist in vivo. Improvement in symptomology in some Long COVID patients, subsequent to SARS-CoV-2 vaccination, provides some indirect evidence of the possible presence of such viral remnant material, which upon host immune stimulation by a vaccine, might help immune cells remove this residual viral material.
4. Prolonged autoimmune response to SARS-CoV-2 infection. The improvement in Long COVID symptomatology in some patients, subsequent to SARS-CoV-2 vaccination, provides some evidence that suggests there is a redirection of the host's immune response, away from self and toward the virus, thus diverting the damaging autoimmune response.
5. Reactivation of other quiescent viruses. One study found Long COVID patients were more likely to have supplemental reactivation of the Epstein-Barr virus, the virus associated with mononucleosis. This finding suggests that SARS-CoV-2 caused reactivation of the Epstein-Barr virus in approximately 3 out of 4 patients with Long COVID, and this may be responsible for at least a portion of Long COVID cases.[24]

Unfortunately, there currently is no definitive diagnostic test for Long COVID. Further, some people with Long COVID have no direct laboratory evidence of prior SARS-CoV-2 infection. There are several reasons for a lack of documentation of a prior COVID-19 infection in patients with Long COVID. Those reasons, theoretically, include asymptomatic disease presentation; a lack of SARS-CoV-2 testing at the time of initial infection; use of SARS-CoV-2 "at home" rapid testing, for which there are no medical records of those results; or negative SARS-CoV-2 test results. One example of a negative test result that could occur during acute infection is SARS-CoV-2 serology (antibody testing). SARS-CoV-2 serology testing may provide a positive result in approximately 90% of people who were infected; therefore, approximately 10% will not have detectable antibodies (nucleocapsid protein), although they may have other evidence of recent infection (e.g., a positive NAAT assay result). Also, since the SARS-CoV-2 antibody response diminishes over time, the timing of the specimen collection could play a role in these cases.[25]

Diagnosis and treatment

Although there are no specific laboratory tests to diagnose Long COVID, testing may still be valuable in assessing symptoms or to point to other causes of symptoms that overlap those of Long COVID. Ruling in or out some other non-COVID-19 causes of a patient's symptoms may be clinically and psychological helpful for an individual patient. For example, headaches and digestive symptomatology have many causes, and their appearance could have been triggered by COVID-19 or be completely unrelated. Thus, patients and their healthcare providers are encouraged, through shared decision-making, to adopt an approach that focuses on appropriate evaluation and goals of improving physical, mental health, and social wellbeing in those suspected of a Long COVID presentation. Because other medical conditions can develop independent of Long COVID, assigning symptoms to Long COVID may mask or delay evaluation of these other medical conditions.

Some medical centers have established Long COVID-19 clinics that specialize in the management of patients with these symptoms. Many social support groups are available online that connect people and provide outstanding assistance. Caution is needed, however, when considering such support avenues because social media has also spurred many support groups that may spread misinformation/disinformation.

Future direction

With more than 65 million confirmed COVID-19 cases (and many million more not confirmed or undiagnosed) in the United States, the shadow of Long COVID will be lengthy, adversely impacting the healthcare of millions of people and healthcare resources needed to serve them. Primary care physicians and specialists need training in Long COVID care. Clinics and other resources need to be quickly developed with wide accessibility.[26] Clinical laboratories will provide a wide spectrum of tests to support the healthcare management of patients with Long COVID.

Currently, we have a poor understanding of the pathogenesis underlying Long COVID. Both basic and clinical research are required to understand risk factors, diagnosis, mitigation (beyond reducing risk of initial infection), and treatment, and management. Fortunately, the National Institutes of Health (NIH) recognizes this challenge. "Most likely it's more than just one condition," said Francis Collins, MD, Director of NIH, which is allocating $470 million for national studies on Long COVID. "The really troubling aspects of this terrible pandemic might be the lingering of this long-tail effect on people," Collins said.[27] With this strong support, we can expect closing many of the gaps in our understanding of Long COVID.

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The long-term health consequences of COVID-19

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1. **Viral infections can be associated with long-term adverse consequences that can result from _____?**
   - ○ direct damage from the primary infection
   - ○ a persistent infection
   - ○ downstream effects of the immune response to the initial infection
   - ○ all of the above

2. **Disease occurring post-initial viral infection ranges in severity.**
   - ○ A. True
   - ○ B. False

3. **Can some people develop serious post-viral sequelae even when viral infections are asymptomatic?**
   - ○ A. Yes
   - ○ B. No

4. **Today, in the worldwide pandemic, how many confirmed COVID-19 cases are there?**
   - ○ 560 million
   - ○ more than 320 million
   - ○ less than 50 million
   - ○ figure not known

5. **Long-term COVID-19 also can be considered a disability, under _____?**
   - ○ The Americans with Disabilities Act (ADA)
   - ○ The President's Proclamation of 2021
   - ○ The CDC guidelines
   - ○ The FDA guidelines

6. **The term "Long COVID," which seems to have stuck as the primary designation of extended symptomatology post primary infection with SARS-CoV-2, was first used by whom?**
   - ○ A. Anthony Fauci, MD
   - ○ B. President Joe Biden
   - ○ C. Elisa Perego
   - ○ D. The surgeon general

7. **Long COVID complications may arise in a wide variety of organ systems including pulmonary, cardiovascular, hematological, pancreatic, dermatological, neurological, and psychological.**
   - ○ True
   - ○ False

8. **Long COVID is defined as having what types of symptoms?**
   - ○ A. a limited number of new symptoms
   - ○ B. a wide range of new, returning, ongoing health problems
   - ○ C. a wild range of new symptoms that disappear quickly
   - ○ D. health problems that reoccur over time

9. **Why is "the minimum four-week time period for prolonged symptom expression" a requirement for a Long COVID diagnosis?**
   - ○ It is not based on scientific analysis.
   - ○ It seems to fit with general clinical observations.
   - ○ It was determined by the Centers for Disease Control and Prevention.
   - ○ It was determined by a laboratorian.

10. **Many weeks after a COVID-19 infection, people may still feel _____.**
    - ○ in a similar fashion that some experience following the flu
    - ○ jittery
    - ○ sweaty
    - ○ insomnia

11. **In approximately what percentage of patients, did a cough last for four weeks or longer?**
    - ○ 10%
    - ○ 2%
    - ○ 5%
    - ○ 12%

12. **Connecting new, returning, or ongoing health problems with a prior COVID-19 episode is _____.**
    - ○ imprecise
    - ○ precise
    - ○ a newly found science
    - ○ none of the above

13. **What did researchers at University of Michigan find when they examined chest X-rays and lung biopsies from patients who had COVID-19?**
    - ○ no evidence of preexisting chronic lung disease
    - ○ evidence of lung cancer
    - ○ evidence of preexisting chronic lung disease
    - ○ A and B

14. **What is the most commonly reported symptom of Long COVID?**
    - ○ fatigue
    - ○ headache
    - ○ shortness of breath
    - ○ cough

15. **Researchers at Mass General Brigham extracted 328,879 clinical notes from 26,117 COVID-19 positive patients. How long was the post-acute infection period?**
    - ○ A. 10-25 days
    - ○ B. 50 days
    - ○ C. 90-100 days
    - ○ D. 51–110 days

16. **Besides the respiratory tract, what other areas can be affected by SARS-CoV-2?**
    - ○ eyesight
    - ○ circulation
    - ○ brain
    - ○ hearing

17. **What are some of SARS-CoV-2's potentially lasting effects?**
    - ○ breathing problems, heart complications
    - ○ chronic kidney impairment, diabetes development
    - ○ stroke, and neurological damage
    - ○ all of the above

18. **In a study of more than 500,000 patient records, researchers found among patients older than 18 years of age a _____ in new diabetes diagnoses in those with COVID-19.**
    - ○ significant increase
    - ○ significant decrease
    - ○ slight decrease
    - ○ slight increase

19. **Long COVID can develop after _____?**
    - ○ a SARS-CoV-2 infection
    - ○ a breakthrough infection following vaccination
    - ○ Both A and B
    - ○ None of the above

20. **Why does Long COVID occur?**
    - ○ direct organ damage due to the primary SARS-CoV-2 infection of cells
    - ○ reactivation of other quiescent viruses
    - ○ prolonged autoimmune response to SARS-CoV-2 infection
    - ○ all of the above

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Anti-Streptolysin O
β-2 Microglobulin
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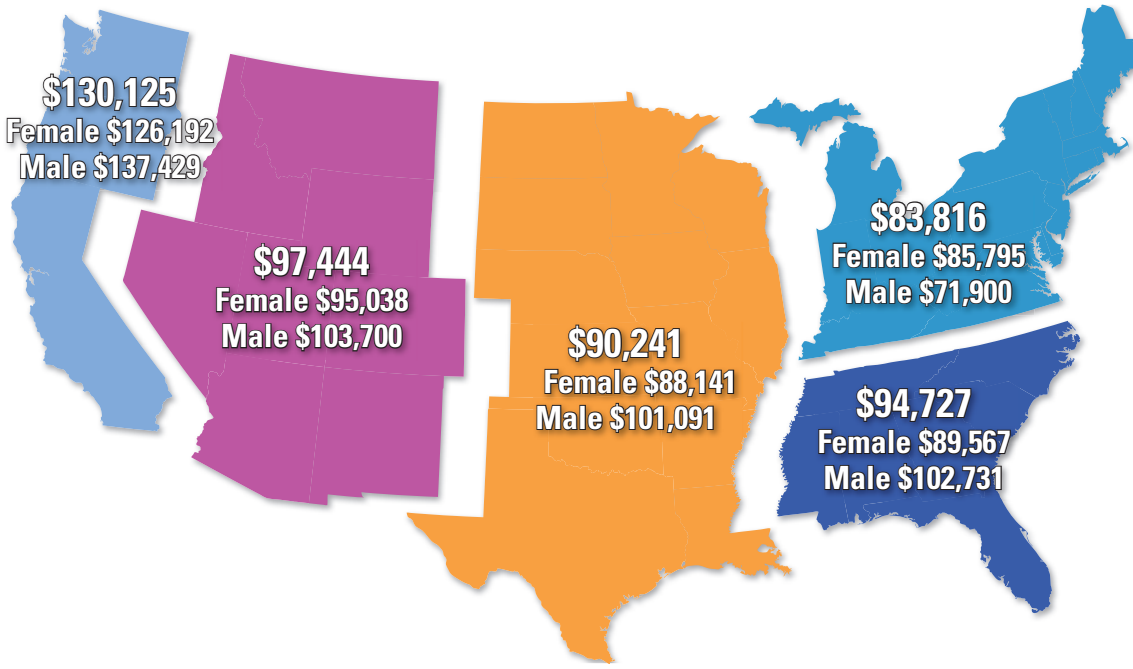


MLO's 2022 Annual Salary Survey of laboratory professionals

By Gail Castanho

The results of Medical Laboratory Observer's 2022 annual salary survey of laboratory professionals indicate a drop in the average salary across all positions; however, some specific job categories reported increases.

According to *MLO's* 2022 salary survey, the average compensation, across all positions, dropped to $92,146 from $97,888 in 2021. Females' salary also showed a drop for 2022, with reported salaries at $90,478, compared to 2021, where females' salary was $95,270. Additionally, salaries for males fell to $98,167 in 2022, as opposed to $103,233 for 2021.

