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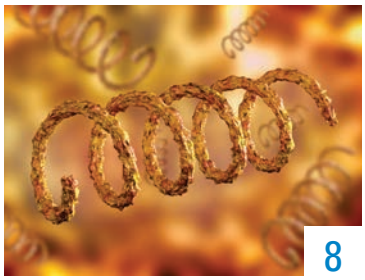

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Not all tests are created equal.

When it comes to results, rapidly mutating viruses can continue to evade quantification with viral load assays that do not have built-in redundancy. Make sure patients receive accurate results. Count on assays trusted in clinical trials for HIV, HBV, and HCV therapeutics since 1996.

Data security

By Christina Wichmann
Senior Editor

In this issue, we published the results of our State of the Industry on Laboratory Data Analytics. Thank you to all who responded to this survey. As can be seen in the results, numerous functions are managed electronically through laboratory information systems (LIS)—patient orders and lab results, patient scheduling, integration with analyzers, quality control activities, and billing, among other functions. Many of the readers of MLO work in labs that are performing millions of tests each year. Suren Avunjian, LigoLab CEO told our author,"Implementing electronic processes is vital if the lab has any significant operational volume and it is looking for efficiency to retain and keep its current customers happy, plus has plans to grow its customer base, expand its test menu, and increase throughput."

While labs are trying to implement electronic processes to keep up with test volumes, maintain customer relationships, support a strong quality assurance program, etc., they also have to deal with cybersecurity issues. The healthcare sector is one of the most targeted industries by cybercriminals. Recently, the U.S. Department of Health and Human Services' Health Sector Cybersecurity Coordination Center (HC3) issued a memo warning that the hacktivist group 'KillNet' is actively targeting the healthcare sector. KillNet is known for its distributed denial of service (DDoS) attacks, which block legitimate users from accessing information systems, devices, and networks. Recent healthcare organizations affected by this group include Cedars-Sinai, Duke University Hospital, University of Michigan Health, Washington University School of Medicine, among others.

Healthcare organizations are also the most targeted in ransomware attacks. Per the *HIPAA Journal*, healthcare ransomware attacks in the United States were estimated at $21 billion in 2020. As I write this, in today's news, Highmark Health suffered a phishing attack that impacted 300,000 individuals and their private information. Highmark discovered that one of its employees was sent a malicious link that led to their email account being compromised.

Phishing emails are one of the most prevalent ways to spread ransomware in healthcare organizations. These emails trick the reader into clicking on a link or opening an attachment that allows cybercriminals to gain access to the employee's computer and begin the process of installing and executing the ransomware program on it.

More than 80% of data breaches involve a human in some way. The U.S. Cybersecurity and Infrastructure Security Agency (CISA) provides the following basic guidelines for individuals' routine technology use:

Think before you click: If a link looks a little off, think before you click. It could be an attempt to get sensitive information or install malware.

- Update your software: Don't delay — if you see a software update notification, act promptly. Better yet, turn on automatic updates.
- Use strong passwords: Use passwords that are long, unique, and randomly generated. Use password managers to generate and remember different, complex passwords for each of your accounts.
- Enable multi-factor authentication: Requiring more than a password and enabling MFA makes you significantly less likely to get hacked.

Reading this information was a reminder for me. I hope it was also useful to you.

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

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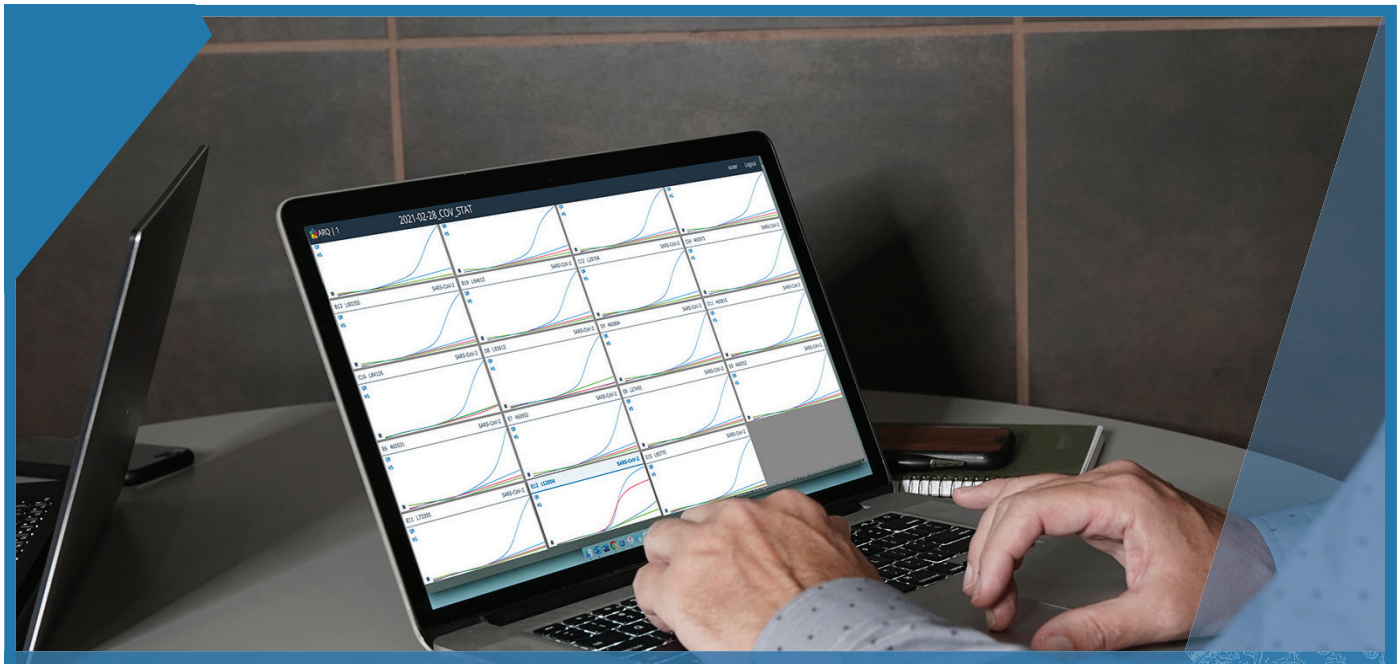

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Fast Facts

A new study, one of the first to look at the link between living in rural America and first-time cases of heart failure, underscores the importance of developing more customized approaches to heart failure prevention among rural residents, particularly black men. The study was largely funded by the National Heart, Lung, and Blood Institute (NHLBI), part of NIH, and the findings, produced in collaboration with Vanderbilt University Medical Center, Nashville, Tennessee, were published in *JAMA Cardiology*.

According to the study:

27,115

adults without heart failure at enrollment, from 12 states, were followed for about 13 years.

20%

of participants lived in rural areas; the remainder lived in urban areas.

19%

higher risk of developing heart failure in adults living in rural areas of the United States compared to their urban counterparts.

34%

of black men living in rural areas have an especially higher risk.

22%

increased risk of heart failure in white women living in rural areas compared to white women in urban areas.

18%

higher risk of heart failure for black women living in rural areas compared to black women in urban areas.

No association was found between rural living and heart failure risk among white men.

Source: https://www.nih.gov/news-events/news-releases/risk-developing-heart-failure-much-higher-rural-areas-vs-urban

Five billion people unprotected from trans fat leading to heart disease

Five billion people globally remain unprotected from harmful trans fat, a new status report from the World Health Organization has found, increasing their risk of heart disease and death.

Currently, 9 of the 16 countries with the highest estimated proportion of coronary heart disease deaths caused by trans fat intake do not have a best-practice policy. They are Australia, Azerbaijan, Bhutan, Ecuador, Egypt, Iran (Islamic Republic of), Nepal, Pakistan and Republic of Korea.

Best-practices in trans fat elimination policies follow specific criteria established by WHO and limit industrially produced trans fat in all settings. There are two best-practice policy alternatives: 1) mandatory national limit of 2 grams of industrially produced trans fat per 100 grams of total fat in all foods; and 2) mandatory national ban on the production or use of partially hydrogenated oils (a major source of trans fat) as an ingredient in all foods.

While most trans fat elimination policies to date have been implemented in higher-income countries (largely in the Americas and in Europe), an increasing number of middle-income countries are implementing or adopting these policies, including Argentina, Bangladesh, India, Paraguay, Philippines and Ukraine. Best-practice policies are also being considered in Mexico, Nigeria and Sri Lanka in 2023. If passed, Nigeria would be the second and most populous country in Africa to put a best-practice trans fat elimination policy in place. No low-income countries have yet adopted a best-practice policy to eliminate trans fat.

In 2023, WHO recommends that countries focus on these four areas: adopting best-practice policy, monitoring and surveillance, healthy oil replacements and advocacy. WHO guidance has been developed to help countries make rapid advances in these areas.

WHO also encourages food manufacturers to eliminate industrially produced trans fat from their products, aligning to the commitment made by the International Food and Beverage Alliance (IFBA).

Mayo Clinic researchers link ovarian cancer to bacteria colonization in microbiome

A specific colonization of microbes in the reproductive tract is commonly found in women with ovarian cancer, according to a new study from Mayo Clinic's Center for Individualized Medicine. The discovery, published in *Scientific Reports*, strengthens evidence that the bacterial component of the microbiome — a community of microorganisms that also consists of viruses, yeasts and fungi — is an important indicator for early detection, diagnosis and prognosis of ovarian cancer.

The study also suggests that a higher accumulation of pathogenic microbes plays a role in treatment outcomes and could be a potential indicator for predicting a patient's prognosis and response to therapy.

For the study, the researchers investigated samples of 30 women undergoing a hysterectomy for ovarian cancer and compared them to samples of 34 women undergoing a hysterectomy for a benign condition. They used high-throughput sequencing to analyze the samples, which were recovered from the lower and upper reproductive tract, peritoneal fluid, urine, and anal microbiome.

In the women with ovarian cancer, the team observed a colonization of disease-causing bacteria, including *Dialister, Corynebacterium, Prevotella and Peptoniphilus*.

Joint Commission announces major standards reduction to provide relief to healthcare organizations

The Joint Commission is eliminating a total of 168 standards (14%) and revising 14 other standards across its accreditation programs to streamline requirements and make them as efficient and impactful on patient safety, quality and equity as possible.

The first tranche of standards deletions and revisions went into effect on January 1. They include six deleted and one revised standard for the Laboratory Accreditation Program.

The standards reduction is the result of The Joint Commission's comprehensive review that was announced in September 2022. The Joint Commission reviewed all its "above-and-beyond" requirements – those that go beyond regulatory requirements of the Centers for Medicare & Medicaid Services (CMS) Conditions of Participation (CoPs) and are not on crosswalks to the CoPs. Specifically, The Joint Commission reviewed each standard to answer:

- Does the requirement still address an important quality and safety issue?
- Is the requirement redundant?
- Are the time and resources needed to comply with the requirement

commensurate with the estimated benefit to patient care and health outcomes?

In addition to a direct review of each standard, The Joint Commission conducted quantitative analyses of scoring patterns and tested for redundancy. Where necessary, The Joint Commission led literature and field reviews and engaged experts within the field.

CMS approved the recommended discontinued standards after confirming they do not diminish any CMS regulatory requirements. Importantly, a second tranche of standards is under consideration for elimination or revision, and a second announcement of burden reduction is anticipated in approximately six months.

Marburg vaccine shows promising results in first-in-human study

A newly published paper in *The Lancet* shows that an experimental vaccine against Marburg virus (MARV) was safe and induced an immune response in a small, first-in-human clinical trial. The vaccine, developed by researchers at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, could someday be an important tool to respond to Marburg virus outbreaks.

This first-in-human, Phase 1 study tested an experimental MARV vaccine candidate, known as cAd3-Marburg, which was developed at NIAID's Vaccine Research Center (VRC). This vaccine uses a modified chimpanzee adenovirus called cAd3, which can no longer replicate or infect cells, and displays a glycoprotein found on the surface of MARV to induce immune responses against the virus. The cAd3 vaccine platform demonstrated a good safety profile in prior clinical trials when used in investigational Ebola virus and Sudan virus vaccines developed by the VRC.

In this study, 40 healthy adult volunteers were enrolled at the Walter Reed Army Institute of Research Clinical Trials Center in Silver Spring, Maryland. They received a single dose of either a low dose of the vaccine (1x1010 particle units) or a higher dose (1x1011 particle units). For safety, the volunteers were enrolled in a dose-escalation plan. Three participants received the lower dose. Then, when they did not exhibit severe adverse reactions after the first seven days, the trial proceeded to enroll the remaining 17 volunteers. The same procedure was also used for the higher dose group. Volunteers were monitored for adverse reactions to the investigational vaccine and evaluated at regular intervals for 48 weeks to track their immune responses.

