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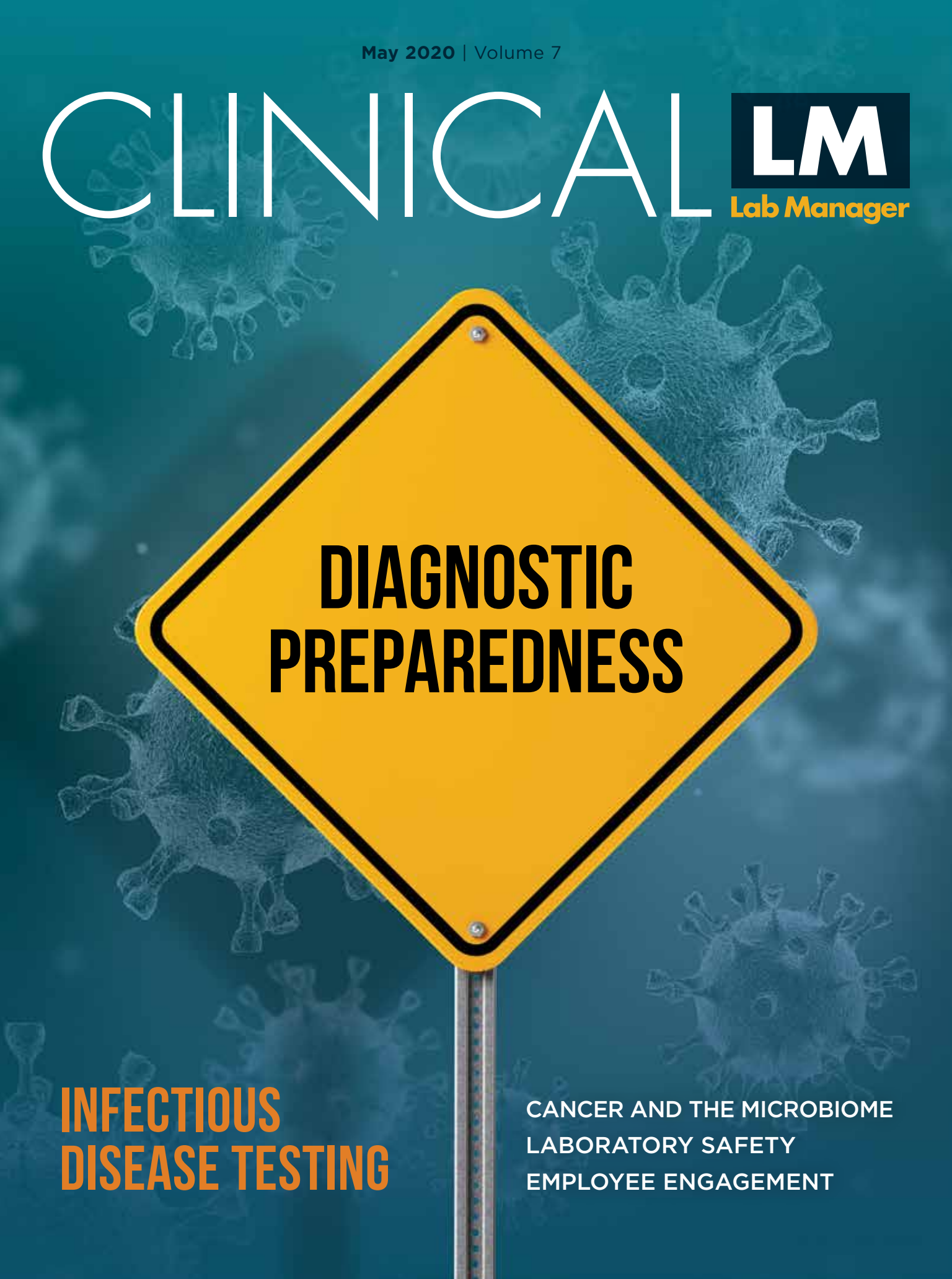
CLINICAL LM Lab Manager



DIAGNOSTIC PREPAREDNESS

INFECTIOUS DISEASE TESTING

CANCER AND THE MICROBIOME
LABORATORY SAFETY
EMPLOYEE ENGAGEMENT

CLINICAL LM Lab Manager

May 2020

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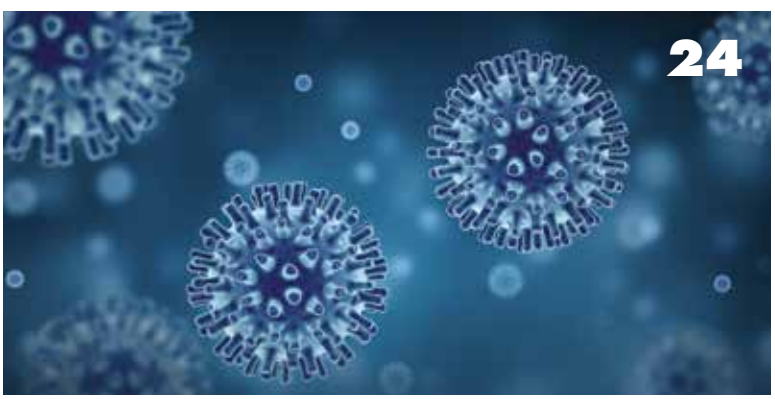


unsung heroes

As the coronavirus pandemic has progressed, the public has been singing the praises of doctors, nurses, and paramedics on the front lines of the crisis.

Lab professionals, who work behind the scenes, are the unsung heroes of the pandemic. They've been tirelessly processing samples and ramping up testing capacity—in many cases, while under pressure to maintain other critical testing operations. Widespread staff shortages and overwhelming workloads put these laboratorians at high risk of laboratory-acquired infection, according to this month's safety feature (page 12) by Karen L. Stiles, SM(ASCP)^{CM} and Suzanne Peters, MT(ASCP).

Despite the incredible efforts and personal risks taken by laboratory workers during health crises like the current one, they rarely get the recognition they deserve. It's no wonder that lab leaders consistently list staff engagement as a key management challenge in *Clinical Lab Manager*'s readership surveys.

Medical Laboratory Professionals Week, which just passed, is the perfect occasion to shine a spotlight on laboratory workers once a year. However, as Patty Eschliman, MHA, MLS(ASCP)DLM, points out in this month's management feature (page 30), "a leader must publicly celebrate his or her team's accomplishments at every opportunity—not just during Lab Week."

We at *Clinical Lab Manager* are committed to exposing the crucial work that goes on in clinical laboratories. In that vein, on page 43, Darryl Elzie, PsyD, MHA, MT(ASCP), CQA(ASQ), brings readers inside a clinical laboratory system and details how staff are managing to ramp up testing, quickly validate instruments, and deal with communication and coordination challenges as they respond to the current pandemic.

This issue also delves into the broader subject of diagnostic preparedness for pandemics. In our cover story (page 14), author Rachel Muenz explores why significant diagnostic gaps exist for many diseases identified by the World Health Organization (WHO) as likely to cause future epidemics. Despite researchers having published a list of recommendations to alleviate many of these diagnostic challenges early last year, Muenz concludes that there is still plenty of work to prepare for the next pandemic.

Coronavirus is at the top of everyone's mind these days, but other diseases shouldn't be forgotten. Around one quarter of the global population is thought to be infected with tuberculosis, cancer remains a leading cause of death worldwide, this year's influenza season has been one of the worst on record. You can read about the current diagnostic challenges, solutions, and advances being made for these and other diseases in this month's issue (see pages 18, 24, and 38).

I'd like to personally thank clinical laboratory professionals for the vital work they do, both inside and outside of the current pandemic.

Stay safe.

Erica Tennenhouse

Erica Tennenhouse, PhD, Managing Editor

managing editor
Erica Tennenhouse, PhD
etennenhouse@clinicallabmanager.com

editorial director
Trevor Henderson, PhD
thenderson@clinicallabmanager.com

associate editor
Rachel Muenz
rmuenz@clinicallabmanager.com

art director
Danielle Gibbons
danielleg@clinicallabmanager.com

contributors
Tracy Wieder, MBA
Karen Stiles, SM(ASCP)^{CM}
Suzanne Peters, MT(ASCP)
Raeesa Gupte, PhD
Suzanne Leech, PhD
Patty Eschliman, MHA, MLS(ASCP)DLM
Margaret E. Blaetz, CLC, MLT(AMT), CCCP(AAPOL)
Laura M. Bolt, PhD
Darryl Elzie, PsyD, MHA, MT(ASCP), CQA(ASQ)
Jing Zhou, MD, PHD

business coordinator
Andrea Cole
andreac@clinicallabmanager.com

eMarketing coordinator
Laura Quevedo
lquevedo@clinicallabmanager.com

scientific technical editor
Michelle Dotzert, PhD
mdotzert@clinicallabmanager.com

digital media coordinator
Catherine Crawford-Brown
ccrawford-brown@clinicallabmanager.com

audience development specialist
Matthew Gale
mgale@clinicallabmanager.com

publisher / sales
Edward Neeb
edwardn@clinicallabmanager.com
203.448.0728

Published by LabX Media Group
president
Bob Kafato
bobk@labmanager.com

managing partner
Mario Di Ubaldi
mariod@labmanager.com

general manager
Ken Piech
kenp@labmanager.com

production manager
Greg Brewer
gregb@labmanager.com

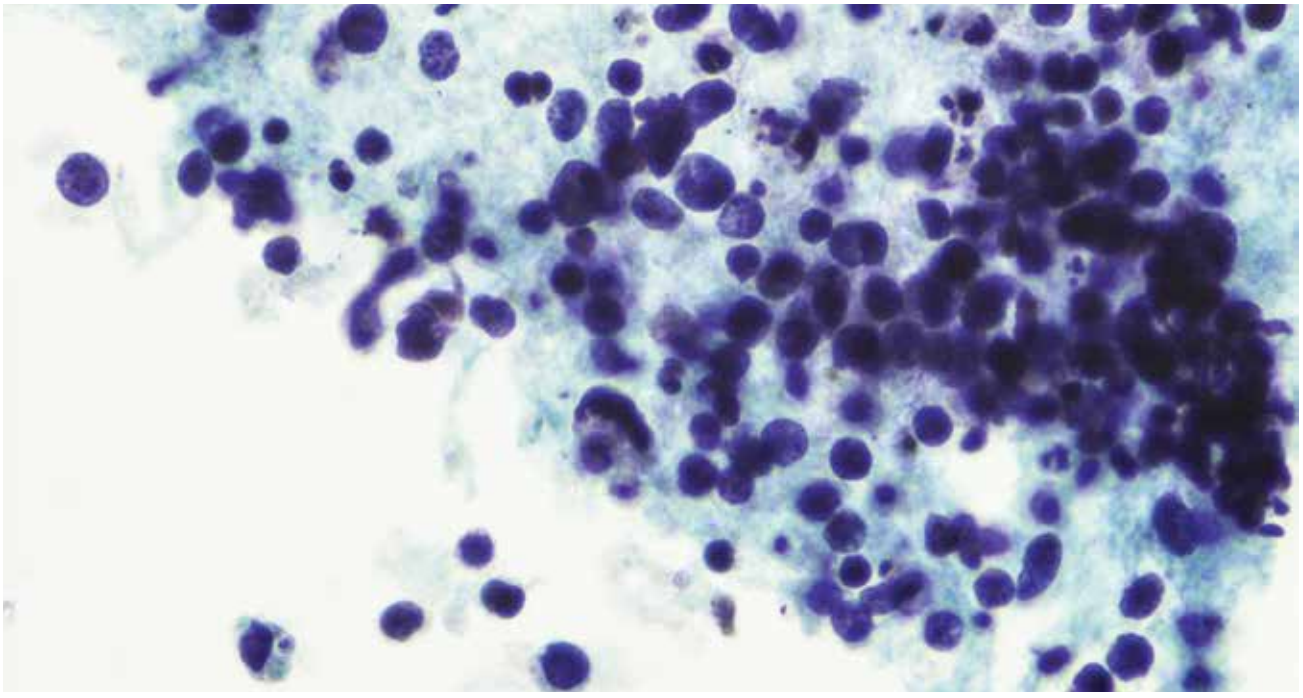
custom article reprints
The YGS Group
labmanager@theygsgroup.com
800.290.5460
717.505.9701 x100

subscription customer service
labmanager@halldata.com

CLINICAL LM Lab Manager

1000 N West Street, Suite 1200
Wilmington, Delaware, 19801
888.781.0328

Our top picks from the literature



Blood Test Detects Dozens of Cancer Types

Researchers have developed the first blood test that can accurately detect more than 50 types of cancer and identify in which tissue the cancer originated, often before there are any clinical signs or symptoms of the disease. The blood test analyzes methylation of cell-free DNA (cfDNA). A machine learning classifier was used to predict the presence of cancer and the type of cancer based on the patterns of methylation in the cfDNA shed by tumors. The classifier analyzed blood samples from 4,316 participants with and without cancer—3,052 in the training set and 1,264 in the validation set—to identify methylation changes, classify the samples as cancer or non-cancer, and identify the tissue of origin. The classifier's performance was consistent in both the training and validation sets, with a false positive rate of 0.7 percent in the validation set, the researchers reported in *Annals of Oncology* in March 2020. In 12 types of cancer that are often the deadliest, the true positive rate was 67.3 percent across clinical stages I, II and III. Detection improved with each cancer stage. Across more than 50 cancer types, the corresponding true positive rates were 18 percent in stage I, 43 percent in stage II, 81 percent in stage III, and 93 percent in stage IV. The researchers say that the targeted methylation test meets the fundamental requirements for a multi-cancer early detection blood test for population-level screening: the ability to detect multiple deadly cancer types with a single test that has a very low false positive rate, and the ability to identify where in the body the cancer is located.

Liu, M. C., et al. "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA." *Annals of Oncology* (2020).

Exaggerated Claims That AI Outperforms Clinicians

Many studies claiming that artificial intelligence is as good as (or better than) human experts at interpreting medical images are of poor quality and are arguably exaggerated, posing a safety risk to patients, researchers warn in a paper published in March 2020 in the *BMJ*. Researchers reviewed the results of published studies over the past 10 years—two eligible randomized clinical trials and 81 non-randomized studies—and compared the performance of a deep learning algorithm in medical imaging with expert clinicians. Of the

non-randomized studies, only nine were prospective and just six were tested in a real-world clinical setting. The average number of human experts in the comparator group was just four, while access to raw data and code was severely limited. More than two thirds (58 of 81) studies were judged to be at high risk of bias, and adherence to recognized reporting standards was often poor. Three quarters (61 studies) stated that performance of AI was at least comparable to (or better than) that of clinicians, and only 31 (38 percent) stated that further prospective studies or trials were needed. The findings raise concerns about the quality of evidence underpinning many of these studies, highlighting the need to improve their design and reporting standards. The researchers say that many of the studies presented arguably exaggerated claims about superior performance of AI to clinicians, which could pose a risk to patient safety.