While the average compensation, across all positions, decreased in 2022, there appears to be a reasonable explanation for this drop. A notable reason has to do with the level of job responsibilities of those who responded. For instance, within the current survey, lab directors responded less than in the previous year (11.9% in 2022, 20.5% in 2021) than medical lab technicians (3.7% in 2022, up from 1.3% in 2021), therefore, causing, perhaps, slightly exaggerated results.

Many participants reported pay increases over the past year, with 73.3% "yes" responses, an improvement over 62.5% from the previous survey in 2021. Respondents also indicated they expected a salary increase in 2022, with 50.6% expressing that thought, a 2-4% rise, whereas 48.4% of 2021 respondents expressed their expected 2-4% increase. A less than 2% anticipated annual increase dropped to 20.2% of the 2022 survey takers, in comparison to 20.8% in 2021. Bonuses where positively affirmed for 2022, at 48.1% over 2021's 38.1%.

AVERAGE ANNUAL BASE SALARY: $92,146

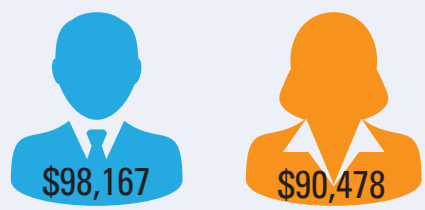
DID YOUR SALARY CHANGE IN 2021?

73% Yes, it increased
24% It remained the same
3% No, it decreased

PERCENTAGE INCREASE EXPECTED OVER LAST YEAR

2.6%

AVERAGE PAY BY GENDER



MALE FEMALE

DID YOU RECIEVE A BONUS IN 2021?

48% Yes
52% No

GENDER OF RESPONDANTS

76% Female
21% Male

3% of survey respondents chose not to disclose their gender

Demographics

Of the 243 survey respondents, where both male and females were represented, the majority were female (76.1%) over 2021's 71.5%. However, the collective percentages of both represented genders were: 37.9% between the ages of 56-65, and 22.6% ages of 46-55. These men and women hold salaried, management positions (74.9%), with the majority working in hospital labs, where an increase to 96.3%, over 2021's average of 93.9% was reported.

Salary changes: ups and downs across positions and locations

While expected annual base salary for 2022 is $92,146, this survey shows that salaries, based on particular positions, fluctuated since 2021 with more salaries dropping, over the past year. Pathologists' salary decreased in 2022, to $147,750, from 2021's $160,000. Microbiologists also saw a decrease in their salary in this 2022 survey, dropping to $70,357, from 2021's $73,750. Lab directors reported a downward trend in their 2022 salary ($123,500), as well, indicating a slight difference from last year's numbers ($126,938). Other areas where salary losses occurred were medical lab technicians, $63,389 for 2022, down from 2021's $65,000; medical laboratory scientists, $63,559, for 2022, dropping from 2021 ($80,500); and chief/asst. chief/medical technologist reporting a salary decrease from 2021 ($86,833), currently at $75,833, for 2022.

In contrast to the descending salary trends above, lab managers/administrators/supervisors' salaries increased from $93,879, in 2021, to $96,246, in 2022. Compliance/quality assurance coordinators and managers' salaries also increased in 2022, to $94,677, over 2021's salary of $87,000. Section managers and department heads also saw an increase in salary for 2022 ($83,735), rather than 2021's salary of $77,703. Lastly, LIS/EHR/EMR managers' salaries, for 2022, rose to $88,083, from 84,500 in 2021.

> Staff shortages continue to plague labs with 43.2% reporting their labs' operational efficiency, was largely impacted, compared to 2021's figure of 26.3%.

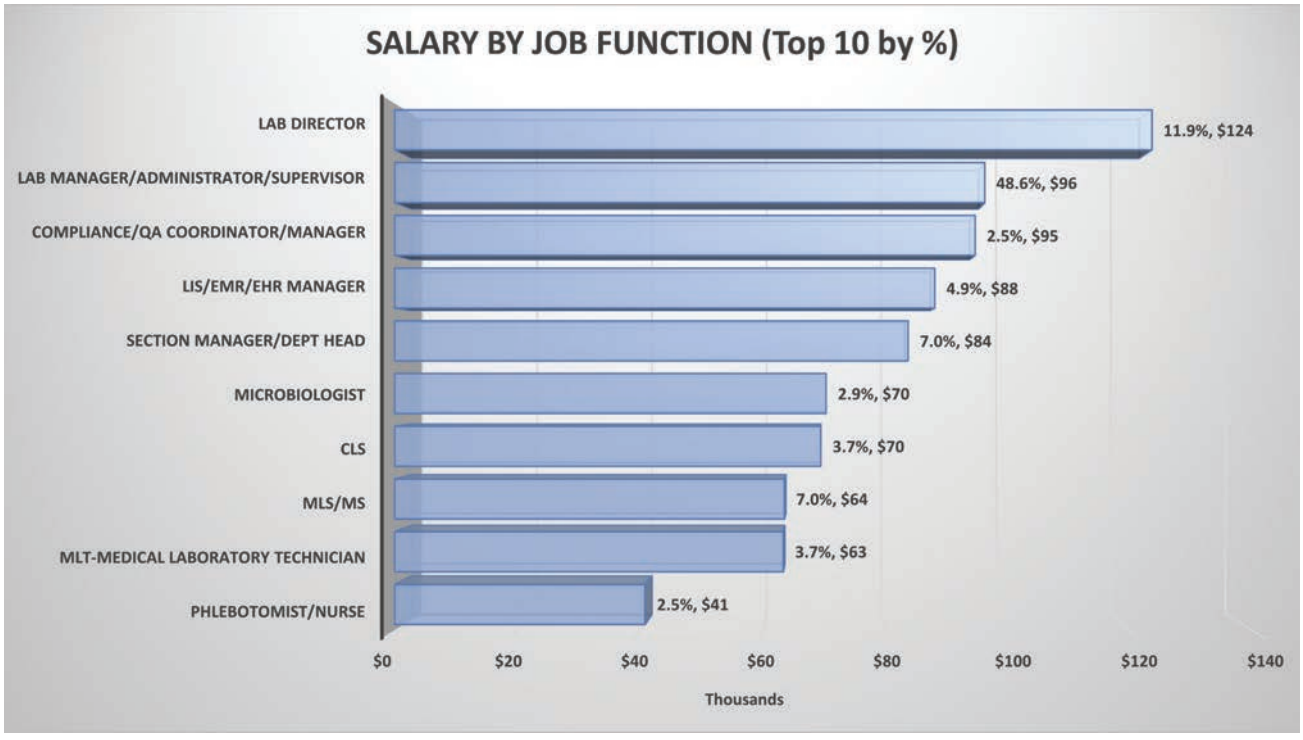
Aligning with the current trend, salaries designated by regions also exhibited fluctuations, with more of a downward tendency, rather than an upward one. The northeast saw a significant downward turn in 2022, with salaries at $83,816, as opposed to 2021's result, $98,110. The central region also experienced a salary drop to $90,241 in 2022, from $92,747 in 2021. The mountain region's salary fell in 2022, to $97,444, from $101,817, in 2021.

Unlike the regions mentioned above, two regions experienced a rise in salary in 2022. The southeast region gained in 2022, with $94,727, over that of 2021 ($92,069). Additionally, the pacific region also experienced an increase in salary in 2022, ($130,125), which outshines the previous year's salary of $129,208.

Lab size and testing volume influence salary

To further clarify the differing salary results for 2022, salaries, based on the number of employees a lab employs, appears as a "mostly" downward trend from 2021. Labs with over 100 employees reported an average salary, for 2022, at $95,536, down from 2021 ($115,873). Labs that employ 51-100 people showed an average salary of $95,052, for 2022, a reduction from $101,535, in 2021. Those labs that have 21-50 employees reported average salaries at $91,052, for 2022, falling below 2021's average of $91,336. Those labs with 1-10 people employed have average salaries of $80,758, whereas 2021's average for salaried employees from the same size lab was $83,128. The only labs experiencing an average salary increase have an average of 11-20 employees, and an average salary of $92,267, in 2022, rather than $86,560, in 2021.

Testing volume of laboratories influenced average salaries in 2022, down, for the most part, from 2021. Labs that performed more than two million tests



experienced a drop in average salary, from $115,516, in 2021, to $109,709, in 2022. The downward trend continues across labs with lower testing volumes.

The only labs where the average salary increased were those with 100,001 to $500,000 tests, where average salaries were $94,173, in 2022, an increase from 2021 ($91,053).

Salary by degree and gender: males surpass females

Among those reporting salary information, degree and gender differences hold evidence that suggests higher average salaries among males, at the post-graduate and bachelor's degree levels.

Males with a post-graduate degree earn, on average, $107,500, a higher salary than females, with the same degree, $106,367. Males with a bachelor's degree, again, earn more than their equally degreed female counterparts. Males earned, on average, $97,833, whereas females earned $91,801. The opposite results appear for employees who hold an associate degree, with females earning higher salaries, on average than males with the same degree. Associate degreed females top males with an average salary of $62,773, to males $55,833.

Job satisfaction is down, at the highest level; job security is on the rise

Those surveyed reported that their job satisfaction was down from 2021, with 32.1% very satisfied, as opposed to 2021 figures (40.7%). However, other categories showed an uptake from 2021:

2022:	Job Satisfaction	2021:
50.2%	somewhat satisfied	48.4%
3.2%	somewhat dissatisfied	8.3%
4.5%	very dissatisfied	2.6%

2022 job security figures demonstrated an increase, at the highest level, with 60.5% reporting they feel very secure in their jobs, up from 54.5% in 2021. However, another increase occurred among those who feel very insecure in their jobs, with 2022's figure (2.9%) rising from 2021 (1%). A drop occurred in the other two categories: 35% somewhat secure (2022) and 1.6% somewhat insecure (2022) from 2021's figures (40.4% somewhat secure and 4.2% somewhat insecure).

Decrease in most benefits

During 2021 and 2022, nearly all respondents said their employers offer health insurance, dental insurance, vision, and a 401K plan or pension. However, overall benefits declined during 2022.

Life insurance showed a drop from 2021 (85.9%) to 2022 (82.7%). Paid time off (PTO) is down from 87.2% in 2021, to 86% in 2022. Disability insurance is also lower in 2022 (75.7%), dipping slightly from 77.6%, in 2021. Flex time, in 2022, fell to 11.1% from 12.2% in 2021. Paid holidays for 2022 also dropped to 58.4%, whereas 2021 showed 62.5%. Childcare is down in 2022 (4.9%), as opposed to 2021's figure of 6.4%.

The only area where benefits increased was overtime, where 2022 figures show 45.3%, over 2021's 30.8%. Additionally, paid COVID-19-specific leave was reported at 30.9% in 2022.

Stacie Bledsoe, Lab Director, The Medical Center, Bowling Green, KY, explained that her lab "offered existing employees incentive pay for covering open shifts."

Education, certifications, and CEUs

Labs, in 2022, as in 2021, continue to employ those workers with a bachelor's degree as their highest level of education.