The trial's safety results were encouraging: There were no serious adverse events, and the experimental vaccine was well-tolerated. One participant in the higher dose group developed a fever following vaccination, but it resolved by the following day. In addition, the investigational vaccine appeared to induce strong, long-lasting immunity to the MARV glycoprotein: 95% of participants in the trial exhibited a robust antibody response after vaccination, and 70% maintained that response for more than 48 weeks.

WHO updates COVID-19 guidelines on masks, treatments and patient care

The World Health Organization (WHO) has updated its guidelines on mask wearing in community settings, COVID-19 treatments, and clinical management. This is part of a continuous process of reviewing such materials, working with guideline development groups composed of independent, international experts who consider the latest available evidence and the changing epidemiology.

WHO continues to recommend the use of masks by the public in specific situations, and this update recommends their use irrespective of the local epidemiological situation, given the current spread of the COVID-19 globally. Masks are recommended following a recent exposure to COVID-19, when someone has or suspects they have COVID-19, when someone is at high-risk of severe COVID-19, and for anyone in a crowded, enclosed, or poorly ventilated space. Previously, WHO recommendations were based on the epidemiological situation.

Similar to previous recommendations, WHO advises that there are other instances when a mask may be suggested, based on a risk assessment. Factors to consider include the local epidemiological trends or rising hospitalization levels, levels of vaccination coverage and immunity in the community, and the setting people find themselves in.

WHO advises that a COVID-19 patient can be discharged from isolation early if they test negative on an antigen-based rapid test.

Without testing, for patients with symptoms, the new guidelines suggest 10 days of isolation from the date of symptom onset. Previously, WHO advised that patients be discharged 10 days after symptom onset, plus at least three additional days since their symptoms had resolved.

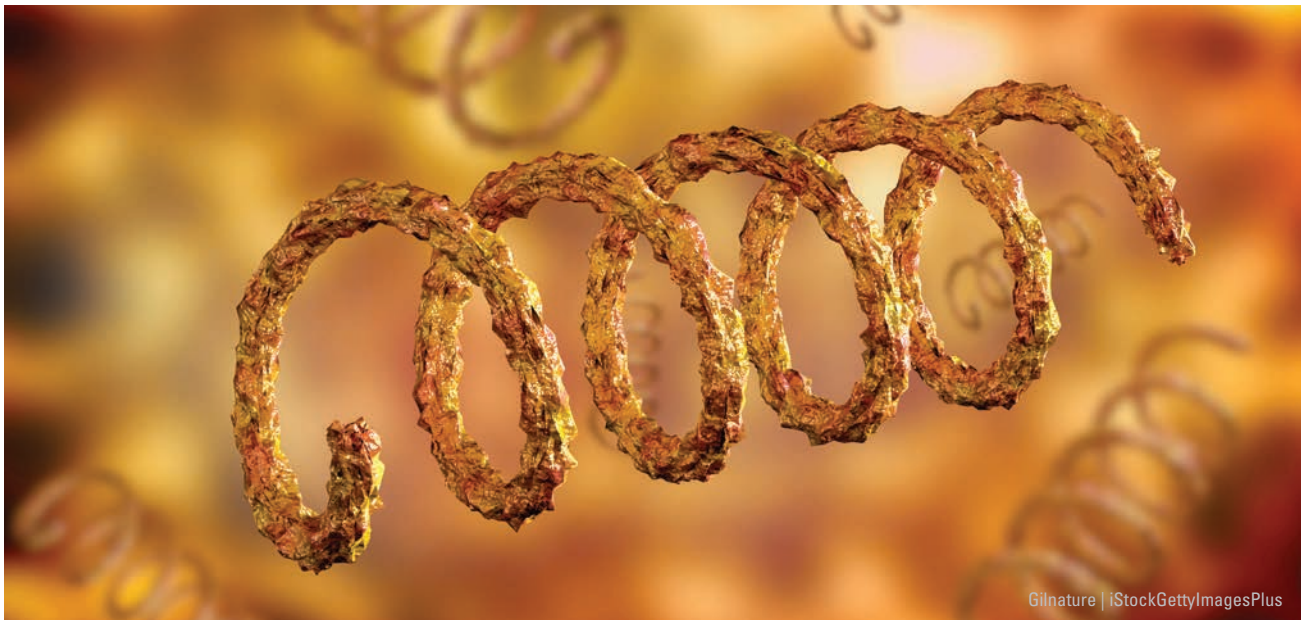
For those who test positive for COVID-19 but do not have any signs or symptoms, WHO now suggests 5 days of isolation in the absence of testing, compared to 10 days previously.

Isolation of people with COVID-19 is an important step in preventing others from being infected. This can be done at home or at a dedicated facility, such as a hospital or clinic.

The evidence considered by the guideline development group showed that people without symptoms are much less likely to transmit the virus than those with symptoms. Although of very low certainty, evidence also showed that people with symptoms discharged at day 5 following symptom onset risked infecting three times more people than those discharged at day 10.

WHO has extended its strong recommendation for the use of nirmatrelvir-ritonavir (also known by its brand name 'Paxlovid').

Pregnant or breastfeeding women with non-severe COVID-19 should consult with their doctor to determine whether they should take this drug, due to 'likely benefits' and a lack of adverse events having been reported.



Syphilis testing: Reverse to move forward

By Jeanne Rhea-McManus, PhD, MBA, DABCC, NRCC and Jim Aguanno, PhD

Syphilis, a sexually transmitted infection caused by the organism *Treponema pallidum*, manifests as a genital ulcerative disease. While the prevalence of syphilis in the United States reached historically low levels in 2000 and 2001, the rate of primary and secondary syphilis has increased almost every year since, up 6.8% between 2019 and 2020 alone.[1]

Syphilis transmission can occur either horizontally or vertically. Sexual transmission (horizontal) of syphilis most commonly occurs through direct contact with a syphilitic sore known as a chancre. In scenarios where a pregnant woman is a carrier of syphilis, vertical transmission to the developing fetus can occur, leading to congenital syphilis with potentially serious consequences to the developing fetus or newborn baby.[2]

Earning CEUs

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LEARNING OBJECTIVES

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

1. Discuss healthcare statistics and the causative agent of syphilis.
2. Describe the different stages of syphilis.
3. Describe detection methods and types of assays for syphilis and their limitations.
4. Discuss the algorithms used in the diagnosis of syphilis and their limitations.

Stages of syphilis disease

The progression of the disease is characterized by primary, secondary, latent, and tertiary stages.[3] The primary stage is typically characterized by the appearance of chancre(s) at the location where syphilis entered the body. These painless sores may last up to six weeks and will heal regardless of treatment. In the absence of treatment, systemic dissemination of *T. pallidum* occurs leading to the appearance of skin rashes and/or mucous membrane lesions that are characteristic of the secondary stage. Similar to primary syphilis, these symptoms will resolve with or without treatment. Without treatment, syphilis remains in the body, and for a period of time there may be no visible signs or symptoms of infection. This stage of infection is characterized as latent syphilis and may last for many years. In rare cases, the disease can progress to tertiary syphilis which occurs 10–30 years after initial infection with potentially fatal consequences. The symptoms associated with tertiary syphilis vary depending on the organ system affected. For example, invasion of the nervous system, visual system, or auditory and/or vestibular system at any stage of infection can lead to neurosyphilis, ocular syphilis, or otosyphilis, respectively.

Testing for syphilis

Syphilis has been called the "great pretender" because it can present very similar to a large variety of other diseases which can sometimes complicate the diagnosis, especially in the later stages.[2] Since syphilis is a chronic and progressive disease associated with significant morbidity and mortality if left untreated, accurate diagnosis and timely initiation of treatment is critical.[2] The diagnosis of syphilis is not based solely on serology, but considers the patient's sexual history, current symptomology, as well as prior syphilis history. Because *T. pallidum* cannot be readily cultured, methods that are able to detect the bacterium

are not widely available leading to the development of other methods for the presumptive diagnosis of syphilis. These alternative methods can generally be grouped into one of two categories: direct detection methods or serologic methods.

Direct detection methods

While direct detection methods provide a definitive diagnosis of syphilis, there is currently no U.S. Food and Drug Administration (FDA) approved or cleared assay for the direct detection of *T. pallidum* available in the United States. Although such methods could provide a critically needed tool for diagnosing the earliest stages of infection, laboratory developed tests (LDTs) are also not widely available or performed at local, reference, or public health labs.

Dark-field microscopy: Using dark-field microscopy (DFM), trained personnel examine wet mounts of exudates from lesions, looking for the characteristic morphology and motility of live *T. Pallidum*.[4] Only specimens collected from primary or secondary lesions are appropriate for detection by DFM as oral specimens are likely to have *Treponema denticola* (normal oral cavity flora), which is morphologically indistinguishable from *T. pallidum*.[4] Although this method is useful at the point-of-care, especially in sexually transmitted disease (STD) clinics, it is not routinely performed on all samples due to a lack of technical skill and/or availability of the required equipment.[5] Timing is also critical as motility begins to disappear approximately 20 minutes after collection.

Molecular assays: A number of nucleic acid amplification tests (NAATs) have been described in the literature targeting a variety of DNA sequences using various methods and have been summarized elsewhere.[6] These tests are generally offered as LDTs, thus is it imperative to ensure that the selected method has been rigorously validated and is always performed with the appropriate quality control material. For specimens collected from mucosal sites, sensitivity of 70% – 95% and specificity of 92% – 98% have been reported.[6] Because the reported sensitivity of molecular assays using blood and cerebrospinal fluid specimens is much lower (24% – 32%),[7] these assays are not recommended for screening an asymptomatic population.

Immunohistochemistry: Several immunohistochemistry (IHC) techniques have been evaluated in formalin-fixed, paraffin-embedded tissue specimens, especially the lesion biopsies from primary and secondary syphilis. The sensitivity of IHC methods range from 49% – 92% for the diagnosis of secondary syphilis.[8] Silver and histological stains are not useful in tertiary disease.[4]

Serologic methods

Given the challenges with direct detection methods, serologic tests remain the mainstay of syphilis diagnosis. Serologic methods include assays that detect either nontreponemal antibodies or antibodies against *T. pallidum* in all stages of infection.

Nontreponemal assays: Nontreponemal assays do not detect antibodies specific for syphilis. Instead, they are based on the ability to detect antibodies against antigens that are released by the cellular damage caused by *T. pallidum* infection or released by the treponeme itself. August Paul von Wasserman developed the first serologic test for syphilis in 1906; the current standard nontreponemal test is the Venereal Disease Research Laboratory (VDRL) slide test, a descendant of the Wasserman test.

The VDRL is a microflocculation test based upon the ability of heat-inactivated serum to flocculate or agglutinate a standardized suspension of reagin (i.e., a purified mixture of cardiolipin, lecithin, and cholesterol). This mixture is placed on a glass slide and viewed at x100 magnification. A sample is interpreted as reactive/positive if clumping is observed and as nonreactive/negative if no clumping is observed.

The rapid plasma reagin (RPR) test is based on a similar principle as the VDRL but is a macroflocculation card-based test.[4] As such, it does not require the use of a microscope to provide an interpretation of the test. Instead, antigen is bound to a carbon particle that is composed of cardiolipin, lecithin, cholesterol particles, and activated charcoal. The presence of a reagin antibody causes agglutination of the antigen, which can be visualized with the naked eye as a black clump against a white background due to co-agglutination of the charcoal particles. If reagin antibodies are not present, no agglutination will be observed.

A similar card-based test is available that uses toluidine red pigment in place of charcoal particles. The toluidine red unheated serum test (TRUST) is reported as reactive/positive when red clumps appear against a white background and is reported as negative/nonreactive if the test mixture remains a faint red color with no observable agglutination.

