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MEDICAL LABORATORY OBSERVER

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Henry Ford Health case study

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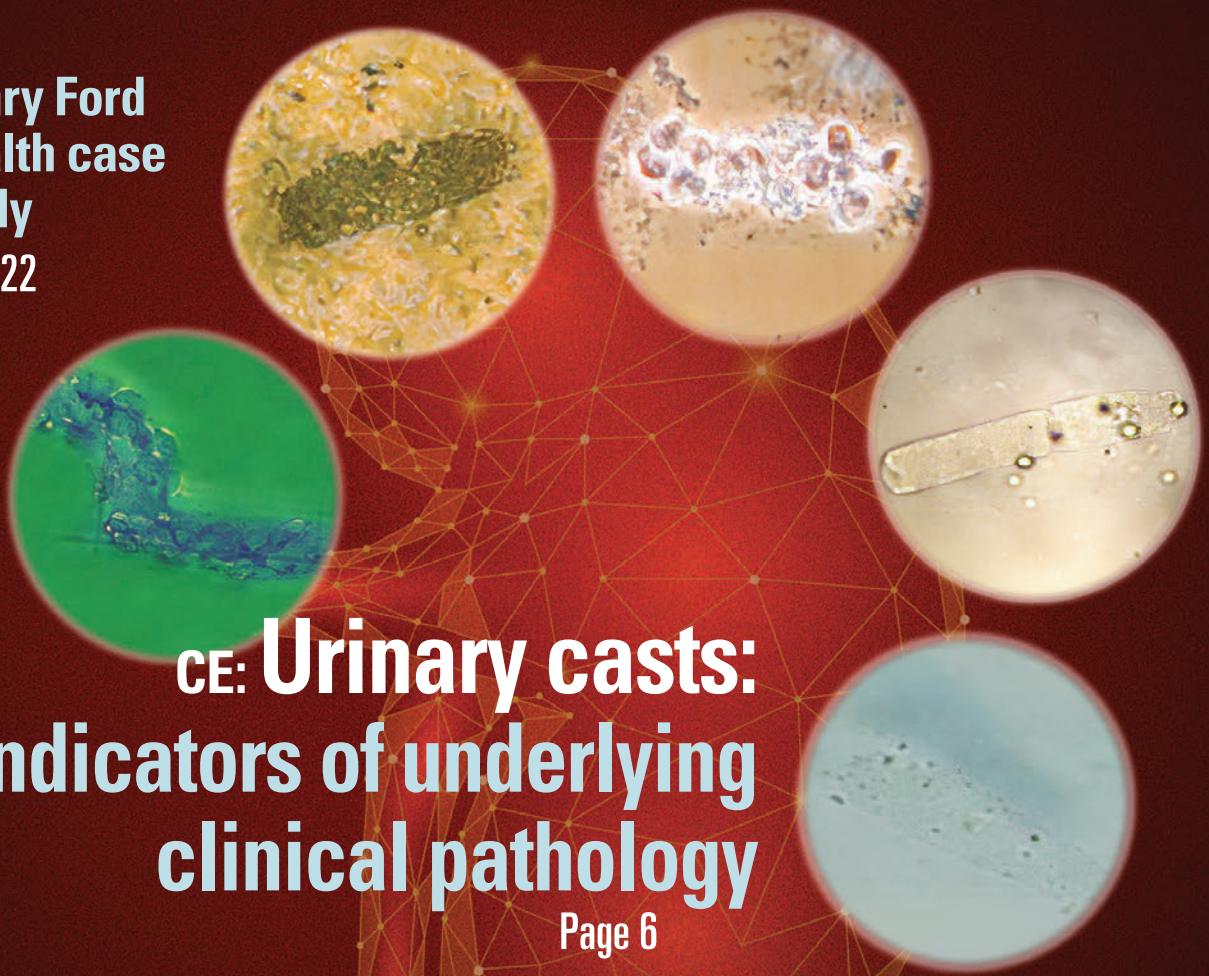

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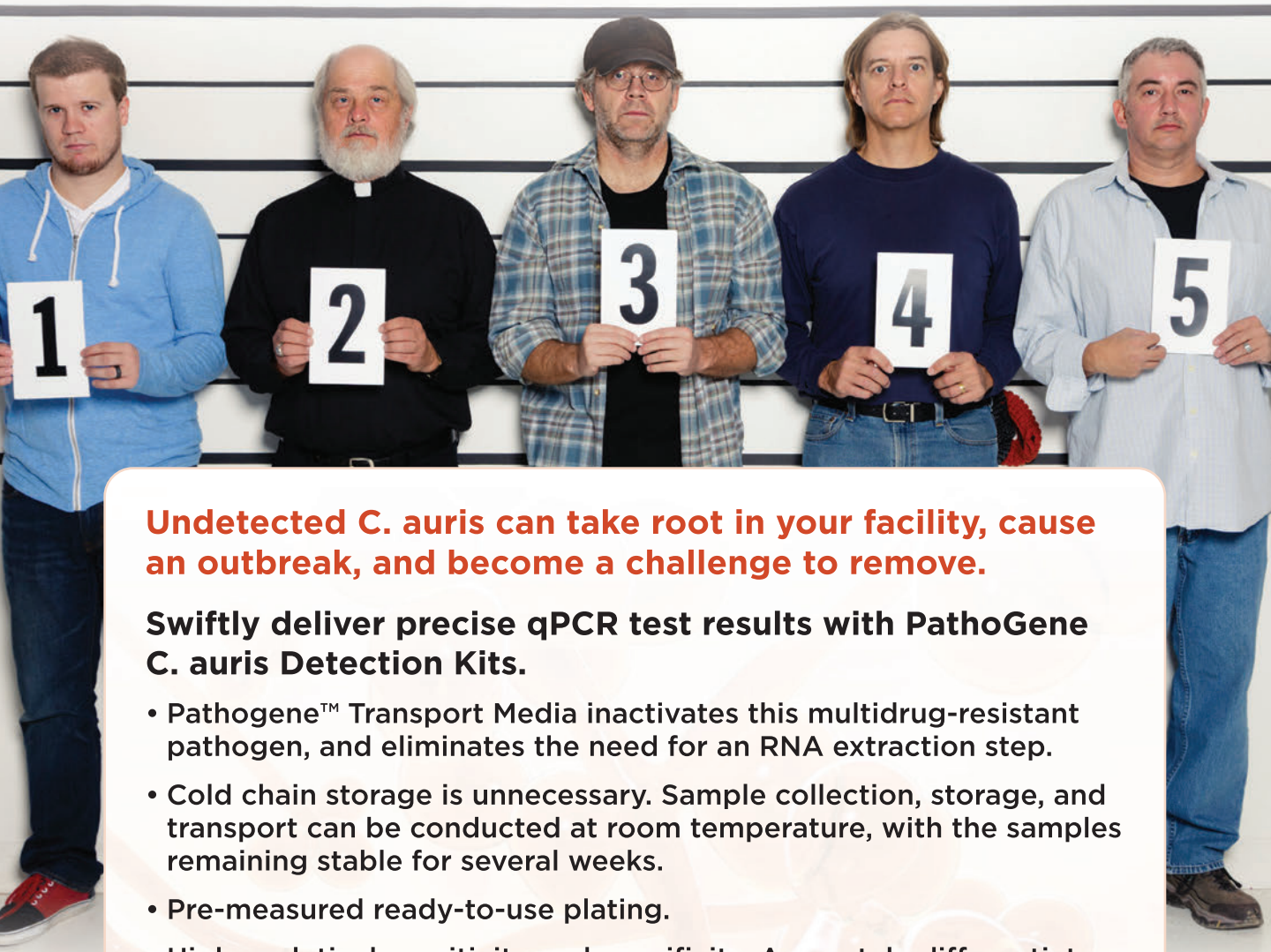

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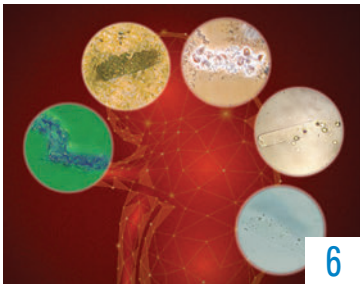

ON THE COVER: Microscopic images courtesy of Sorin Gîju, Ph.D., Clinical Emergency Hospital Timisoara, Romania

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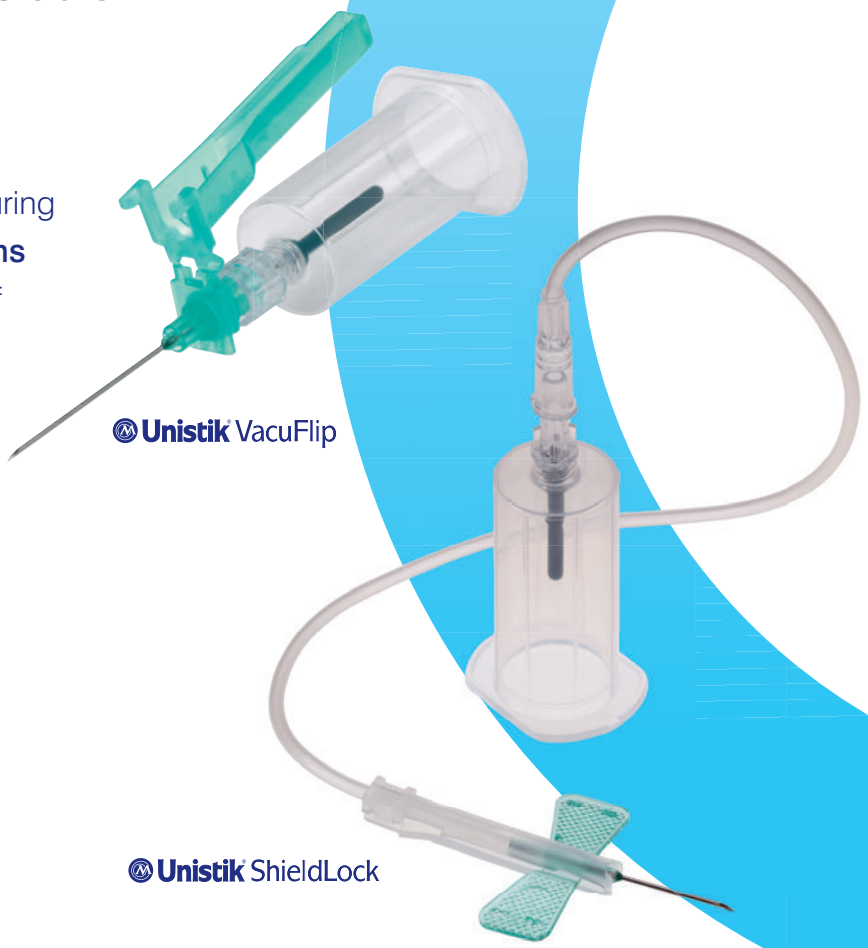

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55 years of laboratory-specific topics

By Christina Wichmann
Editor in Chief

Happy new year! This year, MLO celebrates its 55th year in publication. *Medical Laboratory Observer* was the very first magazine created for laboratorians. In 1968, Medical Economics, publisher of the *Physicians' Desk Reference*, wanted to develop another medically oriented magazine. Two of its staff members spoke to medical experts of all types across America. They later claimed that in nearly every case, they were told, "Go see Ray Gambino."