2022:	Continuing Education	2021:
28.4%	post-graduate degrees	30.4%
58.8%	bachelor's degrees	61.2%
10.3%	associate degrees	7.4%
2.5%	high school diploma	1.0%

In addition to degrees listed above, continuing education units (CEUs) also remain a necessary part of the laboratory world. In 2022, 19.8% logged more than 20 hours of CUEs and 30% logged between 11-20 CEU hours. Bledsoe also indicated the acquisition of CEUs "do not affect salary."

The three most common certifications, from professional organization, remain constant from 2021, with 2022 results revealing the following:

- American Society for Clinical Pathology: 73.7%
- State government: 15.6%
- National Credentialing Agency for Laboratory Personnel (NCA): 11.9%

Tenure results illustrate longevity at the highest level

The current tenure results within the 2022 survey demonstrate consistency of employment, with 21.8% of employees working for more than 30 years with their current employer. Other figures, while not as impressive, still show overall stability within the laboratories surveyed. 2022 results show 8.2% of employees have worked for their current employer for 25-30 years; 10.7% for 20-24 years; 10.3% for 15-19 years; 12.8% for 10-14 years; 12.3% for 6-9 years; 8.2% for 3-5 years; and 15.6% for less than 3 years.

Laboratory operations and management

Those surveyed revealed results regarding the impact of the current shortage of medical personnel, on their labs' operational efficiency, as largely impacted, with 43.2% reporting, compared to 2021's figure of 26.3%. Moderate impact was reported at 40.3%, in 2022, down from 2021 figures (54.2%). Low impact for 2022 (14.8%) was down slightly from 2021 (15.7%). Those reporting no impact to their labs' operational efficiency for 2022 delivered a slight decline (1.6%) from 2021's figure. (3.8%).

Bledsoe also shared how personnel shortages, primarily in the phlebotomy and night shift tech departments, impacted her lab and the solutions that ere implemented.

"We have dealt with phlebotomy and technical staff shortages over the last 2 years," she said. "Since then, our facility has increased our facility minimum wage to be more competitive in the job market for phlebotomy. As far as our technical staff, we have begun a partnership with University of Kentucky's MLS program and were able to retain 2 students as techs. We also started training Medical Laboratory Assistants to do some more non-technical things to assist our techs."

When asked if the current shortage of medical personnel pressed labs to outsource more tests during 2020, 28.4% replied "yes," (up from 22.8% in 2021), and 71.6% said "no."

Conclusion

The MLO salary survey depicts those dedicated, well-educated, adaptable professionals who are, for the most part, secure in their positions, if not as satisfied as they would like. Perhaps the idea of unequal compensation, based on gender, despite the similarities in education, could explain that frustration.

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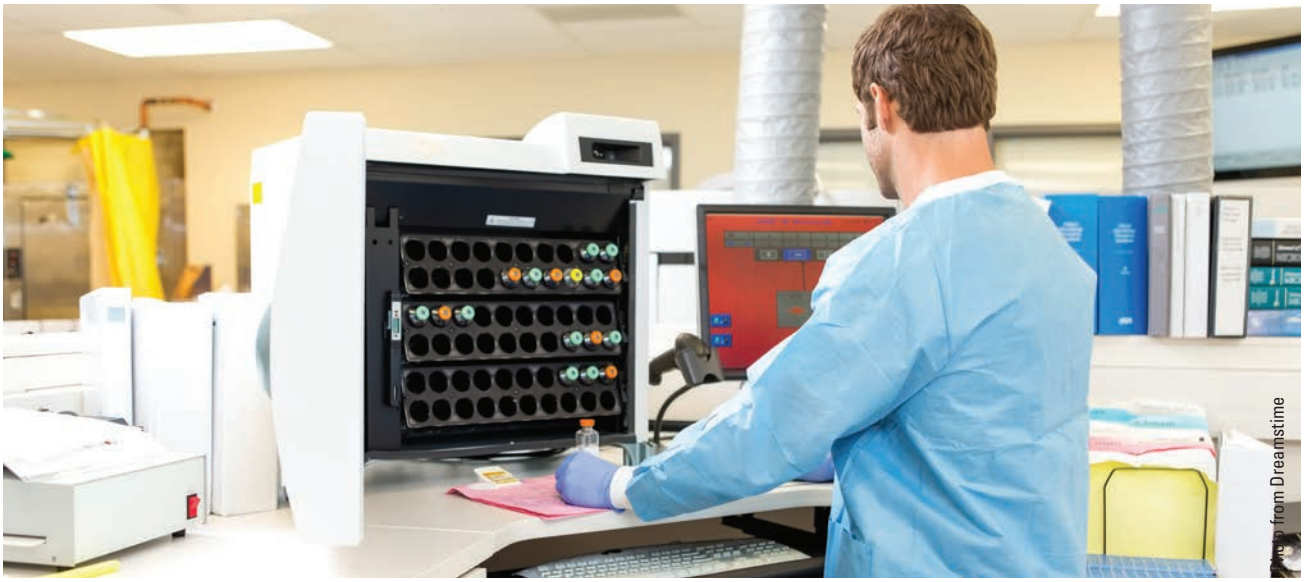

Document review, competency, proficiency testing, and correlation testing are among the standards cited most often during on-site surveys at clinical labs.

What clinical laboratories should do to become survey ready

By Heather Hurley

Laboratories conducting diagnostic testing, classified by the U.S. Food and Drug Administration (FDA) as non-waived, are required to be compliant with the 1988 regulations of the Clinical Laboratory Improvement Amendments (CLIA).[1] In addition, laboratories are required to undergo an assessment of their compliance with CLIA regulations every two years. The Centers for Medicare and Medicaid Services (CMS), which administers the CLIA program, has assigned numerous organizations deeming authority to survey laboratories and assess compliance with these regulations.

These requirements can seem overwhelming. So, how does a healthcare organization keep its laboratory survey ready? In this article, we'll describe some of the most common challenges laboratories face in preparing for an accredidation survey.[2]

Document review

During the on-site survey event, the surveyor will review written documents. Preparing for this part of the assessment is often challenging for organizations.

Below are a few questions to ask yourself and your team to determine if your organization is prepared for an on-site survey event:

- What documentation is required for an on-site survey?
- Do the appropriate personnel have access to the documentation required to perform their duties?
- Is access to the required documentation readily available for review during an on-site survey?
- Is the healthcare organization's documentation organized, whether it is paper or electronic, to easily support the survey process?

Laboratories are required to provide numerous completed documents during the on-site survey including:

- The laboratory personnel report (CMS form 209)
- A test menu including all specialties and subspecialties. The menu also should include proficiency testing (PT) data that is organized by Clinical Laboratory Improvement Amendments (CLIA) number. All pertinent data for the last 24-months should be available for the surveyor, including all worksheets, attestations, and corrective actions.
- A list of tests that do not use PT for verification of precision and accuracy
- Alternate PT results
- An Individual Quality Control Plan (IQCP) for applicable tests, including process improvement data for the last 24-months
- The laboratory's emergency operations plan

Several of these documents are particularly challenging for many laboratory managers.

For example, some healthcare organizations struggle with completing the CMS-209 form that is used by the surveyor to review the qualifications of technical personnel in the laboratory. The form can cause confusion because titles used within a laboratory may not align with the nomenclature used by CLIA to identify roles and qualifications needed to perform testing and provide laboratory oversight.

Before identifying personnel to fulfill supervisory roles, it is important to review the CLIA-defined educational requirements needed to perform laboratory duties based on the level of test complexity. It is also important to review roles for both moderate and high-complexity testing.

Moderate complexity testing requires that healthcare organizations assign the following roles: *Laboratory Director*, *Technical Consultant*, and *Clinical Consultant.* High-complexity testing requires that organizations assign the following roles: *Laboratory Director*, *Technical Supervisor*, *Clinical Consultant*, and *General Supervisor*. Additional information regarding specific qualifications and responsibilities of these roles can be found in the CLIA regulations *Subpart M*.

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Another challenging component of the survey review process is the Individual Quality Control Plan (IQCP). This is a process that consists of three components — Risk Assessment (RA), Quality Control Plan (QCP), and Quality Assurance Plan (QA). All three components must be approved by a *Laboratory Director* **prior** to implementation of the QCP.[3] IQCP approval may be documented by a *Laboratory Director's* signature on each component or on a cover sheet, which specifically indicates that the director reviewed each of the three components. A cover sheet with only one signature is not adequate, as it must stipulate review of all three components.[3]

Standards may contain multiple elements of performance (EPs), including a written checklist, which identifies EPs in which written documentation is required. As the standard states, "The laboratory verifies and documents that the applicant has the education and experience required by the job responsibilities."[3] Proof of this documentation will be reviewed during the on-site survey event. In preparation for the survey, organizations should review the written document checklists by chapter and ensure they have documentation for each of the standards by EP where required.

Competency struggles

Competency continues to be an area where organizations struggle. It remains the number one cited standard, [4] and has held its place on the top-cited list for many years.

So why do organizations struggle with competency? After all, competency standards have been in the CLIA requirements since their inception. It seems the biggest challenge of competency is meeting CLIA requirements about the qualifications associated with a job title, and specifically for *Technical Consultant* for moderate-complexity testing and *Technical Supervisor* for high-complexity testing. Individuals must meet the education requirements and, either, training or experience requirements listed in the CLIA regulations *Subpart M* for each of the specialties and subspecialties performed by the laboratory.

Laboratories must assess and document the competency of laboratory personnel involved in non-waived testing. CMS requires labs to assess six elements for each type of test that each individual performs:

- Routine patient testing assessed through direct observation
- Reading and reporting of test results and review of intermediate test results assessed by monitoring
- Quality control (QC), proficiency testing (PT), and preventive maintenance
- Instrument maintenance and function checks assessed through direct observation
- Test performance assessment
- Problem-solving skills assessment

Problem-solving skills are imperative and are often an overlooked required element of a competency assessment. It is also necessary to ensure that the person performing the competency assessment meets CLIA required qualifications. For example, when performing moderate complexity testing, the individual performing the direct observation of another person performing that test must qualify as a *Technical Consultant*, per the CLIA specified qualifications. It is also important to note that competency is per CLIA certificate, so if staff is performing the same testing using the same instrumentation in different locations, a competency assessment, including all six elements, must be performed at each location.

Commonly cited proficiency testing standards

Standards related to PT are among the top ten annually cited standards. The standard states, "A laboratory will participate in CMS-approved proficiency testing programs for all regulated analytes."[5]

One common basic pitfall is an organization's lack of implementation of a process to address adding a new test to its menu. When a laboratory is adding a new test to its test menu for regulated analytes, it is important to put a process in place to ensure that it adds the new analyte to its PT ordering. Another basic requirement is for the *Laboratory Director* to review each proficiency testing program report, even if testing events are satisfactory and the review is documented. The *Laboratory Director* may delegate this responsibility, in writing, to an individual meeting the CLIA requirements of technical consultant for moderate complexity testing or someone meeting the CLIA requirements for technical supervisor for high-complexity testing.