Nontreponemal assays can be reported as either a qualitative or quantitative result. Because nontreponemal assays recognize antibodies produced in response to cell damage, other causes of membrane damage such as autoimmune disease can stimulate production of nontreponemal antibody making the specificity of nontreponemal assays for syphilis relatively low compared to that of treponemal assays.[2,9] Importantly, however, nontreponemal assays typically become nonreactive/negative with resolution of infection as cell damage resolves and antibodies wane. Thus, nontreponemal assays are used for the purposes of screening populations (see Diagnostic algorithms below) and for the monitoring of disease activity. When nontreponemal tests are used for monitoring treatment response, it is preferable to use the same manufacturer for sequential tests to limit variability in results. Typically, a four-fold change in titer between two nontreponemal test results is considered clinically significant.[3]

A significant limitation of nontreponemal assays is a lack of automation, which leads to their labor-intensive nature. Performance and interpretation of these tests require trained personnel, which can have significant impacts on the workflow for high-volume laboratories. Results from nontreponemal assays can be affected by the subjective judgement of the person running the test and thus lead to high intra- and inter-laboratory variability. Of note, three automated nontreponemal assays are currently FDA cleared. While more studies are needed, the limited data that are available suggest that performance between automated and manual nontreponemal assays is comparable.[10] Nontreponemal assays are also susceptible to false negative results due to a prozone effect where high levels of reagin antibody can inhibit the agglutination reaction. This can be overcome through serial dilutions of a sample, which should be performed in scenarios where clinical suspicion of syphilis is high. Finally, nontreponemal assays have demonstrated limited sensitivity in primary and latent syphilis stages.[4]

Treponemal assays: Infection leads to production of specific antibodies (IgG and IgM) directed against *T. pallidum* antigens Tp15, Tp17, and Tp47 approximately three weeks after infection.[2,4] Treponemal tests are generally qualitative assays designed to detect these antibodies and can be used to confirm exposure to the bacterium. Once positive, treponemal tests usually remain reactive indefinitely and thus cannot be used to differentiate

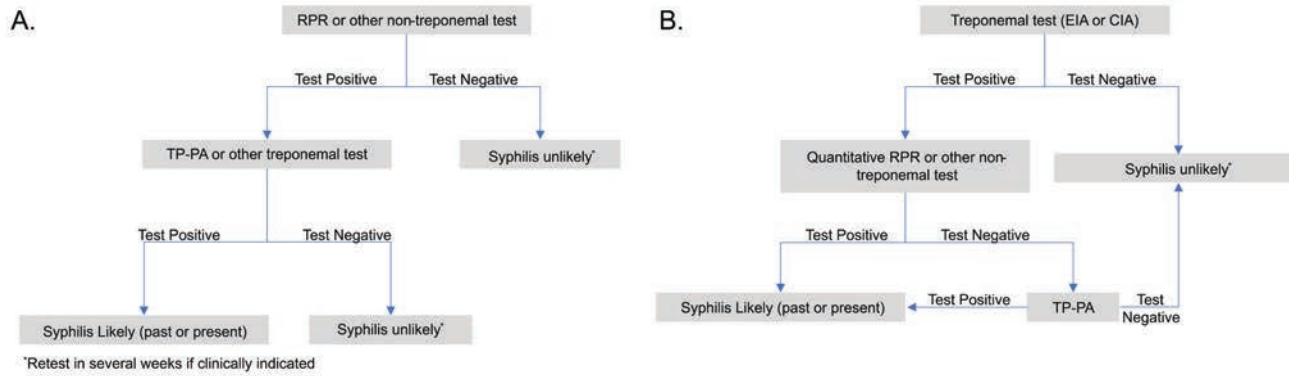

Figure 1. CDC recommended algorithms for (A) traditional or (B) reverse syphilis screening.

between active infection and a previously treated infection nor can they be used to monitor response to treatment.[11]

Typically, treponemal assays have high specificity and possibly higher sensitivity during early and late syphilis stages compared to nontreponemal tests. Manual treponemal assays include the microhemagglutination assay (MHA), fluorescent treponemal antibody absorption assay (FTA-ABS), and the *T. pallidum* particle agglutination (TP-PA). Newer automated assay formats include enzyme immunoassays (EIA), chemiluminescence immunoassays (CIA), multiplex flow immunoassay (MFI), and microbead immunoassays (MBIAs), which provide objective result interpretation with high reproducibility/precision. Although automated methods require expensive instrumentation leading to a higher cost per test than nontreponemal assays, the availability of these FDA-cleared methods provide a high-throughput option for large volume clinical laboratories. Immunoassays for treponemal antibodies demonstrate 100% sensitivity in secondary syphilis, 95.2% –100% sensitivity in early latent syphilis, and 86.8% – 98.5% sensitivity in late latent syphilis.[12]

Treponemal assays are susceptible to false positive results in the presence of inflammatory diseases or other infections. In addition, treponemal assays may detect non-venereal spirochete subspecies (e.g., yaws, bejel, and pinta) as they are antigenically indistinguishable from venereal syphilis.[2]

Diagnostic algorithms

The need for diagnostic algorithms is rooted in absence of a single test that can be used to definitively diagnose untreated syphilis. These diagnostic algorithms typically include the results of both treponemal and nontreponemal assays and the choice of assays and sequence in which they are performed can vary from laboratory to laboratory. Traditional testing algorithms utilize a nontreponemal assay as the initial test and a treponemal assay to confirm.[2] With the development of fully automated, sensitive treponemal assays, many laboratories have adopted a treponemal test as the initial step, with confirmatory testing provided by either a nontreponemal test or sometimes by a second treponemal assay.[13] Initial testing with a treponemal assay is referred to by various names including reverse-sequence testing and the reverse algorithm.

Traditional algorithm: This diagnostic approach begins with a nontreponemal test (**Figure 1A**). If a patient is asymptomatic and receives a negative result, no additional testing is required. Because nontreponemal assays are not specific for syphilis, confirmation of a reactive nontreponemal result using a treponemal assay is necessary to confirm diagnosis. Use of the traditional algorithm continues to be a mainstay in laboratories with low volume of syphilis testing due to the low cost of manual nontreponemal methods.[14] The results of the traditional algorithm show good correlation with disease status and this approach provides a rapid and inexpensive screening method. However, because the sensitivity of nontreponemal tests is lower in early and latent disease there is a risk of missed or delayed diagnosis of syphilis when using the traditional algorithm.[4]

Reverse algorithm: Because modern treponemal immunoassays have demonstrated equivalent sensitivity and specificity to nontreponemal assays (apart from early primary syphilis) combined with their ability to be automated using high-throughput instrumentation, many laboratories have implemented the reverse algorithm (**Figure 1B**). Following this approach to diagnosis, initial screening is performed using a qualitative treponemal assay. A reactive test result is followed by a quantitative nontreponemal test, which provides information on whether the disease is active as well as to establish a baseline for monitoring response to treatment.[13,15,16]

The advantages of the reverse algorithm can include detection of early infection (before nontreponemal antibodies can be detected), latent infection (after nontreponemal antibodies have disappeared), automated workflow, and objective results reporting.[4] Many countries have moved primarily to the reverse algorithm, and some identify it as the preferred approach (specifically using an assay capable of detecting both IgM and IgG,[17]though traditional testing is still common. One concern with reverse testing is the management of discordant results, where the initial treponemal assay is reactive but the nontreponemal is nonreactive. Resolution is important, as this could indicate early infection or late-latent infection in need of treatment, previously treated infection, or a false-positive result. A false positive rate of approximately 0.6% when using the reverse algorithm has been reported in the literature.[14-16] The U.S. Centers for Disease Control and Prevention (CDC) recommends an alternate treponemal test to aid resolution of discordant results when using the reverse algorithm.[2,18] There have been numerous reports of laboratories independently validating a signal strength to cutoff ratio of automated treponemal assays above which there is a high probability of the second confirmatory treponemal test being positive.[14] By using signal-to-cutoff ratio in lieu of additional testing, they report a reduction in unnecessary confirmatory testing and laboratory costs.[14]

Choosing a diagnostic algorithm

The CDC currently recognizes both the traditional and reverse algorithms as acceptable approaches for syphilis screening and diagnosis.[3] Of note, the 2020 European Syphilis Guideline describes a third algorithmic approach that incorporates both

a treponemal test and a nontreponemal test as the primary screening tests.[13] Historically, when both nontreponemal and treponemal assays were only available in manual formats, traditional algorithm approach was justified from both a workflow and cost perspective.[2] The increasing commercial availability of automated treponemal assays offered an alternative option with attractive workflow advantages by screening first with a treponemal assay, followed by a nontreponemal and/or a second treponemal assay (based on a different antigen). The choice of algorithm may largely be driven by the volume of syphilis testing, with low-volume laboratories opting for the more manual and less costly traditional algorithm.[19]

Consideration of the patient population that a laboratory serves is also critical when choosing which algorithm to offer for syphilis testing. For example, data suggests that use of the traditional algorithm can miss untreated cases of syphilis, especially if the patient is in the late latent stage of disease. During this stage, seroreactivity to nontreponemal tests declines and a negative/nonreactive nontreponemal screening test would not be reflexed to a treponemal assay if using the traditional algorithm.[2] Thus, laboratories serving a high-risk population (e.g., STD clinic) may choose to implement the reverse algorithm to reduce the risk of missing a patient with primary or latent syphilis. One caveat to this approach is the potential for an increase in confirmatory testing due to treponemal test positivity that persists in patients with a prior history of treated syphilis.[12]

Studies have demonstrated that utilization of the reverse algorithm maintains equivalent diagnostic accuracy as using the traditional algorithm approach. It is therefore not surprising that may laboratories have opted to reverse the order in which they perform nontreponemal and treponemal assays. Despite the syphilis screening algorithm that is used, communication between laboratories and treating physicians is critical as nuances between the algorithms can lead to confusion when interpreting results. Some laboratories have created a composite report that includes the algorithm used, the specific test methods that were performed, as well as a short interpretative comment that was developed in collaboration between the laboratory and local infectious disease physicians.[14,20] This additional clarification benefits not just physicians but also patients who have the ability to access their lab results immediately via a secure electronic portal.[20]

Summary

Syphilis serology is important for the testing of at-risk populations. Advantages of a reverse-testing algorithm using a sensitive, automated treponemal assay include improved clinical detection and enhanced workflow. It will be interesting to see what, if any, impact that the FDA-cleared automated, nontreponemal assays have on the laboratory's choice in algorithm as more data become available on the overall accuracy of the methods and cost per test.[14]

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Syphilis testing: Reverse to move forward

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TEST QUESTIONS

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1. **Syphilis is caused by _____ _____ and manifests as an _____ disease.**
   - A. *Treponema pallidium*; respiratory
   - B. *Treponema pallidium*; genital ulcerative
   - C. *Neisseria gonorrhoeae*; gastrointestinal
   - D. *Neisseria gonorrhoeae*; genital ulcerative

2. **In the Unites States, the prevalence of primary and secondary syphilis has _____ almost every year since _____.**
   - A. Stayed the same; 2010 and 2011
   - B. Increased; 2000 and 2001
   - C. Decreased; 2000 and 2001
   - D. Increased; 2010 and 2011

3. **Chancres are characteristic of _____ syphilis; while skin rashes and/or mucus membrane lesions are characteristic of _____ syphilis.**
   - A. Primary; secondary
   - B. Secondary; latent
   - C. Latent; tertiary
   - D. Primary; tertiary

4. **Symptoms associated with _____syphilis varies depending on the organ system affected.**
   - A. Primary
   - B. Secondary
   - C. Latent
   - D. Tertiary

5. **Accurate and timely diagnosis of syphilis is critical because it can present similar to other diseases and has a high rate of morbidity and mortality.**
   - A. True
   - B. False

6. **Methods currently used to diagnose syphilis include**
   - A. Direct detection and culture
   - B. Indirect detection and culture
   - C. Direct detection and serologic detection
   - D. None of the above

7. **Direct detection methods include the following**
   - A. Dark-field microscopy, VDRL and molecular assays
   - B. Non-treponemal assays, VDRL and immunohistochemistry
   - C. RPR, VDRL and dark-field microscopy
   - D. Dark-field microscopy, molecular assays and immunohistochemistry

8. **Which direct detection method is not recommended to use in an asymptomatic population?**
   - A. Molecular assays
   - B. Dark-field microscopy
   - C. RPR
   - D. Immunohistochemistry

9. **Which direct detection method is best suited for STD clinics because of the technical skill and specialized equipment needed?**
   - A. Molecular assays
   - B. Dark-field microscopy
   - C. RPR
   - D. Immunohistochemistry

10. **Immunohistochemistry techniques are not useful in diagnosing _____ disease.**
    - A. Primary
    - B. Secondary
    - C. Tertiary
    - D. Latent

11. **Serologic methods only detect nontreponemal antibodies.**
    - A. True
    - B. False

12. **Non-treponemal assays detect**
    - A. *Treponema pallidium*
    - B. Antibodies specific to *Treponema pallidium*
    - C. Antibodies against antigens released by cell damage that *Treponema pallidium* causes
    - D. None of the above

13. **Which test observes macroflocculation?**
    - A. RPR
    - B. Immunoassays
    - C. VDRL
    - D. Dark-field microscopy

14. **Non-treponemal assays are typically used for**
    - A. Screening populations
    - B. Monitoring disease activity
    - C. Monitoring response to treatment
    - D. A and B only

15. **Treponemal assays have high specificity and higher sensitivity during early and late stages of syphilis compared to non-treponemal tests.**
    - A. True
    - B. False

16. **The diagnostic traditional algorithm uses a(n) _____patient and a _____ _____ test to diagnose a negative individual.**
    - A. Symptomatic; negative treponemal
    - B. Symptomatic; negative non-treponemal
    - C. Asymptomatic; negative treponemal
    - D. Asymptomatic; negative non-treponemal

17. **The reverse algorithm uses a**
    - A. Qualitative treponemal assay, followed by a qualitative non-treponemal test
    - B. Quantitative treponemal assay, followed by a quantitative non-treponemal test
    - C. Qualitative treponemal assay, followed by a quantitative non-treponemal test
    - D. None of the above

18. **The _____ has established recommendations to aid in resolution of discordant test results caused by the reverse algorithm approach.**
    - A. WHO
    - B. CDC
    - C. NIH
    - D. All of the above

19. **Laboratories that serve high-risk populations should use the _____ algorithm to reduce the risk of missing a patient with _____ or _____ syphilis.**
    - A. Reverse; primary; latent
    - B. Reverse; secondary; tertiary
    - C. Traditional; primary; latent
    - D. Traditional; secondary; tertiary

20. **To aid in the interpretation of a diagnosis, some laboratories have created a composite report that include(s)**
    - A. Test methods used
    - B. Algorithm used
    - C. A short interpretive comment
    - D. All of the above

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For emerging infectious diseases, reliable controls support QC efforts

By Erica Frew

The spate of recent public health crises, beginning with COVID-19 and including the mpox outbreak that began last year, underscored the importance of quality control measures in clinical laboratory testing. In large outbreaks or pandemics, lab results have to be more than just accurate; they must facilitate useful comparisons across labs, states, and even countries.