Nagendran, Myura, et al. "Artificial intelligence versus clinicians: systematic review of design, reporting standards, and claims of deep learning studies." *BMJ* 368 (2020).

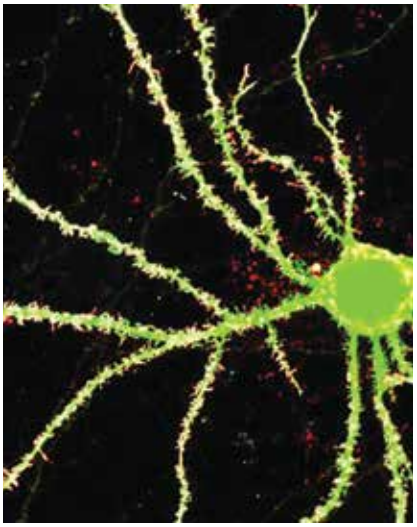
Polygenic Risk Score Does Not Improve Heart Disease Prediction

Polygenic risk score—a genetic assessment that doctors have hoped could predict coronary heart disease (CHD) in patients—is not a useful predictive biomarker for disease risk, according to a study published in February 2020 in the *Journal of the American Medical Association.* The researchers conducted a retrospective cohort study of the predictive accuracy of polygenic risk scores in 7,306 adults of European ancestry ages 45-79. The patients were taken from two large cohort studies, the Atherosclerosis Risk in Communities study and the Multi-Ethnic Study of Atherosclerosis. They found that the polygenic risk score didn't significantly improve prediction of CHD risk in this population. It was no more useful than the conventional method of determining CHD risk, which involves assigning a patient a clinical risk score based on factors including age, gender, cholesterol levels, and tobacco use. Researchers have long sought to reduce cardiovascular mortality by early identification of CHD. The study suggests that polygenic risk scores should not be added to the standard of care for identifying high-risk CHD patients at this time; however, further study is needed to determine whether other populations may benefit from a polygenic risk score.

Mosley, Jonathan D., et al. "Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease." *JAMA* 323.7 (2020): 627-635.

Mutations Help to Explain Sex Difference in Autism Incidence

Researchers have discovered that a single amino acid change in the NLGN4 gene, which has been linked to autism symptoms, may help to explain why autism spectrum disorder (ASD) is more common in males than in females. The findings were published in April 2020 in the journal *Neuron.* Using biochemistry, electrophysiology, and imaging, the researchers compared two NLGN4 genes (one on the X chromosome and one on the Y chromosome), which play an important role in the establishment and maintenance of synapses. They discovered that the proteins encoded by these genes display

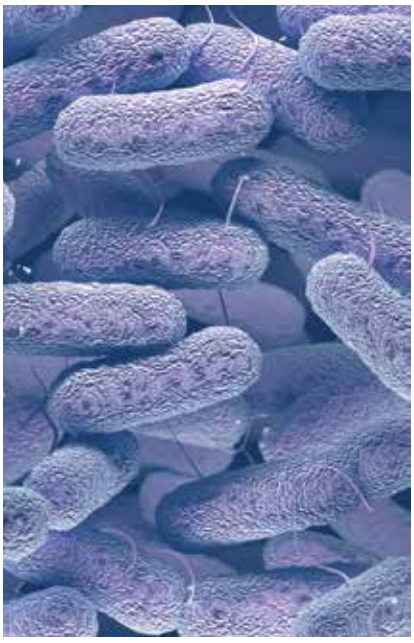


different functions. The NLGN4Y protein is less able to move to the brain cell surface and is therefore unable to assemble and maintain synapses, making it difficult for neurons to send signals to one another. The deficits associated with NLGN4Y are due to a single amino acid difference, the researchers found. They also discovered that the region surrounding that amino acid in NLGN4X is sensitive to mutations in the human population. There are a cluster of variants found in this region in people with ASD and intellectual disability and these mutations result in a deficit in function for NLGN4X that is indistinguishable from NLGN4Y. In females, when one of the NLGN4X genes has a mutation, the other one can often compensate. However, in males, diseases can occur when there is a mutation in NLGN4X because there is no compensation by NLGN4Y. The inability of NLGN4Y to compensate for mutations in NLGN4X may help explain why males, who only have one X chromosome, tend to have a greater incidence of NLGN4X-associated ASD than females.

Nguyen, Thien A., et al. "A Cluster of Autism-Associated Variants on X-Linked NLGN4X Functionally Resemble NLGN4Y." *Neuron* (2020).

AST for High-Priority Pathogens

Researchers have described two unique diagnostic methods to determine phenotypic antibiotic susceptibility of high-priority pathogens in two new papers published in March 2020 in *PLoS Biology*. The two new methods are polymerase-accessibility antibiotic susceptibility testing (pol-aAST) and nuclease-accessibility antibiotic susceptibility testing (nuc-aAST). The pol-aAST uses a polymerase to amplify DNA made accessible after beta-lactam treatment. The pol-aAST was tested on samples containing Enterobacteriaceae species, which are priority pathogens because of the rise in carbapenem-resistant Enterobacteriaceae. The nuc-aAST uses DNase, a DNA-degrading enzyme, to digest DNA that becomes accessible after beta-lactam treatment. The nuc-aAST was validated on samples containing the pathogen Neisseria gonorrhoeae, an urgent threat as categorized by the Centers for Disease Control. Each AST method is rapid, only requiring 15-30 minutes of incubation with the antibiotic, and each uses DNA as the readout, making the methods pathogen specific.

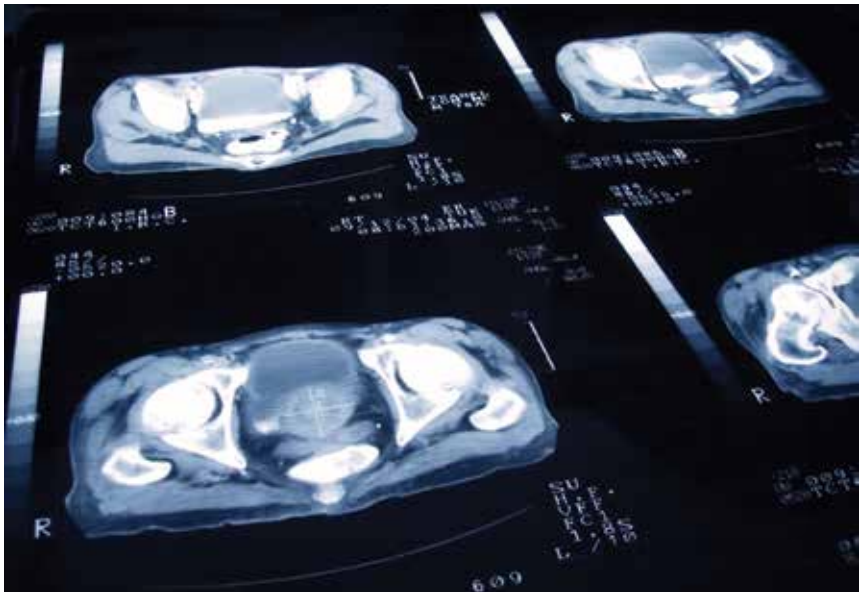


Schoepp, Nathan G., et al. "Differential DNA accessibility to polymerase enables 30-minute phenotypic β-lactam antibiotic susceptibility testing of carbapenem-resistant Enterobacteriaceae." *PLoS Biology* 18.3 (2020): e3000652.

Savela, Emily S., et al. "Surfactant-enhanced DNA accessibility to nuclease accelerates phenotypic β-lactam antibiotic susceptibility testing of Neisseria gonorrhoeae." *PLoS Biology* 18.3 (2020): e3000651.

More Accurate Prostate Cancer Biopsies

Researchers have found that combining MRI-targeted biopsy and 12 core systematic biopsy for men with MRI-visible prostate lesions could help prevent misclassifications of prostate cancer. The standard biopsy method for prostate cancer, which involves taking 12 core samples from different parts of the prostate, is associated with diagnostic inaccuracy that contributes to both under- and overdiagnosis of prostate cancer. Researchers investigated whether adding MRI-targeted biopsy to 12 core systematic biopsy would improve the accuracy of the biopsy results. Doctors performed both 12 core systematic biopsy and MRI-targeted biopsy on 2,103 men with MRI-visible prostate lesions and classified them into one of three grade groups based on the presence of clinically



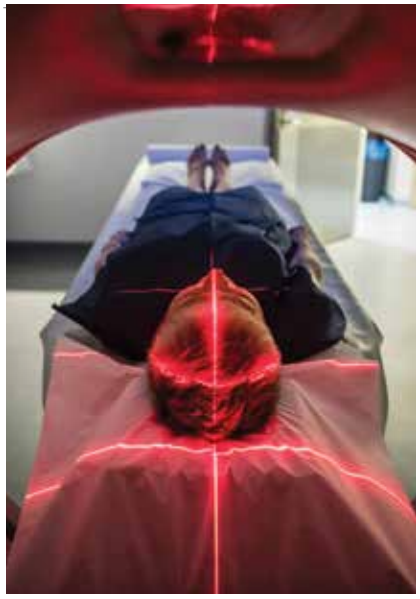
insignificant disease, the presence of cancer with favorable intermediate risk or worse, or the presence of cancer with unfavorable intermediate risk or worse. Of the men who underwent biopsy, 19.2 percent needed a radical prostatectomy. After radical prostatectomy, researchers performed histopathological analysis on the surgical specimens and classified each into one of the three grade groups. They then compared the grade group determined by each biopsy method and with the methods combined to the grade group determined using histopathological analysis. Combining both biopsy methods led to the lowest rate of reclassification with only 3.5 percent of cases being reclassified—far better than the 8.7 percent and 16.8 percent of cases that had to be reclassified when using MRI-targeted biopsy and systematic biopsy respectively. The results, reported in March 2020 *New England Journal of Medicine*, suggest that combining these two biopsy methods could help improve detection of prostate cancer and prevent misclassification of cancer severity.

Ahdoot, Michael, et al. "MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis." *New England Journal of Medicine* 382.10 (2020): 917-928.

Decline in Medical Radiation Exposure

Medical radiation exposure to patients in the US fell by 20 percent between 2006 and 2016, reversing a quarter century-long trend of increasing exposure, according to a study published in March 2020 in the journal *Radiology*. A landmark report published in 2008 found that per capita radiation exposure in the US increased six-fold between 1980 and 2006. In the wake of the report, medical societies enacted initiatives to increase awareness of exposure while equipment manufacturers developed more refined dose modulation technology. The authors of the new study set out to determine how radiation exposure changed in the US from 2006 to 2016. The results showed that the number of radiology examinations performed remained largely unchanged over the 10-year period, even though the US population increased by about 23 million. Estimated annual individual dose from diagnostic and interventional medical procedures fell from 2.9 millisieverts (mSv) in 2006 to 2.3 mSv in 2016, a decrease of approximately 20 percent. A key factor in the reduction was a substantial decrease in the number of nuclear medicine procedures, from 17 million in 2006 to 13.5 million in 2016. CT scans, a major driver of medical radiation exposure, increased from 67 million to 84 million scans over the 10-year period. However, the average individual effective dose from CT procedures dropped by six percent, thanks to the dose modulation techniques now available on most CT scanners and the fact that newer detectors can utilize less radiation to create the same quality images, the researchers say.

Mettler Jr, Fred A., et al. "Patient exposure from radiologic and nuclear medicine procedures in the United States: procedure volume and effective dose for the period 2006–2016." *Radiology* (2020): 192256.



How to Handle a **Laboratory Emergency**

PREVENTION IS CRITICAL, BUT CLINICAL LABORATORY STAFF MUST ALSO BE PREPARED

by Tracy Wieder, MBA

Laboratory safety is about preventing accidents and emergencies in laboratory settings. Laboratory emergencies occur when, despite our best efforts, a serious accident that has the potential to endanger the health of our staff happens anyways. This article will address how to respond to potential emergencies that clinical laboratory staff may encounter.

Would you know what to do if someone in your lab caught on fire? How about if someone were being electrocuted? Let's dive into some of these scenarios.

> "Laboratory emergencies occur when, despite our best efforts, a serious accident that has the potential to endanger the health of our staff happens anyways."

You just spilled a tube of human blood on your lab coat.

What should you do?

Blood and bodily fluids have the potential to spread infectious diseases such as Hepatitis C and HIV to workers who mishandle spills. All bodily fluids should be assumed infectious.

If you spill a tube of human blood on your lab coat, wearing gloves, remove contaminated clothing and place it into a biohazard waste bag. Ensure there is no blood on the floor, benches, or any other clothing. If blood is found on any surfaces, such as floors or countertops, clean them with a 10 percent bleach solution. Remove any additional contaminated clothing and place it in a biohazard waste bag. Put on a new lab coat and dispose of biohazard waste according to your institution's policies.

A member of your lab is unplugging one extension cord from another when his or her metal necklace catches on the exposed prongs of the cord that is still connected to a wall outlet. The employee is thrown to the ground and is actively being electrocuted.

What should you do?

Cut off the electrical supply if it can be done easily and very quickly (e.g., remove the plug from the wall). If the electricity cannot be cut off very quickly, then remove the employee from the electrocution source using a non-conductive material, such as rubber gloves or a wooden dowel. Never touch an employee that is being electrocuted with bare hands as you will also be electrocuted. Then seek medical attention for the employee who was being electrocuted.

Note that extension cords are never recommended in laboratory settings and certainly connecting multiple extension cords together is a huge no-no. Some types of clinical labs, depending on the state where they are located, are prohibited from using extension cords by the regulations that apply to their facility.

You just arrived to work in your lab on a cold winter day. After taking your coat off, you go to the fume hood where you pour 100 percent ethanol into a 1L beaker. You then wipe your hands on your wool sweater just before reaching back into the fume hood to turn on a hot plate. Suddenly a shock of static electricity ignites the ethanol fumes in the hood and your clothes catch fire.

What should you do?