Dr. Gambino was the laboratory director of Englewood Hospital's Pathology Department in New Jersey. As a member of the American Society for Clinical Pathologists' education programs, Dr. Gambino ran a yearly seminar to teach pathologists how to manage a lab. He also trained residents at another nearby hospital to round out their pathology training with a focus on laboratory medicine. The Medical Economics staff picked Dr. Gambino's brain for new ideas for a magazine.

Dr. Gambino told them that they shouldn't try to compete directly against scientific journals, but rather cover laboratory-related topics that scientific journals never do. Nobody spoke to or for the laboratory professionals he elaborated. The idea flourished and Dr. Gambino became the editorial consultant for the new publication — *Medical Laboratory Observer* — in 1969. What began as a bi-monthly publication evolved into a monthly one that is still true to its roots. MLO is a leader in providing relevant content to its laboratory readership, and I am proud to be a part of it. If you have best practice or lessons learned content that you would like to share with your peers in an article, please reach out to me.

One of MLO's traditions is the annual Lab of the Year award. Please refer to page seven. We are now accepting applications for our 2024 Lab of the Year, which celebrates medical laboratories that demonstrate their extraordinary commitment to quality patient care. This is a highly anticipated feature in the magazine, and we hope you will consider applying! Submission requirements are at https://www.mlo-online.com/documents/document/53073100/2024-loycall-for-entries.

Lastly, I want to share with you a couple changes to the Continuing Education feature in MLO beginning this month. Very few of our readers complete a paper test and mail that to our partner Northern Illinois University for P.A.C.E. credit. To save NIU staff time and money going forward, we will only be offering the test online, which is how most readers complete the CE for credit. This will also save us on printing costs. Another change is the length of time the tests will remain active. That time frame is currently 18 months. It will be shortened a bit to 12 months. Tests published before January 2024 will still maintain the 18 month deadline as published at the time. MLO has a variety of CEs available on our website (www.mlo-online.com/ce).

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

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PUBLISHER Chris Driscoll
cdriscoll@endeavorb2b.com
EDITOR IN CHIEF Christina Wichmann
cwichmann@mlo-online.com
MANAGING EDITOR Erin Brady
ebrady@endeavorb2b.com
PRODUCTION MANAGER Edward Bartlett
ART DIRECTOR Patti Connors
AUDIENCE DEVELOPMENT/LIST RENTALS
Laura Moulton | lmoulton@endeavorb2b.com
ADVERTISING SERVICES MANAGER
Karen Runion | krunion@endeavorb2b.com

ADVERTISING
DIRECTOR OF SALES
EAST COAST/MIDWEST SALES, CLASSIFIEDS
Carol Vovcsko
(941) 321-2873 | cvovcsko@mlo-online.com
SOUTH/WEST COAST/ILLINOIS SALES
Lora Harrell
(941) 328-3707 | lharrell@mlo-online.com

30 Burton Hills Blvd., Suite 185
Nashville, TN 37215
800-547-7377 | www.mlo-online.com

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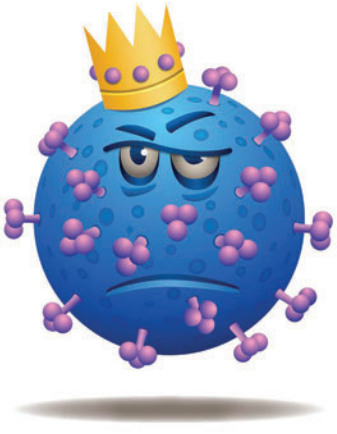

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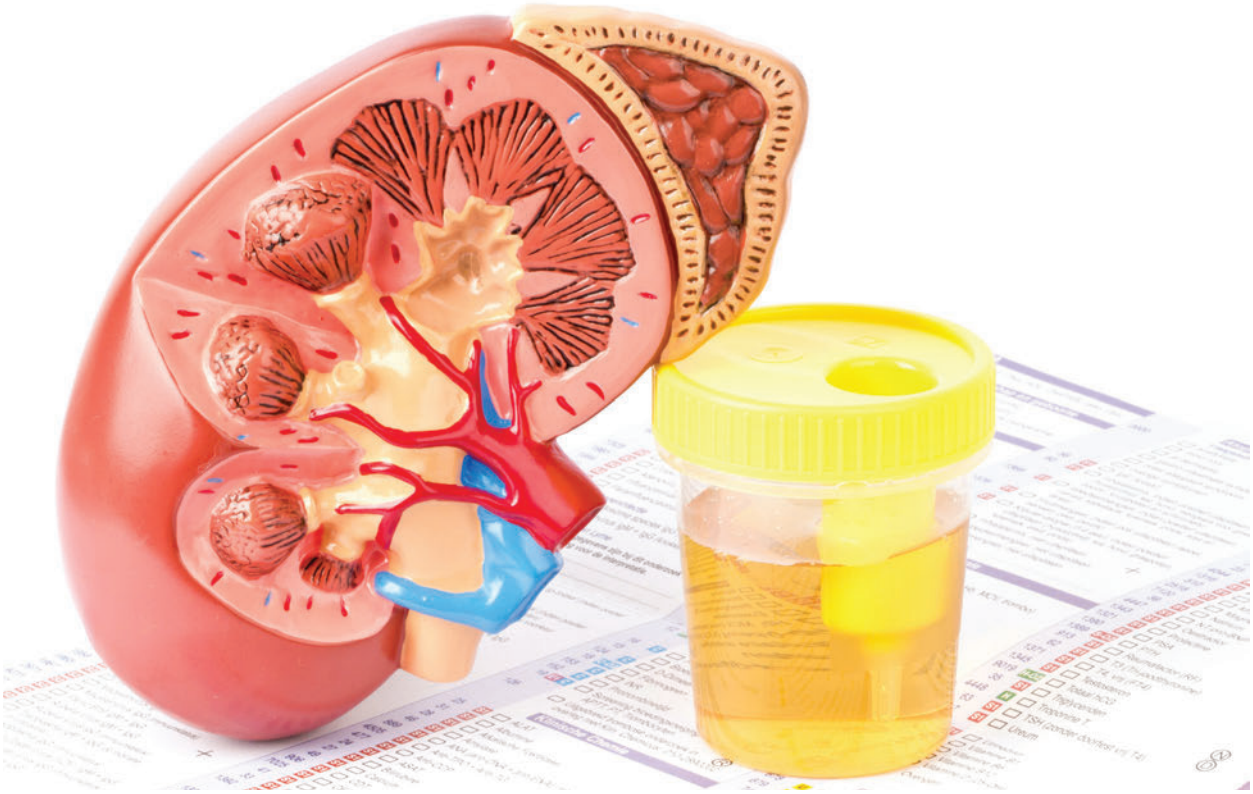

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Urinary casts: Indicators of underlying clinical pathology

By Paul R. Morris, MD, MA

The kidneys, two fist-sized, bean-shaped organs, reside just below the rib cage in the back of the abdomen under the liver. Properly functioning kidneys are essential for maintaining overall health. Unfortunately, for millions of people around the world, kidney diseases interrupt kidney function, leading to high morbidity and mortality.

Kidney disease

Chronic kidney disease (CKD), the most common type of kidney disease, occurs slowly over a long period of time, getting progressively worse. Currently, an estimated 13.4% of the global population is affected by CKD at all stages and 10.6% for moderate to advanced stages.[1] Globally, kidney diseases have risen from the world's 13th leading cause of death to the 10th, and mortality has increased from 813,000 in 2000 to 1.3 million in 2019.[2] Over 6 million adults have been diagnosed with CKD in the United States alone, where it is also the 10th leading cause of death.[3]

Structural changes, genetics, and comorbidities all may play a role in determining CKD risk. More than 30% of adults with diabetes and 20% of adults with hypertension may have CKD.[4] Other causes include heart disease, obesity, and a family history of kidney failure.[5]

One of the challenges with identifying and treating CKD, is that early disease is often without symptoms—90% of patients don't know that their kidneys are damaged.[6] Fortunately, most cases of CKD can be detected by simple urine and blood tests. As with most medical conditions, early detection leads to better patient outcomes.[6]

The renal system

The kidneys, along with the ureters, bladder, and urethra, comprise the renal system. Kidneys serve several vital functions—they filter blood to remove wastes and toxins, remove excess water from the bloodstream and produce renin to help maintain blood pressure, produce erythropoietin to maintain a healthy level of red blood cells, balance salts in the body, and convert dietary vitamin D to its biologically active form, calcitriol, to regulate calcium. Kidneys filter about 200 quarts of fluid every day; 99% of that fluid is reused in the body, while the remaining 1% is converted to urine.[7]

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LEARNING OBJECTIVES

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

1. List disease statistics of CKD in the global and U.S. populations.
2. Discuss the function and parts of the renal system.
3. Identify and define the components of a urinalysis.
4. Discuss key findings in a urinalysis that help to diagnose CKD.

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Unfiltered blood enters the kidney through the renal artery, which then branches into progressively smaller blood vessels until it reaches one of the more than 1 million nephrons in the kidney. Nephrons are the microscopic functional unit of the kidney, and each is comprised of a nephron and a tubule. (See **Figure 1**.) Inside the nephron, the glomerulus, a network of capillaries enclosed within a sac (Bowman's capsule), filters water and solutes from the blood. Smaller molecules, wastes, and fluids pass through the glomerulus and into the tubules, which ultimately feed into the Loop of Henle, a U-shaped structure where water and sodium chloride are resorbed from the filtrate. Larger molecules and cells stay in the blood.[8] Wastes from the filtrate exit as concentrated urine through the ureter to the bladder and filtered blood returns to the body via the renal vein.

CKD and other kidney diseases can be identified on urinalysis. Acute kidney disease (AKI), which occurs over days or even hours, results in the retention of nitrogenous wastes. Kidney stones and pyelonephritis (kidney infection) both cause severe pain. Nephrotic syndrome presents with heavy proteinuria and lipuria. Others include glomerulonephritis, autoimmune conditions, kidney stones, and polycystic kidney disease.