Of all the factors that go into quality control and quality assurance in clinical laboratories, the most important might also be the most humble: control material. Reliable, high-quality controls make it possible to ensure accurate results, proper workflow procedures, and instrument performance. Without such controls, there can be little confidence in the outcome of any lab procedure.

Unfortunately, COVID-19 and mpox both illustrated the tremendous challenges in establishing access to high-quality controls for emerging infectious diseases or even new outbreaks of known diseases. In these situations, many clinical labs look to secure residual positive samples from other facilities to help in the development and validation of their own tests. But with so much simultaneous demand for these samples, they are notoriously difficult to acquire and typically cannot be relied upon for a steady supply of control material. In addition, positive samples can be infectious and increase the risk to lab technicians.

In new outbreaks, a better approach could come from synthetic molecular controls. These can be designed quickly and easily from the pathogen's genome sequence, making it possible to start development as soon as the source of the outbreak is identified. Because they are synthetic, they can be manufactured in high volumes to provide a steady, reliable supply for testing.

The roles of controls

Before diving into the specific challenges seen with COVID-19 and mpox testing, it is worth a quick review of the various types of molecular controls and how they are used by clinical labs. In general, they can be broken down into three broad groups.

The first group, positive and negative controls, tends to be the most familiar. These controls are designed so they always deliver positive results (or always deliver negative results) in a correctly

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> "As cases spread around the world, labs in every country and state found themselves competing with each other for critical testing supplies, including control material."

performed assay. Useful for a variety of QC checks throughout the testing process, these controls are essential in the analytical phase as test results are being generated.

The second and third groups of controls are intended to confirm processes more than results. Controls may be internal or external, exogenous or endogenous. These controls are often combined to give the best view of the entire testing workflow. For example, internal controls move with the sample for confirmation of how certain phases of the assay worked, while external controls are kept separate from the sample and are processed in parallel to reflect the performance of the entire workflow. Introducing controls very early — in some cases as soon as the initial sample is collected — can help increase confidence in all of the processes that contribute to each patient's test results.

COVID-19 testing

By early 2020, the enormous challenges clinical laboratories would face in COVID-19 testing were already becoming clear. As cases spread around the world, labs in every country and state found themselves competing with each other for critical testing supplies, including control material. There were nowhere near enough residual positive samples to allow all labs to develop their own tests, and of course in the early days there were no commercially available alternatives.

As labs increasingly faced staffing shortages — due in part to sickness among workers and in part to social distancing requirements or lockdowns — the risk of using infectious positive samples as controls was pronounced. Few labs could afford to lose staff members even temporarily to COVID-19 infections as they raced to meet the demand for test results.

Beyond testing clinical samples, some labs were also testing wastewater samples to help with community surveillance efforts. Wastewater surveillance has been quite helpful in predicting new surges in cases, often indicating regional spikes in the SARS-CoV-2 virus days or weeks before test positivity rates begin to rise. But testing wastewater comes with its own challenges. The sample goes through so many processing steps to capture the tiny fraction of viral RNA in vast quantities of water, and many process controls are not robust enough to function properly from sample collection all the way through to analysis.

The release of synthetic molecular controls addressed challenges for testing both clinical samples and wastewater samples. "Armored" versions of these controls have a protective casing that allows them to be put through harsh processing steps without any loss of performance. Manufacturing of commercially available controls at scale helped ease the supply chain constraints experienced by so many laboratories early in the pandemic. Having synthetic alternatives to controls based on positive samples also made the workflow safer for technicians and helped to reduce the risk of on-the-job infection.

Mpox testing

Much like the early days of COVID-19, the start of the mpox outbreak last year revealed the testing limitations of clinical laboratories for an emerging disease. The first major outbreak outside of Africa, mpox came to continents and countries where labs had never needed to test for it.

Unlike COVID-19, though, the constraints for mpox testing lasted for months. New York City quickly became an epicenter of the outbreak in the United States. In a city filled with hospitals and clinical lab facilities, only 10 people could be tested *per day* well into the third month of the outbreak.[1] Much of that testing bottleneck was created by the lack of reference materials and other critical assay components.

Testing capacity has improved significantly, for a number of reasons. Last summer, the U.S. Centers for Disease Control and Prevention teamed up with several commercial laboratories, a move that increased the number of tests that could be run each week across the country by ten-fold.[2] Later, the U.S. Food & Drug Administration was permitted to issue emergency use authorizations, streamlining the process for commercially developed tests to reach clinical labs. Finally, companies began releasing synthetic molecular controls that could be used for mpox tests, which addressed supply constraints many labs had faced.

Rapid control development

Sadly, COVID-19 and mpox are not flukes. Public health experts have spent years warning about the rising incidence of infectious diseases, particularly those brought into the human population from animals. Changes in climate and habitat, among others, are bringing humans and wild animals into contact more than ever. Spillover pathogens are an inevitable consequence.

Whether it's a new infectious disease like COVID-19, or an existing one that spreads to a new area like mpox, one thing is clear: clinical laboratories need every advantage to ramp up testing in the earliest stages of an outbreak. General surveillance and screening programs could help, as would faster adoption of emergency use authorization protocols in regulatory agencies.

Synthetic molecular controls have a contribution to make too. They can be designed as soon as a pathogen's genome sequence is known, and they offer a safer and more accessible alternative to other molecular controls. They can be used as positive or negative controls as well as process controls to give laboratory teams increased confidence in their workflows and test results. Collectively, all of these measures could help labs respond more quickly to new infectious disease threats — and do so with reliable results thanks to careful quality control.

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Advances in personalized medicine: Prognostic testing in patient management

By Katherine Soreng, PhD

Laboratory tests inform most clinical decisions and are essential for optimal patient management. Most existing assays are diagnostic, supporting determination of the presence or absence of a disease or condition at the time of testing. As we move into the era of personalized (or precision) medicine, testing at the individual level for disease progression or response will become increasingly important, enabling tailored management to improve individual outcomes. Foretelling disease course or risk-assessment necessitates tests or scores validated for predictive performance, including assays with specific prognostic data and claims.

Prognostic testing indicates risk of future events, such as disease progression or recurrence and is typically based on outcome data over a defined period (e.g., five years).[1] Prognostic testing is sometimes divided into "prognostic" to predict the natural course of disease and thus who might benefit from treatment, and "predictive" to indicate outcomes with treatment. Frequently, the terms are used interchangeably. To better guide patients' treatment choices and drive improved outcomes, prognostic testing is increasingly being integrated into the management of a small but expanding number of diseases, including breast cancer, cardiovascular, and liver disease.

Prognostic testing in breast cancer

One in eight. The number of women who will receive a diagnosis of breast cancer in the United States. While recent and encouraging data shows survival rates are improving,[2] breast cancer remains a highly heterogeneous disease involving multiple treatment decisions from the moment of diagnosis. Early breast cancer is increasingly treatable but requires determinations such as if chemotherapy is likely to be beneficial in the adjuvant (post-surgical) setting. Is there a difference in individual outcomes at five or ten years if electing to forgo chemotherapy (and its associated risks) with early disease or is treatment always beneficial?

In the case of early breast cancer, genetic information from the tumor itself can now be added to traditional risk factors such as tumor stage, size, and hormone receptor status. Complex molecular tests utilizing gene expression profiling can analyze multiple ribonucleic acid (RNA) transcripts in the individual tumor and generate a mathematical risk score (typically grouped as high, intermediate, or low) that incorporates longitudinal outcomes study data to predict risk or benefit of treatment.[3,4]

Tumor profiling following a breast cancer diagnosis contrasts with other molecular risk testing such as BRCA 1 and 2 (breast cancer gene 1 and breast cancer gene 2) that is associated with risk of cancer occurrence based on mutations in the individual's genomic DNA. Following surgical removal, the patient's tumor is analyzed for gene expression specific to that individual's cancer. Differing tumor-specific molecular profiles have been associated with risk of recurrence, the benefit of chemotherapy, or the extension of adjuvant endocrine therapy. For example, a score can indicate as little as one percent benefit if electing for chemotherapy in the adjuvant setting, supporting a decision to forgo treatment and avoid the concomitant risks. Alternatively, a high score can predict improved outcomes with treatment. While only one component in the complex management of breast cancer, an expanding number of prognostic molecular tests are increasingly recommended in guidelines,[4,5] integrated into management, and are gaining reimbursement from insurers.

Prognostic testing in cancer incorporates multiple approaches

Other markers employed prognostically in breast cancer include estrogen receptor (ER) and HER2 positivity used to predict benefit of antiestrogen and anti-HER2 therapies. Ki67 immunohistochemistry, a marker of breast cancer proliferation, is finding prognostic usefulness, including a recent recommendation for use in ER-positive, HER-2 negative early breast cancer with limited or no node involvement.[6]

On-going research continues to investigate promising new prognostic and predictive biomarkers for breast and other cancers. Current research includes circulating tumor DNA (ctDNA), micro RNAs, and circulating tumor cells.[7] One promising biomarker is the mutational status of the estrogen receptor (ESR1) for predicting the emergence of resistance to aromatase inhibitors in HR-positive advanced breast cancer.[8] Other investigations include biomarkers for predicting response to radiotherapy treatment and specific forms of chemotherapy. Prognostic testing in the field of oncology is a leading example for the potential of personalized medicine to customize clinical management and enhance individual outcomes.

Differentiating risk assessment tools from prognostic assays

It is important to distinguish tests that are diagnostic but can be incorporated into a risk-assessment tool versus an assay with a specific claim or authorization such as prognostic gene expression profiling. While molecular assays comprise most current tests with specific prognostic claims and applications, a small but growing number of blood-based tests, including immunoassays, are anticipated/have achieved FDA-authorization specific to a prognostic use. However, diagnostic assays can be incorporated into scoring tools for risk prediction, for example to estimate probabilities for cardiovascular disease (CVD).[9] CVD risk scores typically incorporate clinical findings and other information such as history, age, and gender along with diagnostic assay results.

Prognostic testing in CVD

Cardiovascular disease (CVD) risk scores are increasingly being utilized in both acute and nonacute applications. In the outpatient setting, assessment tools such as the American College of Cardiology/ American Heart Association ASCVD risk estimator or the Framingham CVD risk score integrate diagnostic test results such as total cholesterol and HDL into the multifactorial calculator. The ACC/AHA and Framingham risk scores predict the likelihood of a CVD event or coronary heart disease over a 10-year period, so they can be utilized as a prevention strategy to mitigate disease through proper interventions such as therapy or lifestyle modifications. While it is well-accepted that high cholesterol or low HDL portends risk, it is the aggregate risk-assessment score that is prognostic versus the diagnostic assay values.

Related CVD risk scores can also be highly useful in the acute setting.[10] Most chest pain patients with signs and symptoms of a non-ST elevated myocardial infarction (NSTEMI) are not experiencing a myocardial infarction, but it must be safely ruled out prior to discharge or assessment for alternate etiologies. While serial changes in high-sensitivity troponin are utilized in the diagnostic pathway, risk scores such as HEART or TIMI that include troponin are often incorporated in the assessment and can be especially useful for the low-risk rule-out. While used to aid risk-assessment in a scoring tool, the troponin assay remains a diagnostic test.

Intriguingly, however, high-sensitivity cardiac troponin assays are being investigated as a direct marker of risk, and in Europe some have achieved a specific prognostic claim utilizing values well below the diagnostic threshold of the 99th percentile. The use of high-sensitivity cardiac troponin assays has been recently recommended for CVD risk prognostication in the general population.[11,12] While currently no high-sensitivity assays in the United States have been cleared by the FDA with a prognostic claim, it is an area of active research.