Drop to the ground, roll, and smother the fire with a fire blanket or lab coat. After the flames are put out, the elevated temperature of the skin continues to cause damage. Run the skin under cold water for 20 minutes to bring the temperature down. Then seek medical care.

It is important to note that static electricity can be an ignition source. In this scenario, the lab worker wiped his or her hands on a wool sweater, which can cause static electricity. In addition, cold temperatures make air dry, which can also cause static electricity. The best way to prevent static electricity is to increase the humidity in the air.

You walk into a pathology lab at your institution to ask a friend a question. Just as you walk in, you bump into a lab bench and a glass thermometer falls onto the floor and breaks. Since this is not your lab, you do not know what type of thermometer (mercury or alcohol) it was.

What should you do?

Most thermometers in today's lab facilities are filled with alcohol, rather than mercury; however, it certainly is possible that a mercury thermometer is being used in the lab as they are more accurate for measuring higher temperatures than alcohol thermometers.

Mercury is silver in color. It is highly toxic to the brain and nervous system and particularly fatal to fetuses. Alcohol thermometers are not toxic and the alcohol is usually colored red or blue for easy visualization. If you do not see any silver beads on the floor and only observe a red or blue liquid, you can clean the spill up using gloves and paper towels, being careful not to cut yourself on the broken glass, and dispose of clean-up materials in the lab's broken-glass disposal container. If you see silver mercury beads on the floor, then you need to take great care in cleaning up the broken thermometer and mercury:

1. Put on latex or vinyl gloves. Place two garbage bags outside of the contaminated area and bring another one with you inside the contaminated area to use during clean-up.

2. Using paper towels, carefully pick up the larger pieces of glass and wrap the paper towel around the glass pieces. Place the paper towels with glass inside into the trash bag you brought with you into the contaminated zone.

3. Use stiff cardboard or index cards to sweep smaller pieces of glass and mercury beads into a pile. Shine a flashlight onto the area of the spill as well as surrounding areas to

help identify beads of mercury that may have traveled away from the area of the original accident. Be sure to check very carefully looking into hard-to-reach areas (cracks and corners) to locate all mercury beads. Use paper towels to clean up the remaining glass and small beads of mercury and place them into the trash bag.

"Would you know what to do if someone in your lab caught on fire? How about if someone were being electrocuted?"

4. Sprinkle sulfur powder over the area of the mercury spill and rub it into the contaminated area, paying special attention to cracks and corners. Sulfur powder binds with mercury to clean up any remaining mercury particles that you were not able to identify. Clean the sulfur/mercury combination up well with several rounds of paper towels dampened in water. Place all items into the garbage bag.

5. Carefully remove your latex/vinyl gloves and place them into the trash bag. Place any shoes or clothes that came into direct contact with mercury during the clean-up into the trash bag.

6. Carefully seal the trash bag. Then place this trash bag into a non-contaminated trash bag and seal the second trash bag well.

7. Contact your institution's environmental health and safety group immediately to inform them that you have cleaned up a mercury spill and follow their procedures for disposing of the waste bag.

8. Place all clothes or shoes that did not come into direct contact with the mercury into the second fresh garbage bag and take the bag outside. Remove items from the trash bag and air them out outside for at least 24 hours. Once the items are aired out, you may wash them and wear them again.

If you do not have the proper supplies to clean up the spill, move away from the contaminated area immediately and call your environmental health and safety group for assistance with clean up. Notify all lab staff to stay out of the room.

You just splashed hydrochloric acid in your eyes.

What should you do?

Immediately move to an eyewash station. If you cannot see well enough to do that, call for your lab mates to help you. Rinse your eyes for at least 15 minutes, holding your eyelids open. Remove any contaminated clothing and then seek medical care.

A member of your lab just slipped on some water on the floor, fell straight onto his or her back, and cannot get up.

What should you do?

Immediately call 911 and give them your location. Do not move the person who has fallen as you do not know how severe the injuries may be. Approach your lab mate carefully, so as not to fall yourself. If your lab mate is conscious, calmly instruct him or her not to move and explain that help is on its way. Keep your lab mate as still and calm as possible until help arrives.

These are just a few of the vast number of emergency scenarios that you may face in your day-to-day work in the lab. I urge all labs to discuss past emergencies as well as current near-misses and current emergencies, in an effort to continually learn and improve their emergency responses.

Practice is also crucial. It's a great idea to conduct regular emergency drills so staff can practice what to do in the event of these emergency scenarios. Lab safety is important and prevention is key, but we are all human and mistakes happen. In the end, we need to know what to do when, despite our best efforts, the worst happens.

Tracy Wieder *has worked in the field of biomedical research for 30 years, starting as a lab technician, then moving into lab manager roles, lab director roles, and finally into her current role overseeing all research laboratories at the University of Miami Sylvester Comprehensive Cancer Center.*

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Safety Measures to Prevent Laboratory-Acquired Infection

DIAGNOSTIC LABORATORIES MUST IMPROVE THEIR LEVEL OF SAFETY TO PROTECT LABORATORIANS FROM INFECTION

by Karen Stiles, SM(ASCP)^{CM} and Suzanne Peters, MT(ASCP)

On March 11, 2020, the World Health Organization (WHO) declared COVID-19—the disease caused by the virus SARS-CoV-2—a global pandemic. As COVID-19 has developed into a community-spread disease in the US, our clinical and public health laboratories (PHLs) are becoming overwhelmed. The purpose of this article is to encourage all diagnostic laboratories to improve their level of safety, for the sake of their laboratorians, in order to prevent the possibility of a laboratory-acquired infection.

Due to lab staff shortages, overwhelming workloads, and lack of funding, laboratorians are at high risk for infection if not fully prepared. Only a small percentage of clinical laboratories have performed documented risk assessments on hazardous procedures or implemented effective training in biosafety. Laboratorians complete annual training in blood-borne pathogens, but biosafety training tends to be overlooked or only mentioned upon hire. Additionally, biosafety and use of personal protective equipment (PPE) or the biosafety cabinet (BSC) are not built into the laboratory competency program where laboratorians are observed for breach of safe PPE or BSC usage. Despite the Centers for Disease Control and Prevention's (CDC's) three-year effort to incorporate a culture of safety by hiring a biosafety officer, it placed focus on enhancing the PHL biosafety and may not have fully involved clinical diagnostic laboratories.

Public health laboratories have a key role to play, not only to lobby Centers for Medicare and Medicaid Services (CMS) and College of American Pathologists (CAP) for safer regulations, but also to connect with clinical laboratories in each state, train on risk assessments and biosafety, and assist in the incorporation of competency policies regarding biosafety and PPE measurements. Currently, there is little regulatory oversight for a laboratory to attain biosafety to its fullest extent. Accrediting agencies must be asked to be more comprehensive in their biosafety checklist/inspection process. Safety in clinical laboratory settings must be immediately improved in order to be prepared for the imminent threat of a COVID-19 outbreak. Clinical laboratories must voluntarily boost their safety by implementing all possible safety precautions.

With the introduction of Ebola in the US, PPE requirements were enhanced with the use of risk assessments. The Association of Public Health Laboratories released risk assessment best practices, which detailed key components including workforce needs, risk characterization, and risk mitigation. Two points of highest risk for self-contamination were insufficient hand hygiene and unsafe removal of gloves and masks. Clinical laboratories can apply the lessons learned from Ebola to the current COVID-19 outbreak. It is imperative to perform risk assessments on all laboratory procedures in which the virus may be present in specimens. The risk assessment must be written and documented by lab managers, who must ensure laboratory staff has been consistently trained. Competency in PPE donning, use, and doffing, and other risk-mitigating procedures developed by the administration should be routinely assessed. This documentation

may be required during an Occupational Safety and Health Administration (OSHA) investigation of a laboratory-acquired infection, particularly in the case of a death.

Laboratorians should understand the concept of using biosafety level (BSL) 3 practices in a clinical BSL-2 laboratory. BSL-3 practices require protection of eyes and mouth with the use of N95 respirators and disposable face shields, in addition to universal precautions of impermeable lab coats and gloves. Few laboratories have incorporated N95s into their inventory unless tuberculosis is processed on-site. Laboratories and clinics would benefit from providing inventory and continued use of the N95 respirators when performing rapid detection tests. Microbiology laboratories can benefit from using N95s in the BSC when ruling out a suspect hazardous pathogen such as *Brucella* or *Francisella*. The CDC states that surgical masks are an option in the laboratory, but this type of mask is designed more to prevent an infectious person from spreading the virus, and less for protection of the lab staff wearing the mask. The main advantage of surgical masks is that they keep the laboratorian from touching the face. Due to the shortage of N95 respirators, surgical masks may be the only option at this time in the laboratory.

The workflow within the BSC should be articulated in the written laboratory policy to include disinfection of all specimen collection devices after removal from biohazard bags (each specimen should be transported in individual bags after collection), placing absorbent pads under the work area, working from clean to dirty side, covering all tubes with absorbent squares when opening, disinfecting gloves multiple times, and ideally providing a trained observer to point out risk during a procedure. Multiple glove changes inside the BSC or immediately at exit of the cabinet should be written into policy. Staff must mindfully remove gloves every time they exit the BSC, even if it's only to obtain something forgotten. This is a critical time when laboratorians must make improvements, such as adding centrifuges with closed rotors in their clinical settings. These are typically not used due to cost or space, but is it worth the cost of a laboratory-acquired infection?

Lab management should be encouraged to monitor PPE usage and to voluntarily incorporate extensive biosafety tasks into the competency program, even if it is not detailed in federal requirements. PHLs can provide assistance on risk assessment to help clinical laboratories go beyond the individualized quality control plan, and fully document a risk assessment with steps to mitigate each risk. Portions can be incorporated into the Laboratory Response Network training currently taught in the clinical laboratory setting. In order for PHLs to play a larger role with clinical laboratories within the state, the additional federal funding is necessary to promote better training. No other organizations can instill these practices like PHLs, as they provide education and consultation for the clinical laboratories.

Now is the time for laboratorians to take safety into their own hands. Employers should provide every possible PPE measure, as well as administrative and engineering controls (including safer centrifuges) to keep staff safe, but each individual laboratorian must also be willing to take responsibility to protect themselves. Unfortunately, the virus causing the COVID-19 disease is new and not well understood. Obviously, this specific coronavirus may not require the full precautions for Ebola, but until the scientific world knows exactly how dangerous this virus is, laboratories must take an abundance of precaution. Ebola taught all health care facilities extreme measures to enhance safety during patient management and laboratories must follow suit. Eventually, PHLs can be a principal resource to guide clinical settings but not without additional federal funding. Only funding can improve training efforts to teach risk assessments and biosafety measures to mitigate the risks to clinical laboratory staff.

***Karen Stiles**, SM(ASCP)^{CM}, is the state training coordinator for the Nebraska Public Health Laboratory and serves as the liaison to over 85 clinical laboratories in the state. She is responsible for continuing education and training for all clinical laboratories across Nebraska in the areas of preparedness, including agents of bioterrorism, chemical terrorism preparedness, and packaging and shipping of infectious substances.*

***Susanne Peters**, MT(ASCP), has enjoyed working in various departments on the UNMC/Nebraska Medicine Campus for the past twenty years. Her roles have included medical laboratory scientist in the clinical microbiology laboratory as well as the Nebraska Public Health Laboratory during the Ebola outbreak, infection preventionist, and her current role as clinical trials analyst in the clinical research center. www.suemadsenpeters.com*

This article was authored by the Clinical Laboratory Management Association (CLMA), an international association providing support, resources, and advocacy in the clinical laboratory industry. For more information and discussion on COVID-19 related to laboratory professionals, please visit www.clma.org/covid-19.

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Diagnostic Preparedness for Pandemics

WHAT NEEDS TO BE DONE TO ENSURE LABS HAVE PROPER DIAGNOSTIC TOOLS FOR FUTURE OUTBREAKS **by Rachel Muenz**

Despite years of warnings of such a pandemic occurring from public health authorities and researchers, the world was caught off guard by the novel coronavirus, SARS-CoV-2. Diagnostic testing to track the spread of the virus has lagged behind in most countries, leading to delays in putting critical measures, such as social distancing, in place.

Unfortunately, this likely won't be the last pathogen to pose such a challenge to health care systems. What needs to be done to ensure labs are prepared for the next pandemic? Which pathogens are likely to cause the next outbreak? What diagnostic options currently exist for such pathogens, if any?

Citing the World Health Organization's R&D Blueprint for Epidemic Preparedness, an analysis published last year in *BMJ Global Health* outlines 10 diseases and

WHO PRIORITY DISEASES
COVID-19
Crimean-Congo hemorrhagic fever (CCHF)*
Ebola virus disease
Marburg virus disease
Lassa fever*
Middle East respiratory syndrome coronavirus (MERS-CoV)
Severe Acute Respiratory Syndrome (SARS)
Nipah disease*
Henipavirus disease*
Rift Valley fever*
Zika*

*Indicates diseases with major diagnostic gaps, according to the *BMJ Global Health* article[1]

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pathogens likely to cause future epidemics. Of those, six have "significant diagnostic gaps," according to the article.[1] Since the novel coronavirus outbreak, COVID-19 has now been added to that list (see the table on the previous page for the diseases currently included in the list).

The WHO also lists "Disease X" as a threat which, according to its website, "represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease. The R&D Blueprint explicitly seeks to enable early cross-cutting R&D preparedness that is also relevant for an unknown Disease X.'"

Why diagnostic gaps exist

According to the *BMJ Global Health article*, none of the six WHO priority diseases with significant diagnostic gaps (CCHF, Lassa fever, Nipah disease, Henipavirus disease, Rift Valley fever, and Zika) have WHO-approved diagnostics. The remaining priority diseases face diagnostic challenges of their own, including limited availability of tests. We have already seen a significant diagnostic gap with COVID-19, which health authorities and diagnostics companies are quickly trying to close.

"Governments worldwide have not made pandemic preparedness a financial priority."