Additionally, a thorough corrective action is required for any unsuccessful PT event. This often offers healthcare organizations the opportunity for improvement. When organizations respond to unsuccessful PT by merely documenting "Repeated and OK" or "Random Error," it does not foster improvement. Instead, a full investigation should be conducted to ensure patient samples performed during the same time frame were not affected. PT samples should be integrated into the laboratory's normal workflow and rotated among staff performing patient testing.[6]

Healthcare organizations should follow a normal testing process for PT samples, until the process requires that the sample be sent to another laboratory for validation. PT samples cannot be sent to another laboratory for testing. Sending samples to another laboratory for testing is considered PT referral and carries significant consequences, per the CLIA regulations. It is also important to remember that PT samples are specific to the CLIA certificate.[7,8]

Correlation deficiencies

Correlation, or comparison testing, also is high on the list of most-cited standards. Correlations are required when the same test is performed on different instruments, by different methods, and/or in different locations.[9] The goal of correlation testing is to ensure that results for the same test will be equivalent — no matter what instrument, method, or location is involved.

Some typical observations from surveyors include the following: correlations are not performed every six months, or at all; failure to correlate automated and manual differentials; and failure to correlate point-of-care testing locations, the emergency department, or other locations with the main laboratory.

It is imperative that healthcare organizations plan well in advance for their laboratory survey. Hours dedicated to preparation will certainly pay off, resulting in a successful laboratory survey that overcomes obstacles and meets necessary requirements.

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Heather Hurley is the Executive Director of Laboratory Accreditation at The Joint Commission. In this role, Hurley leads business strategies and activities, including the development and implementation of products and services for The Joint Commission's Laboratory Accreditation Program, Patient Blood-Management Certification and Integrated Care Certification.

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Bringing on the next wave of spatially resolved transcriptomics

By Jiang He, PhD

Diseases often originate in highly specific regions or cell types within the body. Why? Because healthy cells are not uniform: there are hundreds of different cell types that display different characteristics, perform different roles, and malfunction in equally diverse ways. But those errors don't occur in a vacuum — all cells are influenced by their location within a tissue.

As scientists seek to understand the origins of human disease, there is a growing movement to catalog all the cells in the human body while preserving spatial context — a field of study called spatial biology or spatial genomics. In spatial biology, scientists use a combination of molecular profiling and imaging techniques to produce an atlas of the cells and cell types in a tissue. Cells may be cataloged based on their transcriptome, proteome, metabolome, and their metabolic flux within intact tissue samples to preserve the spatial context of the information. Getting the full picture requires a large quantity of high-quality data that has, until recently, been slow to acquire. But now, spatial biology is experiencing a step change, thanks to a new generation of advanced spatial genomics technologies that expand the quantity and quality of information that can be gained from a single experiment.

While spatial genomics tools are not yet common in clinical labs, they likely will be soon. The depth and detail of data that spatial genomics tools can efficiently capture offer countless opportunities for establishing new biomarkers for diagnostic testing. Furthermore, spatial genomics instruments generate nuanced, high-volume results that could expand what is possible through precision medicine. Here, we'll discuss the science behind an emerging spatial genomics technology, massively multiplexed single-molecule imaging technology, followed by some of its potential clinical applications.

Setting a higher standard for data collection

Resolution matters. Scientists need spatial techniques that are capable of distinguishing individual cells to identify which cell types are altered in a diseased state. Techniques with single-cell resolution can help characterize underlying molecular changes, visualize morphology and behavioral changes, and identify relationships with neighboring cells. Together, these valuable data points are essential to improving our understanding of biological systems and using that to advance human health.

Time is of the essence. To capture spatial genomic data, scientists need tools that can capture high-resolution cellular and molecular information while preserving spatial context. But to capture this data at a scale on par with the vast number of cells in the human body, high-throughput strategies are critical. So far, conventional imaging-based methods, such as RNA FISH, that preserve spatial context have not been high throughput enough to make cell atlasing commonplace. On the other hand, sequencing-based spatial genomics technologies on the market don't offer true single cell resolution and often suffer from poor sensitivity. However, a new class of imaging-based spatial genomics methods that map cells based on their gene expression — i.e., their transcriptomes — show great promise.

Here we will discuss one such emerging spatial genomics technology. Massively multiplexed single-molecule imaging technology enables researchers to accelerate the cell atlasing process by mapping whole tissues at single-cell resolution on an unprecedented scale and massively multiplexed level **(Figure 1)**.[1] A growing number of groups across the United States are using this technology to produce cell atlases relevant to their physiological area of interest, with more on the way.[2-5] Based on their achievements, it is possible to imagine a day when it will be routine to generate reference maps that unlock the cellular and molecular mechanisms underlying any disease.

Visualizing gene expression

Massively multiplexed single-molecule imaging technology is based on FISH (Fluorescence In Situ Hybridization), a highly sensitive and quantitative way to measure gene expression.[6] In FISH assays, RNA probes hybridize to gene transcripts within the cells of a tissue. These tagged transcripts are then imaged to visualize their location. While powerful in specific settings, these methods face a major technological challenge: it is difficult to visualize more than four gene species simultaneously, as the multiplexing power is dependent on how many spectrally distinct fluorophores can be used in a single experiment.

In contrast, massively multiplexed single-molecule imaging technology has not only overcome these challenges but has also pushed the limits of the volume and quality of available data. It employs strategies from a highly sensitive, single-molecule variation of FISH **(Figure 2)** [7]capable of visualizing individual transcripts. By combining smFISH with combinatorial labeling, sequential imaging, and error-robust barcoding strategies, massively multiplexed single-molecule imaging technology can massively multiplex the number of genes that can be imaged per experiment. Together, the stepwise approach to massively multiplexed single-molecule imaging technology experiments (outlined below) enables scientists to spatially profile the expression of hundreds to thousands of genes across whole tissues. It identifies individual transcripts at the highest detection efficiency available and resolves their location at subcellular, nanometer-scale resolution. With the location and quantity of gene transcripts recorded, this spatially resolved RNA-profiling data gives a physical picture of the cell or tissue of interest.

The science behind massively multiplexed single-molecule imaging technology

Design: To set up a massively multiplexed single-molecule imaging technology experiment, researchers must first select a gene panel of hundreds to thousands of genes of interest. An error-robust binary barcode, a series of "0" and "1," is assigned to each gene of interest. Then, encoding probes, which effectively imprint the desired barcode onto each RNA species, are generated to hybridize to each gene species in the panel, and at least 20 different encoding probes are used for each gene. This multi-probe strategy produces an exceptionally high detection efficiency that is an order of magnitude higher than other spatial technologies; it faithfully identifies target RNA molecules, even those transcribed at very low frequen-

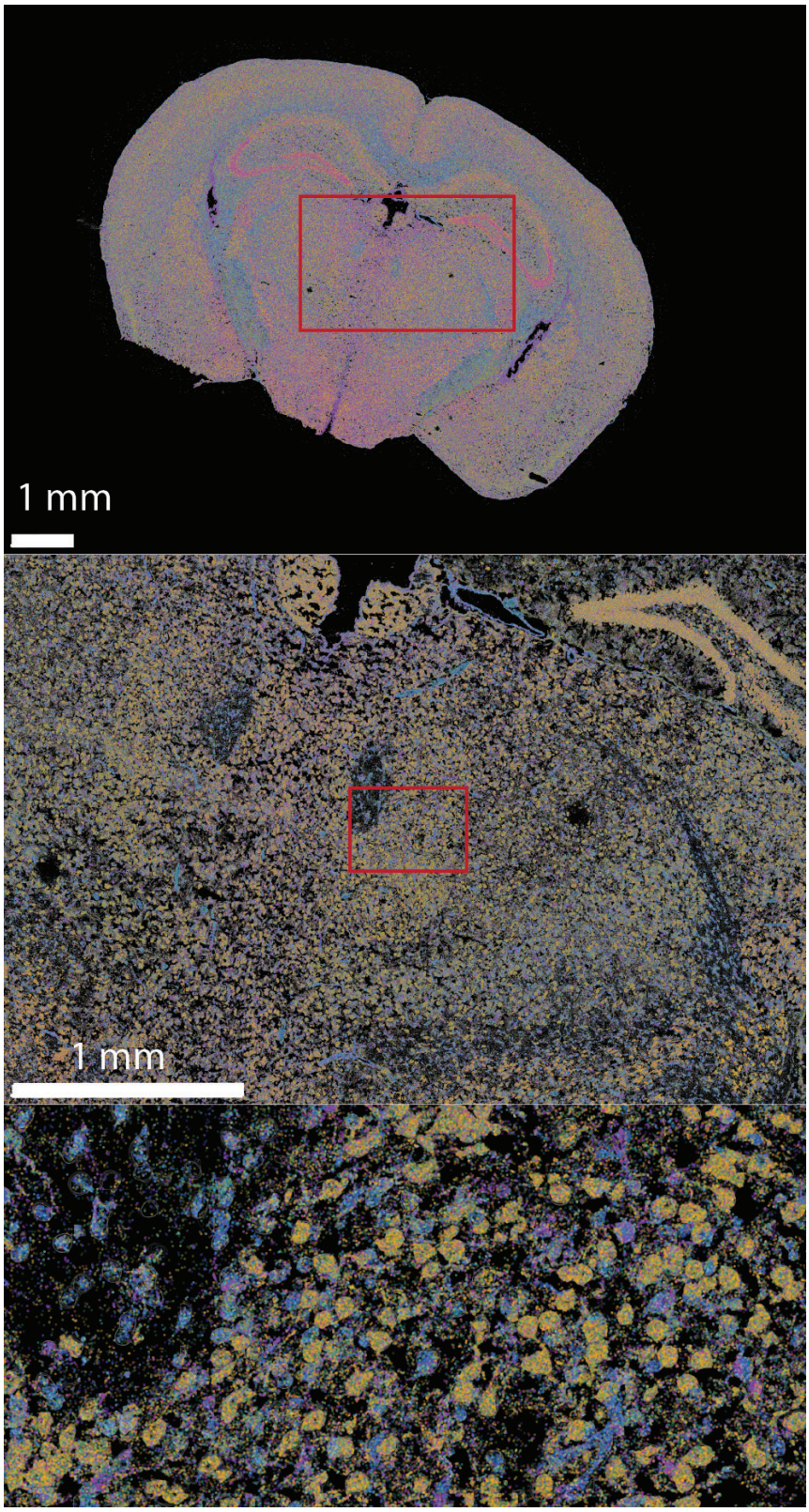

Figure 1. A full mouse brain coronal slice undergoes massively multiplexed single-molecule imaging technology measurement: Massively multiplexed single-molecule imaging technology measurements capture information about target genes of different colors with subcellular resolution. The data may be viewed as a whole (top), zoomed in to observe patterns across neighboring cell populations (center), or zoomed in to view transcripts within individual cells.

cies. The probes are also designed so that fluorescent labels can hybridize in a combinatorial fashion, allowing for a massively multiplexed experiment.

Capture: To run a massively multiplexed single-molecule imaging technology experiment, scientists must prepare a tissue slice or cell culture sample and stain it with the library of gene panel probes. Then, the sample must go through a series of steps where it is hybridized with a set of fluorescent readout probes, imaged, washed to remove the fluorescent signal, and then treated with another set of fluorescent readout probes. These steps are repeated until all bits in the binary barcode are imaged, and the optical barcode generated from this process will be used to resolve the quantity and location of each transcript. The amount of time that it takes to capture massively multiplexed single-molecule imaging technology measurements varies depending on the size of the gene panel being probed and the area size of tissue slices being imaged in the sample, but in general, each slice of a sample will take a day to complete.