Prognostic testing in liver disease: A growing urgency

Greater than 100 million people in the United States suffer (most unknowingly) from chronic liver disease (CLD), the leading cause being nonalcoholic fatty liver disease (NAFLD) affecting up to an estimated 30% of the U.S. population.[13] NAFLD encompasses a spectrum of liver pathology, from simple steatosis (fatty liver) to higher-risk disease associated with advancing fibrosis,

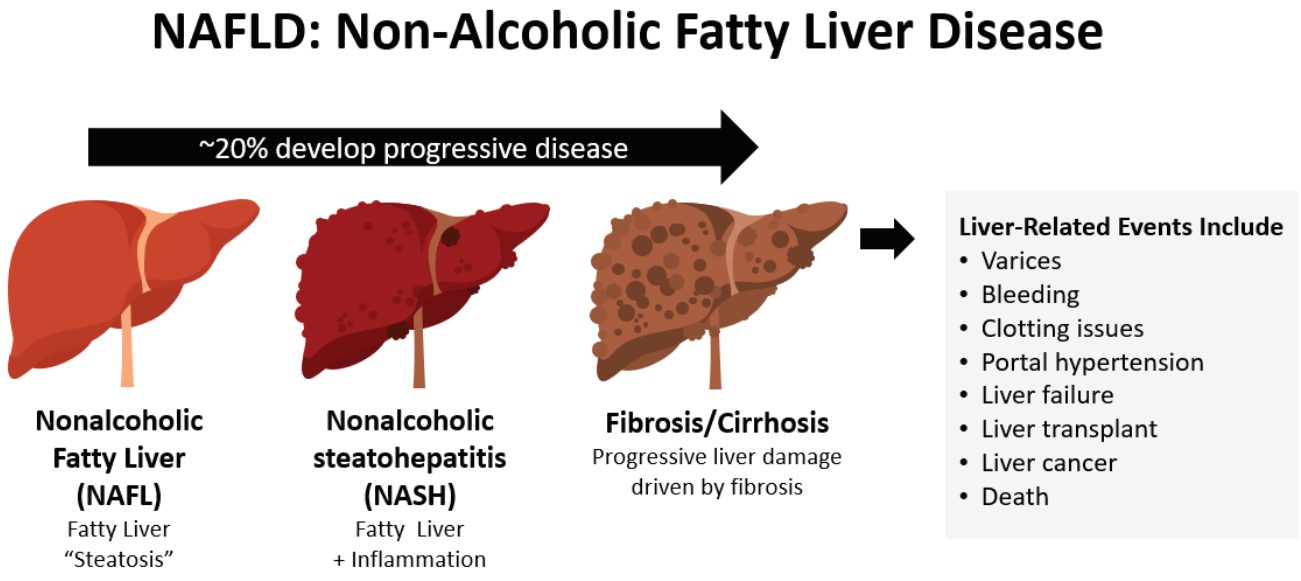


Figure 1.

cirrhosis, liver failure, or hepatocellular carcinoma. **(See Figure 1.)** Comorbidities such as obesity, diabetes, and the metabolic syndrome increase risk for NAFLD and disease progression and include "lean NAFLD" occurring in non-obese individuals.[13,14] About 25% of people with fatty liver will develop nonalcoholic steatohepatitis (NASH), an inflammatory form more likely to advance to cirrhosis and liver failure.

Factors such as genetics, the gut microbiome, diet, and lifestyle are contributing variables associated with disease progression.[15,16] Identifying progressors from non-progressors is challenging due to the frequently silent nature of advancing damage and the sheer numbers of those with fatty liver. Moreover, a significant majority of patients with steatosis and/or elevated liver enzymes do not develop progressive disease, and many with high-risk disease may have normal liver enzyme levels.[17]

The need for earlier identification

Of paramount concern is the high frequency of those diagnosed only after cirrhotic decompensation where few options besides transplant exist, and hospitalization for complications are frequent.[18] The need for an effective risk-stratification strategy in NAFLD is critical, as earlier identification and intervention can limit or reverse disease, even some cases of compensated cirrhosis. Moreover, promising pharmacologic treatments for NAFLD and NASH are in late-stage development and may soon become available.[16] But what is a good strategy to optimize outpatient management and prevent unnecessary referrals, hospitalizations, and deaths associated with cirrhosis? For that, it is important to understand the underlying pathology.

Liver fibrosis and disease progression

Evidence clearly shows it is not inflammation but rather the active formation of scar tissue—fibrosis—that is the strongest predictor of disease advancement.[19-21] Fibrosis is more likely to occur with inflammation (NASH), although may occur in its apparent absence. Fibrosis is a natural part of the wound healing process, with damage (fibrogenesis) existing in a balance with tissue repair mechanisms (fibrolysis). With chronic exacerbation, that balance is altered, damage overwhelms repair and healthy liver tissue is increasingly injured and scarred.

Evaluation for evidence of active fibrosis is a proven means of risk-assessment; techniques include biopsy and noninvasive testing (NIT) using imaging or biomarkers.[22-24] Biomarker testing methods include measurement for direct markers that indicate active fibrosis or indirect markers related to inflammation or damage.

Liver fibrosis and biopsy

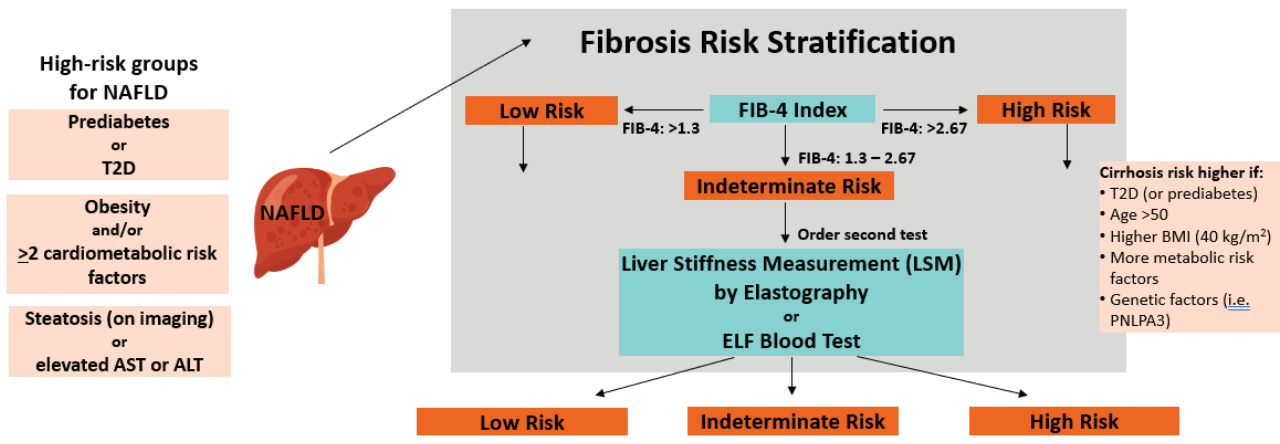
Histopathology (liver biopsy) has been the historical standard to indicate inflammation (activity or grade) and fibrosis (staging) for disease severity. A scoring system (commonly stages 0–4 with 4 indicating cirrhosis) is typically reported. While biopsy is a diagnostic technique, data show it is also predictive of disease progression, with higher stages associated with elevated risk.[19-21] However, biopsy has significant limitations including invasiveness and risk, sampling error, and inter-observer variability.[25] To better address the unmet clinical need, including high-volume testing, NITs using imaging for elastography or for direct biomarkers of fibrosis have recently been incorporated into U.S. guidelines for risk-assessment in NAFLD.[14,15]

NITs for liver fibrosis and risk-prediction

As fibrosis often proceeds slowly (though some are fast progressors), identification of active fibrosis indicates elevated risk. Successful intervention is linked with disease reversal and improved outcomes but must be timely (prior to decompensated cirrhosis).[26-28] As higher-risk patients (including those with obesity and/or diabetes) are most likely to be seen initially in primary care or endocrinology settings, testing recommendations target these clinicians. Algorithms in the United States designed for cirrhosis prevention include a simple blood-based NIT (FIB-4 index) for the initial screening and secondary NIT testing for additional risk-stratification and referral decisions.[14,15] **(See Figure 2.)**

NITs: Blood based vs. imaging

NITs for liver fibrosis fall into two general categories: blood-based biomarkers or imaging for "liver stiffness" (elastogra-



Adapted from Cusi, K. et al. Clinical Practice Guidelines. May 1, 2022, Vol. 28, Issue 5, P528-562

Figure 2.

phy).[22-24] Imaging includes ultrasound/ultrasonic or MRI-based techniques that can assess for liver stiffness, as advancing fibrosis produces progressively less flexible tissue. Blood-based NITs include those using indirect markers (such as inflammatory markers or markers of liver dysfunction associated with fibrotic damage), or direct markers of fibrosis involved in fibrogenesis and/or fibrinolysis. Both imaging (liver elastography) and serum-based direct markers (using the enhanced liver fibrosis [ELF] blood test, which automatically measures three direct markers to produce a numeric risk score) are included as NIT options following an elevated FIB-4.[14,15] ELF is the first blood-based test to receive De Novo authorization from the FDA as a prognostic assay in NASH, though others are in development.[29] In the United States, the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis. The ELF test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to NASH to assess the likelihood of progression to cirrhosis and liver-related clinical events.

Conclusion

A growing number of promising assays with specific prognostic utility across diverse disease states are anticipated in the coming years and include neurology, cardiac, liver disease, and cancer as active areas of investigation. Additionally, AI-assisted risk algorithms are showing promise across a range of morbidities. The increasing availability of risk-assessment tools and assays is expected to advance the promise of personalized medicine and reduce hospitalization and patient burden.

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Digital pathology and clinical testing: Considerations for a successful integration

By Lisa-Jean Clifford

Digital pathology has very quickly simply become pathology. It is not considered the future and there is no longer a question of whether it will take root, it is being deployed and used in laboratories across the globe. Those who have not already deployed some form of digital technology are either in implementation, assessing the available solutions, or developing their plans for beginning their digital path.

There are several things to consider when implementing a digital solution and workflow and not the least of these are the integration into a clinical testing environment. In this article, I will be focusing on the key items to examine and provide a framework for consideration. This framework will vary depending upon the type of laboratory/facility and the use cases (just clinical; clinical and education; clinical and research; clinical, education, and research; etc.) but it can be adapted. To realize the true benefits of digital, flexibility is key — both in the vendor and solution you select — and in your implementation and use of it. Keep in mind that the focus in this article is for clinical integration.

Items to evaluate internally

Workflow: What is the current, manual workflow. Gathering and documenting the current process from the time a requisition and the associated specimen(s) are received until the case is signed out is key to outlining which areas need to be adapted for digital workflows. The goal can either be to closely replicate the existing workflow or to optimize workflows with digital. These are two very different approaches, and each should be considered when determining your business goals and objectives. The decision here will also have an impact on the solution(s) you select and the way they are implemented.

There are many small items in this category that have a major impact on integration — such as slide labels, naming conventions, barcodes, case distribution, how to work in both glass and digital workflows simultaneously (the assumption is that you will not be going to a 100% digital workflow immediately).

Integration of AI algorithms: Will you be using artificial intelligence (AI) algorithms? Are they approved by the U.S. Food and Drug Administration (FDA) or will they be validated as an aide to the pathologist only? You will need to identify which cases, customers, or pathologists they will be used with. What is your business model for these? Will you be charging extra for their use if you are doing the professional component (PC) work as outreach business or as consultation, for example?

Phased deployment: You will need to determine if you are doing a phased approach to your deployment/integration (highly recommended). With a phased approach you can decide how you would like that to be broken out and some of the more common choices are: By case type, by specimen type, by customer, by pathologist(s), by percentage of overall cases (i.e., 20% of all case volumes to start then increasing over a set time frame).

Some organizations will decide that they would like to break the workflow into a phased approach, depending upon the completeness and robustness of the solution they select. If a full digital solution, then you may decide to start with just integrating the workflow portion for case accessioning and continue to do the final reporting in your laboratory information system (LIS); then, for a Phase II, do the full bidirectional integration that includes results.

Location: Starting with the location(s) of your scanners to the locations you are supporting, there are physical and virtual integration considerations. This includes the types of work you are performing — is it global, technical only, professional only, internal only, or do you have outreach clients and/or do you do consults? In these cases, there are other ways to tackle the integration within your organization's clinical work. For example, if you are doing the technical component (TC) work, then providing secure access to your customer's cases for them to perform the PC side digitally can have a significant impact on cost savings and turnaround times. The same is true if you are doing the PC side of the work and someone else is performing the TC side. By simply having an interfaced scanner at their location, the cases will be available to you for interpretation as soon as they make and scan the glass. Again, avoiding the packing, shipping/courier, and tracking.

There are also the lab applications involved to consider if you are a multi-site entity. Do you have multiple electronic medical records (EMRs), LISs, etc.? Do they all need to be integrated, or do you already have some consolidated in your ordering and reporting processes implemented? Be sure that the digital solution (and vendor) you select are flexible enough to accommodate different scenarios so there is minimal or no reworking required. This will equal less disruption and faster deployments.