There are several reasons why such large gaps exist in the creation of diagnostic tests for these diseases and pathogens. The key challenges to diagnostic preparedness that the authors outline are: fragmented and unreliable funding pathways; limited access to specimens and reagents; inadequate diagnostic testing capacity at both national and community levels of health care; and lack of incentives for companies to develop and manufacture diagnostics for priority pathogens during non-outbreak periods.[1]

Funding issues

Lack of funding for diagnostics research and laboratories has been shown to be a key problem in recent outbreaks, as pointed out by Seth Berkley, chief executive officer of Gavi, the Vaccine Alliance, in a 2018 *Science* editorial. Without accurate, fast, and reliable tests in developing countries, confirming and even properly diagnosing cases of Ebola during the beginning of the 2014 outbreak and of yellow fever in 2016 and 2017 was difficult and allowed those diseases to spread.[2]

Even in wealthier countries, properly funding diagnostics in preparation for future pandemics is an issue. Governments worldwide have not made pandemic preparedness a financial priority, according to a 2019 report by the World Bank Group.[3] While the report said there was "increasing momentum" in many countries to create pandemic preparedness plans and identify weak points, it also pointed out that "little progress has been made in paying for these plans and integrating them into national budgets."

Inadequate testing capacity

Lab capacity is already limited in developing countries, which often don't have enough trained staff and supplies, and also lack adequate testing labs. Coupled with the lack of rapid diagnostic test kits that can be used in the field without training, delays in testing that allow disease to spread are inevitable. A deficiency of supplies and key reagents for testing kits was an issue during the outbreak of yellow fever in Nigeria in 2016-17.[2]

Developed countries also suffer from insufficient testing capacity, as we've seen in both the US and Canada during the current COVID-19 outbreak. A lack of supplies and key reagents for testing kits has been a critical problem in the US and other countries dealing with COVID-19, with the US only having 23 test kits per million people at one point and continually struggling with test backlogs.[4,5]

Lack of incentives for R&D between outbreaks

Now that COVID-19 has turned into a pandemic, governments around the world are pouring money into developing diagnostic tests for the coronavirus. But prior to the outbreak, overall funding in R&D relating to pandemic preparedness left something to be desired, according to the World Bank report. The report gave governments a yellow "traffic light" ranking when it came to "Mobilizing funding for R&D for new product development and to strengthen clinical research capacities" stating that "Global, regional, and national preparedness R&D is insufficient; innovative financing approaches are needed."[3]

Solutions for better diagnostic pandemic preparedness

The authors of the *BMJ Global Health* article say that solving these diagnostic challenges will involve many people in both public and private health care coordinating to implement "a holistic approach to diagnostics preparedness." Their key recommendations include:

- Boosting diagnostic capacity, including health care worker education and surveillance of priority pathogens
- Developing diagnostics that require minimal sample preparation and training, and developing platforms that can rapidly adopt new assays
- Establishing a coordinating body for diagnostic funding
- Creating business models that incentivize manufacturers by offsetting losses during non-outbreak years
- Providing funding for stockpiling of tests
- Expanding the network of expert personnel and labs to enable knowledge sharing and a rapid response during outbreaks
- Preselecting suppliers of diagnostic materials for outbreak situations
- Implementing surveillance laboratory networks
- Educating health care workers on the importance of real-time reporting
- Looking into how solutions to similar challenges in vaccine development could be expanded to cover diagnostics

Despite these recommendations being published over a year ago, it is clear, based on the current coronavirus pandemic, that there is still work to do in the area of diagnostic preparedness for pandemics. The best efforts of WHO and other health authorities seem to have fallen on deaf ears when it comes to encouraging governments to invest in diagnostics R&D.

At the same time, there are encouraging signs, based on how these public health groups and others are coordinating efforts to handle the challenges of COVID-19 so far. For example, the Foundation for Innovative New Diagnostics (FIND), WHO, and their partners are working together to help low- and middle-income countries with "training, technical assistance, and capacity building to ensure access to accurate and high-quality diagnostic testing for SARS-CoV-2. [6] The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), an international network of 28 major research funding organizations that helps ensure a quick response to outbreaks of infectious disease, is also coordinating with WHO to support the creation of better COVID-19 diagnostics.

> "Solving these diagnostic challenges will involve many people in both public and private health care coordinating to implement a holistic approach to diagnostics preparedness."

Hopefully, once the COVID-19 pandemic has subsided, governments will recognize the critical need to fund rapid diagnostics and act accordingly to support the efforts of public health and research groups worldwide in preparing for the next pandemic.

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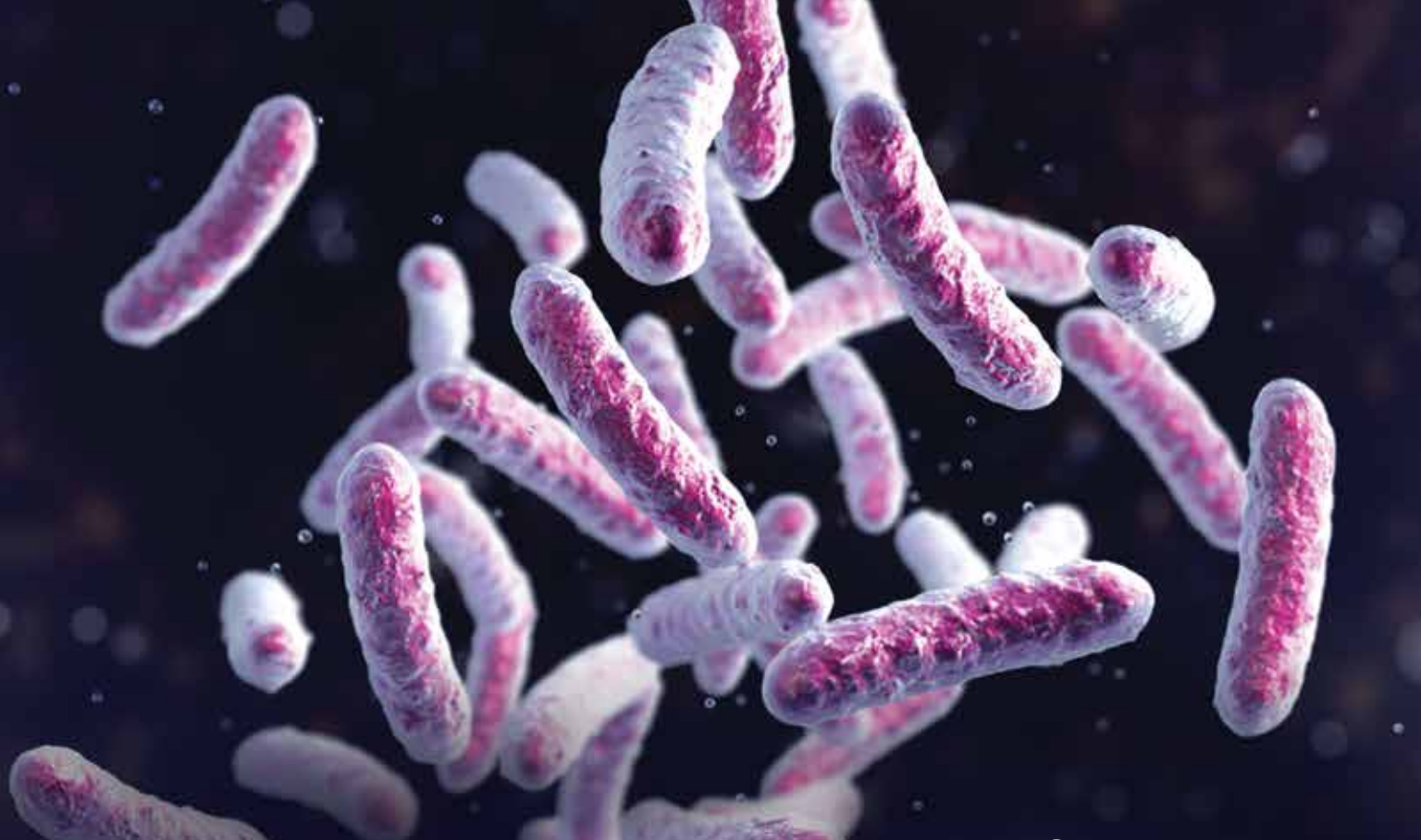
***Rachel Muenz** is an associate editor at* Clinical Lab Manager.



Molecular Tools for Tuberculosis Testing

NOVEL DIAGNOSTIC APPROACHES FOR ACCURATE, COMPREHENSIVE, AND ACCELERATED RESULTS

by Raeesa Gupte, PhD

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (MTB), is a major global health problem. According to the World Health Organization (WHO), an estimated 10 million people contracted TB in 2018 and 1.5 million died of it.[1] Approximately 30 countries contribute to 87 percent of the global TB burden. In these countries, TB is commonly diagnosed using sputum smear microscopy and bacterial culture.

Smear microscopy produces rapid results but is limited by low sensitivity and specificity. It can neither distinguish between *Mycobacterium* species nor provide information on drug resistance. More sensitive than microscopy, culture remains the gold standard in TB detection. However, it requires adequate laboratory infrastructure and takes four to eight weeks to produce conclusive results.

Rapid and accurate detection is crucial in initiating treatment and reducing disease transmission. Advances in microbiology and genetics have led to the development of novel molecular diagnostic tools.

Molecular diagnostic tests

Molecular diagnostics are more accurate than microscopy and significantly faster than culture methods. They are capable of detecting mutations associated with

drug resistance and may also be used on non-respiratory specimens. Commercially available and upcoming molecular testing technologies are discussed below.

Nucleic acid amplification tests (NAATs)

Polymerase chain reaction (PCR) or reverse transcriptase PCR (RT-PCR) are among the most common molecular diagnostic tests for TB. Several commercial and laboratory-developed tests are available. These tests target sequences from genes encoding 16S rRNA, IS6110, hsp65, and dnaJ among others.[2,3] The WHO recommends using a MTB/RIF test as the initial diagnostic test for simultaneous detection of TB and drug resistance. The assay amplifies a fragment of the ß subunit of MTB RNA polymerase (rpoB) and probes it for rifampicin resistance-associated mutations. In a systematic review of 27 studies, the MTB/RIF test demonstrated pooled specificity of 99 percent and 89 percent sensitivity in smear positive samples or 67 percent sensitivity in smear-negative samples. Pooled sensitivity of the assay for smear-positive and culture-positive samples was 98 percent.[4] It had a pooled sensitivity of 94 percent and sensitivity of 98 percent in detecting rifampicin resistance. The test provides results in less than two hours.

Unlike PCR-based assays, loop-mediated isothermal amplification (LAMP) does not require a thermal cycler. LAMP is a highly sensitive method that amplifies target DNA at a constant temperature using a set of four specially designed primers and DNA polymerase with strand displacement activity. Due to the large output of amplification products, the result can be qualitatively observed by the naked eye or quantified using turbidity, colorimetry, or fluorescence detection methods.[5] A meta-analysis of 13 studies showed that TB-LAMP had similar specificity but higher sensitivity than both sputum smear microscopy and the MTB/RIF assay.[6] Therefore, the WHO recommends using this test as a replacement for microscopy during the diagnosis of pulmonary TB in symptomatic adults. Several LAMP-based assays have now been developed that target the *gyrB*, *rrs*, *rim*, *IS6110*, *hspX*, *mpb64* and *sdaA* genes of MTB. These tests can provide results within one hour.

Whole genome sequencing (WGS)

WGS enables detection of single nucleotide polymorphisms, insertions, and deletions in the entire genome of an organism. Therefore, it can provide information on disease transmission, bacterial evolution, and drug resistance. For WGS analysis, MTB strains obtained from clinical samples (such as sputum) are grown in culture. DNA is extracted from the cultured isolates. Following enzymatic processing, the multiple DNA fragments obtained are sequenced in parallel. The individual fragments are then mapped to a reference genome in order to identify specific alterations in the genetic code of the test organism.[7]

> "Rapid and accurate detection is crucial in initiating treatment and reducing disease transmission."

A systematic review of 20 publications reported high specificity and sensitivity (pooled estimates over 95 percent) of WGS in detecting resistance to the first-line drugs rifampicin and isoniazid.[8] However, these studies rely on bacterial culture that may delay results by several weeks. Direct WGS of sputum provided results on drug resistance within five days, compared to 11 days using cultured isolates. However, only 74 percent of sputum samples generated whole genomes of adequate quality compared to 100 percent of cultured samples.[9] Therefore, the diagnostic workflow needs to be optimized before WGS is routinely used for clinical decisions.

CRISPR-based diagnostics

Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) proteins have been extensively used for gene editing owing to their ability to function as molecular scissors. The discovery of the Cas12 and Cas13 family of proteins has spurred the development of CRISPR-based diagnostics. These diagnostics harness the "collateral cleavage" potential of Cas12 and Cas13. The endonuclease activity of Cas12 cleaves DNA and Cas13 cleaves RNA. The Cas proteins are coupled to guide RNA that targets a complementary sequence within a pathogen's genome. The Cas proteins are activated once they cleave the targeted nucleotide sequence and continue to cleave nearby non-targeted DNA or RNA sequences. The reaction is visualized by introducing DNA and RNA reporters that fluoresce when cleaved.

A CRISPR-MTB assay was developed recently.[10] DNA extracted from clinical samples was amplified at

constant temperature using recombinase polymerase amplification. The amplified product was added to the CRISPR reaction mix containing Cas12a, guide RNA, and fluorescent reporter DNA. In order to enhance test sensitivity, guide RNA targeted the *IS6110* gene since each MTB genome contains six to 10 copies of this gene. The CRISPR-MTB assay detected pulmonary TB with 90 percent sensitivity and had overall specificity of 98 percent. Results were obtained within 1.5 hours on average. Efforts are underway to develop a lateral flow assay that uses a simple paper test strip for point-of-care testing in low resource settings.[11]

Pros and cons of molecular testing technologies

Rapid turn-around time of NAAT systems facilitates testing and treatment initiation in the same visit, reducing cases of loss to follow up. LAMP tests are cost-effective and do not need specially trained personnel or elaborate infrastructure. This makes them ideal for use in resource-limited settings for point-of-care testing. Although several NAATs are available for testing MTB resistance to first-line drugs, drug susceptibility tests for second-line agents are limited. In countries with high TB burden, second-line drugs become crucial in treatment. With the ability to comprehensively detect multiple drug resistance genes at once, WGS may play an important role in such clinical settings.

"Culture remains the gold standard in TB detection; however, it requires adequate laboratory infrastructure and takes four to eight weeks to produce conclusive results."

The major limitation of PCR-based NAATs such as the MTB/RIF assay is their need for specialized instruments like thermal cyclers. The cost of test cartridges, advanced instrumentation, and availability of trained personnel are drawbacks for resource-limited countries with high TB burden. Similarly, WGS suffers from high costs associated with computing infrastructure and bioinformatics training. No commercial WGS kits are available and the diagnostic workflow needs to be optimized. In addition, the slow growth of bacterial culture may delay treatment initiation and lead to poor health outcomes. However, enrichment of DNA directly from clinical samples is challenging. Lastly, CRISPR-based diagnostic tests are still in their infancy. They need to undergo extensive optimization and standardization before their clinical validity is established.