Urinalysis

Laboratory testing can provide timely information for identification and comprehensive therapeutic interventions to help drastically improve patient outcomes. Cost-effective[9] and usually noninvasive,[10] urinalysis provides critical information in the early detection of many diseases, including kidney disease. Considered to be the first developed laboratory test,[10] routine urinalysis can be used to screen for underlying health conditions such as diabetes, urinary tract infections, and kidney disease. It can also be used to monitor disease and disease treatment.

The three main components of urinalysis are macroscopic examination of the sample, chemical analysis, and microscopic examination of the urine sediment. Additional tests including microbiology and cytology may also be performed. The presence of crystals, casts, and blood cells in the urine sediment provides vital information for both diagnosis and prognosis.

Macroscopic examination

Macroscopic evaluation of urine is simply a visual examination. Macroscopic analysis of urine is done by visually inspecting the physical appearance of the urine. Normal urine is light yellow and clear. Macroscopic urinalysis notes the amount, color, and clarity of the urine as well as any other visible characteristics of the urine such as the presence of blood or blood clots, precipitates, or sediments.

Unusual colors may indicate infection, liver dysfunction, or drug use,[11] while turbidity may suggest infection or the presence of RBCs.[12]

Urine chemistry

Done to measure levels of certain substances such as proteins, sugars, ketone, and bilirubin, urine chemistry can be used to help diagnose and monitor a variety of health conditions including diabetes, urinary tract infections, and kidney disease.

CKD is divided into five stages based on the estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR). Albumin, a protein normally found in the blood, is involved in building muscles, repairing tissues, and fighting infections. In a normal kidney, albumin cannot pass through the kidney's filter and into the urine, but in a diseased kidney, albumin leaks through the filter. Creatinine is a waste product of protein metabolism—from food or from normal muscle cell turnover and is normally found in both serum and urine. If the kidneys are not functioning properly, the urine level of creatinine decreases. To ensure that the urine concentration doesn't interfere with the determination of albumin levels, the uACR test is done. The uACR is a ratio between urine albumin and serum creatinine; a uACR greater than 30 mg(albumin)/g(creatinine) is indicative of albuminuria—excessive protein in the urine.[13] eGFR is a calculation based on serum creatinine levels and shows how well the kidneys are filtering toxins and wastes from the blood.[14] A normal eGFR is above 60 mL/min/1.73m^2, and a normal uACR is below 30 mg/g.[14] Falling eGFR numbers and rising uACR numbers are indicators of progressing disease.

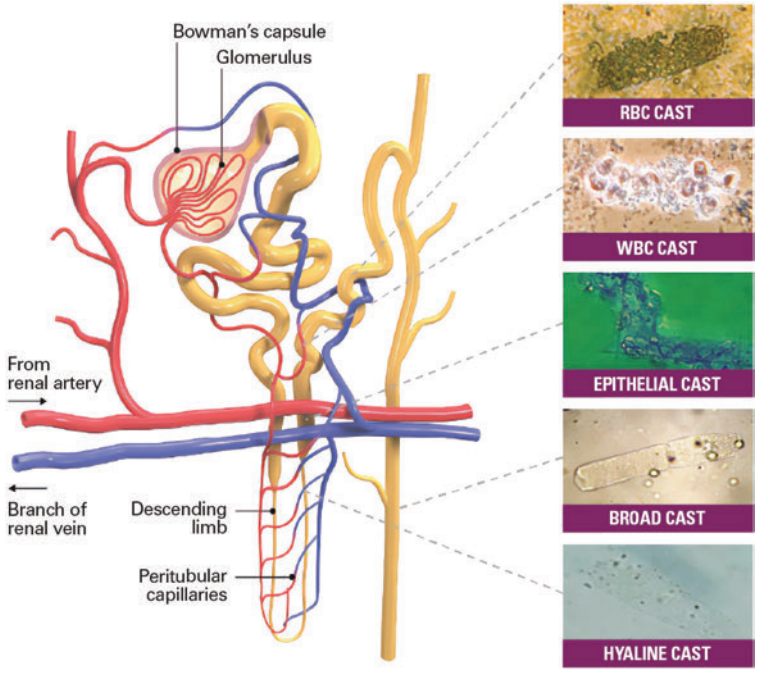

Figure 1. Microscopic images courtesy of Sorin Gîju, Ph.D., Clinical Emergency Hospital Timisoara, Romania.

Urine microscopy

Urine microscopy is a common test in the clinical laboratory and is used to evaluate cells, casts, and crystals in the urine. While it is not uncommon to find some epithelial cells in the urine, an increased number may be a sign of trauma, inflammation, or infection in the urinary tract. Similarly, bacterial or yeast in the sample suggest an underlying renal system infection. Blood cells in the urine may be benign—for example, as a result of heavy exercise—but may also indicate a more serious disorder such as a severe infection or urinary tract cancer.[15] The presence of urine casts often portend a more serious underlying kidney condition and may be one of the first early indicators of underlying kidney disease.

MLO LAB OF THE YEAR 2024

CALL FOR ENTRIES

MLO's Lab of the Year Award celebrates medical laboratories that demonstrate their extraordinary commitment to quality patient care. Submissions will be judged on achievements in five areas. A panel of judges selected from MLO's Editorial Advisory Board will select the winner and two runners-up. All will be featured in the April 2024 issue of MLO, in print and online, and awarded a display wall plaque, with the winner featured on the issue cover.

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MLO LAB OF THE YEAR 2024

MLO MEDICAL LABORATORY OBSERVER

Casts

Urinary casts are cylindrical mucoprotein particles that arise from the distal convoluted tubule or collecting duct during periods of urinary concentration or stasis. All casts have a core matrix glycoprotein, uromodulin, that is secreted by renal tubular cells in the ascending arm of the Loop of Henle.[12] Trapped contents in the tubule lumen intermix with the uromodulin, and eventually, the tubule-shaped cast is excreted in the urine. Different casts are comprised of different components and are formed in different areas of the tubule (See **Figure 1**), which may be helpful in determining clinical significance. Urine cast formation is influenced by the pH, concentration, and temperature of the urine—as well as by the presence of drugs or underlying genetic conditions.

And while having some casts in the urine sediment may be normal, the type and number of casts may indicate the presence of renal disease[12] and can be detected and characterized using automated urinalysis. The clinical significance of some of the most common casts is shown in **Table 1** below.

Conclusion

Advancements in automation are streamlining the urinalysis laboratory workflow and improving laboratory efficiency to take the subjectivity out of urinalysis. Integrated automated urinalysis systems with automated urine microscopy and auto-particle recognition software provide numeric counts and digital image results and can also auto-classify particles based on size, shape, contrast, and texture and assist with particle sub-categorization. The insights gained from urinalysis with sensitive cast identification are facilitating partnerships between laboratorians and clinicians to identify kidney disease in a timely manner—allowing them to focus their time on the most critical patients.

Casts	Clinical significance
Hyaline	Hyaline casts, the most common type of urinary casts, are composed of mucoproteins. Like granular casts and RBC casts, hyaline casts may be a normal finding following strenuous exercise. They are also found in those using diuretics. Clinically, though, hyaline casts are indicative of pyelonephritis and CKD.
Granular	Granular casts are a key indicator of acute tubular necrosis or advanced renal disease. The granules inside the casts are formed after decomposition of cells in the cast or a tubule. The appearance of granular casts may vary from coarse granules including cell particles to fine granules that are turning to waxy casts. While the presence of granular casts is usually clinically significant, a small number of granular casts may be present after intense physical activities.
Cellular	Cellular casts include those comprised of red blood cells (RBCs), white blood cells (WBCs), and epithelial cells. RBC and WBC casts are implicated in glomerular dysfunction and nephron inflammation or kidney infection, respectively. Epithelial casts, which form by inclusion or adherence of desquamated epithelial cells to the tubule lining, have a broad range of clinical significance from acute tubular necrosis to kidney disease to toxic nephropathy from heavy metal ingestion.
Waxy	Waxy casts, the largest of the casts, occur in patients with chronic kidney diseases and are indicative of tubule damage. These casts are comprised of a variety of cell types but have a homogenous structure. Occasionally, granular matter is found within waxy casts. Waxy casts are often seen as broad casts, having a greater diameter than most casts.
Fatty	Fatty casts are comprised of fat- or lipid-laden cells. They are formed by the breakdown of lipid-rich epithelial cells and have a Maltese cross pattern under polarized light. Fatty casts are clinically significant for nephrotic syndrome, kidney disease, hypothyroidism, or toxic renal poisoning.

Table 1. Most common urinary casts.

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Dr. Paul R. Morris earned his medical degree from Boston University. He completed his residency in Pathology at Duke and fellowship in Blood Banking/Transfusion Medicine at the University of North Carolina. Dr. Morris has over twenty years of experience in blood and tissue banking, reference laboratories, and the in-vitro diagnostics industry. He currently is the Medical Director for **Beckman Coulter Diagnostics** and **Life Sciences** focusing on risk management and new product development.