Validation: Do not forget your validation as part of the clinical-use process. Some solutions can help automate this as part of their capabilities. However, you will need to have your cases set for the validation process, and this can be done simultaneous to your implementation, saving a great deal of time.

Items to evaluate externally

Integration of AI algorithms: Which algorithms are you looking to incorporate? From which vendor(s)? There are several vendors who provide machine learning (ML), image analysis (IA), and AI algorithms for a variety of uses from diagnostic aids to tumor identification, counting, and metastasis prediction to quantification and grading. They come in first read (precalculated), ROI (region of interest invoked) and second read (QA/QC). When identifying which one(s) you are interested in incorporating within your organization, things to consider are the use cases and their ability to be seamlessly integrated within your workflow platform. It does not provide a large advantage to have to use each different algorithm in a separate application, window, or workflow.

Are you looking to develop your own? There are certainly scenarios where you may have the desire or a unique assay in house that you would like to leverage AI for and there are also vendors who provide a platform that enables you to easily create and validate your own for internal use.

Lab application integration: Not all applications, especially older or legacy

applications, are as open and readily able to integrate well with other applications. This can be a bit of a limiting factor in the useability and true interoperability between your digital solution and your LIS. However, there are definitely ways to work around this. Many entities are working with their LIS and EMR vendors to encourage better interoperability and others are actually making changes to more current, open technologies. There are large gains in efficiency and uses of digital and AI even with truncated interfacing options from less open LISs. However, the significant benefits and gains are in a truly interoperable, bidirectional ecosystem.

Image storage and archival: As of now, the requirement is still for storage of glass, not digital images. And though many of us believe it is only a matter of time before that changes, the decisions regarding whether to store, what to store, and how long to store are those of the laboratory or administration. I have seen clients who choose not to store beyond the completion of the case — they feel that if they need to rescan, they will just recall the glass and rescan. I have seen clients who take advantage of the digital solution provider's long term (archival storage) for anywhere from 10 years to indefinitely and then there are those who prefer to offload long-term storage to a third party such as Microsoft Azure or Google. There is no wrong answer. There is only the planning and understanding of the costs and benefits of each form. If utilizing a third-party information management system vendor, you will want to ensure that your vendor is able to integrate bidirectionally (sending and recalling) those images for your historical cases.

Conclusion

Remember, the adoption and use of digital workflows and AI in clinical diagnostics and laboratories is at its inception point. Choosing a vendor and solution that is flexible, nimble, easily customizable and robust are key for your ability to continue to grow on that platform as the technological advances will continue to evolve and be developed for decades to come. See **Figure 1** for an image of an ideal, full digital framework and environment.

Lisa-Jean Clifford, is COO and Chief Strategy Officer of **Gestalt Diagnostics**. Clifford has more than 20 years of experience in high-tech industries, with over 15 of them specifically in high-tech healthcare.

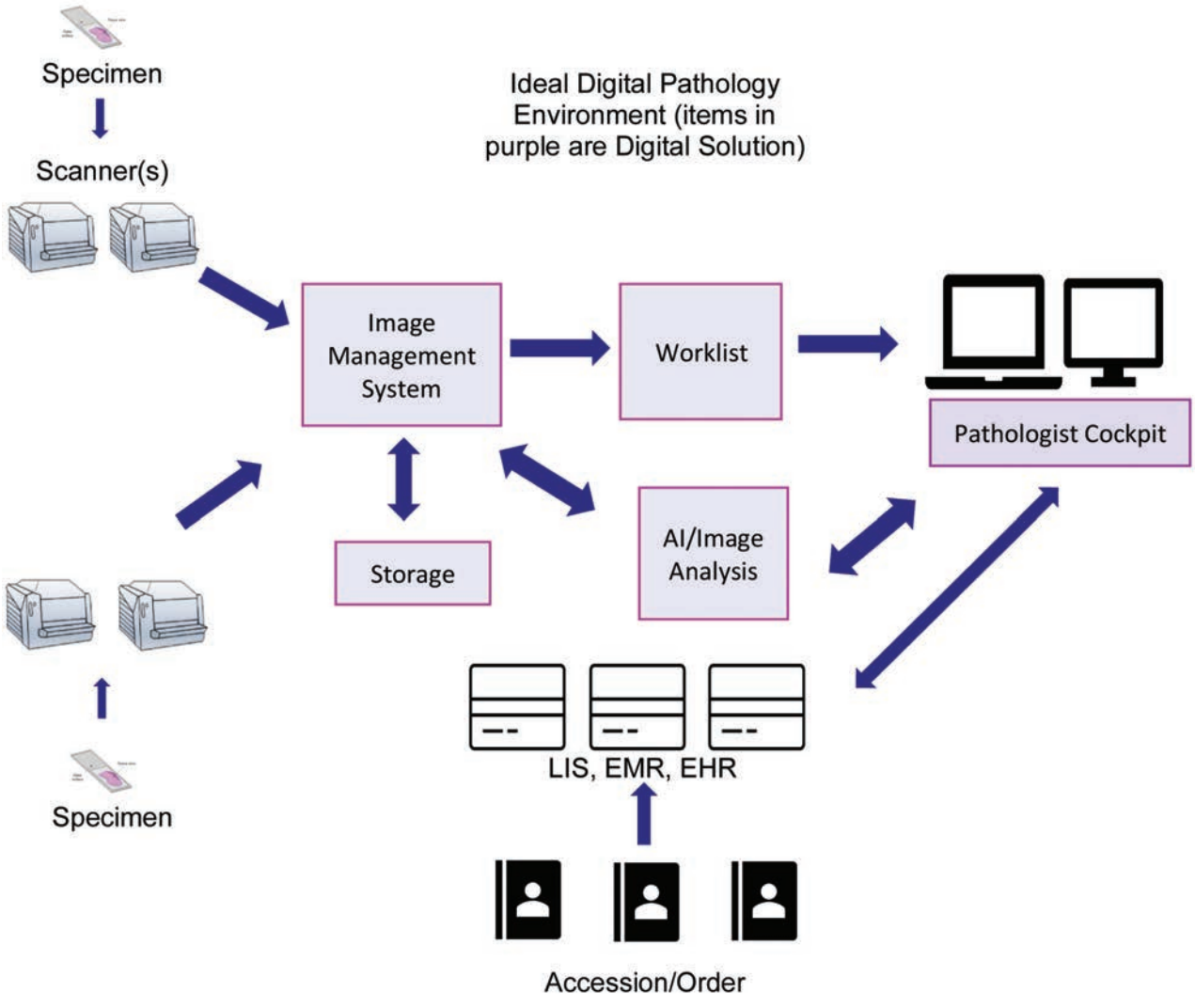


Figure 1.

STATE OF THE INDUSTRY
Laboratory Data Analytics

By Kara Nadeau

With increasing cost pressures, labor shortages, and continued supply disruptions, it is more important than ever for medical laboratory leaders to have access to actionable analytics on their operational and financial performance.

"I think of the lab as an information system in its essence," said Alastair "Ali" Dunnett, Director, Laboratory, Carle Health, based in Urbana, Illinois. As a medical technologist by training, Dunnett says he has a strong interest in informatics and works to get the most value out of his lab's information systems. He stated:

"This is my 35th year in healthcare and I find it to be an exciting time if you're interested in informatics, as we now have the horsepower, software, and clever people who are figuring out how to integrate disparate pieces of information. The lab has far more useful information than people realize. If you really get the hood up, there's quite a lot in there you can use to answer questions and gain insight."

Alastair "Ali" Dunnett

To understand how lab teams are leveraging their systems and data to measure performance and make improvements, *Medical Laboratory Observer* issued its second annual State of the Industry (SOI) survey on laboratory data analytics.

The majority of those surveyed this year are employed in a lab administration position (69%), with nearly half being lab managers, administrators, or supervisors (47%); 12% lab directors; and 9% section heads or department managers.

Most work in hospital labs (63%), one-quarter (25%) in independent labs or physician office labs, with the others spread out across other categories of facilities (e.g., group practice, government/public health, medical school/MedTech, etc.).

There was broad representation across lab sizes and volumes, with 22% working in labs with 1–10 employees, 10% in labs with 11–20 employees, 19% in labs with 21-50 employees, 25% in labs with 51–100 employees, and 24% in labs with more than 100 employees. Respondents were fairly equally distributed across labs performing from 1,000,001 to over 2,000,0000 tests per year (35%), 100,001 to 1,000,000 tests per year (35%), and less than 100,000 tests per year (29%).

For a qualitative assessment, *MLO* also interviewed medical lab professionals and technology providers on the topic of clinical data analytics, specifically challenges and opportunities around process automation, data capture and planning and forecasting.

Laboratory information system (LIS) platforms

There was little change since last year when it comes to the type of laboratory information systems (LIS) medical lab professionals report to be using, with 39% using stand-alone systems (38% in 2022) and 61% modules within enterprise-wide electronic health record (EHR) systems (62% in 2022).

There was a slight increase in those using cloud-based LIS infrastructure (28% in 2023 compared with 24% in 2022), while the majority still use in-house software/servers (73% in 2023 compared with 76% in 2022).

Electronic processes in the LIS

When asked what functions were electronic through their LIS solutions, electronic orders and results (87%) and integration with analyzers (71%) topped the list. More than half of respondents said they had electronic billing/revenue cycle management (56%) and QA/QC (52%) processes.

About one-third said they have electronic processes through the LIS for regulatory compliance/reporting (31%), point-of-care testing (POCT) management (34%), and scheduling (31%). Fewer had moved from manual to electronic processes for inventory control/supply chain management (17%) or customer service (15%).

OakLeaf-Pine Grove Family Medicine in Eau Claire, Wisconsin is a small clinic with a rotation of four doctors at one location and five at another. Roxie Caswell, MLT for the clinic, commented on her lab's automation journey:

"Prior to 2017, our only computer system was to make patient appointments. Everything in the lab was on paper forms that then were given to the physicians and eventually pasted in the patients' charts. In the fall of 2017, our two clinics along with other small clinics in the area bonded together with a hospital in town and we had Epic installed in computers in our clinics."

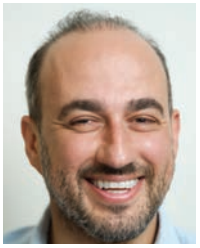
Roxie Caswell, MLT

Caswell explained how schedules and lab orders are processed through Epic, with orders then released into their LIS. They manually enter all other tests into the LIS, which are then transferred into patients' charts in Epic.

"Because a lot of our lab tests are waived tests, I don't see any more tests being electronically resulted in our LIS," said Caswell. "Through the LIS, all our hematology controls are kept within the system, and we are able to pull up Levy-Jennings charts for our controls. We are also able to bring up test volumes and other pertinent information that we need."

"Implementing electronic processes is vital if the lab has any significant operational volume and if it is looking for efficiency to retain and keep its current customers happy, plus has plans to grow its customer base, expand its test menu, and increase throughput," said Suren Avunjian, LigoLab CEO.

"Human intervention in the laboratory and manual workflow can only take you so far before the potential for mistakes and bottlenecks become major issues and threats to the business," he added. "Modern laboratories eliminate this risk by automating core processes and introducing interoperability with analyzers, EHRs, and third-party services like billing companies."



Suren Avunjian

"Automation is not only incredibly more efficient, but it is more effective," said Marci Dop, VP, Enterprise Laboratory Operations, ELLKAY. "An automatic patient matching process could be looking at 20 or more criteria to ensure an accurate match, whereas a manual process would not evaluate that many criteria. Imagine if your lab was able to reduce the number of duplicate registrations generated from processing blood in a bag."

Interoperability and data integration challenges

While automation is key to greater efficiency and accuracy, over half of survey respondents (51%) said interoperability and data integration issues with other LIS or EHR are a stumbling block to implementing electronic processes at their labs. This was up from 46% in 2022.

The Carle Health lab team performs 3–3.5 million tests annually, serving collaboratively 600–700 beds in a community of 1.2 million patients. As Dunnett explained, they are not new to information systems, having total lab automation with integrated modalities across coagulation, chemistry and hematology. Yet he acknowledged how data integration and system operability continue to be a major challenge in the lab industry because of the "niche or narrow solutions" that have been introduced over the years.

"Lab teams have long been responsible for pulling together islands of information," explained Dunnett. "For many years we have used a tool for reporting some analysis. It helps with turnaround times (TAT), volume statistics, activity reporting, and productivity (staff and instrument – for capacity management). But it's still essentially a very static tool that has its limitations. Now that we have total lab automation, we can consolidate more information so we can look at things more broadly across the board. A significant evolution but not where we ultimately want to be."

"The lack of standardization across various systems presents a unique challenge to labs," said Dop. "Even within the same health system, there are labs operating on different systems. This disparity

makes interoperability between systems difficult and makes the use of machine learning imperative."