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***Raeesa Gupte**, PhD, is a freelance science writer and editor specializing in evidence-based medicine, neurological disorders, and translational diagnostics.*

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PREVENTING FALSE POSITIVES AND FALSE NEGATIVES IN PCR

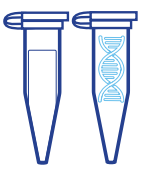
PCR IS A SENSITIVE TECHNIQUE THAT REQUIRES APPROPRIATE PRECAUTIONS AND CONTROLS TO ENSURE ACCURATE RESULTS

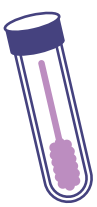
Polymerase chain reaction (PCR) and reverse transcription PCR (RT-PCR) offer an extremely high level of sensitivity, and as such, are suitable as diagnostic assays for viral and bacterial pathogens, as well as for genetic testing applications. However, given the high sensitivity of these techniques, there is the risk of false positive results (detection of non-targeted sequences) and false negative results (failure to detect targeted sequences). Fortunately, there are many ways to reduce the risk of false positives and false negatives to ensure more accurate results.

FALSE POSITIVES

Factors Contributing to False Positives

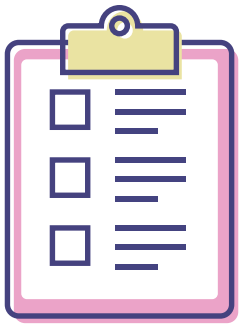
- The large number of target organisms present in clinical specimens.
- Repeated amplification of the same target sequence, which leads to accumulation of amplification products in the laboratory environment.
- Introduction of contaminants during collection, transport, or processing.





PREVENTION

- Include a negative control to ensure no contaminating nucleic acids have been introduced to the master mix. Obtaining a negative result with the control indicates no contamination has occurred.
- Designate separate areas of the laboratory for sample and reagent preparation, amplification, and analysis, and implement a unidirectional workflow.
- Maintain a clean workspace and clean all surfaces in the PCR area with 70% ethanol.
- Ultraviolet (UV) irradiation may be used to inactivate contaminating nucleic acids present on supplies via thymidine dimer formation.
- Enzymatic methods, including the use of Uracil-DNA glycosylase (UNG), are effective for contamination control. UNG specifically degrades products following PCR, leaving only native nucleic acid templates for amplification.
- Perform routine cleaning and extensive monitoring, including performing PCR on all reagents, and work station swabs.
- Adhere to proper sampling and handling techniques, such as wearing gloves, using sterile collection instruments and vessels (and avoiding touching the inside), and maintaining proper temperature control throughout transport.

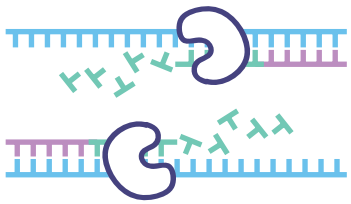


FALSE NEGATIVES

Factors Contributing to False Negatives

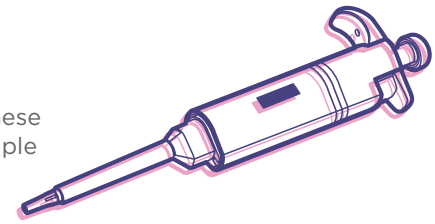
- Improper sample collection/transport.
- Nucleic acid degradation during shipping or storage.
- Poorly timed specimen collection.
- Errors in sample extraction.

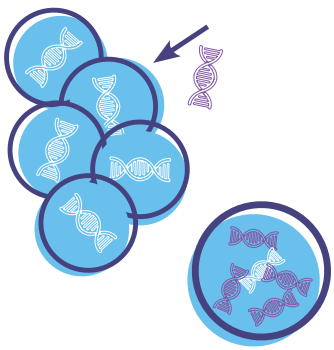
- Presence of amplification inhibitors in the specimen, which interfere at different steps throughout PCR analysis. Inhibition is a leading cause of assay failure as inhibitors may interact directly with DNA or block polymerase activity.
  - Inhibitors found in blood, serum, or plasma samples: immunoglobulin G (IgG), hemoglobin, lactoferrin, anticoagulants such as heparin, hormones, and antiviral substances such as acyclovir.
  - Inhibitors found in urine samples: urea.
  - Inhibitors found in stool and fecal samples: polysaccharides, chlorophyll, bile salts, urea, glycolipids, hemoglobin, and heparin.



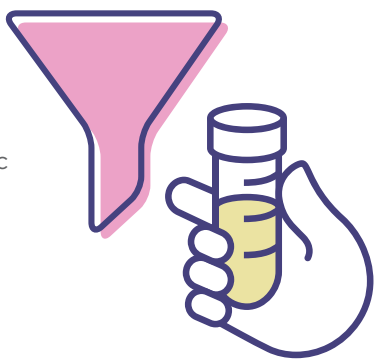
PREVENTION

- Include an endogenous internal positive control. These genes occur within the specimen (β-actin, for example is a host genome sequence).

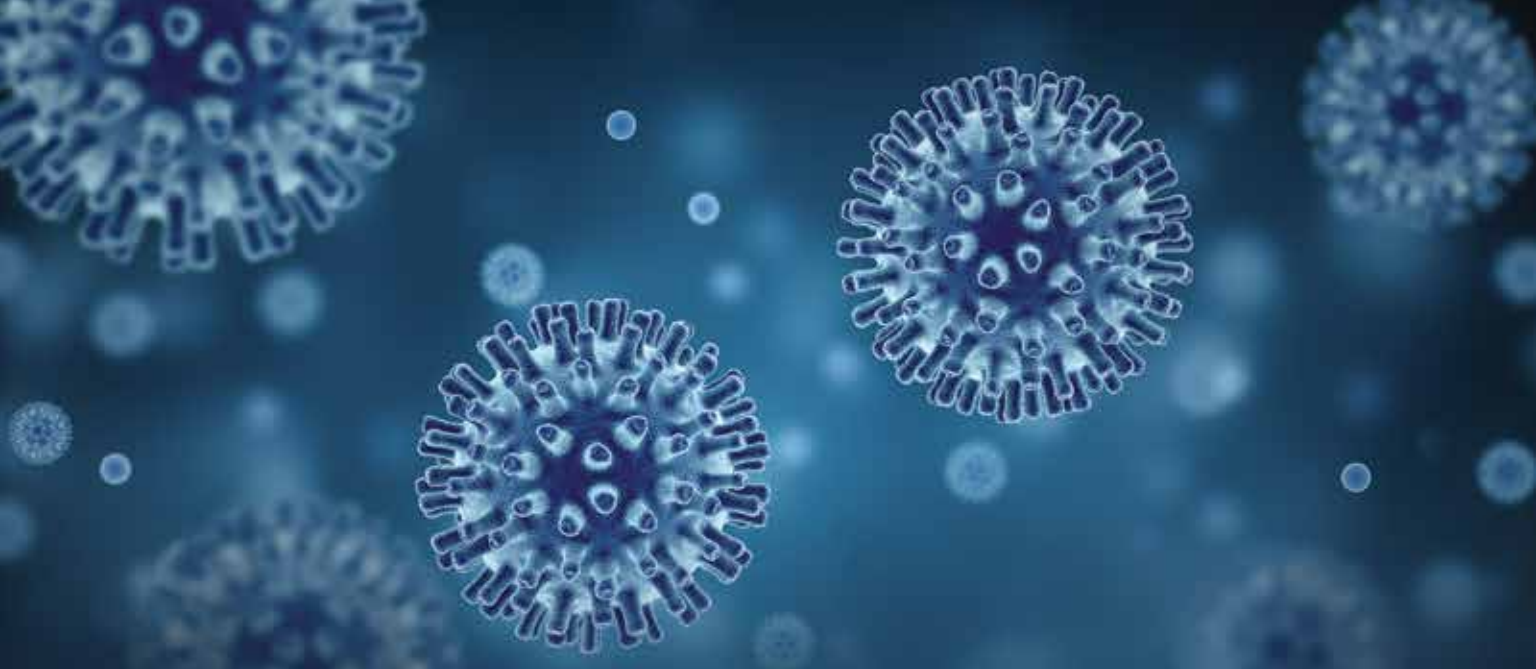




- Spike samples with an exogenous internal control. These may be homologous, consisting of an artificial primer template and the same primer binding sites as the target pathogen sequence, or heterologous, designed with unique primers and probes.



- Remove inhibitors:
  - Employ appropriate sample processing and nucleic acid extraction methods.
  - Select an appropriate DNA polymerase to reduce the risk of inhibitors impairing polymerase enzyme activity.
  - Urea may be removed from urine samples with dialysis or ultrafiltration.



Influenza Diagnostic Methods: RT-PCR vs. RIDTs

RT-PCR IS CONSIDERED THE GOLD STANDARD, BUT CERTAIN SITUATIONS MAY CALL FOR THE USE OF RIDTS **by Suzanne Leech, PhD**

Rapid and accurate diagnosis of influenza can save lives by facilitating early treatment, save money by preventing inappropriate treatment, and prevent epidemics by minimizing viral transmission.

For accurate diagnosis, reverse transcription PCR (RT-PCR) is considered the gold standard. Rapid influenza diagnostic tests (RIDTs), although fast and convenient, often produce false-negative results. In fact, the WHO recommends that "in general, the use of RIDTs in hospitalized patients should not be encouraged where RT-PCR or immunofluorescence assays for influenza are available."

And yet, both the CDC and the WHO include RIDTs in their repertoire of recommended diagnostic tools. This article explores the two very different tests and discusses when and why clinicians choose one or the other.

Ease of use and portability

RIDTs are simple-to-use dipsticks, cards, or cassettes that do not require laboratory conditions or extensive training—a huge benefit to isolated clinics with minimal staff and laboratory equipment. Their size makes them easily transportable and, when kept between 4°C and 30°C, RIDTs are viable for around 18 months.

RT-PCR, in contrast, must be performed by highly trained staff using bulky, expensive equipment in dedicated laboratories. In the US, the tests must be performed at accredited clinical laboratories and in developing countries, clinics may need to send samples many miles to diagnostic centers.

Speed of diagnosis

The greatest benefit of the RIDTs is the short test time: less than 15 minutes, compared to one to eight hours for RT-PCR. RIDTs are point-of-care (POC) tests, so samples do not have to be sent to centralized laboratories; therefore, clinicians can start anti viral treatment much sooner, which is vital for high-risk patients. The CDC recommends that clinics should not wait for laboratory confirmation of influenza before beginning antiviral treatment.

Specificity and sensitivity

RT-PCR is considered the most accurate method of diagnosis, with 90 to 100 percent sensitivity and specificity depending on the strain, patient age, and day of testing.[1] The PCR method may have slightly reduced sensitivity

after day three of infection in adults, but it performs better than other tests at this time.[2] By using primers specific to RNA sequences, RT-PCR can confirm influenza as well as distinguish between strains and subtypes. Further analysis can identify a strain's susceptibility to anti viral agents, a useful resource during an epidemic. However, laboratorians must update primers regularly to keep up with antigenic shift and maintain test reliability.

RIDTs have a specificity of 90 to 95 percent, resulting in few false-positives.[3] Their reported sensitivity varies from as low as 4.4 percent to 100 percent, and most often between 40 and 70 percent,[4] so false-negatives are common, especially during peak influenza seasons. RIDTs display much higher sensitivity if used within the first three days of infection, or within seven days for children. Most kits can distinguish between influenza A and B but not subtypes within A or B: In 2009, RIDTs could not distinguish pandemic H1N1 influenza A infection from the seasonal influenza A viruses.

Cost

RIDTs cost around $20 each, while RT-PCR tests are higher at $90, and real-time RT-PCR is significantly more. Transportation costs for isolated clinics increases the price of RT-PCR further. For many clinics in the developing world, RIDTs are the only affordable tests available.

In addition, a study of health insurance claims in the US revealed that use of antiviral drugs dropped by almost 50 percent when RIDTs were used to diagnose influenza compared to no clinical test.[5] The average cost of treatment when RIDTs were used was $62.46 compared to $192.83 after medical diagnosis without RIDTs. In 2003, the total medical cost of influenza in the US was an estimated $10.4 billion; clearly, further use of RIDTs could make a substantial impact on this expenditure.

Controversies and limitations

The high variance in RIDT sensitivity is a result of myriad factors such as influenza type, viral titer, patient age-group, sample source, and experience and ability of the tester. Studies into RIDTs often vary in these factors, as well as in the RIDT kit used. It is very difficult, therefore, to assess the sensitivity accurately until more standardized studies are deployed.

Several new RIDTs have been developed with improved sensitivity. On the other hand, faster and more portable POC tests based on nucleic acid amplification technologies may someday provide clinic-based molecular testing comparable to RT-PCR. At around $50 per test, these POC tests are more expensive than RIDTs and require accurate and careful sample collection and expensive reading equipment. Sensitivities for these rapid molecular tests are more variable than traditional RT-PCR tests, so are not yet considered an adequate replacement.

Choice of test

Ultimately, the choice between the RIDT and RT-PCR methods is based on several factors. In an understaffed, ill-equipped clinic, or in the peak of an epidemic, RIDTs may be employed to confirm the influenza type for some of the patients presenting with influenza-like symptoms, but with the majority receiving treatment without confirmed testing. In such a situation, samples are collected for laboratory testing, using the RT-PCR gold standard to confirm infection type and subtype, for future reference and for use in epidemic recording and control.

In less manic times, RIDTs are a useful, inexpensive, and rapid method of confirming influenza, and in some clinics, they may be the only diagnostic tool available. When a negative RIDT result is obtained, clinicians must take other factors—such as exposure, risk of infection, severity of illness, and differential diagnosis—into account when deciding whether treatment or further testing is required.

Researchers have yet to confirm the benefits that newer tests can provide. If they are able to overcome the limitations of the current methods successfully, they will inevitably become the next must-have influenza diagnostic tools

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***Suzanne Leech**, PhD, is a freelance science and medical writer. She has a background in parasitology, multiple sclerosis research, and clinical chemistry research and development.*

SARSTEDT

THE KEY TO LOWERING DIAGNOSTIC BLOOD LOSS

Patient blood management encompasses several strategies to minimize blood loss, but the most obvious solution is also the most effective

It's a surprisingly common story in ICUs across the country: A patient is admitted for an illness, receives blood draw after blood draw for diagnostics tests during the stay, and winds up with hospital-acquired anemia. In fact, up to 85 percent of patients that spend more than a week in the ICU require a blood transfusion.[1] To reduce this massive need for transfusions during hospital stays, many hospitals are making great effort to streamline various aspects of patient blood collection.