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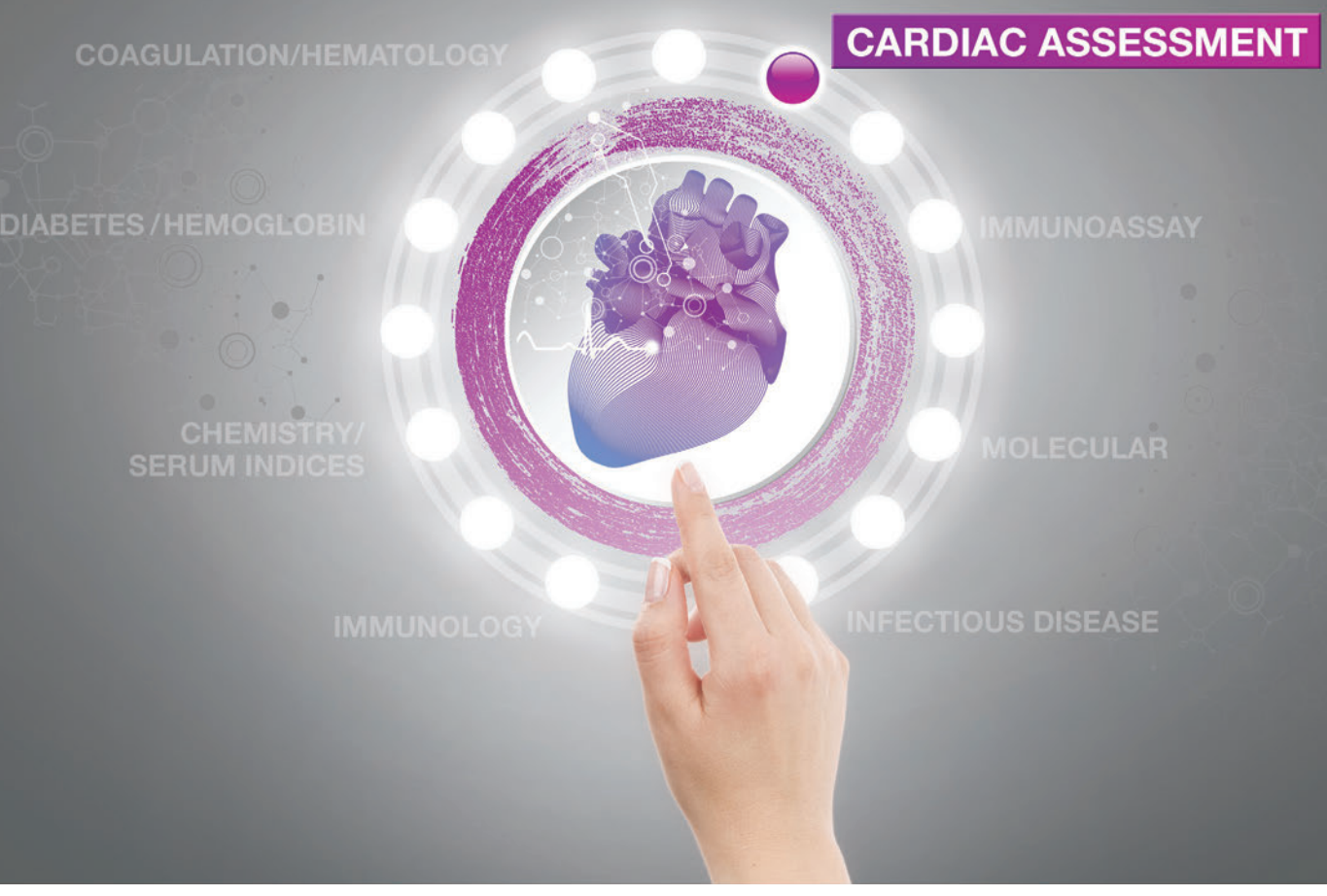

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Point-of-care testing is the next step for respiratory infections

By Dhaval Waghela

After years of centralization in the clinical testing realm, the field is in the midst of a shift toward decentralization. This trend supports the goals of diagnostic stewardship and getting the right test to the right patient at the right time.

While point-of-care testing has been an option for some clinical situations for many years—rapid flu or rapid strep tests performed at primary care offices are good examples—the need for the full spectrum of testing options was starkly revealed during the COVID-19 pandemic. There was an obvious need for high-quality molecular tests that could be run in hospital laboratories and in reference laboratories. But with all of these clinical laboratories overwhelmed with testing demand, there was an equally clear need for point-of-care options, particularly at-home testing that made it possible for people to get a fairly accurate reading of whether they were contagious so they could take appropriate isolation measures to keep others safe.

For some healthcare situations, this is the model that will serve the entire clinical laboratory community best going forward: a hub-and-spoke approach that allows for all the benefits of centralized testing as well as the advantages made possible through decentralized testing.

While clinical lab testing is well established, it's in point-of-care testing where innovation is needed most. Decentralized testing options must have accuracy approaching that of standard clinical lab tests, but they will also require the speed and ease of use that patients and healthcare professionals have come to expect from the era of rapid antigen tests.

Point-of-care testing in the past

To understand where point-of-care testing needs to evolve, it is worth looking at how it has been implemented in the past. Based on prior examples, it is understandable that many members of the clinical laboratory community may be skeptical that decentralized testing could ever produce truly reliable and useful results.

Perhaps the best-known examples of point-of-care testing involve the rapid antigen tests that have been used for influenza and group A streptococci. These lateral flow tests became popular among primary care physicians and urgent care clinics for their speed, often delivering results in 10 to 15 minutes. But within the clinical lab community, these tests became known for their lack of sensitivity, with a high rate of false negatives that sent many contagious patients home believing they didn't need to worry about spreading infection.

In several meta-analyses of these tests, sensitivity for rapid influenza A and B testing was 67.5% at best and 51% at worst.[1] Sensitivity was lower for influenza B than influenza A, and lower for adults than children.

Due to sensitivity issues, many physicians regularly sent negative test samples to clinical laboratories for confirmatory molecular testing, as recommended by the U.S. Centers for Disease Control and Prevention.[1] But even that was deemed inadvisable by the Infectious Diseases Society of America (IDSA), which in 2019 published new guidelines for flu testing in which they recommended against the use of rapid antigen tests.[2] Instead, the IDSA now recommends the use of rapid molecular tests, which can generate results in an hour or less—still providing same-day answers for patients and physicians but with extremely high accuracy.

Respiratory testing should be first

While decentralized testing will be useful for a broad range of healthcare needs, it is likely that the first area where it will make a major impact is in respiratory infections. For a number of reasons, this will be the perfect test case to evaluate the utility of this model.

Respiratory testing capacity has always been unpredictable due to its seasonal nature. In summertime, testing ebbs for flu and respiratory syncytial virus (RSV). But in the winter, hospital labs can be overwhelmed by demand for these tests, leaving little bandwidth to manage all of the other clinical tests that have to be run. A reliable point-of-care test for the most common causes of respiratory infections would make it possible to offload much of the peak respiratory testing demand to pharmacies or urgent care clinics, freeing up the hospital laboratory staff to focus on testing for seriously ill patients. When flu, COVID-19, or RSV are at unusually high levels, hospitals might even set up tents or screening stations outside where patients could be given a point-of-care test, allowing those who are not sick enough to be admitted to get the answers they need while avoiding a testing burden on the central lab.

A decentralized model would also help in this space because respiratory infections are highly transmissible. If patients could get accurate results at home, at an urgent care facility, at a primary care office, or at a pharmacy, they could take appropriate measures to avoid infecting others. Each patient who stays safely at home could represent the end of a transmission chain, rather than the continuation of it. Point-of-care testing could reduce community spread and keep more people healthier.

Finally, respiratory testing has been primed for a decentralized approach thanks to advances from the COVID-19 pandemic. Substantial technology development for rapid molecular platforms—including molecular tests that could be performed by patients in their own homes—has paved the way for increased familiarity with point-of-care tests.

How decentralized testing fits

For optimal results, point-of-care platforms should be integrated into the testing strategy established by a clinical laboratory. Clinical lab teams know best where and how decentralized modes of testing could complement hospital and reference lab testing in their communities, with specific attention paid to the needs of their patient population. For labs serving a large elderly population, for example, perhaps setting up a point-of-care test platform in the local senior center or pharmacy would be most convenient and effective. Clinical labs have tracking data on which customers are submitting requests for testing, and this knowledge will be essential for ensuring that point-of-care testing is rolled out in the best way for the population they serve.

A combination approach could work for healthcare systems such as integrated delivery networks. Hospital labs would continue to run respiratory tests for admitted patients, while point-of-care tests could be used in urgent care and outpatient facilities to expand testing venues without increasing capacity in existing labs. In this case, using the same point-of-care platform in all of these sites would ensure consistency of results no matter where testing is performed.

In addition, point-of-care testing could be deployed for rural communities and remote facilities associated with integrated delivery networks to provide a better standard of care.

What's next

It is clear that the testing market is shifting, and that decentralized testing options will be important for managing patient health going forward. With that said, though, point-of-care tests have much to accomplish before they can be broadly adopted. Technology development will be important to ensure accuracy on par with traditional molecular assays, ease of use so even lay people can operate the tests, minimal hands-on time to avoid creating a new testing burden outside the lab, and rapid results for optimal utility. Just as importantly, these developers will also have to collect data about how these platforms are used and what errors might arise to continually hone these new tests for mainstream use.

While that innovation happens—and it is happening, driven in large part by what the laboratory community learned from the COVID-19 pandemic—it will be important for clinical laboratories to begin thinking about how they could implement the best point-of-care options for respiratory testing in their own healthcare facilities. Any concerns about reducing revenues within the clinical lab can start to be addressed in the planning phase as leaders find ways to attribute point-of-care testing revenues to the clinical lab overseeing these platforms. Early adopters who figure out the best way to combine centralized and decentralized testing options for their patient populations will help establish efficient and effective models that can eventually be implemented in healthcare systems around the world.

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Dhaval Waghela serves as senior product manager at **Diasorin**, where he oversees product development and innovation for a variety of clinical testing needs.

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A holistic approach to error prevention in the clinical laboratory

By Stephen Bishop, MBA, MS, CLS, MLS(ASCP)^{CM}, CPHQ

In the world of clinical laboratory testing, precision and accuracy are paramount because laboratory results can have a critical impact on patient safety, so preventing errors is non-negotiable. Yet, the challenge for laboratory leaders lies not only in the sophistication of the tests performed, or the selection of appropriate tests, but also in the intricacies between technology, systems, and human capital. To address this complex challenge, a comprehensive strategy that encompasses structural, technological, and cultural measures is essential. From meticulous policies and procedures, or advanced hardware and relevant software, to fostering a culture of open communication, psychological safety, and continuous improvement, the integration of these elements creates a holistic defense against the errors in the clinical laboratory, ensuring the reliability and integrity of test results.

Errors in the total testing process

The total testing process (TTP) involves multiple steps to ensure accurate and reliable results. This journey comprises pre-analytical, analytical, and post-analytical phases and demands meticulous attention to detail at every turn. It begins with healthcare providers ordering specific tests, followed by the collection and proper labeling of patient specimens. After transportation to the laboratory, specimens undergo processing, and tests are performed. The generated data is analyzed, and results are reported to healthcare providers for interpretation in the context of patient information. Diagnostic decisions are made based on the results, and the data is archived for reference and quality assurance.

In the pre-analytical phase, errors emerge from specimen handling, utilization, ordering, transportation, collection, and patient identification. A misstep at any of these preliminary stages can cast a long shadow, influencing the reliability of subsequent test results. Analytical errors, on the other hand, may arise from a variety of sources, including reagent issues, calibration discrepancies, quality control, and instrumental malfunctions. These errors have the potential to skew results, introducing inaccuracies that, if undetected, could lead to misguided clinical decisions.

The post-analytical phase, often regarded as the final frontier before results reach the clinician's hands, is not exempt from its share of challenges. Data entry and management errors, miscalculations, and reporting inaccuracies pose threats to the integrity of the diagnostic process. Whether it be calling critical values erroneously or overlooking essential delta checks, the post-analytical realm demands an extra layer of scrutiny. Moreover, measurement conversion errors and misinterpretations further underscore the fragility of this intricate process.

As laboratories strive for excellence, understanding and mitigating errors across the entire total testing process becomes imperative—where the journey from specimen to result is not merely a sequence of steps, but a delicate orchestration of precision and diligence.