"Interoperability is still a huge issue," said Lisa-Jean Clifford, COO & Chief Strategy Officer, Gestalt. "Most legacy and some newer applications are either not able to be fully open or interoperable or the companies themselves have a closed, restrictive and competitive philosophy. This is outdated thinking that impedes innovation and forward movement - the very movement that healthcare organizations are demanding more often. We are seeing this expectation when it comes to being able to truly leverage the benefits of new technologies, such as digital pathology and AI."


Lisa-Jean Clifford

Clifford said labs are often challenged with being able to implement electronic processes for two main reasons, in her experience. One is they approach the process by trying to mimic their current, manual processes and workflow, as she explained:

"In this situation, they are missing the point — and the benefits — of technological advancements and automated, electronic workflows. The point is to optimize workflows and break out of the tedious, manual often outdated processes, not to re-create them by simply automating it."

"Lab management or project managers should be taking the opportunity to take a step back, analyze the capabilities of the technology, and determine how they can best leverage these to leap outside their current norm," Clifford continued. "Often, the vendors you are working with will be best able to guide you on the benefits and intended workflow or implementation of these solutions, ensuring that you achieve the optimal outcome and ROI. If they can't, they may not be the right technology partner. Another option is to hire a consultant with expertise in technology and optimizing workflows. This can be beneficial if you are struggling with internal politics, thought processes, or simply with being too close to the situation to see the bigger picture."

Clifford noted how having many different functional areas involved in the process is another challenge labs face when trying to implement electronic processes:

"There are often conflicting objectives from different departments and functional areas. These can create a situation where personalities are at play and the business objectives aren't necessarily the focus. It is essential that key objectives are met for each functional area, but these should be clearly defined (e.g., security, access, user rights) but be careful not to involve the 'how' in the discussions. By clearly defining the requirements and the goals, then the core functional area (the lab) can define what they need and how to achieve it while meeting the key underlying needs of other areas."

Avunjian cautions labs to avoid adding multiple vendors and multiple electronic systems as this approach won't necessarily solve the interoperability and data integration barriers that exist. He stated:

"Instead of multiple systems and bolted-on modules, lab managers should seek out laboratory information system vendors that offer all-in-one solutions and one source of truth for all laboratory informatics. This is the only way to achieve the desired end-to-end data integrity and maximized connectivity. Examples of this all-in-one approach are LIS systems that feature interwoven modules and interface engines that share the same software structure, and that have the support of expert teams of interface engineers."

Data analytics for operational performance

While only 12% of lab professionals surveyed said they are utilizing data analytics for all aspects of their operations, a deeper dive into the responses reveals overall greater interest in analytics capability improvements. Nearly half of those surveyed (49%) said they are utilizing data analytics for some aspects of their operations and planning more, up from 42% in 2022. Among those who have not yet used data analytics in any significant way, 23% said they want to start, up from 16% in 2022.

Only 6% of respondents said they are not using data analytics and have no plans to start soon (down from 16% in 2022). Additionally, 10% said they are utilizing data analytics for some aspects of operations and not planning more (up from 8% in 2022).

Independent Consulting Lab Director Martha Casassa said none of the organizations she has worked for in the past three years as a Traveling Director had instituted a formal analytics program.


Martha Casassa

"Laboratory-specific metrics are pulled on a monthly basis primarily manually from the LIS," she explained. "I have not seen analytics modules offered by LIS vendors. Most often, they are third party software layered over an LIS. Analyzer middleware will provide some analysis, but only for the data they are handling — not for the entire lab."

"Some newer installations (within the past few years) offer dashboards providing limited analytics," she continued. "Much of the analytics software available has been third-party originating primarily for those laboratories performing a high volume of outreach testing and needing to monitor performance for their customers. More recently, instrument

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vendors are offering analytics through their middleware. However, the output is constrained to the data coming through the middleware. The software is not integrated to pull data from the LIS to provide whole-lab analytics. While helpful, these available systems provide a limited view of the laboratory's operations."

Among respondents with data analytics tools, 69% said they were integrated with the LIS (up from 65% in 2022) and 31% said they use a separate tool (down from 35% in 2022). With regards to how often the data for analytics is refreshed, 32% said weekly, 31% in real-time, 28% daily, 5% in minutes, and 3% in hours.

The most common operational performance indicators that labs measure according to the survey results are turnaround time (72%), cost per test (51%) and staff productivity goals (46%), followed by billable tests versus performed tests (35%) and medical necessity (33%). Indicators for unnecessary tests was lower down on the list at 16%.

"As labs become more aware of the possibilities offered by data analysis, we're seeing an increased number of requests from labs looking to gain access to their data in a consumable and actionable format. But we've found that very few labs are confident in their ability to extract data from the LIS, manipulate the data, and to implement protocol changes to improve workflow," said Jennifer Sanderson MS, CTT+, MLS(ASCP)CM, Sr. Global Marketing Team Lead, Workflow Solutions, Siemens Healthcare Diagnostics. "As such, we've been acting in a consultative role in most instances where operational performance is concerned, assisting with data assessment, and later determining and implementing operational improvements to improve workflow protocols."

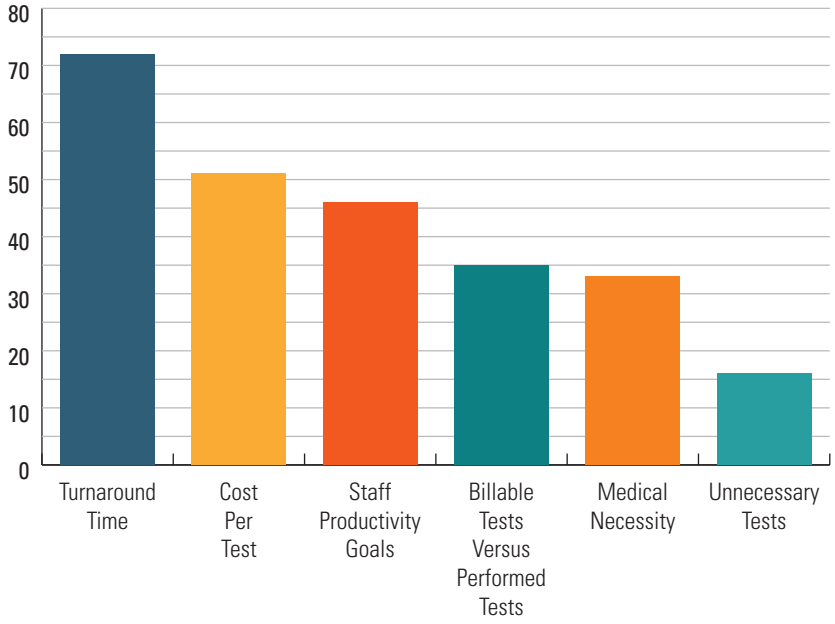
"Business analytics are relatively new in the lab, but they are quickly gaining traction as lab directors are looking to data to help combat budget cuts, shrinking staffs, and the explosive growth in testing volumes," Sanderson added.

Jennifer Sanderson MS, CTT+, MLS(ASCP)CM

She shared success stories from labs that have implemented analytics programs, like Atellica Process Manager, in developing new protocols to make staff and testing processes more efficient. One customer reconfigured their testing protocols using reagent efficiency data from Atellica Process Manager, resulting in annual operational savings of more than $50,000. Another Lab Director, in this case in a community hospital lab, determined they could eliminate the lab's urgent care testing station and POC devices with a few changes to workflow and testing protocols.

"In several instances, we've seen other labs dramatically reduce repeat testing, significantly improve TAT and labor efficiency, and realize notable cost savings by limiting reagent waste, among other improvements," said Sanderson. "In the future, we expect additional operational enhancements to be realized by artificial intelligence. There is great potential for data to more profoundly enhance tube routing, sample stops, and other workflows based on aggregate historical performance data."

Most common operational performance indicators that labs measure



Data and analytics for COVID-19 and influenza

Over half (54%) of survey respondents said they are tracking the number of tests performed specifically for COVID-19, while only 17% said they tracked the number of tests performed for influenza.

More than half (54%) also track positive and negative test results for COVID-19 (up from 42% in 2022). In fact, reported tracked metrics for COVID-19 were up in all categories queried in the survey:

- Turnaround time 38% (21% 2022)
- Types of tests performed 31% (3% 2022)
- Supplies used/inventory management 29% (8% 2022)
- Cost per test 21% (3% 2022)

Ionized Magnesium (Mg^{++})
A Critical Piece of the Electrolyte Puzzle

Electrolytes (Na^+, K^+, Ca^{++}, Cl^-) are all measured as ions because that is their only clinically active form. Now Mg^{++} can be measured the same way.

Ionized Magnesium (Mg^{++}), not Total Magnesium (tMg), is the only physiologically active form of magnesium. Magnesium bound to protein, or chelated to phosphate, citrate, sulfate, or carbonate is inactive.

tMg is an unreliable substitute for Mg^{++}. Mg^{++} may be abnormal while tMg is normal, and vice versa.[1,2]

Mg^{++}, and Ca^{++} can now be measured in the lab or at the point of care to provide a complete electrolyte analysis: Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, HCO_3^-

If you are measuring K^+ and Ca^{++}, you should also be measuring Mg^{++}

Mg^{++}, Ca^{++}, and K^+ ion abnormalities are common in critical care medicine.

Mg^{++}, Ca^{++}, and K^+ ions are interdependent and play a role in numerous disease processes, including diabetes, hypertension, kidney disease, cardiovascular disease, cardiac arrhythmia, and sepsis.

Mg^{++} is a vasodilator, Ca^{++} is a vasoconstrictor. Both are synergistic in maintaining vascular and bronchial smooth muscle tone.

Mg^{++} ion is an antagonist to Ca^{++} ion entry into cardiomyocytes.[3]

Serial monitoring of Mg^{++}, Ca^{++}, and K^+ ions are all important in correcting or avoiding cardiac arrhythmias and cardiomyocyte necrosis.[4,5,6]

Hypokalemia may be unresponsive to potassium repletion unless hypomagnesemia is first corrected.[7]

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Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, pH, Hct

Contact us for a bibliography of more than 25 recent publications about the importance of Mg^{++} in disease processes.

Mg^{++}

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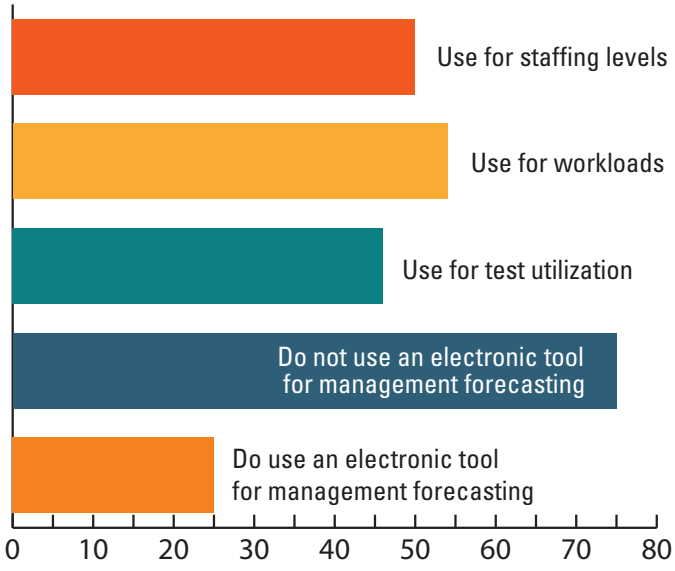
Management forecasting efforts and capabilities



Planning and forecasting

MLO questioned lab professionals about their management forecasting efforts and capabilities. Half (50%) use forecasting for staffing levels (down from 55% in 2022), 54% for workloads (down from 57% in 2022), and 46% for test utilization (down from 68% in 2022). Three-quarters (75%) said they do not use an electronic tool for management forecasting, while 25% said they do.

"I don't think (management forecasting) is something labs can do on their own. That's one of the big problems," said Dunnett. "Lab vendors come to me and say, 'I can help with lab utilization' and candidly they can't. What they can do is produce reports telling us what was performed, which I call 'activity reporting' but you can't guide decisions until you get upstream from the lab for insights into the patient's condition and context for the clinician's decisions. What we need is a lab, electronic medical record (EMR) and prescriber partnership solution."

Dunnett noted how a hospital's business intelligence team typically does not want the kind of granular level detail that the lab needs to satisfy its own operational needs. "We give them the tip of data iceberg, the rest of it is what we use in the department for operations and management," he explained.

To dig deeper into lab data for meaningful reporting, Dunnett said his lab has employed a team member specialized in structured query language who has access to the data layer in the EMR and lab system.

"The beauty of having that SQL writer sit between the two systems is she can pull granular detail that we never dreamed of having and never programmed or planned to give to the EMR," Dunnett continued. "She can juxtapose it alongside our data to answer a question, which is what it's all about."