Hospitals are intent on reducing blood transfusions because they can harm patients and they're costly. The patients most likely to become anemic during a hospital stay belong to the populations most vulnerable to the risks associated with transfusions, such as children and the elderly. Those risks include transmission of infectious diseases and adverse reactions to transfusions.[2,3] The costs associated with transfusions arise from the direct cost of allogeneic blood units, extended hospital stays for patients receiving transfusions, extra work in blood transfusion labs and nursing units, and potential costs of adverse events related to the transfusion.

Patient blood management (PBM) has become a popular term around hospitals. The broad aim of PBM is to improve patient care, and its specific goal is to ensure that individuals tasked with handling patient blood do so in ways that maintain hemoglobin concentrations and minimize anemia and the need for transfusions. PBM efforts commonly implemented by hospitals include: finding biomarkers of anemia-induced tissue hypoxia to detect it earlier; better defining the thresholds for treating anemic patients with transfusion for specific patient populations; better use of banked specimens; reduction of the number of rejected specimens for laboratory testing due to specimen integrity issues; and reduction of diagnostic blood volumes.[4] While all of these PBM strategies have merit, arguably the simplest way to reduce anemia and the subsequent need for transfusion is to collect less blood from patients in the first place.

Staggering amounts of blood get collected from hospital patients for diagnostic testing. Critically ill patients can lose 40 to 70 ml of blood per day and between 300 and 500 ml over a week-long hospital stay. Far less blood is actually required—as little as 10-20 µl per test is sufficient for diagnostic tests, using modern instruments.

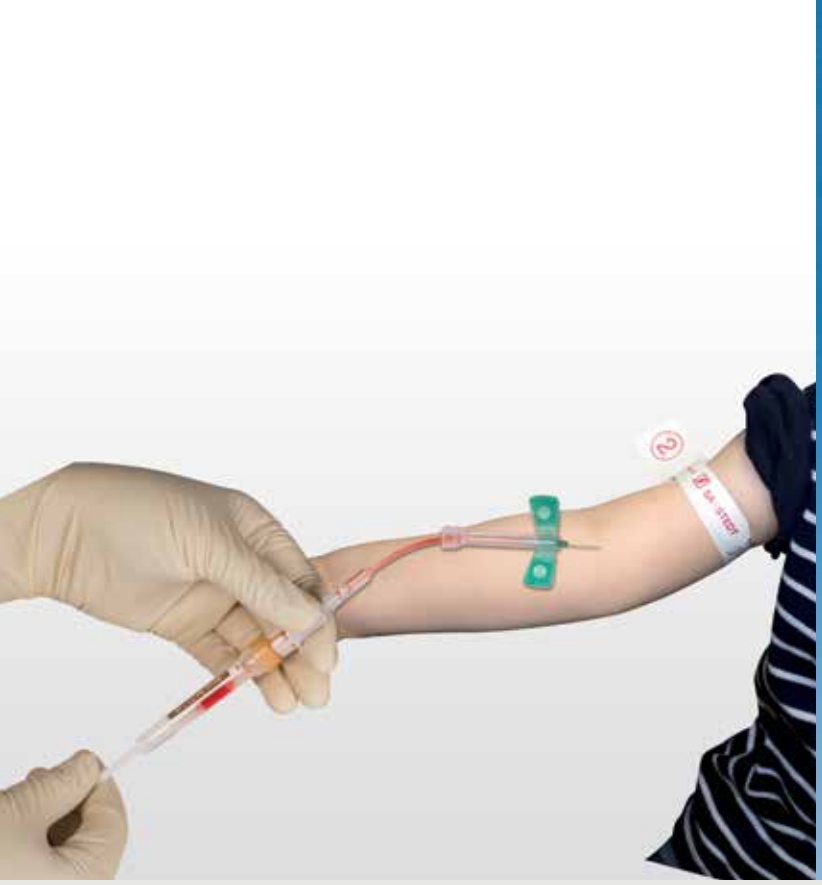
Up to 85 percent of patients that spend more than a week in the ICU develop hospital-acquired anemia and require a blood transfusion.

Yet it is common practice to fill large-volume tubes, regardless of which tests have been ordered or the amount of sample required for them, so excess blood collection is inevitable. However, there is now growing focus, especially among children's hospitals, on lowering the blood volumes collected.

The size of tube used for collection largely dictates the volume of blood that patients lose. Standard tubes lead to unnecessarily high levels of diagnostic blood loss; conversely, using the smallest tube size available serves to minimize diagnostic blood loss. Although one study found that smaller blood collection tubes lead to increased error rates,[5] the recollection rate is also higher when using larger tubes; thus, smaller tubes result in overall lower blood volumes collected from patients.

Ranging from 1.1 ml to 1.8 ml, SARSTEDT's S-Monovette® PBM tubes collect over 40 percent less blood volume than traditional tubes. These small blood volumes get drawn directly into a treated syringe-like tube, which enables a more controlled, gentle collection than a pre-evacuated tube and doesn't require subsequent transfer compared to a standard syringe. Filling the 1.1 ml S-Monovette® halfway brings volumes down to what could previously only be achieved with capillary collection, but with the added benefits of obtaining high-quality venous blood without compromising the specimen or introducing additional handling steps. The low-volume tubes, either directly or when placed into carrier tubes, conform to standard dimensions, allowing the S-Monovette® to be easily adapted to analyzers already in the lab.

Hospitals that adopt small-volume tubes reduce diagnostic blood loss, which in turn lowers the incidence of hospital-acquired anemia among patients and serves to decrease transfusion rates.[6] Better PBM with the help of small-volume tubes can therefore enable hospitals to achieve two of their most critical aims: to save money and to improve patient safety.



Patient blood management (PBM) aims to ensure that individuals tasked with handling patient blood do so in ways that maintain hemoglobin concentrations and minimize anemia and the need for transfusions.

Small-volume tubes serve to minimize diagnostic blood loss. SARSTEDT's S-Monovette® PBM tubes collect over 40 percent less blood volume than traditional tubes, helping hospitals reduce diagnostic blood loss and, ultimately, decrease transfusion rates.

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Employee Engagement:
The Role of the Laboratory Leader

KEEPING EMPLOYEES ENGAGED IS MORE THAN A NUMBERS GAME

by Patty Eschliman, MHA, MLS(ASCP)DLM

Every year, the employee engagement survey rolls around. During this time, I think back to everything my clinical laboratory team has accomplished over the year and feel pretty good about their engagement. Why, then, do the survey results not always align with my own analysis?

Two years ago, I overheard my niece, a frustrated teacher, complain that her creativity in the classroom had been replaced with a demand to meet state testing scores. This "teach to test" mentality made me wonder if I had lost sight of my team in my quest for numbers. It was that day that I adopted a new approach to leadership—one focused on building meaningful relationships with each and every member on my team. And one that did not rely on employee engagement surveys.

The role of the leader

Numerous studies have identified the impact a leader can have on an employee's level of mental and physical health. A recent survey by Gallup of more than one million US workers found that 75 percent of those who voluntarily left their jobs did so not because of job dissatisfaction but because of their managers.[1] It is clear that the interpersonal relationships and the culture created by you as a leader can either encourage self-determination or cause distrust and a sense of hopelessness. In fact, another survey of 90,000 workers found that the primary element that drives employee engagement is the belief that the leader cares about the employee's wellbeing.[2]

Building relationships with employees is totally within your control as a leader. Showing your team gratitude through genuine acts of caring makes them feel appreciated. Never underestimate the value of a hand-written thank you note mailed to your team member's home. Get to know each member on your team and in doing so, become comfortable with vulnerability; it is impossible to build a relationship with someone if you are not willing to share. Every morning at the end of our shift change huddle, we do a gratitude lightning round. Everyone around the circle shares one thing they are grateful for. It has changed us. The entire team now knows the everyday joys, struggles, fears, and celebrations of their teammates as well as mine. It builds trust and connection and allows the team to see each other as flawed, yet lovable human beings. Developing trust within your team is essential to establishing team loyalty, job satisfaction, and connectedness. All of these, in turn, drive employee retention.

Starting off on the right foot

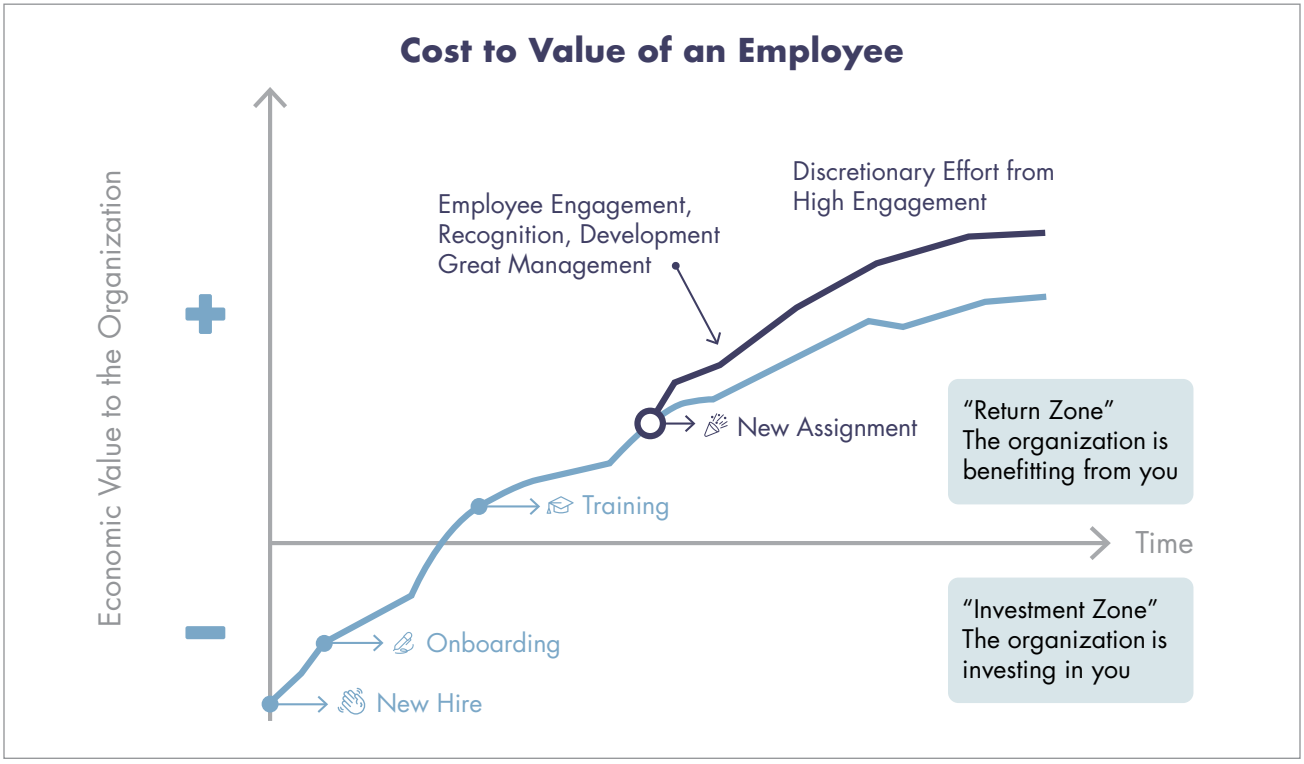
With the ever-increasing shortage of medical laboratory professionals, employee retention has never been more important. Starting in 1970, the number of accredited US medical laboratory training programs, both MLS and MLT, declined from nearly 1,000 to less than 450 in 2006.[3] It wasn't until 2008 that programs began to rebound, but it has not been enough. According to the National Accrediting Agency for Clinical Laboratory Science, the number of MLS/MLT accredited programs in 2019 had only reached 476—an addition of 26 programs in 13 years.[4] This decline in training programs does not paint a pretty picture for the future of laboratory staffing.

"With the ever-increasing shortage of medical laboratory professionals, employee retention has never been more important."

While hiring the first warm body may be tempting, it is important to screen for relationship potential during the interview process. Remain protective of your team by searching for a good personality fit. Quality laboratory skills are obviously important, but these skills can be taught; attitude, positive energy, and a desire to work in teams cannot.

Once you find and hire that employee, the onboarding process will make an immediate impact on whether or not the new team member feels like he or she belongs. A sense of belonging reduces anxiety, builds trust, and gives individuals permission to be themselves. This, in turn, fosters honest communication and authentic relationship building.

The graph on the next page shows what happens to new employees if, shortly after training, they are tasked with an assignment or responsibility.[5] Being handed projects demonstrates trust and encouragement for new employees and you can see the impact it has on their level of engagement. Greater engagement builds confidence, which positively impacts the team by improving morale and departmental success. Anticipating this opportunity and choosing a project ahead of time based on the skills and desires of the new employee is imperative for savvy leaders committed to employee engagement.



▲Source: Bersin, Josh. "Employee retention now a big issue: Why the tide has turned." *Bersin by Deloitte* (2013).

Continued engagement

If you currently work as a clinical laboratory professional, you will undoubtedly agree that there are few things more meaningful than providing patients with medical answers and helping clinicians make appropriate patient care decisions. It is unfortunate but very common for clinical laboratory staff to lose sight of the meaning in their work. Most of this misdirection comes from the way clinical laboratory staff are sometimes treated by non-lab personnel. Those who do not understand the level of training and knowledge it takes to perform high-quality medical lab testing often view it as a commodity. This is a prime opportunity to educate.

> "A leader must publicly celebrate his or her team's accomplishments at every opportunity—not just during Lab Week."

A leader must publicly celebrate his or her team's accomplishments at every opportunity—not just during Lab Week. Building relationships outside of the lab and thereby creating understanding of who we are and what we do increases respect and improves behavior. Have new clinical hires tour the lab. Engage your team to sit on interdisciplinary task forces or act as non-lab department liaisons, creating presentations that foster the collaboration needed to meet the needs of patients. It is no longer an option to stay in the basement. We do great work and it is up to us to shine the light!