Three pillars of prevention

To prevent errors effectively, laboratory leaders must adopt a proactive stance, implementing rigorous measures and fostering a culture that places a premium on error reduction through three pillars: structural prevention, technological

prevention, and cultural prevention. In this intricate management of science and diligence, the pursuit of error prevention in the clinical laboratory emerges not merely as a task, but as a solemn commitment to the well-being and trust of the patients relying on the precision of diagnostic outcomes.

Structural prevention establishes the foundation for a robust defense against errors. Detailed policies and procedures, spanning testing protocols, quality control measures, and standardized operating procedures, provide a structured framework that guides laboratory operations. Regular assessments of the laboratory's Quality Assurance/Quality Management (QA/QM) plan ensure that these structures remain dynamic, adaptive, and aligned with the evolving landscape of healthcare. Structural prevention sets the stage for systematic checks and balances, creating an environment where errors are less likely to occur due to procedural lapses or ambiguities.

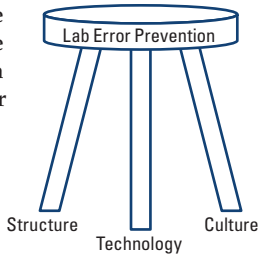

Figure 1.

Technological prevention introduces a layer of sophistication, leveraging hardware, software, and information systems to fortify the laboratory's defenses. Advanced hardware, such as positive patient identification systems and barcoding solutions, enhances accuracy in specimen handling and processing. Automated temperature monitoring and quality control applications bring precision to critical aspects of testing, reducing the likelihood of errors stemming from environmental or procedural fluctuations. Laboratory information systems (LIS) play a crucial role, ensuring correct builds and seamless integration of testing platforms, diminishing the risk of errors associated with data transfer and interpretation.

Cultural prevention, the third pillar, represents the human aspect of a holistic defense against errors. Cultivating a culture of laboratory safety and continuous improvement establishes a philosophy where every team member actively contributes to error prevention and where the laboratory leadership fosters psychological safety. Effective feedback mechanisms, coupled with routine competency checks and ongoing training, create a dynamic learning environment where errors are not only addressed but serve as catalysts for improvement, as opposed to punishment.

Putting it all together

Laboratorians are entrusted with the responsibility of ensuring the integrity and precision of the diagnostic process, making the implementation of the three pillars of prevention—structural, technological, and cultural—a crucial endeavor.

To fortify the structural foundation, leaders should invest in developing and regularly updating comprehensive policies and procedures. These documents should serve as living guides, reflecting the latest industry standards, and continuously evolving to address emerging challenges. At the same time, a proactive approach involves routinely assessing the Quality Assurance/Quality Management (QA/QM) plan, ensuring that it aligns with the laboratory's goals and regulatory requirements. Laboratory leaders need to be intimately familiar with the laboratory's QA/QM plan and regularly assess it for improvement. This continual scrutiny ensures that structural preventive measures remain robust, adaptive, and relevant.

Technological advancements offer a powerful arsenal in the fight against errors. Laboratory leaders should prioritize investments in cutting-edge hardware and software solutions. Positive patient identification systems, barcoding technology, and advanced communication systems bolster accuracy in specimen handling and result reporting. Automated temperature and humidity monitoring applications, quality control interfaces, and cybersecurity measures also contribute to the integrity of laboratory processes. Additionally, a focus on optimizing the laboratory information systems (LIS) ensures correct builds and seamless integration with testing platforms, which can further minimize the risk of errors related to data interpretation.

Cultural prevention, the often undervalued yet highly effective pillar, demands intentional leadership. Laboratory leaders should foster a culture that places all forms of safety at the forefront and embraces continuous improvement as a collective mission. Establishing open communication channels encourages team members to voice concerns and report errors without fear of retribution. Creating effective feedback systems, along with routine competency assessments beyond what CLIA requires, instills a mindset of perpetual learning and growth. Laboratory leaders must champion the concept of total quality management, making quality assurance a shared responsibility among all team members. By embedding these cultural values into the fabric of daily operations, leaders inspire a collective commitment to laboratory excellence and patient safety.

Final remarks

The synergy of these three pillars is vital to effective error mitigation. The structural, technological, and cultural elements are interdependent, each reinforcing the others to create a resilient defense against the complexities of the total testing process. It is important to note that if one is neglected, the remaining two pillars can only be partially effective.

Like a three-legged stool (**Figure 1**), each pillar plays a crucial role, contributing to the stability and effectiveness of the overall preventive framework. If one pillar fails, the consequences can resonate throughout the entire laboratory system. A deficiency in structural measures may lead to procedural ambiguities and lapses, compromising the reliability of testing processes. Technological shortcomings could introduce inaccuracies, jeopardizing the interpretation of results and the security of data. A lapse in the cultural pillar will result in communication breakdowns, diminished vigilance, and a declining sense of collective responsibility for quality assurance. The interconnection of these pillars underscores the importance of maintaining equilibrium; any imbalance has the potential to weaken the laboratory's ability to safeguard against errors, which ultimately impacts patient care.

Embracing these pillars requires a strategic, forward-thinking approach—one that recognizes errors as multifaceted challenges and addresses them comprehensively. As leaders commit to the implementation of these preventive measures, they not only safeguard the integrity of laboratory results, but also foster a culture of excellence, innovation, and unwavering dedication to providing the highest standards of patient care.

Stephen Bishop, MBA, MS, CLS, MLS(ASCP)CM, CPHQ is currently the Director of Laboratory Services at **Dignity Health California Hospital Medical Center**, located in downtown Los Angeles, CA. Stephen is passionate about healthcare leadership, clinical laboratory education, and process improvement.

Urine-specific gravity: Specific clinical relevance

By Hillary Threatt CPhT, MDT (AMT), MSc

The goal of urine is to eliminate urea and other byproducts from the body. Specific gravity, also known as relative density, is defined as finding the ratio between the density of substances versus the density of solution. This is distinguishable from the precision of osmolarity as osmolarity defines an exact number based on the particles within a density and is not subject to change based on weights.[1] For laboratories, urinary analysis (uranalysis) uses urine-specific gravity (USG) as a timely estimate for finding the concentration of byproducts within a patient's urine. Urine-specific gravity is the ratio of the density of urine to the density of water (**Figure 1**). When interpreting results for uranalysis, USG provides information on a kidney's ability to filter, the status of hydration in patients, and identifies plausible long-term health conditions such as diabetes insipidus or loss of renal tubular abilities.

$$\left(\frac{\textit{Number and Size of Solutes}}{\textit{Density of Solution Compared to Water}} \right)$$

Figure 1. The equation for urine-specific gravity.

The base of any urine sample is the discarded water from a patient's body containing waste urea, traces of various hormones, vitamins, drug metabolites, and other organic and inorganic solutes. Aside from urea, the organic components in a sample may include creatinine, uric acid, hippuric acid, urobilin, and other carbon-based byproducts. The inorganic components in urine samples include, but are not limited to, sodium chloride, potassium, sulfate, phosphate, ammonium, magnesium, and calcium.[2]

Kidneys selectively reabsorb chemicals, minerals, and water through glomerular filtration. This process is conducted individually by roughly one million nephrons per kidney, which filters blood through a cluster of branching red blood vessels called the glomerulus. The nephrons return necessary substances including salt, glucose, and water, back to the blood while removing waste through the ureter. The amount of waste excreted in urine is determined by the osmotic gradient in the medulla; the water is regulated by the naturally occurring antidiuretic hormone (ADH), which is regulated by the renin-angiotensin-aldosterone system that controls the flow of blood to and within the kidney.[3,4] ADH accomplishes regulation by binding to the receptors on principal cells. Principal cells account for two-thirds of the cell type in the initial collecting tubule of kidneys, whereas intercalated cells account for the other third.[5] When ADH attaches itself onto the receptors, the integral membrane proteins, aquaporins, change shape allowing for water to pass through. The water is reabsorbed through the renal collecting tubule due to the higher concentration gradient in the medullary interstitium.[3,4] When ADH levels become high, tubular walls become more permeable; when ADH levels are low, the impermeable tubular walls retain water leading to diluted urine.

A kidney's reabsorption ability is one of the first renal functions impaired for diabetic patients. In addition, urinary tract issues and inflammation of different areas of the kidneys will also lead to impairment.[6] The ratio at which substances are excreted notifies healthcare professionals of hydration, plausible kidney problems, and other underlying conditions. Risk factors affecting kidneys can be separated into two cate-

gories — controllable and non-controllable. Non-controllable factors are predetermined and cannot change in an individual such as age, race, sex, and genetic history. However, among the controllable factors are hydration, diet, and medicine, which affect the concentration of solutes in urine.

Factors affecting urinary-specific gravity

Hydration is the largest controllable factor to impact USG. Higher water intake correlates to lower USG due to a higher volume of discarded water to solutes in urine; inversely, lower hydration raises USG due to a higher concentration of solutes in a lower urine volume.[2] Depending on a patient's diet, the contents may alter USG. In a 2023 study, the biomarkers USG and creatinine-adjustments were analyzed.[7] This study showed that while creatinine-adjustments in serum and urine both provided information of kidney function, USG could be used as a parameter for correcting hydration status in patients.[7]

Routine medicine is an important factor that can alter an otherwise "normal" reading. Depending on how a drug reaches the activation site will determine the impact on USG. Diuretic medications, described as "water pills," have three different binding methods to reach their activation site and remove excess salt, water, and sometimes potassium by increasing excretion.[8] Increasing the amount of water excreted in the body and removing the smaller ions lowers the USG in patients. Blood pressure medications, in particular alpha-blockers, will also increase urination. Alpha-blockers will interact with receptors resulting in smooth muscles to vasoconstrict or by blocking receptors that will cause vasodilation.[9] Other types of blood pressure medications such as calcium channel blockers will yield similar effects by increasing secretion. Without increasing fluid intake, or proper maintenance, a patient can quickly become dehydrated.

When secretion increases to abnormal amounts, known as polyuria, it can reflect certain healthcare conditions. Diabetes mellitus is a condition caused by defects within the pancreatic production of insulin or the function of insulin. The result is an increase in glucose concentrations seen throughout the body floating in the liver and bloodstream. To counteract the excess floating glucose that cannot be reabsorbed or used, the body increases the excretion rate to remove the excess glucose.[2] The urine excreted is highly concentrated and turbid due to glucose, but smaller in volume due to polyuria resulting in a higher USG. Diabetes insipidus is another condition that results in polyuria but is caused by the reduction of ADH or decreased response of ADH.[10] The resulting urine is highly diluted due to aquaporins remaining shut and not allowing water to properly reabsorb back into the kidney and body. In special populations, such as pregnant women, USG is used as a biomarker to determine risk factors. In a retrospective cohort study of gestational diabetes mellitus (GDM), 1,769 pregnant women from January 2015 to December 2018 were evaluated using UA, UN, and USG. GDM was diagnosed based on the 2010 diagnostic criteria of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG). The study concluded that higher levels of USG along with serum uric

acid and a higher composite kidney function biomarker were positively and independently associated with an increased risk of GDM.[11] See **Table 1** for a general summary of factors affecting USG.