Analysis and visualization: A single massively multiplexed single-molecule imaging technology experiment produces numeric data and images that are largely analyzed using computational methods. Software must be used to compile the different rounds of imaging data to decode the fluorescent signal, determine the barcode, and match it with the preassigned binary barcode of every individual RNA molecule in the sample. This process produces a massive body of data about the location and identity of hundreds of millions of RNA species distributed throughout hundreds of thousands of cells. Furthermore, massively multiplexed single-molecule imaging technology images provide information about cell shape, cell size, and cells' interactions with their neighbors.

Massively multiplexed single molecular imaging technology in action

The technology was recently used to generate a receptor map of the mouse brain.[8] The dataset revealed new information about the expression of over four hundred GPCRs — a vast class of transmembrane signaling proteins, many of which have been implicated in various neurodegenerative disorders. Although GPCRs come in an incredibly diverse array of "flavors," they are expressed at such low levels that their function was only partially understood. It was largely unclear which cell

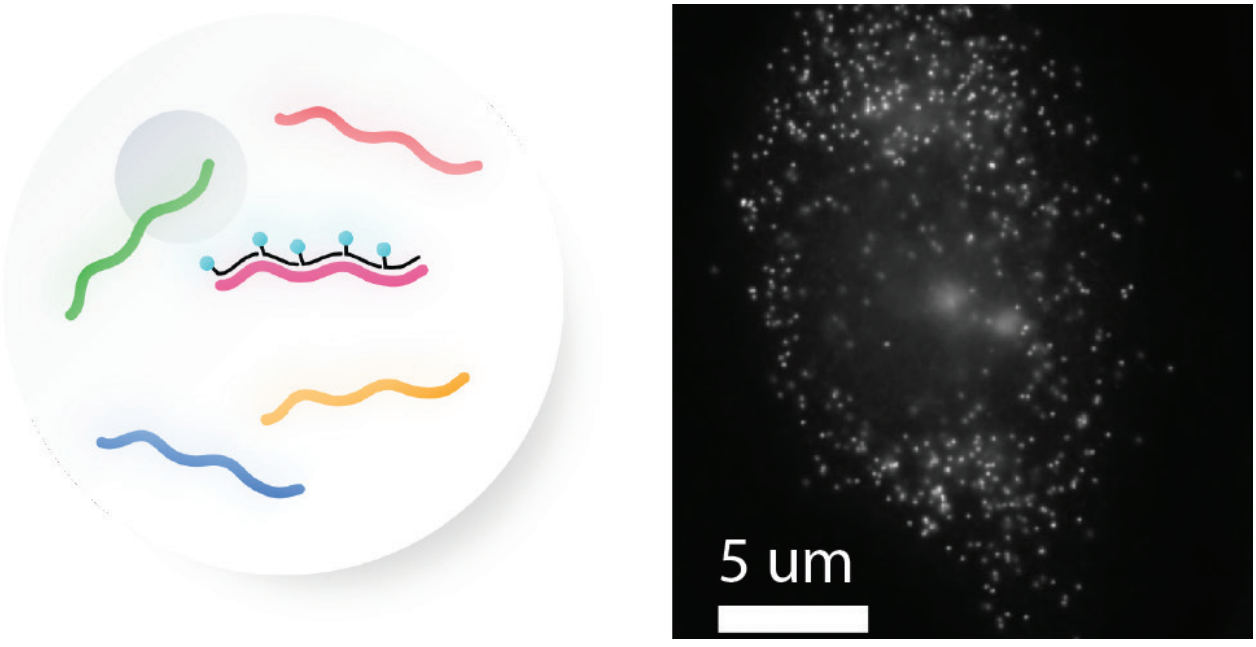

Figure 2: Measuring individual transcript copies using smFISH: schematic (left) and fluorescent image (right). For smFISH, multiple probes adhere to a target transcript (pink) to amplify the fluorescent signal and make it possible to distinguish individual RNA molecules as a single point using a high-resolution microscope. Fluorescent points may be counted to be quantified. Massively multiplexed single-molecule imaging technology employs a similar strategy, but additional multiplexing tactics allow hundreds to thousands of genes to be measured simultaneously.

types express these proteins, information which would provide vital clues as to their roles in the brain. Now, however, the massively multiplexed single-molecule imaging technology-generated cell atlas has revealed where GPCRs are expressed. Armed with this information, researchers can begin unraveling these genes' role and examine how their expression changes in disease-associated cell types. Down the line, this data may serve as a springboard to guide the clinical development of new diagnostics for neurological disease.

But the brain is just the beginning. As more labs use massively multiplexed single-molecule imaging technology to map both healthy tissue and tissue representing a variety of disease states, these will serve as reference maps for the field. Together, these maps will provide an unprecedented view into the cell and molecular changes that occur as a result of disease that may soon aid in a new generation of clinical diagnostics.

Clinical applications on the horizon

Massively multiplexed single-molecule imaging technology stands to make a dramatic impact in the clinic thanks to its massively multiplexing capabilities and the high-volume information it produces. It can readily profile hundreds to thousands of biomarkers at the same time, which could facilitate the biomarker discovery process for developing new diagnostic tests. Specifically, by profiling groups of biomarkers simultaneously, clinical labs could potentially use the data it captures to stratify patients for therapeutic intervention. With test results offering a more fine-tuned evaluation of a patient's disease, clinicians may be better able to optimize treatment, determine prognosis, and predict and monitor treatment response. Furthermore, massively multiplexed single-molecule imaging technology-generated cell atlases can also map and catalog different cell types and characterize cell state and function in complex tissue. This information can provide an additional level of insight into how genes function and how different cell types work together in healthy versus diseased tissue, illuminating new physiological hallmarks that that can be used in tissue pathology. Overall, massively multiplexed single-molecule imaging technology evaluation may represent a new generation of clinical testing that empowers labs to deliver more personalized, detailed diagnoses, with the potential to elevate medical care and enable new generation of precision medicine that will advance human health.

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Jiang He is Co-Founder and Director of Scientific Affairs at **Vizgen**, a Cambridge, MA-based company, which holds the patents for MERFISH and has commercialized the MERSCOPE Platform.

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Rapid diagnostics are the critical link to improving sepsis care and addressing AMR

By Temitayo Famoroti, MD, MPH, MMed; Muhsen Alkurdi, BSMG, ICBB; Aparna Ahuja, MD, PGDip Hosp Mgment, DCH&FW,IFCAP

Sepsis is a life-threatening organ dysfunction, which is caused by the dysregulated host response to infection.[1] It is a spectrum that starts from bacteremia, the presence of viable bacteria in the bloodstream, which might progress to sepsis that, in addition to bacteremia, includes organ dysfunction.[2] The final stage may lead to septic shock, a condition where the patient exhibits poor blood hypoperfusion, despite adequate intravascular fluid resuscitation.[2] Sepsis causes the death of nearly 270,000 Americans annually[3] and claims more lives each year than the top three cancers combined (lung, colorectal, breast).[4] The extended time from symptom presentation to appropriate therapy remains a major contributor to poor patient outcomes and the proliferation of antimicrobial resistance (AMR).[5] For every hour of delay in time to appropriate therapy, survival decreases by 7.6% during septic shock.[5]

Intersection of COVID-19 and sepsis

Since late 2019, the global COVID-19 pandemic[6] has significantly added to the burden of sepsis.[7] Individuals who are hospitalized with COVID-19 have shown to be more prone to secondary bacterial and fungal infections.[7] These secondary bacterial and fungal infections are likely to occur in a significant portion of critically ill hospitalized patients with COVID-19.[7] Hospitalized COVID-19 patients are at a 22% increased risk of developing sepsis and 113% more likely to experience septic shock when compared to hospitalized influenza patients, and the overall inpatient mortality incidence was also found to be much higher when compared to those hospitalized influenza patients (15.8% vs. 4.1%).[8]

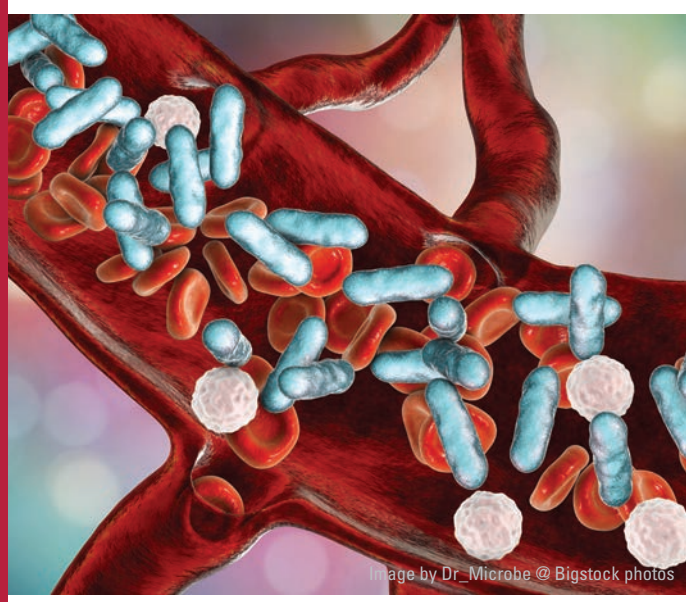
Image by Dr_Microbe @ Bigstock photos

Unnecessary treatment for bacterial and fungal infections is common in patients with COVID-19.[9] As a result, the overuse of antibiotics incurred during the pandemic may have long term ramifications for increased antimicrobial resistance.[9] The clinical conditions of sepsis and COVID-19 may lead to irrational and prolonged antibiotic use, which may lead to the development of anti-microbial resistance (AMR),[9] whereby microbiological pathogens become resistant to the common antimicrobial agents, necessitating the use of the newer and more expensive drugs.[10]

The global threat of antimicrobial resistance (AMR)

According to the World Health Organization (WHO),"the persistent failure to develop, manufacture, and distribute effective new antibiotics is further fueling the impact of antimicrobial resistance (AMR)[11] and threatens our ability to successfully treat bacterial infections."[11,12] Every year, 700,000 people die of AMR, and if no action is taken, the death toll because of AMR could rise to as many as 10 million, annually by 2050[12] and cause a 3.8% reduction in annual gross domestic product (GDP).[12] This global threat has created room for innovation in the terrain of rapid diagnostic tests to combat the development and spread of drug resistance bacteria. There is a federal challenge/competition, with a prize of $20 million, a joint effort between the National Institutes of Health and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR) to address the issue of AMR.[13]

The challenge calls for new, innovative, and novel laboratory diagnostic tests that identify and characterize antibiotic-resistant bacteria, to reduce the unnecessary use of antibiotics, a major cause of antibiotic resistance.[13] It is important to note that diagnostic tests play an important role in the prevention and inappropriate use of antibiotics because they assist in the selection of the most effective therapy, thereby reducing the risk for antibiotic resistance.[14]

Laboratory diagnoses of sepsis causing pathogens

The gold standard for the detection of sepsis-causing pathogens is a blood culture (BC),[15] which requires a higher blood volume for testing, up to 30 ml with multiple culture sets.[15] This has been in use since the inception of early microbiological diagnosis and has served patients with sepsis well, but there are issues that include the delayed resulting of specimens of up to 3 days, cross contamination, and the impact of prior antibiotics use on the likelihood of pathogen detection that could further impact the management of the patient.[15]

There are numerous other tests, apart from BC, which are non-specific such as the complete blood count (CBC) that identifies an increase in the white blood cells (WBC), signifying an infection, and a reduction of the WBC may also indicate the individual is at risk of developing an infection.[16] The elevated lactate level is another non-specific method of managing sepsis patients, though lactate levels may also be elevated in other situations such as intense exercise or heart failure.[16,17]

Another non-specific test is the C-reactive protein (CRP) that the body produces when there is an inflammation, and several other conditions can cause inflammation, including infections.[16,17] Procalcitonin (PCT) is a protein in blood that rises if there is a bacterial infection, but it does not identify the specific bacterial

Sepsis Fast Facts

In a typical year:

- At least 1.7 million adults in America develop sepsis
- Nearly 270,000 Americans die as a result of sepsis
- 1 in 3 patients who dies in a hospital has sepsis
- Sepsis, or the infection causing sepsis, starts outside of the hospital in nearly 87% of cases.