Providing opportunities for career growth is another engagement driver. It used to be that several positions in the lab allowed employees an opportunity for advancement. Now, much of the laboratory leadership ladder is gone. There are fewer bench leads, fewer supervisors, and sometimes only one manager. If this is your situation, you must look at other ways of developing intrinsic motivation. One idea is to create a ladder of accomplishments where scientists can achieve different promotional levels by engaging in projects of incremental impact. At the first level, a project

would have a positive impact for the laboratory department. Next is a project that creates value for the hospital, then the health care system, and at the last level, the laboratory industry. This strategy encourages laboratory quality, hospital and system efficiencies, and professional growth while also building relationships and encouraging volunteerism on a national level. Incorporate the organization's core values into these achievements and you now have a recipe for company loyalty and retention. Sprinkle in a pay raise at each level and you will have an added layer of extrinsic motivation on top of the employee's internal drive to succeed.

"One of the most challenging aspects of leadership is knowing who can be coached up to their full potential and who needs to be let go."

Make sure employees have plenty of opportunities for learning. Even if you do not have the funds to send someone to a conference, it takes very few resources to put together a PowerPoint and teach your team new skills. Bring in speakers from other hospitals to share their successes or subscribe to an online education program.

An employee's engagement is heavily influenced by the attitudes of other team members. Working alongside committed and happy people is just, well, more engaging. A recent Gallup survey found that only 34 percent of the US working population over the age of 18 is fully engaged while 50 percent is not.[6] Who is left? The 16 percent that are actively disengaged. These are the disrupters on your team that are preventing the unengaged from moving toward full engagement and placing the fully engaged at risk.

One of the most challenging aspects of leadership is knowing who can be coached up to their full potential and who needs to be let go. Up to 80 percent of your time can be spent on trying to change those who either refuse or cannot change.[7] This only leaves 20 percent of your time to show gratitude and develop positive relationships in your team. Do your best to flip these numbers around. The staff that jump at the challenge and become engaged deserve your attention and recognition. Not giving in and keeping the pressure on for those who do not engage should eventually lead to your disciplinary action programs where most people self-select and leave before termination.

Being a leader that is focused on building meaningful relationships and creating a culture of open communication where co-workers are appreciated, and all contributions are valued, will encourage engagement and create a personal bond that makes employees want to stay. This won't stay as a secret for long! As word spreads, it will also create a positive reputation within your community and act as a recruiting tool for others who want to join such a welcoming and quality-driven team.

Moving away from the numbers game and focusing instead on building authentic caring relationships within my team has paid off. Incidentally, my employee engagement scores have increased significantly two years in a row! But more importantly, I can see their engagement every day—my team is much more cohesive, they support each other, there are fewer patient errors, and I have far fewer attendance issues. I also enjoy hearing their laughter and friendly banter.

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***Patty Eschliman** is a laboratory manager at Saint Luke's South Hospital in Overland Park, KS. With more than 35 years of laboratory experience, she also serves as a certified professional coach and energy leadership master practitioner.*

Getting on Track with Quality Assessments

LABORATORIES OFTEN STRUGGLE WITH QUALITY ASSESSMENTS BECAUSE THEY DON'T FULLY UNDERSTAND THE IMPACT THESE REVIEWS CAN HAVE ON PATIENT CARE

by Margaret E. Blaetz, CLC, MLT(AMT), CCCP(AAPOL)

An estimated 70 percent of health care decisions are based on laboratory test results. To ensure that all test results are as accurate as possible, the performing laboratory is required to follow certain protocols and practices outlined by the federal government, including those related to laboratory quality.

Some laboratories struggle with quality assessments because they don't fully understand the benefit and impact these reviews can have on patient care. This article will break down quality assessments in simple terms to get you started on the right track.

"A quality assessment is more than just a routine check of activities to assess if they were performed correctly; it should assess how all activities are performed and how they can be improved."

Laboratory quality

Clinical Laboratory Improvement Act (CLIA) 42 CFR 493 laboratory requirements state that each laboratory issued a certificate must maintain a quality assurance and quality control program adequate and appropriate for the validity and reliability of the laboratory examinations.[1] Updates made to CLIA in 2003 describe a quality systems approach to laboratory operations in which all the procedures, processes, policies, and resources in place to achieve high quality laboratory testing are bundled together and defined as quality systems.[1]

Accreditation agencies such as the Commission on Office Laboratory Accreditation (COLA) and the College of American Pathologists (CAP) define their requirements for quality with more detail. Quality assessment (QA), as defined by COLA, is a "planned, ongoing review process that observes and evaluates the quality of all laboratory-related processes and activities."[2] Quality management (QM), the quality program required by CAP, is designed to improve patient service through established activities and mechanisms to monitor and evaluate quality.

Performance of QA (COLA) requires careful observation and examination of the tasks that are performed every day. Data about these tasks are gathered over time and reviewed, with a focus on detecting patterns of events in an in-depth analysis and evaluation. A QA is more than just a routine check of activities to assess if they were performed correctly; it should assess how all activities are performed and how they can be improved.

CAP requires quality management to be a dynamic process which will be reviewed annually and updated as necessary. The goals of a QM program include the assessment that all the services provided by the laboratory and areas of the laboratory contribute to the overall delivery of excellent medical care.[3]

For the purposes of this article, the terms quality assessment, quality assurance, and quality management will be used interchangeably.

Performing quality assessments

When performing quality assessments, the laboratory processes requiring evaluation can be broken down into four sections: the pre-analytical, analytical, and post-analytical phases of testing, plus general laboratory actions not related directly to daily specimen testing.

The pre-analytical phase is the period before the samples are tested. It includes test ordering, specimen collection and labeling, and the transport, storage, and processing of the samples. Evaluation of quality in the pre-analytical period may be difficult because specimens are often collected outside the laboratory performing the testing. Detailed specimen collection and transportation instructions are critical. Specimens received outside of the specified collection and transportation instructions must be rejected and documented. Specimens that are incorrectly labeled should not be processed and the original collection site should be notified immediately. In order to improve quality in the pre-analytical phase, a strong educational component is needed to follow up on all rejected specimens. Documentation of these educational opportunities should be part of the quality assessment.

The analytical phase includes actions such as equipment calibration and maintenance, quality control, test performance, and result review and interpretation. Problems with any of these actions can have a negative impact on the quality of the result. Tight control of the quality of these processes can be maintained with supervisory oversight. In addition, many analyzers have lock-out features prohibiting test performance when calibration, maintenance, and quality control are not performed.

The post-analytical phase includes result reporting, corrected reports, record retention, and specimen retention (if applicable). Result reporting often refers to the time it takes for a test to be performed and results to be charted, also known as turnaround time. In hospital laboratories, turnaround time for STAT testing is high priority. However, in many physician office laboratories, turnaround time is less relevant because testing is performed immediately after collection. Selecting quality measures pertinent to your laboratory's quality measures should be a key focus when developing and reviewing QA.

In addition to the testing phases, general laboratory actions are also a critical part of quality in the laboratory. Assessment of personnel competency must be performed six months after new employees are trained, one year after training, and annually thereafter. Documentation of competency is required. Proficiency testing

Required Competency	How to Assess
Test performance	Direct observation
Test recording and reporting	Review records
Quality control, proficiency testing, and maintenance recording	Review records
Instrument maintenance	Direct observation
Blind sample testing	Proficiency testing
Problem solving skills	Review relevant documentation

▲Competency assessments must cover these six categories

records and results should be reviewed, and all corrective actions must be documented. All data interfaces must be validated before being placed into action. Interfaces should also be checked when updates or enhancements are installed and periodically in between. Additional factors such as safety, communication, and receipt of complaints should also be documented and investigated.

Quality review meetings

QA review meetings are an integral part of the quality assessment. During these meetings, QA is reviewed and discussed. When QA measures do not meet the expected threshold for acceptability, a plan of correction should be reviewed. Reviewing these measures and the associated plan of correction within a group provides an opportunity for others to offer suggestions and ideas to help improve the quality. Many actions within the laboratory cross from one department to another. Sharing information and ideas across the laboratory disciplines will help produce a positive outcome for the entire laboratory.

Evaluating all laboratory activities for a short period (e.g. monthly) is not enough to tell how the laboratory operates on an ongoing basis. Quality assessments should detect errors over a period of time (e.g. three, six, and nine-month intervals). These timeframes allow implementation of corrective actions that not only solve the initial problem but also prevent the errors from repeating. The laboratory can also review key areas more frequently and implement a method to catch errors before they happen.

When problems are found, ongoing observation should continue. A QA review should concentrate on the recurrent issues. Comparing performance over time should reveal if changes in staffing, workload, or other factors influence the problem. Ultimately, identifying the root cause of the problem will allow the laboratory to uncover what is really wrong. Since the quality program is designed to improve patient care, the program should continuously identify and monitor potential problems or concerns that may interfere with optimal services.

Currently selected quality monitors should be reviewed periodically. If the data indicate that the laboratory repeatedly meets or exceeds the performance benchmark, a new quality monitor should be selected, or the benchmark should be re-evaluated. Quality monitors do not only pertain to correction of errors; they should also be designed to lead to improvement of laboratory services.

Typically, the laboratory director delegates quality measures to the laboratory supervisory team or an individual assigned directly for these monitors. COLA suggests all laboratory technical and non-technical staff be included in the discussions about quality monitors. These staff members should have a full understanding of the processes performed during each phase of the workflow. They may have insight into problems that arise and should be able to offer suggestions for opportunities for improvement.

"Since the quality program is designed to improve patient care, the program should continuously identify and monitor potential problems or concerns that may interfere with optimal services."

Ultimately, whether the laboratory has a CLIA certificate of compliance or is accredited by COLA or CAP, the purpose is the same. The laboratory should evaluate all phases of testing—pre-analytic, analytic and post-analytic, as well as general laboratory actions—to ensure the highest quality of laboratory work and patient care.

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Margaret Blaetz *is a seasoned laboratorian with more than 30 years' experience. Margaret's background includes hospital, physician office, and reference laboratories throughout New Jersey. Margaret is the owner and technical consultant for East Coast Clinical Consultants, LLC.*


Sandrine Miller-Montgomery, PharmD, PhD

ASK THE EXPERT

Cancer and the Microbiome

by Laura M. Bolt, PhD

Sandrine Miller-Montgomery, PharmD, PhD, is the executive director for the Center for Microbiome Innovation and professor of the practice in bioengineering at the University of California (UC) San Diego. Her team is focused on expanding industry and academic collaborations of microbiome research in various domains such as clinical application (e.g. new drug pathway identification, novel diagnostic biomarkers identification), environmental science (e.g. identification of natural products from ocean sediment), and the consumer world (e.g. the role of nutrition and diet on our microbiome and metabolome). She also serves as president and CEO of Micronoma Inc.—a start-up out of UC San Diego focusing on early cancer detection using liquid biopsy targeting microbiome biomarkers.

Q: How does an individual's microbiome relate to their cancer susceptibility and cancer progression?

A: It's important to keep in mind that human beings do not have just one microbiome, they have many that are very different from each other. For example, the skin microbiome is affected by how much you wash your hands and what kind of lotion you're using. The gut microbiome is affected by what you eat. When we're talking about cancer and the microbiome, we are adding an additional level of microbiome study—the microbiome of the cancer, which is very different from the microbiome of the human body. And that's one of the main points in our recent *Nature* paper.

Q: What were the main findings of your recent *Nature* paper?

A: Our first discovery confirmed that cancer tissues are not sterile. Then, we also tested whether the microbiome of the cancer tissue was identical to the adjacent tissue. For lung cancer, we tested whether the microbiome of the lung cancer tissue was different from the microbiome of the healthy adjacent lung tissue. We found that the answer was yes—the cancer had a different microbial signature and the signature was very specific. Then we tried to determine if, by looking at the signature, we could tell if it was lung cancer or breast cancer or prostate cancer. We used a machine learning system and didn't tell the machine learning system the origin of the tissue we tested. We found that by looking only at the microbial signatures, we could differentiate not only between the cancer and the adjacent healthy tissue, but we could also differentiate which tissue the cancer is coming from. What was really the cherry on the cake was that when we started looking at blood samples, trying to see if we could detect microbial signatures in them, we found that in some cases, the model could predict with very high accuracy—98 percent or higher—what kind of cancer the patient had, whether it was lung or prostate. Our paper is about the various microbiomes that we have in the body's healthy tissue and in cancer tissue, and the specificity of cancer microbiomes. When it comes to cancer, our findings on the specificity of the microbial signature can enable us to develop a new diagnostic tool.

> "If we go back in history, microbes were ignored and not understood as being an important component of our interaction with the world, but little by little, their importance has been starting to emerge."

Q: Why are bacteria present in cancer tissues?

A: We don't know why the bacteria are there. For example, are they recruited by tumor tissue so that the bacteria can go and digest things invading their environment, like metabolites for example, or are they there because they are a defensive mechanism by the host? We don't know yet, and like everything in science, it is likely going to be dependent on the type of cancer. Some cancers may recruit, and some may be attacked by the bacteria. We will likely find it to be a combination of host defence and the tumor trying to shelter itself and thrive.

Q: Can you tell me about your company Micronoma?

A: I co-founded a company called Micronoma along with part of the team on the *Nature* paper. When we started looking at the data used in the paper early in 2018, we realized that it was probably wise to file a patent. So, we filed two IPs at the end of that year, and we started the company in 2019, while we were still generating more data for the paper. Advancing the use of microbial DNA in disease diagnostics is Micronoma's primary objective as a company. Micronoma is developing the diagnostic assay for cancer detection specifically from blood samples—an assay using microbial markers.

"We need to make sure that the entire oncological community understands that the microbiome of cancer is important, and that we need to avoid contamination of patient samples when they are removed from the body."

Q: How long have we known about the potential for an individual's microbiome to impact their cancer therapies?

A: If we go back in history, microbes were ignored and not understood as being an important component of our interaction with the world, but little by little, their importance has been starting to emerge and is starting to be explored in the microbiome field of science. The fact that the human tissue microbiome has an impact on cancer treatment was discovered in 2017, when it was demonstrated that certain drugs acted differently in responsive and non-responsive patients based on their microbiome profile. The impact of the microbiome on the effectiveness of cancer therapy has been emerging for a couple of years now. However, only the host microbiome was being looked at because, at the time, nobody had looked into the microbiome of the cancer. It was unknown that cancer had a microbiome of its own.

Q: Do you think the microbiome will be given consideration in clinical oncology practice in the future?