Common tests for measuring USG

USG is measured through refractometry or reagent test strips.[12] When the quantity of urine cannot fill a small container, refractometry provides an advantage in clinical settings. Refractometry works through a refractive index meaning the measurement of how much light bends or refracts upon entering a material.[13] In clinical refractometry, a prism measures the velocity of light in the air and compares it to the velocity of light in the urine. Refractometry requires only one to two drops to cover the entirety of the prism. The concentration of dissolved particles present in the solution determines velocity and angle due to light passing through the solution. The wavelength of light used in a sample can affect the reading, however, in a laboratory setting these variables are consistent and less likely to affect readings. One of the advantages of refractometry is that it does not require specific temperature to provide accurate information; between 15°C to 38°C is enough to ensure accurate results.

Reagent strips are analyzed through manual hand dips or urinalysis automation such as the Clinitek system. The reagent pad of the strips utilizes bromothymol blue as the indicator. The color changes in Multistix and Chemstrip function on the dissociation constant (pKa) in alkaline mediums. The color shift changes from alkaline blue at 1.000 to acidic yellow at 1.030 as the USG rises. Higher concentrations lead to more released hydrogen ions causing acidic conditions. Based on a 24-hour urine collection, the typical range for USG in a healthy individual is from 1.015 to 1.025.[2] A limitation of reagent strips is protein content; if protein reaches 100 to 750 mg/dL it may cause false elevated USG readings.

Analyzing special cases

USG is considered in other assessments of physiology. Metabolomics is the study of small molecules within a biological sample. The applications of metabolomics can be used to study the relationship between diet and the organism; in other cases, clinical evaluations of diseased states.[14] In a 2019 comprehensive assessment of various samples and studies, urine specimens were analyzed for preanalytical factors and how they influenced the metabolomic states. The urine concentration produced from a single patient can change drastically from sample to sample. The assessment of urine can account for some variation by normalizing metabolite levels. The goal of normalization is to reduce the variation of nonbiological variations from biological variations. Specifically in urine, samples are normalized through creatinine, osmolarity, or specific gravity.[15] The paper looked at three studies where normalization was used at three different times during a procedure and evaluated for consistency and accuracy.

USG is dependent on the size and number of particles present within a solution. When evaluating renal function, it gives a fast, approximate state of patients and possible risk factors. Determining therapies and treatments should not rely solely on USG, but when used as an approximate tool, in addition to other markers, it can help provide fast and timely treatment and assessments.

Condition	High USG	Low USG
Renal artery stenosis (Narrowed artery)	■	
Diuretics		■
Diabetes Insipidus		■
Diabetes Mellitus	■	
High glucose content in Urine (Glycosuria)	■	
Impaired renal function		■
Heart Failure	■	
Dehydration	■	
Over hydration		■

Table 1. Factors affecting USG.

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Hillary Threatt is a medical technologist working at **Quest Diagnostics laboratories**. Much of Hillary's time is spent working in clinical chemistry, hematology, coagulation, urinalysis, and blood banking. Her national certificates include molecular diagnostics technologist and pharmacy technician. With eight years of medical experience under her belt, Hillary's experiences also extend to research working under IRB protocol, and a Biotechnology master's thesis based on identifying mechanisms in Enterobacterales.

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Unlocking profit potential: Transforming hospital labs from cost centers to profit generators

By Alex Mitchell

Many administrators and C-suite executives tend to view their labs as an essential service, but not necessarily a profit-generating arm. This has led to a prevailing trend where lab directors outsource profitable testing to large reference labs, missing out on the opportunity to run these tests in-house for profit.

"Oftentimes, there is a lack of entrepreneurial thinking among hospital administrators with regard to their hospital laboratories," says Jon Harol, President of Lighthouse Lab Services, a medical lab management, recruiting, and consulting firm. Despite the potential to bring profitable testing in-house, some health systems are outsourcing testing or selling their labs outright instead of exploring solutions to make them more profitable. Instead of accepting the status quo, Harol believes hospital labs should explore insourcing certain esoteric testing by focusing on adding high-margin tests that can both offset the cost of routine essential services and produce a profit for their hospitals in the long run.

"If you require a lab to be able to service patients 24/7 with a broad test menu, it's very hard to operate that on a profitable model given reimbursement assigned for many of those tests by federal and commercial payers," Harol says. "If you get so in the weeds that you only perform the low-margin testing and completely pass over higher-margin testing, that's the worst-case scenario." Some of the testing opportunities Harol cites include toxicology confirmation testing utilizing liquid chromatography-mass spectrometry (LCMS) and next-generation sequencing for cancer.

Challenges faced by hospital labs

Harol and his leadership team at Lighthouse recently conducted a panel of four hospital laboratory directors to try to better understand the challenges they face when advocating to add new lines of testing. Chief among the roadblocks cited by these leaders is the limited amount of time directors and lab managers can commit to compiling the business case for how new lines of testing can benefit their hospital's bottom line, especially when considering many of these directors may lack a business background. Other challenges cited include the following:

Understaffing: This was the chief concern raised by each lab director since staff constraints limit their capacity to take on new testing while managing existing responsibilities. Key staffing challenges include difficult shifts/schedules, pay scale restraints, and low morale causing churn.

Skill set and validation: Esoteric testing often requires specialized skills for validation, and many hospital labs lack the necessary personnel with the required expertise and certifications, especially in smaller rural settings.

Capital approval: Getting approval for the capital required for new equipment, such as LCMS, often proves to be a significant hurdle. Those surveyed for this study each said they lack a seat at the table to properly advocate for themselves or raise these issues with their C-suite.

Lack of space: Many hospital labs face constraints due to limited lab space, potentially hindering the incorporation of new testing lines or required staff. One potential solution is to utilize space outside of the core lab for esoteric testing alongside the necessary courier infrastructure to support it.

Little incentive for existing staff: Due to the issue of existing staff already being stretched thin, panel members said there is sometimes little direct incentive for their teams to add new testing since they will be required to oversee it and will likely receive no additional support or compensation in the short term.

Making the business case

"For inpatient-only labs, bringing in new esoteric testing depends largely on the size of the hospital," says Roger Newbury, Managing Director of Legend Consulting Group, which specializes in performing operational assessments for labs. Reviewing monthly send-out reports and the actual reference costs can help determine whether bringing this testing in-house makes sense for a given hospital lab.

"In order to make this successful, labs need to fully understand their costs and actual reimbursements, thoroughly analyzing the data for a better-informed decision," Newbury says. "They need to work off the test reimbursements versus billed amount — reimbursement by carrier (payer) is the only valid data point."

Harol echoes this point, adding that many lab directors can benefit from an advocate in their corner who can make the business case for why a particular test could lead to profit down the line for a hospital. "If a test is being sent out, in order to figure out whether it makes sense to bring it in-house, a lab director needs the time to make that case, aside from their day-to-day duties," Harol says. "Oftentimes, it's more than they have time and energy to commit to."

Another opportunity: Strengthening outreach programs

"Hospital labs should also look to strengthen their outreach programs to collect potential high-margin testing that often doesn't reach their facilities due to local, in-network physicians directly sending samples to commercial labs," Harol says. "Developing effective communication and outreach strategies to reach these physician practices can address this issue, ensuring that profitable testing stays within the hospital system."

Overcoming these challenges: A proposed solution

Both Harol and Newbury say the solution to this advocacy and data issue is for hospital labs to partner with third-party groups who can provide the equipment, staff, and expertise needed to insource esoteric testing into hospital labs. Lab directors interviewed for the Lighthouse panel said they would be open to exploring a collaborative approach with a profit-sharing model, aligning incentives for both parties.

"When correctly armed with factual data, coupled with the right partner to provide the resources necessary to reconfigure the workflow without costing labs any funds, a very compelling argument can be made about adding this type of business," Newbury says.

Looking ahead: Unlocking the full potential of hospital labs

In short, hospital labs should seek to shift their perspective, explore profitable in-house testing, and consider collaborative solutions with outside experts when their resources to advocate and build a business case for their labs are stretched thin. By addressing staffing, skill set, capital request, space, and outreach challenges, hospital labs have the potential to transform into profit-generating entities rather than be viewed simply as cost centers.

"Bringing profitable testing into the lab solves many of the issues currently plaguing labs today," Harol notes. "Instead, health systems are selling their labs. We want to change that trend and the perception of hospital lab profitability as a whole."

Alex Mitchell is Marketing Communications Manager at **Lighthouse Lab Services**. He works to keep the team and their clients abreast of industry news and changes that could impact their operations or revenue. Alex also manages Lighthouse's educational content, including monthly webinars, blogs, and industry newsletters.

Henry Ford Health

Henry Ford Health: A leader in physician wellness, automation, and process improvement

By Michael Kalinowski

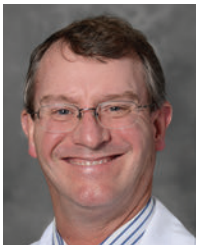
It's a question that many in the clinical laboratory C-suite are asking. How do we handle all-time-high testing volumes while also addressing the negative effects of growing caseloads and understaffing on the collective mental health of our medical laboratory personnel? Physician burnout and a lack of qualified laboratory technologists were pre-pandemic issues that have turned into full-blown crises within the industry.[1,2] In terms of burnout, the numbers are very troubling. A recent poll by the American Society of Clinical Pathology (ASCP) revealed that burnout is widespread, with 71.4 percent of practicing pathologists saying they have felt burnout at some point on the job. Another 32.9 percent responded by saying that burnout was a current problem.

Anxiety and stress are on the rise thanks to several factors, with the most pressing issue being a lack of qualified personnel to assist pathologists with their unrelenting caseloads. It is estimated that the clinical lab industry is short some 25,000 laboratory technologists even as employable candidate numbers continue to plummet. Add to that, industrywide struggles with budgets impacted by the pandemic, inflation in the form of rising supply costs, and more expected reimbursement cuts, and you can understand how burnout is now a real threat to the profession.

But all is not lost. Some within the industry have been able to successfully navigate these uncertain times with programs that target burnout, understaffing, and inefficient processes. Henry Ford Health, one of the nation's leading and largest healthcare providers with more than 1,900 physicians among its approximately 33,000 employees, has incorporated a wellness program, automation in the laboratory, and Lean management to navigate today's staffing issues. What follows is a look at the steps taken by the organization as a whole, and the Pathology Informatics department in particular, to guard against physician burnout and understaffing.