Source: Centers for Disease Control and Prevention.[3]

pathogen. Other tests are Prothrombin time and partial thromboplastin time (PT and PTT), platelet count, and d-dimer.[16, 17]

Rapid diagnostic test (RDT)

The ideal rapid diagnostic test (RDT) would potentially have advantages that include rapid and reliable results, low detection limits, high-throughput testing, and specific organism detection directly from a clinical specimen.[18] There are numerous U.S. Food and Drug Administration (FDA) approved molecular diagnostic tests for detecting sepsis causing pathogens,[18] some are culture independent tests such as the magnetic resonance (T2MR), metagenomic shotgun sequencing methods, and nucleic acid amplification platforms. There are also the culture dependent platforms or post-culture, meaning it relies on the BC result before it can be tested on such a diagnostic platform such as MALDI-TOF MS, Real-time multiplex PCR, and in situ hybridization.[18] Culture is the standard for pathogen detection, but in recent times, culture independent diagnostic tests are increasingly used due to their advantages such as rapid detection of organisms, which is critical to clinical decision making.[19]

The newer rapid diagnostic tests (RDT) could shorten the time to the detection of pathogens, and this could potentially lead to faster initiation of appropriate and targeted therapy,[19, 20, 21] shortening the time of unnecessarydrugs,[19] thereby, reducing the time of exposure to ineffective medicine. This may reduce the chances of developing AMR.[19, 20, 21] All these could have an impact on the rate of mortality, length of stay (LOS) in the hospital, and a reduction in cost of both drugs and bed occupancy per patient.[19, 20, 21]

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STATE OF THE INDUSTRY

Using data analytics to improve performance and patient care

By Linda Wilson

Many lab managers are using data analytics to measure and manage operational and clinical performance.

"We are basically a service line that provides data. We are absolutely buried with data every day. The data analytics piece is absolutely critical for us to get that data in a usable format, in a timely manner, so we can provide good information back to the providers," said Bill Remillard, Laboratory Director for four hospitals in the Inland Northwest Washington service area for Providence, a 52-hospital health system operating in five western states.

Bill Remillard

To find out more about how labs, like the ones at Providence, are compiling and using data to improve performance, *Medical Laboratory Observer* created a State of the Industry (SOI) survey on clinical data analytics. It is the first of four SOI surveys and associated articles that *MLO* plans to produce in 2022. (*MLO* has been producing a series of four SOI reports annually since it launched this survey research in 2020.)

In the 2022 survey, most survey respondents were in administration: 45% were lab managers, administrators, or supervisors; 12% were lab directors; and 6% were section heads or department supervisors. A small number were in other administrative roles, such as in QA/QC, information technology, or point of care.

They were distributed across a range of lab sizes. A total of 22% work in labs with 1-10 employees, 16% work in labs with 11-20 employees, 16% work in labs with 21-50 employees, 21% work in labs with 51-100 employees, and 26% work in labs with more than 100 employees.

Most survey respondents (71%) work in hospital labs, while physician's office labs and independent labs each accounted for 11% of participants, and group practice labs accounted for 4%.

THE LIS

The laboratory information system (LIS) is the hub of labs' electronic processes, and it is the starting point for collecting and storing data used in analytics.

While an on-premises software deployment is still the most common architecture for an LIS, cloud-based systems are slowly becoming more common at labs, according to the results of *MLO's* SOI survey. The percentage of survey participants working at labs using a cloud-based LIS increased to 24% in 2022, up from 17% in 2021. The percentage of labs with an on-premises infrastructure was 76% in the 2022 SOI survey, dropping from 83% in 2021.

In 2022, most labs (62%) used LIS software that is part of an electronic health record (EMR), compared with 38% with a stand-alone LIS. The breakdown was virtually the same in 2021: 61% with an enterprise-wide system and 39% with a stand-alone LIS.

Labs have automated a variety of clinical processes using LIS functionality. For example, nearly all (95%) use the LIS for electronic orders and results, compared with 92% in 2021. The majority of survey participants in 2022 also have integrated their analyzers with the LIS (72%) and rely on the LIS for QA/QC processes (70%). Automated billing and revenue cycle processes also were common in 2022 (60%), compared with 58% in 2021.

Other functions were not as likely to be automated through the LIS. Slightly more than one third (39%) of the SOI respondents in 2022 use a module for point-of-care testing, 29% use it for regulatory compliance and reporting, 26% for scheduling, 27% for customer service, and 15%

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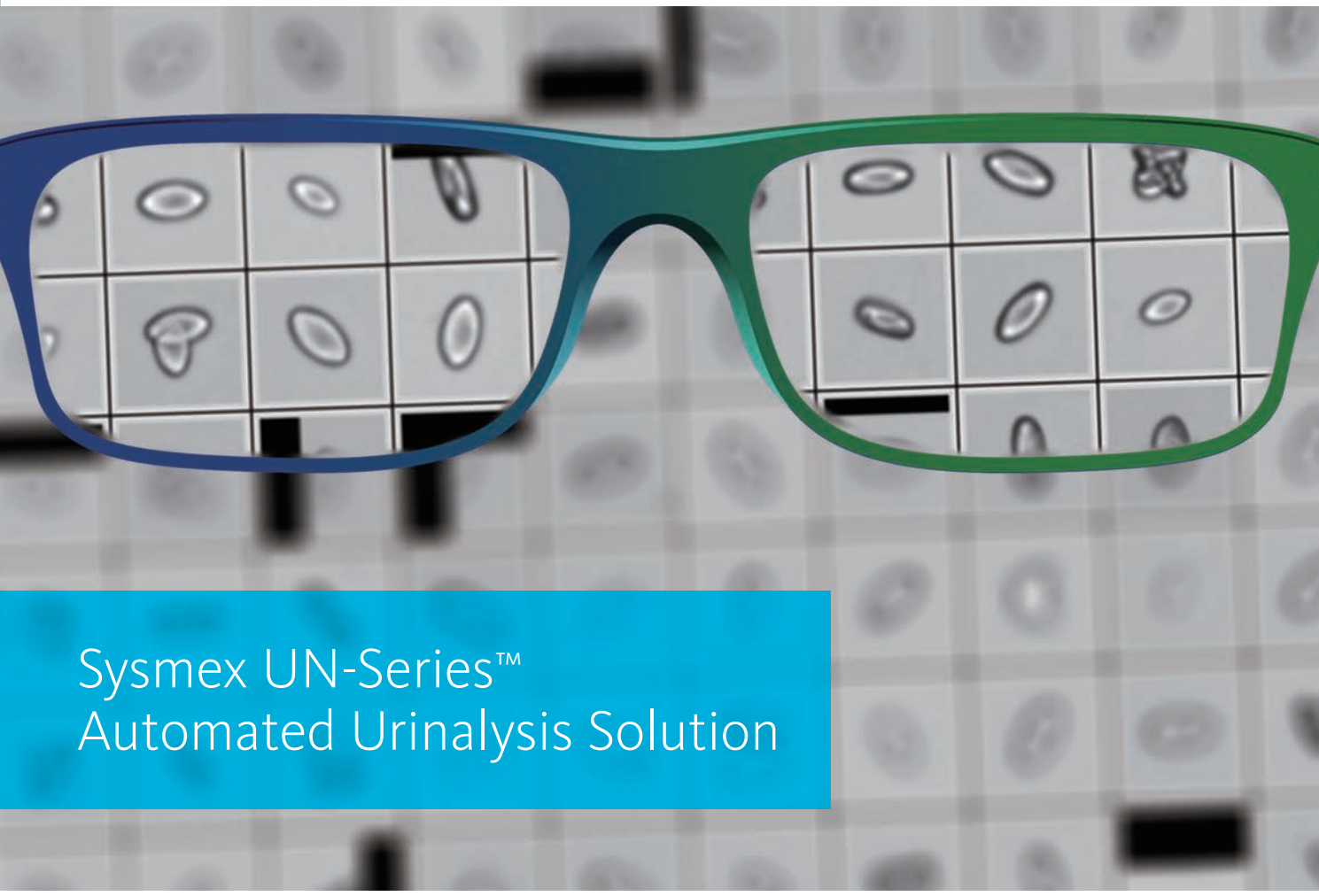

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David Nichols, MBA, President and Founder of the Nichols Management Group, a consulting firm, said that automating some of these processes is not a top priority for many lab managers.

For example, Nichols said he thinks that labs do not place enough emphasis on nurturing customer relationships, so it is not surprising that few have automated those processes or developed standardized performance measures. "That's kind of a no brainer in most industries, and we, labs, are significantly behind in that regard," he said.


David Nichols

Kim Futrell, MT(ASCP), MSHI, Senior Strategic Marketing Manager, Orchard Software, said she expects more labs to adopt the functionality in their LIS for regulatory reporting and compliance. "In my experience both at Orchard and as a laboratory manager, there are a multitude of features in the LIS that support regulatory compliance reporting, so if this functionality is not currently being used by the majority, I would expect it to be the largest area of growth because much of the functionality is already within the top LISs. Features like data mining, QC tracking, audit trails, and rules-based decision support can automate a great deal of regulatory requirements.


Kim Futrell

"In addition, COVID-19 has brought some urgent reporting needs that the LIS can support from a regulatory stance. COVID-19 is a required state reportable, and manual reporting on a massive scale with severe staffing shortages results in delayed and inaccurate statistics," Futrell said.

Labs also might be more likely to automate compliance activities in response to federal regulations governing the Promoting Interoperability program, she added. The Centers for Medicare and Medicaid Services (CMS) now places more emphasis in that program on public health reporting than was the case in the past, Futrell added.

TOP STRATEGIC PRIORITIES

When survey participants were asked about their top strategic IT priority for the next three years, the most common answer was infrastructure and platform development — the option selected by 30% in 2022 and 31% in 2021. A total of 26% chose data analytics optimization to support lab management as the top priority in the 2022 survey, compared with 25% in 2021; while 22% chose a new LIS in 2022, compared with 13% in 2021.

Revenue cycle management optimization became a less popular strategic priority, declining to 9% in 2022, compared with 17% in 2021. Very few chose a point-of-care testing product as their top priority in 2022 (3%) or 2021 (6%).

TAPPING INTO DATA ANALYTICS

No matter what their strategic priority is, most labs already are using data analytics to monitor and manage lab operations. In the 2022 SOI survey, 42% of survey respondents said they are "utilizing data analytics for some aspects, and we're planning more," while 17% said they are "utilizing data analytics for all aspects of lab management," and 8% said they are "utilizing data analytics for some aspects, and we are not planning more."