A: Now that we better understand the link between host tissue microbiota and cancer tissue microbiota, treatments that take these elements into consideration are going to be happening more and more. One of the first things is we need is to make sure that the entire oncological community understands that the microbiome of cancer is important, and that we need to avoid contamination of patient samples when they are removed from the body. This is not current practise because no one has known that microbes were important. When it comes to surgery, we hope that we're going to be able to make a difference in the way that samples are removed so that they are not contaminated and so that they can be analyzed more accurately for microbiota.

Q: What are the key research questions that need to be explored regarding cancer and the microbiome?

A: We need to focus not just on the cancer and the microbiome—we need to look at cancer and the microbiome with the host immune system entering the equation. Once we learn more about the host immune response to the microbiome and/or the cancer, that will likely be when we will be able to make further discovery. Right now, the research is focused on the host response as a stand-alone and trying to develop pathways of genetic offense. But now with our *Nature* paper, we're adding a new component, which is the cancer microbiome. The cancer microbiome may be triggering some immune responses or turning down some immune responses that are favorable to the cancer. That's likely where we'll find some new research pathways.

***Laura M. Bolt**, PhD, is a writer, researcher, and university-level educator based in Toronto, Canada. She holds degrees from the University of Cambridge (UK), University of Toronto, and Queen's University (Canada).*

solutions FOR THE CLINICAL LAB

From assays to analyzers, these are some of the latest and greatest products for use in clinical research and diagnostic labs

EKF β-KETONE AND GLUCOSE POC ANALYZER

EKF Diagnostics announced a new addition to its diabetes care portfolio in the US. The STAT-Site WB is a dual-use whole blood β-ketone and glucose meter for professional use in the management of diabetes. The new FDA CLIA-waived handheld analyzer reliably and efficiently delivers results within five to 10 seconds and can be used in point-of-care (POC) and certificate of waiver settings, such as physicians' offices, clinics, and other non-traditional laboratory locations. As a dual analyte measurement system, the STAT-Site WB can quantitatively measure β-ketone (beta-hydroxybutyrate or BHB) from both fresh capillary and venous whole blood in 10 seconds. In addition, it delivers quantitative measurements in five seconds for glucose in fresh capillary, venous, and also neonatal whole blood. Results are reported on its clear LCD screen and up to 400 can be stored in memory; these can be downloaded using a simple mini USB cable.

PERKINELMER PG-SEQ™ RAPID NON-INVASIVE PREIMPLANTATION GENETIC TESTING KIT

PerkinElmer, Inc. introduced its PG-Seq™ rapid non-invasive preimplantation genetic testing for aneuploidy (PGT-A) kit. This solution tests spent embryo culture media for chromosomal abnormalities during *in vitro* fertilization (IVF) treatment. PGT-A is used to identify viable embryos, so the transfer or storage of embryos with an incorrect number of chromosomes can be avoided, as those typically lead to failed IVF cycles. Traditionally, PGT-A requires a biopsy of a developing embryo by creating an opening in the outer coating prior to removal and testing of a few cells. However, recent studies have shown that an embryo releases small amounts of DNA into the culture media in which it is growing, allowing the surrounding fluid to be genetically tested instead. PerkinElmer's PG-Seq rapid non-invasive PGT-A kit is specifically designed for this type of sample, which enables embryos to remain fully intact. The new non-invasive kit tests the spent embryo culture media to accurately detect aneuploidies, as well as structural rearrangements, including unbalanced translocations and segmental errors. The kit is a modified version of the new PG-Seq rapid kit, a three-hour sample preparation workflow—less than half of the sample preparation time compared to the PG-Seq kit 2.0 workflow.

VERICHEM LABORATORIES LIQUID STABLE BILIRUBIN REFERENCE STANDARDS

A line of liquid stable, protein based, bilirubin reference materials is now available from Verichem Laboratories. The bilirubin standard kit and the optional bilirubin standard-level F are specifically designed and intended for CLIA calibration verification of total and direct bilirubin assays with any wet chemistry clinical testing systems. The ready-to-use bilirubin standards are treated as patient specimens, with no preparation or diluents required. All have had their assigned concentration levels verified with the Doumas reference method, and the included certificate of analysis provides verification data using pure crystalline bilirubin reference material. The standard's unique protein-based formulation, along with a set point design using CLSI EP06-A linearity protocol, are critical for the determination of the testing method's accuracy, sensitivity, linearity, and reportable range. All of the standard materials are conveniently packaged in amber serum vials with rubber-lined closures containing five milliliters of standard at each level. The bilirubin standard kit contains five concentration levels, while the extended range level F also contains two vials of with a 30 mg/dL concentration level.

ORTHO CLINICAL DIAGNOSTICS VITROS® XT 3400 CHEMISTRY SYSTEM

Ortho Clinical Diagnostics announced the launch and availability of the VITROS® XT 3400 Chemistry System, which completes the company's VITROS® XT Solutions, a comprehensive suite of lab solutions that help labs obtain consistently fast, accurate and reliable results. The new VITROS XT 3400 Chemistry System, like the VITROS XT 7600 Integrated System, simultaneously performs two tests frequently ordered together on one VITROS® XT MicroSlide, a multi-layered, postage-stamp sized slide which filters out lipids and proteins that can impact the quality of results, and offers an up-to-40 percent higher throughput than current slides. Double assay processing offers a 25 percent faster turnaround time on a common panel of assays, with an average processing time of 7.5 minutes compared to about 10 minutes for other industry options. Further, the XT MicroSlide allows for the lowest sample volume at 2.7µl. Reduction in external factors that may impact results further ensures the accuracy of VITROS XT Solutions results. Ortho's proprietary "dry" chemistry technology does not require water to run, eliminating the risk that poor water quality could impact results. In addition, single-use tips and cuvettes eliminate the risk for both sample and reagent carryover.

THERMO SCIENTIFIC CASCADION SM CLINICAL ANALYZER WITH 25-HYDROXY VITAMIN D ASSAY

Thermo Fisher Scientific announced that its Thermo Scientific Cascadion SM Clinical Analyzer is now commercially available in the US with the Cascadion SM 25-Hydroxy Vitamin D assay. Designed to deliver accurate, traceable measurements of vitamin D2 (ergocalciferol) and D3 (cholecalciferol), this serum assay reports total vitamin D results alongside its components. Clinical laboratories can now benefit from a complete system bringing the accuracy, sensitivity, and specificity benefits of Thermo Fisher's gold standard liquid chromatography-tandem mass spectrometry (LC-MS/MS) technology into routine clinical workflows. Incorporating sample processing, LC separation, and MS detection capabilities in a single solution, the Cascadion system is fully automated and enables load-up and walkaway sample management, eliminating the need for multiple connected components. The system offers end-to-end automation that is easy to use by any qualified laboratory personnel with minimal training, thus streamlining and optimizing the analytical process. The Cascadion system analyzes samples directly from qualified primary blood collection tubes, while the Cascadion SM 25-Hydroxy Vitamin D assay incorporates fully barcoded components, all traceable to a specific result. The vitamin D calibrators and controls are traceable according to the National Institute of Standards and Technology and assay calibration remains stable for up to 30 days.

SIEMENS HEALTHINEERS RAPIDPOINT® 500E BLOOD GAS ANALYZER

Siemens Healthineers announced that its latest critical care testing solution, the RAPIDPoint® 500e blood gas analyzer, has received clearance from the US FDA. The analyzer generates blood gas, electrolyte, metabolite, CO-oximetry, and neonatal bilirubin results, which are used to diagnose and monitor critically ill patients in the intensive care unit, operating room, or emergency room. Already available in countries requiring the CE mark, the RAPIDPoint 500e blood gas analyzer is now available for critical care testing in the US. The RAPIDPoint 500e blood gas analyzer is an essential instrument supporting COVID-19 response efforts, where blood gas testing plays a critical role in managing infected patients and monitoring their respiratory distress. Routine blood gas testing is also performed when patients require mechanical ventilation. Arterial blood gas tests provide the status of a patient's oxygenation levels and enable health care providers to determine whether adjustments to ventilator settings or other treatments are required. The RAPIDPoint 500e Blood Gas Analyzer integrates seamlessly into hospital networks with the Siemens Healthineers Point of Care Ecosystem™, which offers convenient, remote management of operators and devices located across multiple sites.

Big Ideas About the Clinical Industry

Single-Cell Proteomics: From Concept to Reality

Single-cell functional proteomics is accelerating cancer immunology research and could improve clinical outcomes

by Jing Zhou, MD, PHD

In the competitive world of cancer immunology, researchers are always searching for better ways to discover the cellular drivers of immune responses. Researchers have been dreaming about the ability to look at functional proteins from single cells for decades. The most urgent efforts in cancer immunology involve characterizing the complexity of tumor-immune interactions and include increasing tumor-antigen potency and modulating the host environment. These efforts are challenged by difficulty in detecting, understanding, and characterizing each immune cell's function.

The current technologies used to analyze cell function can miss key information that can only be obtained by single-cell functional proteomics. For example, bulk cytokine analysis averages serum protein information from all cells and masks cytokine-driven cellular response differences between those that respond to the therapy and those that do not. Flow cytometry-based systems are often used to surface phenotype for many surface markers or to look at a few blocked cytokines within the cell, without detecting what's truly being secreted from live single cells or identifying highly polyfunctional cell subsets that are associated with quality immune responses. To achieve the dream of complete cellular characterization, single-cell functional proteomics is needed to define the functional phenotype of each cell by the secreted, or extracellular, cytokines that dictate the response of each cell to the tumor.

Single-cell functional proteomics has uncovered unique correlative pre-clinical and clinical immune biomarkers, allowing researchers to differentiate mechanistic information in the competitive clinical world of immuno-oncology. In recent studies, single-cell functional biomarkers have revealed the cellular drivers of response in cancer immunology, gene edited cell therapies, and immune suppression from the host environment.

As the only functional cellular analysis tool with correlative biomarkers at single-cell resolution, IsoPlexis' highly multiplexed single-cell cytokine detection system has produced multiple correlative data sets in bispecifics, solid tumor checkpoint inhibitors, next generation cell therapies, and more. IsoPlexis' IsoLight system is the only technology able to detect the range of functional extracellular proteins (30+ cytokines) per live single cell. This single-cell functional phenotyping technology is essential to researchers looking for complete characterization of cellular response.

Many researchers and institutions are already using single-cell functional proteomics to help accelerate their cancer immunology programs by allowing them to make more informed decisions based on true cellular function. A recent commentary in the journal *Blood* concluded "by using single-cell analyses, heterogeneity may actually improve clinical outcomes."

***Jing Zhou**, MD, PhD, is the chief scientific officer at IsoPlexis. She has led multiple studies with various biopharma and trial center leaders, particularly in the immuno-oncology space, to develop single-cell polyfunctional metrics that can distinguish and predict patient response to CAR-T and antibody-based cancer immunotherapies. Prior to IsoPlexis, she was an immunologist at the Yale School of Medicine with expertise in defining phenotype and functionality of immune cells in diseased and healthy settings, with 30+ scientific publications in leading journals. Jing earned her medical degree in clinical medicine from Bengbu Medical College, MS and PhD in immunology from Shanghai Jiao Tong University, and has been the principal investigator of NIH, AHA, and Yale University grants.*

Inside a Clinical Lab During the COVID-19 Pandemic

Laboratories are challenged to maintain testing quality and efficiency amid an increased demand for service and the ever-changing dynamics of the pandemic

by Darryl Elzie, PsyD, MHA, MT(ASCP), CQA(ASQ)

The COVID-19 pandemic has challenged the health care industry across the spectrum in the effort to deliver patient care. The challenges have been particularly stark for our laboratory system, Sentara Healthcare, in meeting the need to provide accurate, reliable testing, not only for COVID-19, but also for all other patient testing. Amid the increasing demand for services and the ever-changing dynamics of the pandemic, our laboratory system's goal is to maintain testing quality and efficiency.

Our laboratory system quickly responded to the crisis by setting up a Laboratory Incident Command Center (LICC) to direct the flow of information across 18 labs. Clear communication is critical to the coordination of supplies and other resources across a large multi-state health care system, especially when the situation on the ground is continuously changing. Having a central command to discuss issues from different perspectives contributed to arriving at the best answers.

The LICC is manned by the laboratory administrative directors and the system quality coordinators. Numerous reports are generated daily and shared with the laboratory managers and administrators throughout the system through video conferencing. During the daily morning report, laboratory managers are provided information on the highlights, problems, and solutions to issues that arise in an attempt to provide testing for patients and answers to health care providers. The phone lines are continuously ringing with questions from all across the system.

The LICC also keeps track of the daily volume of tests and swabs used, the level of personal protective equipment supplies, and handles even small issues like a label printer not printing in the emergency room. With the shelter-in-place order from the state and the closing of schools, there have been additional staffing variables requiring solutions.

In the beginning, the issue of blood utilization was a concern. To avoid a possible blood shortage, elective surgeries were categorized on a tier system to prioritize only those needing to be performed to eliminate harm to patients. Another issue involving blood was that our health care system frequently promotes and assists the American Red Cross in blood drives. The blood drives usually involve mobile units; however, it was quickly noticed that using mobile units would reduce the number of people able to donate because of the need to practice social distancing. Fortunately, our local hotels and restaurants stepped up and volunteered their spaces for blood donation locations.

In response to the increased public demand for testing, our health care system set up four tents for drive-in public COVID-19 sample collection. Dedicated laboratory employees assist health care providers from our medical group in swabbing patients arriving to get tested for COVID-19. Despite inclement weather, these committed medical workers continue to provide essential services to the public.

Our laboratory system also decided to do something about one of the biggest problems of the pandemic—the lack of testing. Our molecular scientific director worked tirelessly to set up a lab in a former lab office with new equipment to start onsite testing. Despite experiencing the same obstacles as the rest of the nation in getting the reagents needed for testing, our laboratory was able to get an instrument validated and up and running in about a week. In addition, we've also begun implementing a plan to bring in a larger instrument to increase our testing capacity.

The laboratory professionals in our system have certainly answered the call of the nation in adapting and sacrificing to continuously provide quality patient care.

***Darryl Elzie**, PsyD, MHA, MT(ASCP), CQA(ASQ), has been an ASCP medical technologist for over 30 years and has been performing CAP inspections for 15+ years. He is also a certified quality auditor (ASQ). He currently works for Sentara Healthcare. Darryl provides laboratory quality oversight for four hospitals, one ambulatory care center, and supports laboratory quality throughout the Sentara system.*

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