There are significant challenges everywhere

J. Mark M Tuthill, MD, is the Division Head of Pathology Informatics at Henry Ford Health. He is a leading voice for pathology informatics and believes that patient care is directly enhanced by applying information technology to pathology and laboratory medicine. Tuthill leads a department that manages medical laboratory testing for 5 acute care hospitals and 263 ambulatory sites located throughout central and southeast Michigan. In a recent interview, he was asked to describe how burnout and staffing challenges have affected the medical group.


J. Mark M Tuthill, MD

"There are significant challenges everywhere," he said. "It's something that I'm very concerned about." Tuthill said that a lack of available pathologists and a slowing pipeline in areas of pathology means current practitioners are forced to do more with less and that ultimately puts everyone at risk for burnout. "Look at what pathology labs have to do now to hire and retain staff. It goes beyond just bringing in med techs. The main challenge is finding qualified personnel to hire in the first place," he said. The reasons for this are well known. The med tech pipeline has been undermined by universities that lack interest and appreciation for what they do, and when compared to nurses with equivalent training and experience, these technologists are compensated at roughly 50 cents on the dollar.

Tuthill said that the industry is still in a recovery mode economically post-pandemic. That coupled with increasing requirements for compensation is making a difficult situation even worse for everyone in healthcare.

The We Care Physician Wellness Program

For Tuthill and other members of the Henry Ford leadership team, physician burnout is not a new concept. He sits on a wellness committee that pre-dates the pandemic. The We Care Physician Wellness Program[3] was first established by Lisa MacLean, MD, the medical group's Chief Clinical Wellness Officer, in 2017.


Lisa MacLean, MD

At the time, a program like this was uncommon, but even back then Tuthill saw the need for it. "We were already recognizing signs of physician stress and burnout, plus a lack of availability for individuals who support physician activities. As a leadership group, we realized the need for wellness activities, especially for the professional staff," he said.

So, even though the physicians at Henry Ford were consistently reporting burnout rates lower than the national average, Tuthill said a decision was made to do more, and a committee was formed with MacLean taking a leading role. According to MacLean, the overall strategy behind the wellness program was based on an existing Stanford model that recognized the need for a systemwide approach and a focus on the systemic problems that exist in healthcare and drive burnout. In those early days, her principal role was to both ask questions and listen to her colleagues. "It was important that I approach the role with humility," she said. "There were others within the organization who also had a passion for this work, and I needed to harness their energy and add them to my small army of people tasked with preventing and mitigating burnout while also improving overall well-being."

For MacLean, taking on this role was a natural next step after years of preparation. She first developed an interest in wellness and education as a Residency Program Director of Psychiatry at Henry Ford Hospital early in her career. From there, she further pursued her interest by becoming the Associate Dean of Students at Wayne State School of Medicine in 2012.

While at Wayne State, MacLean witnessed firsthand the negative impact that the curriculum and delivery of medical education were having on student well-being. Thats where she also became fully aware of the importance of having easy access to mental health support. "As I worked in that role to develop health and wellness programming for the students, I further fell in love with the work," said MacLean, who also acknowledged her struggles with burnout during this point in her medical journey. "I felt that I had an important voice to bring to the table and wanted to further envelop myself in this work."

After five years of refining her program at Wayne State, MacLean was ready for a change. Thats when she contacted Henry Ford Health and shared a white paper with leadership that outlined her plans and why they should hire her to lead a wellness program. Henry Ford Health did just that in 2017, and the creation of MacLean's position coincided with a mandate from the Accreditation Council for Graduate Medical Education calling for all institutions that sponsor residency and fellowship programs to have wellness programming.

"My journey began there, and I can attest that it's been challenging work, especially in the context of all the systemic healthcare delivery problems that currently exist," stated MacLean. "No doubt, medicine attracts high-achieving, resilient, gritty people but when they are placed into situations that do not allow them to do the work that matters the most, and they are not working at the top of their license, this drives distress and burnout."

MacLean says the coronavirus pandemic hugely impacted healthcare and providers in a very palpable way. She says she's still seeing the effects of this today. "I'm seeing more exhaustion, angst, and suffering than before," she said. "Many feel the system is the problem. I agree that the system is problematic, but I also feel that, as individuals, we need to strive to control what we can and pay attention to what we do. How we interact, how we show up, and how we take responsibility for our self-care."

Creating a happier workforce

At Henry Ford Health, the wellness program is run by physicians for physicians. The primary goal is to optimize healthy coping strategies and help physicians find a good work–life balance that will allow them to deliver high-quality care and find greater satisfaction in their careers and lives. "It's all about creating a happier workforce," said Tuthill. "We try to identify the issues and take actionable steps to correct them, so colleagues don't take patient work home with them when they leave work." Tuthill also noted that the program provides emotional and psychiatric help discreetly so those experiencing high-stress levels, anxiety, and/or depression can get the help they need without being placed in jeopardy for doing so.

Since the advent of the program, Henry Ford Health leadership has supported the hiring of a health psychologist for psychotherapy and two psychiatrists for medication support. Additionally, the group has changed its credentialing questionnaire by removing a question asking about a clinician's mental health treatment history. Also noteworthy is the fact that the medical group has updated its vacation policy, so physicians now get the maximum amount of vacation after 10 years of service. "We strive to break down walls and barriers and open doors so that people who need mental health treatment can easily seek it," said MacLean.

> A key component of the Henry Ford Production System is the empowerment of every employee to improve their work product or service.

In Tuthill's experience, even a little gesture of kindness in the form of a wellness cart with clowns, balloons, and candy can make people feel valued and appreciated. "Our carts travel around the health system, visiting departments and floors. It makes you stop and think about wellness, and this is a primary goal for the committee. We want our colleagues and our healthcare system to take ownership of wellness. To be more mindful and intentional about their well-being," said Tuthill.

The role of automation and pathology informatics

It's unfortunate, but most often true in all forms of business: When budgets are strained, non-value-added services and human resources are cut to make up the difference. Tuthill acknowledged that this is a scenario many pathology labs are facing today. Even under the weight of burnout and understaffing, human resources are being targeted. Doing more with less is nothing new for anyone who has spent time in a clinical laboratory, but how can these businesses survive and even thrive during turbulent times?

For Henry Ford Health, it starts with automation.

"If we didn't have the automated chemistry line and the automated staining solutions in histology, and if we weren't extensively using barcode technology to drive all of our interactions with these assets, we wouldn't be able to keep the lab running," said Tuthill. "Without automation, we'd be closing our doors."

Tuthill also suggested that labs with well-deployed technology in areas like digital pathology, molecular technology, and lab automation may have an edge in the retention and recruitment of staff. "In the end, it comes down to automating processes and eliminating defects by standardizing work and using lab analytics," he said. "The two are interrelated." Simply stated, without lab analytics, you cannot see where the problems are.

"Some of these problems live deep under the hood, and it takes a lot of effort to get under the hood and find them," he said. Tuthill used a label issue problem as an example. During recent quality assurance work on the automation line, his department identified a pre-analytic problem. The lab was receiving defective tubes that had unreadable labels. This resulted in the need to reprocess all of those samples in the defective tubes. According to Tuthill, this minor issue could have translated into a $200,000 annual cost if it wasn't caught. However, the issue was solved with regular printer maintenance and adjustments to the formatting of the label.

"Identifying simple things like this and then focusing efforts to solve the problem, most organizations don't have the wherewithal to do this," said Tuthill. "It's something we've committed to because we know if we fix these problems, we're going to save time and staff requirements."

The Henry Ford Production System and its adaption of Lean management

At Henry Ford Health, the commitment to being a world-class laboratory organization dedicated to a lean culture and relentless improvement dates back to 2005. That's when leadership first integrated the concept of the Henry Ford Production System into their lab operations to eliminate wasteful practices and innovate more efficient processes that focus on the needs of the patient.[4]

"There's nothing that information technology likes better than lean quality management because it gets people to use our systems efficiently and consistently, and that allows us to identify defects and resolve them," said Tuthill, who also noted that keeping the present lean culture intact is in itself a tremendous effort because of inevitable staff turnover and retraining.

A key component of the Henry Ford Production System is the empowerment of every employee to improve their work product or service. Every employee has a voice and is incentivized to seek continuous improvement at his or her level of work. "Finding ways to improve efficiency allows us to do what we do," concluded Tuthill. "With our very defined culture, all staff members can take ownership of their roles, identify deficiencies in standardized processes, and work to solve them in the most efficient manner possible."

That brings to mind a phrase first attributed to Henry Ford back in 1918: 'Quality is what counts, and nothing but quality.' That phrase remains a guiding principle for Tuthill and his pathology informatics team, and they strive to live up to this standard every day.

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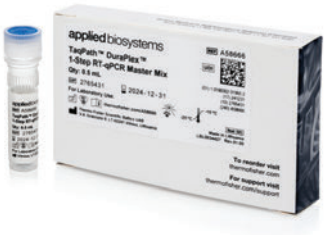

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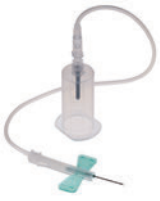

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Factors to consider in molecular diagnostics testing during the preanalytical phase

By Dr. Eric Gonzalez Garcia

Molecular diagnostics applies techniques of molecular biology to diagnose disease, as well as predict its course; select appropriate treatments; and monitor treatments' effectiveness.[1] Testing within this medical field often involves a complex workflow of many steps that are prone to variability. Different factors can influence this variability, and if they are not controlled, they could alter specimen integrity and thus lead to patient misdiagnosis.

The preanalytical phase plays an important role in the entire workflow followed in molecular diagnostics, with steps that include ordering of the test, as well as the collection, transport, storage, and processing of the sample. This last step, which comprises the extraction of the molecular target, is a fundamental method in molecular biology, as it is the beginning of downstream processes and product development, including diagnostic kits. Errors made in each of these steps can have a significant impact on the correct diagnosis of a patient. This review analyzes important variables in these preanalytical phase steps that have an impact on molecular diagnostics testing.

Test ordering and patient health status

Medical specialists request molecular tests to enable them to reach a diagnosis and to choose a treatment strategy. In this regard, physicians requesting a molecular test should be aware of the limitations of such tests in management and decision making, as well as the cost–benefit ratio.