On the other hand, 16% of respondents in 2022 said they "are not using data analytics for lab management, and we have no plans to start in the near future," and 16% said they "have not used data analytics yet in any significant way, but we want to start."

To improve the uptake of data analytics, organizations should push standardized reports or electronic dashboards out to managers, rather than expecting them to build custom reports, Nichols recommends. "It has to be easy and automatic. Managers aren't going to spend their time querying a database," he said.

Tim Bickley, VP of Sales for Visiun, said, "Laboratory analytics shoud provide the lab's leadership with the ability to run a report on demand or automate reports with a scheduler. Not only should the automated reports be set up on a scheduler, laboratories should be able to set outlier criteria, so they are made aware of when they are not meeting a key performance metric."

Some labs are monitoring performance, but they aren't using automated tools for data analytics. One example is 26-bed Anson (TX) General Hospital. Laboratory Director William Lee monitors turnaround time and test utilization through the LIS. He tracks cost per test using a spreadsheet in which he figures in the cost

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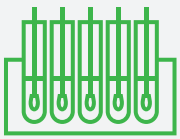

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of reagents, labor, and non-chargeable items such as test tubes. He updates the spreadsheet every two weeks.

FREQUENCY OF REFRESHING DATA

Another way to improve the uptake of analytics is to provide current data. Labs refresh their data for analytics with varying amounts of frequency, but, overall, the industry appears to be moving in the direction of real-time data. According to the results of the *MLO* SOI survey, 41% were using real-time data in 2022, compared with 29% in 2021.

For those not using real-time data, the frequency varied. In the 2022 survey, 24% said they refreshed their data weekly, compared to 33% in 2021; 24% refreshed data daily in 2022, compared to 28% in 2021; 4% refreshed data hourly in 2022, compared with 2% in 2021; and 7% refreshed data in minutes in 2022, compared with 8% in 2021.

To slice and dice the data, many labs rely on electronic tools. In 2022, 65% of respondents used a tool that is integrated with the LIS and 35% used a separate tool. The breakdown was identical in the 2021 survey.

KEY PERFORMANCE INDICATORS

Labs also are using data analytics to track a variety of key performance indicators (KPIs). The most common KPI, not surprisingly, is turnaround time (TAT), which 90% of survey respondents in 2022 said they track, up from 80% in the 2021 survey.

Other KPIs that survey respondents said they track include quality improvement initiatives (67% in 2022 and 74% in 2021), cost per test (58% in 2022 and 63% in 2021), billable tests versus performed tests (48% in 2022 and 53% in 2021), staff productivity goals (47% in 2022 and 42% in 2021), medical necessity (34% in 2022 and 30% in 2021), and unnecessary tests (22% in 2022 and 30% in 2021).

As Remillard explains, "Our quality metrics and productivity metrics provide an excellent foundation to know if our current staffing and test performance goals are meeting our patients' needs."

One example is appropriate test utilization. Providence actively monitors what tests providers request for hospital patients to make sure the tests are related to inpatient care and that the results will be ready before the patient is discharged. For example, genetic testing should only be requested for newborns. Otherwise, the tests should be ordered on an outpatient basis after the patient is discharged, he said.

These guidelines help ensure that payers will approve the charges and pay the health system for the tests, Remillard said.

Providence's labs in inland Washington also track utilization of blood products for transfusions. The goals are to ensure that transfusions occur only when medically appropriate and to prevent blood products from being wasted. For example, Providence tracks how many units of blood are ordered for each procedure to discourage providers from ordering more units of blood than necessary.

The labs also match up orders for blood products with patients' medical information, such as hemoglobin or platelet levels, to help ensure that providers order transfusions appropriately.

In addition to testing-process metrics, Nichols said labs should use data analytics to manage the supply chain, particularly related to

utilization and spoilage. "Supply costs are going up in the industry really fast," he said.

FORECASTING THE FUTURE

Of all the resources that go into diagnostic testing, lab managers have the most difficulty forecasting staffing needs.

At least that is the case in the short term, or the next three years, survey participants said.

In both the 2022 and 2021 *MLO* SOI surveys, majorities of respondents ranked staffing as the most challenging need to forecast. On a scale of 1-5, with 5 being the "least challenging," 76% of respondents in 2022 ranked staffing with a 1, or "most challenging." In 2021, 56% ranked staffing with a 1.

These findings are not surprising, given fluctuating testing demands in molecular testing and increasing demand for testing from an aging population. Those challenges are compounded by the lab industry's ongoing difficulty finding enough employees to fill all shifts.

In its 2020 survey report on staffing, the American Society for Clinical Pathology found that the national vacancy rate was highest, at 12.7%, for chemistry/toxicology and lowest, at 3.9%, for cytology. Other departments with relatively high vacancy rates in the study were immunology (11.2%), phlebotomy (11.1%), blood bank (10.4%), core lab (10.3%), LIS/QA/PI (10.3%), and flow cytometry (10.1%).[1]

To forecast staffing needs, Maggie Morrissey, Director of Recruiting at Lighthouse Lab Services, suggests labs measure how many samples a day are run by their techs, so they can see, on average, how many samples one tech can run. "With that information, they should be able to calculate how many techs to hire based on the expected volume of samples," she said.

Nichols said that tracking overtime is important because this information can help spotlight problems to tackle, such as inadequate compensation or a dirty and crowded space. "In general, significant overtime is a management issue," he said.

Forecasting resource needs other than staffing is less challenging, survey participants said. For example, only 26% ranked funding challenges with a "1," or most challenging, on a scale of 1 to 5, and only 7% assigned "1" to forecasting technology needs. A minority of participants chose "1" for forecasting training (13%) or ROI/costs (13%).

DATA ANALYTICS AND COVID-19

COVID-19 also has been an area of intense focus for tracking and analyzing metrics.

Remillard said, "Use of data analytics has been crucial in dealing with the COVID pandemic. We are closely monitoring positivity rates and testing workloads to ensure adequate inventories throughout our system. We have a weekly system wide laboratory command center where we discuss testing needs and strategies in all 5 states where Providence has hospital ministries."

Another example is the trio of interactive infectious disease dashboards that TriCore Reference Laboratories makes available to providers and the public in New Mexico, based on the company's diagnostic testing activity. The first dashboard provides a week-at-a-glance of 13 of the most common respiratory infections and the current week's positive count. The second dashboard is a deeper dive into respiratory disease trends and the third dashboard is a heat map display.[2]

MLO's survey participants also are monitoring their pandemic response. When asked what measures they are tracking related to COVID-19 testing, 42% said positive and negative test results, 23% said number of tests performed, 21% said turnaround time, and 8% said supplies used/inventory management. Type of test performed and cost per test were each tracked by 3% of survey respondents.

Nichols said he expects COVID-19 testing volume to decline by 75% in 2022, if no new variants emerge, making inventory management particularly crucial. "I would urge people to monitor their inventories and look at what kind of expiration dates there are for various kits in their labs." He also says that if labs choose to carry excess inventory because of uncertain demand, they should only do that for one analyzer platform.

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Clostridioides difficile in inflammatory bowel disease

By Jodie Y. Lee, MS, MBA, and David M. Lyerly, PhD

The intestinal microbiota in the human large intestine is a highly specialized ecosystem that has evolved over millions of years. Here reside trillions of anaerobic bacteria comprising more than 1,000 species — many more than in the small intestine.

This community maintains a healthy symbiotic relationship with us, with the total number of bacterial cells and genes vastly outnumbering the number of human cells and genes in the body. Our large intestine provides a little over 6 square feet of living space in an oxygen-free environment for the anaerobes while these bacteria supply us with basic physiological and biochemical functions to keep us healthy and safe.

The microbiota is a virtual organ that interacts with other body organs, but much of how this interaction occurs remains poorly understood. We do know, however, that the microbiota provides key functions such as tightly regulated immune homeostasis, metabolic activities such as bile acid metabolism and hormonal balance, and neuronal interaction of the gut-brain axis that involves neurotransmitters and inflammatory signals.

When this diverse ecosystem is disrupted, our health can be endangered. This phenomenon is well illustrated with two diseases, inflammatory bowel disease (IBD) and *C. difficile* infection (CDI). These diseases have very different etiologies, but both are triggered by a dysbiotic (i.e., imbalanced) intestinal microbiota. It is critical that efforts continue to understand the role of the microbiota in these diseases and others like them because dysbiotic-related diseases are major burdens to healthcare. CDI, for example, is the primary hospital-acquired infection in the U.S. and Europe, resulting in hundreds of thousands of cases and tens of thousands of deaths annually. About 25% of patients experience "recurring" CDI. IBD, which is not an infection but instead a chronic, possibly autoimmune, condition, affects 2-3 million people in the U.S., either as Crohn's Disease or ulcerative colitis. IBD is becoming a more global disease as countries become more industrialized.

The challenge of diagnosing CDI in an IBD patient

CDI and IBD present with similar clinical features that include diarrhea, abdominal pain/tenderness, and inflammation, but they require very different therapies. CDI, typically triggered by antibiotic therapy, can be effectively treated in most instances with other antibiotics, primarily vancomycin or fidaxomicin. IBD, on the other hand, usually requires corticosteroids for Crohn's Disease or salicylates for ulcerative colitis. Without an accurate diagnosis, inappropriate treatment with either disease may lead to a life-threatening event. Diagnosing a patient with CDI or an IBD patient who is flaring is challenging enough. But when an IBD patient tests positive for *C. difficile*, the challenge becomes even greater. Is it CDI or an IBD flare? Recurrent bouts of either disease can further complicate the diagnosis.

Distinct etiologies of CDI and IBD

C. difficile is a prototypical opportunistic pathogen that infects the large intestine. The organism is a gram-positive, anaerobic, spore-forming bacterium that is virulent because of the potent toxins it produces. Fortunately, *C. difficil*e cannot grow in the intestine when there is a healthy, diverse microbiota present. However, when the microbiota is disrupted, most often by antibiotics, the spores which have entered the patient by the fecal-oral route germinate into actively growing vegetative cells. Clearly, it is the disruption of the microbiota that triggers the onset of CDI. The vegetative cells grow to high numbers because the healthy competing microbiota has been killed by the antibiotics, and there is very little competition for nutrients required by *C. difficile*.[1] As this pathogen grows in the large intestine, it produces toxins A and B, both of which are large glucosylating toxins that damage the intestinal mucosa by shutting down the intracellular cytoskeletal system. In addition, the toxins trigger inflammation through several mechanisms that include direct chemotactic activity and cellular damage. CDI can range from mild, self-limiting diarrhea to severe life-threatening colitis.

IBD is a chronic and relapsing intestinal disease, probably autoimmune in origin. The two primary forms of IBD, Crohn's Disease and ulcerative colitis, have slightly different clinical features. Crohn's Disease occurs more commonly in younger adults and tends to involve multiple layers of the mucosa anywhere along the intestinal tract. Ulcerative colitis is localized to the colon and rectum, involves more superficial ulceration and inflammation of the mucosa, and attacks a wider age group. There is a genetic predisposition to IBD, and some putative genetic markers have been identified that help to explain why, for example, family members of a Crohn's patient have a greater likelihood of developing the disease.