Errors in test ordering are due to a variety of reasons and are commonly the result of simple mistakes, such as unnecessarily repeating a test, forgetting to order a test, or simply ordering the wrong test. The implementation of electronic medical records systems has contributed to reducing these errors, resulting in a decrease in duplicate orders, as well as reduced costs and fewer issues with preauthorization.[2] Additionally, diagnostic stewardship programs in areas like infectious diseases can assist not only in guiding test ordering, but also in speeding up test results and their interpretation.[3,4,5]

A patient's health status also plays a role in the results of molecular diagnostic tests. Patients receiving antiviral treatment are monitored for treatment efficacy by nucleic acid amplification tests (NAAT), where viral loads decrease to low or undetectable levels with treatment. In the case of a CMV (cytomegalovirus) infection, for example, viral load has been also used not only for its prognostication, but also as a guidance for preemptive therapy and an indication of the risk of clinical relapse or drug resistance.[6] A similar effect on disease management is applied to HIV patients undergoing preexposure prophylaxis, who in addition to showing a reduced viral load may present a delayed seroconversion, which hinders the detection of HIV RNA and antibodies.[7,8] In cases of an acute viral infection like COVID-19, patients experience evident symptoms, and the viral load is at detectable levels. However, testing during the early phases of a latent period can lead to false negative results if there are low levels of viral particles; it is therefore important to consider replication dynamics when performing molecular testing.[9]

Sample adequacy, collection, transport, and storage

When a patient is suspected of having an infection, various factors can influence a test's efficacy in diagnosing them. False positives may be caused by lingering traces of viral DNA or RNA, specimen contamination, or other complications.

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False negatives are also possible, largely caused by improper sample collection and handling.[3]

Hemolysis of blood samples is the most frequent pre-analytical interference and a major source of error leading to unreliable test results. The effect of in vitro hemolysis should be considered in the fields of cancer diagnostics and non-invasive prenatal testing. In this sense, the release of genomic DNA from non-tumor and maternal white blood cells can lead to underestimation of the tumor DNA and fetal DNA fractions, respectively, in hemolyzed samples.[10]

The adequacy of the collection method used is of paramount importance when assessing the quality of molecular amplification methods in clinical diagnostics. In blood and bone marrow specimens, clotting must be inhibited, with EDTA and citrate being commonly used for this purpose. Specimen collection systems containing citrate dilute the specimen by 10%, while heparin (routinely 14.3 IU/ml of whole blood) inhibits amplification in concentrations as low as 0.05 IU per reaction volume.[11] Components of whole human blood (WHB), like immunoglobulin G, hemoglobin and lactoferrin can also act as PCR inhibitors. Additionally, it may be possible to completely inhibit *Taq* DNA and Ampli*Taq* Gold, common polymerases used for PCR, in the presence of less than 0.2% WHB, when direct PCR is performed.[12] PCR inhibitors generally act through the inactivation of DNA polymerases, binding of DNA polymerase co-factors, or degradation of target nucleic acids and/or primers.[13]

Collected blood can be used directly (whole blood) or be fractionated into serum, plasma, or buffy coat. If the fractions are not intended for short term usage, they should be divided into multiple aliquots in small vials and stored in freezers to avoid multiple freeze-thaw cycles. Whole blood can be temporarily stored at room temperature for up to 24 hours, or in the refrigerator (2°C – 8°C) for a maximum of 72 hours. After this time, genomic DNA (gDNA) will degrade.[14] If this time is exceeded, the erythrocytes should be removed, since the heme group can inhibit the PCR.

As for RNA, whole blood should be collected in tubes containing an RNA stabilizer. If this is not possible, the specimen should be placed on ice immediately after collection and transported to the laboratory for RNA extraction. The quick addition of RNase inhibitors is also an established step in the preanalytical phase when working with RNA assays.

When compared to whole blood plasma, serum is less favorable in molecular diagnostics due to its lower DNA yield. However, it may be suitable for evaluating gDNA. For DNA or RNA studies, serum should be shipped frozen on dry ice and stored at -20°C.[15,16]

Plasma DNA concentrations gradually decrease over time and can be delayed by keeping the samples stored at a temperature ranging between 2°C to 8°C. Evaluation of the effects of different storage temperatures on RNA and DNA levels in unfiltered plasma showed that storage of samples at 4°C yielded stable RNA levels for up to 24 hours, while DNA levels were stable at both 4°C and room temperature for 24 hours.[17]

Buffy coats, as a layer enriched in white blood cells, are commonly used as a source of nucleic acids for molecular assays. If DNA extraction from buffy coat is performed within days, it is recommended to isolate it and store at -70°C or lower.[18] If, however, DNA isolation occurs immediately after collection, it can be stored long term (for up to 9 years) in a deep-frozen state (-80°C).[19] Additionally, resuspending the separated buffy coat in TRIzol and immediately cryopreserving it at -80°C is very effective for extracting RNA of high purity and quality that is suitable for sequencing.[20]

Sample processing

Preparing a sample for molecular testing requires different processes in which the sample is mixed with reagents for extraction, stability, and amplification. Some samples, such as sputum and saliva, are difficult to process due to their high viscosity, making them difficult to handle in laboratories with automated platforms. These samples can cause pipetting errors and contamination. To prevent this from happening, homogenization procedures are implemented to liquify the sample prior to nucleic acid extraction, which can include proteinase K or dithiothreitol,[21] as well as a mechanical disruption by glass bead beating.[22]

Although working with viscous samples can cause issues in automated platforms, there are many benefits to working in an automated fashion as it can improve throughput, reproducibility, and maximize the laboratory technician's time for data analysis. Additionally, the risk of sample contamination can be reduced, as well as environmental contamination of the laboratory, with potentially infectious material.

Additional pretreatments that can have a positive impact on sample processing and downstream molecular testing involve work with pathogen inactivating agents. A chemical commonly used for this purpose is guanidinium thiocyanate, which is the main component of nucleic acid extraction kits. Buffers containing it destabilize the viral envelope and eliminate cellular nucleases, while maintaining the structure of DNA and RNA for subsequent molecular biology analysis in lower biosafety level facilities.[23] Other methods include thermal inactivation, UV radiation, and the use of formaldehyde.[24,25,26]

Conclusion

The preanalytical phase of the molecular diagnostics workflow is complex and requires meticulous attention to best practice, as sample quality forms the basis for accurate patient diagnosis and treatment. While the field of molecular diagnostics constantly evolves, the preanalytical phase will continue to influence its effectiveness and trajectory.

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Eric Gonzalez Garcia received his doctorate in Technical Chemistry at Vienna University of Technology in 2019. He is currently serving as Global Product Manager for Molecular Diagnostics Systems at **Greiner Bio-One**, a global company specializing in the development, production, and distribution of high-quality laboratory products.

INDEX OF ADVERTISERS

LABORATORY INNOVATOR

Lab Services in an award-winning healthcare system

By Christina Wichmann

Mary Colaizzi is the Director of Laboratory Services at **Edward-Elmhurst Health**. Before being promoted to Director of Laboratory Services in July 2021, Mary was System Manager over Edward and Elmhurst Laboratories with responsibility over Core Laboratory and Blood Bank. In addition to the above responsibilities, Mary also managed the satellite laboratory that supports the emergency room in Plainfield, Illinois. Mary's laboratory responsibilities included supporting the supervisors with day-to-day operations along with financial and regulatory responsibilities.

Prior to joining Edward-Elmhurst Health (EEH) in 2014, Mary was Director of Laboratory in Palmdale, California with financial and regulatory responsibilities.

Mary graduated from Benedictine University in Lisle, IL.

Could you describe the customer service attributes of your laboratories that you are most proud of?

I am most proud of our customer service staff. They are experienced and extremely knowledgeable about the laboratory. Our customer service center is located at our Elmhurst laboratory and the team fields calls for both Edward and Elmhurst laboratories. The team will investigate issues prior to handing off concerns to the departments. A recent example was forwarded to our leadership: "kudos" from a LabCorp employee who stated that Chiquila is extremely knowledgeable and will take the time to read all notes and will use all the tools provided before reaching out, in addition, she is very polite and always has a positive attitude.

Are there particular lessons learned you can share with other laboratory directors on reducing laboratory errors?

In March of 2020 our laboratory created a Quality Coordinator position as a system role between Edward and Elmhurst. We were honored to hire Michelle Irving into this role who held various positions that supported the laboratory over the past 12 years. Michelle has a passion for quality and has enhanced our quality program.

Each month we discuss our quality metrics at each hospital and then compare Edward and Elmhurst to each other. This is a nice way to understand challenges that each hospital may be facing and discuss opportunities to improve processes. Some lessons that we have learned over the years is that we need to have all instruments interfaced to reduce manual entry and human error. In addition, we have a very supportive laboratory IT team — most of this team are MLS's that understand workflow within the laboratories.

What is the current vacancy rate at your lab? What strategies have you found to be successful in recruiting and retaining staff?

Currently, our vacancy rate is 5.8% with 12 FTE openings across both Edward and Elmhurst laboratories. During the pandemic, we experienced a vacancy rate as high as 24%. Last November as we were experiencing staff burnout, we needed to hire agency staff to fill the void. Over the past 10–11 months, as new staff have come on board, we were able to end the contracts with our agency staff. We are very thankful that we were able to find agency staff to lessen the burden on our employees.

In the past 6–8 months, we worked very hard on strengthening the onboarding process in the lab. As new employees finish the hospital orientation, we have their second day on the job as a lab orientation in a group setting. For example, if we have five new hires in a week across both Edward and Elmhurst, we gather all the new employees at one location to go through the mandatory safety and new hires mandatory modules together. The supervisors will rotate the education and take the team to lunch. This is a nice way to connect with the new employees. In addition, it's a nice way to connect leadership to all department staff to get to know each other better. Our leaders are expected to check-in with the new staff members on a weekly basis and document how their training is proceeding and what they need in order to make the transition more seamless. In addition, we ask "what can we do better?"

Some strategies that we have implemented over the past two years are quarterly "Round Table" discussions with a few staff members from each department. This forum is about 4–5 staff members, we talk openly with their supervisor, manager, and director to discuss what is going well, what obstacles or processes are needing some attention, etc. We start the conversation with "This is a safe place, and we are here to listen, nothing is off limits."

Do you have strategies you can share for getting new tests and equipment approved for your laboratories?

Edward and Elmhurst merged with Northshore in January 2022; over the past (almost) two years we have engaged in conversations to learn from each other. Then, in May of 2023, the whole laboratory system is now under one VP of all the laboratories to better align across the whole NS-EEH system. With the new laboratory organizational structure, we have opportunities to better align standardization across the system and obtain better vendor contracts. Most recently, all eight acute care hospitals have standardized Diagnostica Stago Coagulation instrumentation and soon will all align with Grifols automation in our blood banks.

We are beginning to look at redundancies across the system especially with some of our lower-volume tests. We immediately found approximately 20 send-out tests that we can send to a sister hospital to save over $100K per year by keeping the testing within our system.

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