IBD patients carry *C. difficile* at increased rates and are more at-risk for CDI

Persons with IBD have a less diverse intestinal microbiota. There is a reduction in the number of anti-inflammatory members of the microbiota such as the *Firmicutes* accompanied by higher numbers of pro-inflammatory members such as *Bacteroidetes*.[2] This reduction in diversity is a key characteristic of IBD and represents a triggering event for carriage of *C. difficile* by IBD patients. Because of the higher carriage, there is an accompanying increased risk of CDI.[3]

In one study, the prevalence of CDI was 37.3 per 1000 in patients with ulcerative colitis, 10.9 per 1000 in patients with Crohn's Disease, and 4.5 per 1000 among patients without IBD.[4] In the UK, where CDI rates have decreased over the past 10 years, complications of CDI in IBD patients also have decreased.[5] In addition to clinical epidemiological data, recent research in mouse models has shown that the onset of IBD is a predisposing factor for both *C. difficile* colonization and CDI.[6] Additional new information indicates that the risk of CDI in IBD patients is increased by factors such as healthcare exposures, nonsteroidal anti-inflammatory drugs, colonic vs intestinal involvement, and whether they are transplant recipients. IBD patients with CDI are at higher risk for complications, IBD flares,

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colectomies, and death than patients without IBD.[7]

Inflammatory markers help identify severe IBD and CDI but do not distinguish between the diseases

With some diseases, the presence of inflammation can be a distinguishing clinical feature. IBD, for example, can be differentiated from irritable bowel syndrome, which has overlapping clinical features, but which is noninflammatory. In the case of both CDI and IBD, however, inflammation is a clinical hallmark, and the presence or absence of inflammation is not a differentiating feature. In both diseases, peripheral white blood cell counts and fecal biomarkers of inflammation (e.g., fecal lactoferrin released from infiltrating leukocytes) are elevated. The increase in these inflammatory markers during CDI, more so than the fecal bacterial burden, correlates with severity.[8]

With CDI, there is accompanying involvement of inflammasomes that play a role in proinflammatory cytokines, but it is unclear whether CDI-associated cytokines may serve as surrogate markers for the disease. With IBD, neutrophil-to-lymphocyte ratios have been examined as a means of establishing a diagnosis of IBD along with severity.[9] However, there is no clear indication that this approach may help differentiate CDI from an IBD flare.

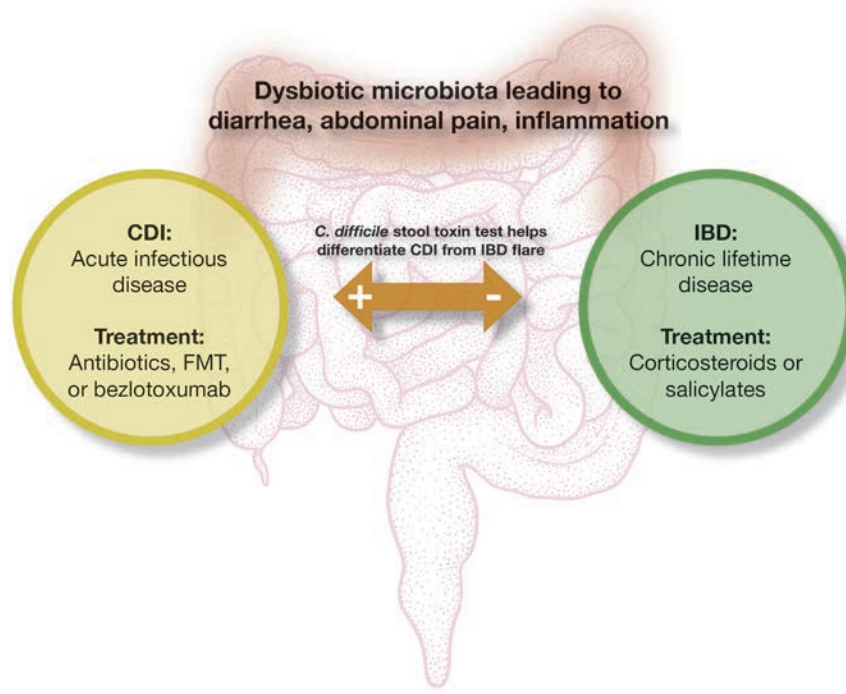

Figure 1. CDI and IBD are two unrelated diseases that are triggered by a dysbiotic intestinal microbiota. The use of a stool toxin test can help identify CDI in a patient with IBD, resulting in appropriate therapy for the infection.

Laboratory tests help distinguish CDI from IBD

Widely used tests for *C. difficile* and its disease include PCR and glutamate dehydrogenase (GDH), both of which detect the organism, and stool toxin, which detects toxins A and B. PCR is very sensitive, but the high sensitivity results in lower positive predictive values because *C. difficile* carriage is common. GDH can detect actively growing bacteria, but the test does not differentiate between toxigenic and nontoxigenic strains, which do not cause disease. For CDI, patient clinical history in conjunction with toxin detection offers higher positive predictive values than either PCR or GDH testing. Microbiology and gastroenterology societies now recommend an algorithm approach that consists of PCR or GDH screen coupled with toxin testing for accurate diagnosis of CDI.

These recommendations have been extended to aid in the diagnosis of CDI in IBD patients. Recent guidelines and recommendations report that the detection of stool toxin helps to accurately diagnose CDI in IBD patients.[10,11] Further, the recommendations state that IBD patients who flare should be tested for CDI and for recurrent CDI if the diarrhea and colitis symptoms persist. A negative PCR or GDH result can help rule out CDI in an IBD patient.[12,13] If the toxin test is positive, treatment with vancomycin or fidaxomicin should be considered. If the patient's condition does not improve within several days, then additional clinical workup for an IBD flare should be considered.

Fecal microbiota transplantation (FMT) can restore homeostasis

Efforts to restore the intestinal microbiota in patients with CDI and IBD through fecal microbiota transplantation (FMT) have met with varying levels of success. In patients with recurrent CDI, FMT has a high success rate. Multiple companies are actively researching ways to improve the technology of FMT. The approaches range from using fecal emulsions obtained from donors who have been rigorously tested for the absence of *C. difficile* and other pathogens to efforts that consist of well-defined bacterial populations delivered in pill form.

The fecal emulsion approach relies on the collection, screening, and shipping of fecal specimens and the preparation of samples for instillation in patients. The procedure has reported success rates >90%. Clinical studies on more defined combinations of bacteria that are curative and that prevent recurrent CDI are promising. With treatment of IBD, FMT results have not been as spectacular. Even so, clinical research still is underway on the utility of FMT as a treatment in IBD patients.[14] IBD may be less responsive to FMT and more challenging than CDI because the goal is to establish a more diverse microbiota than what currently exists in an IBD patient rather than simply replacing the microbiota, the goal in a CDI patient. FMT has been recommended as a treatment for IBD patients who are toxin-positive with recurrent CDI.[11,15]

Conclusions

IBD and CDI are intestinal diseases that present with similar clinical features but have very different etiologies. Both are the result of a dysbiotic intestinal microbiota. In CDI, the microbiota becomes dysbiotic after antibiotics or other medications/conditions that disrupt the microbiota, setting up the possibility of disease. In IBD, the cause of the dysbiosis is unclear, but significant disruption of the microbiota is evident. As a result, IBD patients have a higher likelihood of being colonized with *C. difficile* and developing CDI. Because of the similar clinical features and the higher rates of carriers and CDI in IBD

patients, it can be difficult to distinguish a true CDI infection from an IBD flare. Recent recommendations include the detection of *C. difficile* toxin as an aid in the diagnosis of CDI in IBD patients.

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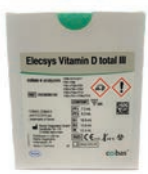

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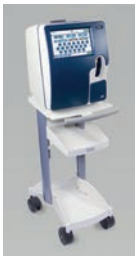

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LABORATORY INNOVATOR

Insights from Innovators:
Laboratory outreach, molecular diagnostics, and automation

By Gail Castanho

After tabulating the results from the 2022 Salary Survey, further clarification was needed to cull the results from some supplemental questions, added only a couple of years ago.

The answers to these questions will provide additional information for our readers, concerning these specific areas:

Laboratory Outreach

1. Which of the following have been a focus of your laboratory's outreach efforts?

Survey takers responded to the question, "Which have been the focus of your laboratory's outreach efforts?" with the following results, illustrating the priority given to physician practices (58%), over other areas:

- Physician practices: 58%
- Nursing homes: 43.2%
- Community members: 37%
- Home care: 26.7%
- Other laboratories: 21%
- None - no outreach efforts: 19.8%
- Minimal outreach efforts: 11.5%
- Other: 2.1%

Molecular Diagnostics

2. Which areas of your lab have embraced molecular diagnostics?

Surveyed lab personnel were asked to report on which areas of their labs have embraced molecular diagnostics in 2022:

- Most areas, including microbiology, showed a slight decrease in results, with that area showing results at 77%, down from 80.4% in 2021.
- Chemistry was also down, for 2022 (12.3%), compared with 14.1% in 2021.
- Hematology showed a minor decrease from 2021 (6.4%), as well, with a 2022 result of 4.5%.
- The area where 2022 results showed improvement, from 2021, was blood banks , at 4.5% (up from 2.9%in 2021).

Automation

3. Did your lab automate or further automate new procedures in 2021?

When questioned, those surveyed reported that their labs automated, or further automated new procedures during the previous year, 50.2% said "yes," compared to the 2021 survey (50.6%).

Impact of COVID-19 on laboratories in 2022

4. How was your lab department affected by the COVID-19 pandemic?

Laboratorians answered the question relating to how their lab department was affected by the COVID-19 pandemic, in 2022:

- As expected, the highest area affected by COVID-19 was increased testing, at 67.9%.
- Also anticipated, was the area involving reorganizing and evaluating supply usage and storage, which was reported at 53.9%.
- Reassigning lab employees to other areas was conveyed at 36.6%.
- Reviewed test and utilization costs and reimbursement levels were 28.8%;
- furloughed lab employees were at 25.9%, and
- updated processing policies were identified at 25.1%.

The two areas with the lowest percentages were focusing on certifications (2.9%) and 0% reported for closing the department.

The Accurate. Sustainable. **Molecular** Solution.

Testing beyond COVID for respiratory season.

With Solana, you can sustain your molecular testing of critical assays for which you might be considering alternate methods. Coupled with the power of Virena® cloud based analytics, you can quickly implement a more complete solution to protect the health of your patients and your facility.

Compact footprint
9.4" x 9.4" x 5.9"
Deployable *practically anywhere*

For more information contact
Quidel Inside Sales at 858.431.5814

Easy, flexible workflow – Integrated seamlessly for single specimen or high-throughput batching up to 12 tests at a time

Minimal training – Get up and running quickly

QUIDEL | Solana®

with the power of Virena

Enhanced diagnostics featuring data analytics and surveillance

*SARS-CoV-2	GAS
Influenza A+B	GBS
RSV + hMPV	HSV 1+2/VZV
Respiratory Viral Panel	Bordetella Complete
Strep Complete	Trichomonas
C. difficile	

*THIS TEST IS AVAILABLE FOR SALE IN THE USA UNDER EMERGENCY USE AUTHORIZATION. The Solana SARS-CoV-2 Assay has not been FDA cleared or approved, but has been authorized by the FDA under an Emergency Use Authorization (EUA) for use by authorized laboratories for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens. This assay is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless authorization is terminated or revoked sooner.

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