Dunnett says they can create reports that include a patient's data from the EMR so they have richer detail on their condition and history. Next, they put it alongside the frequency of ordering certain tests to see if there is pattern to how tests are utilized in the management of that type of patient.

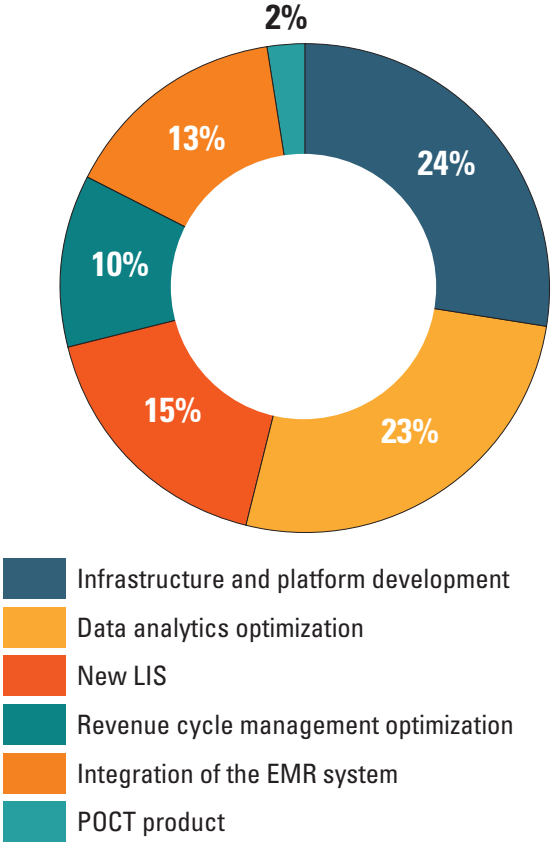
Looking ahead

To understand how lab professionals are preparing for the future, we asked for their top strategic information technology (IT) priorities for their organizations in the next three years.

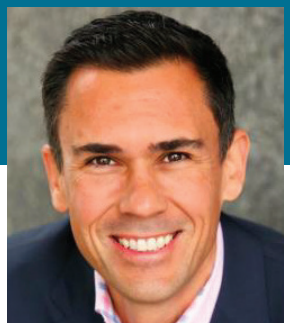
The results were similar to last year's survey, with infrastructure and platform development (24%) and data analytics optimization to support lab management (23%) highest on the list, followed by new LIS (15%), revenue cycle management optimization (10%), and integration of the EMR system (13%). POCT product was the least selected priority (2%).

Among the 12% selecting "other," several cited HER-related initiatives, including the implementation of a new EHR system, transition from one EHR platform to

Top strategic information technology (IT) priorities



The Importance of Innovation in Molecular Diagnostics



Fernando Beils
Vice President and General Manager
qPCR Instruments

An Interview with Fernando Beils, Vice President and General Manager, qPCR Instruments, Thermo Fisher Scientific

In this interview we discussed the Applied Biosystem QuantStudio Real Time PCR Ecosystem and Thermo Fisher Scientific's commitment for innovation for molecular diagnostics.

Fernando joined Thermo Fisher Scientific in 2018 as vice president and general manager of toxicology, therapy drug monitoring, and quality controls after more than 20 years holding a number of leadership roles at Siemens Healthineers. In 2022, he began supporting qPCR instruments as part of Genetic Sciences. After obtaining his MBA in Germany, Fernando held several positions in strategy, finance, operations, and sales and marketing in medical imaging, *in vitro* diagnostic (IVD) point of care (POC), microbiology, and molecular diagnostics.

Overall, IVD tests influence about 70% of all clinical decisions and they amount to about 5% of the healthcare costs, Beils said. He further discussed the importance of molecular diagnostics and the role that Thermo Fisher had in the industry in this executive interview with the *Medical Laboratory Observer* editorial team.

Can you discuss the importance of innovation in molecular diagnostics and the role Thermo Fisher plays in the MDx industry?

Molecular diagnostic testing moved to the forefront of present-day clinical practice and through the pandemic gained attention and acknowledgment in public health.

Real-time PCR (qPCR) evolved to be the gold standard in infectious disease testing—with further evolution over next-generation sequencing (NGS) into digital PCR, which allows you a powerful combination to monitor and treat patients suffering with cancer.

We play a role being the market leader in PCR technologies, offering microarray (MA), capillary electrophoresis (CE), NGS, and POC in decentralized testing. We cover all aspects through technology, tests, key components, and ingredients to provide superb patient care for the clinical research community. We enable optimal workflow operations, with error elimination, in a fast and safe manner supporting our customers to save time and cost.

How is Thermo Fisher's commitment to innovation translating into new products this year?

After the launch of our solution for digital PCR, the Applied Biosystems™ QuantStudio™ Absolute Q™ Digital PCR System, we ensured the compliance of the Applied Biosystems™ QuantStudio™ product family: the QuantStudio™ 5 Dx Real-Time PCR System and the flagship QuantStudio™ 7 Pro Dx Real-Time PCR System with IVD regulations in both the US and EU. Furthermore, this summer we launched the new Applied Biosystems™ Diomni™ Software, an ecosystem which stands also in compliance with IVD regulations in the US and In Vitro Diagnostic Regulation (IVDR) in Europe.

Can you explain the importance of IVDR compliance and how Thermo Fisher is addressing this need?

The EU made the decision to move toward new standards of regulation for medical devices. The IVDR is built around providing patient safety with reliable results. This translates that IVD equipment providers need a safe and reliable workflow and data interpretation to ensure that the results of molecular diagnostic tests are supporting patient safety and data privacy. We therefore adapted our flagship instruments to meet this new standard and took into account that the movement of data is IVDR-safe. Diomni Software is also compliant with the IVDR standard.

Can you tell us more about the buzz around the Diomni Software ecosystem?

It is about the digital customer experience. Diomni Software is intelligent, integrated qPCR software – accessible and run by your browser. It offers multi-unit and fast qPCR workflows with innovative and AI-powered applications. It speeds up your routine and provides actionable qPCR-based results to enhance healthcare delivery and outcomes. Besides diagnostics, Diomni Software is also addressing the needs in research, academia, and pharma/biotech to improve the workflow and control your data.

For clinical applications, in a nutshell, Diomni Software is about simplifying and accelerating your workflow to clinical results—reducing time, cost, and errors, and protecting your data. Quality control is a major focus. Diomni Software future-proofs the laboratory and is also scalable while being compliant with the regulatory standards. Diomni Software empowers you to trace and track all your samples through the qPCR workflow from the patient, over liquid handling, sample prep, qPCR analysis, and automation of results, up to the integration into the laboratory information system (LIS). You can connect as many instruments as you would like with one single entry point. Through the efficiency of Diomni Software, you are also reducing the carbon footprint and making more space in your lab.

Thinking about the future—is Diomni Software targeting only qPCR workflows?

We foresee that Diomni Software will include further elements of molecular diagnostic technologies like sequencing, NGS, and microarray analysis, and could expand even further into immunochemistry and LC-MS. Diomni Software is aiming to provide all intelligence to support our partners and customers – ultimately to enable them to make this world healthier.

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QuantStudio 5 Dx and QuantStudio 7 Pro Dx Real Time PCR Systems and Diomni Software are for *In Vitro* Diagnostic Use.

The QuantStudio Absolute Q system is For Research Use Only. Not for use in diagnostic procedures.

another, and EHR/LIS optimization. Others stated they were upgrading their LIS solutions, and one respondent said they were automating the validation of lab results.

Avunjian said accessioning client orders is at the top of the list for labs when it comes to automation:

"Moving from manual order processing to an electronic interface directly translates to more efficiency and productivity because it eliminates typographical errors, increases throughput, and improves turnaround time. We also see many of our lab partners moving toward electronic processing to support automated billing, digital pathology, the automatic assignment of cases to pathologists, and the automatic assignment of case numbers based on factors like the client, physician, location, and test type."

Dop believes the inbound registration and order process should be one of the top priorities for a lab that is still manually processing laboratory requisitions. She stated:

"When a lab has specimens coming in from outside the organization without automation, they are registering patients in the systems manually and then also manually placing the orders. This leaves room for errors with faulty patient matching, incomplete or incorrect insurance information, or even just misinterpretation from bad handwriting. When patients are registered electronically via inbound interfaces to the laboratory, the system matches the patient or creates a new one in seconds, it files their insurance information and passes the order to the LIS. This frees up staff time on the pre- and post-analytic side of processing the specimen."

Dop said once labs are beyond automation of patient registration and ordering, she sees electronic compendium standardization becoming a trend in the lab market.

"The healthcare industry still does not have standard nomenclature for tests across EHRs, practices, insurances, etc., so every one of a lab's clients may call a test by a different name," Dop explained. "Many of our partners have listed this challenge as a key inhibitor in their workflow. For example, a clinician orders a CBC. This shows up as a hemogram in another system, another system may type is out as complete blood count, or just abbreviated as a CBC."

"In the absence of a standardized compendium, machine learning and test code mapping will be key to allow for these multiple iterations to be identified as the same test," she added. "When this identification can be done automatically, this allows the order to flow from one system to another without manual intervention. Without automation, more staff are required on the front end of an order to interpret and process orders."

Lab professionals who took part in the survey also weighed in on the challenges faced in their planning and forecasting environments in the next three years, rating the following factors on a five-point scale: funding, staffing, technology, training, ROI/costs, with "1" being the most challenging and "5" the least challenging.

Looking at the most challenging factors in terms of those that ranked highest as a 1 or 2 on the scale:

- Staffing was at the top of the list at 85% of respondents ranking it as a 1 or 2 (down from 91% in 2022)
- Funding at 56% (up from 49% in 2022)
- ROI-costs at 24% (down from 41% in 2022)
- Training at 19% (down from 38% in 2022)

Dop said resources remain a challenge for labs across the country, noting how they are being required to provide more data and information without additional resources to gain access to that information. She commented:

"The implementation of electronic processes is not just an investment for the lab, but it is also an investment of staff time and resources. It can be a difficult sale to leadership to make the investment of moving from manual to electronic processes due to what is required to make it happen. However, no matter which processes are moving away from manual, labs will see the return on investment in increased reimbursements, an improved workflow for staff, and efficiency gains that we have seen reduce the need for a number of FTE in many cases."

Casassa noted how IT security and hospital budgets are typically not favorable for third-party packages; therefore, it is incumbent upon LIS vendors to develop modules that are integrated into their existing software and can provide whole-lab data with drill downs available by specialty section (i.e., chemistry, hematology, microbiology, etc.).

"They need to adopt the middleware concepts and expand on them," she explained. "Outreach systems may still be required as the monitoring and metrics provided are distinct for the outreach business. Laboratory leaders need basic day-to-day operational metrics on a real-time basis to optimize sample processing and workflow, analyzer usage and needs, and especially staffing in light of the industry-wide shortage of laboratory scientists. Customized current dashboards of key metrics should be available to all levels of laboratory leaders."

She concluded: "Directors, managers, supervisors, schedulers, etc. should be educated in their use for more eyes on the data providing more opportunities to improve — the goal of analytics."

Kara Nadeau, has 20+ years of experience as a healthcare/medical/technology writer, having served medical device and pharmaceutical manufacturers, healthcare facilities, software and service providers, non-profit organizations and industry associations.

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Improve the health of populations by empowering physicians to deliver optimal patient care through unified health information

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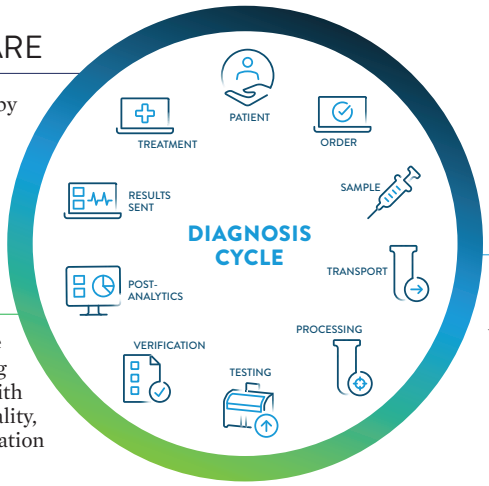
Improve patient experience and secure the lab as a trusted advisor by elevating IVD testing and decision making with integrated diagnostic, clinical, quality, and workflow information



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Liquid biopsies: Brilliant potential but highly workflow dependent

By Uwe Oelmueller, Dr. rer. nat and Nedal Safwat, PhD

Since becoming commercially available over the last 10–15 years, liquid biopsies have been enthusiastically embraced, particularly for noninvasive prenatal screening and increasingly for oncology diagnostics. Liquid biopsies also are emerging as helpful tools for monitoring transplant patients, and a range of other conditions and diseases are following. Strengthening every link in the process — from sample to insight — is key to expanding clinical use of liquid biopsies.

Delivering patient benefits today

Unquestionably, liquid biopsies — still a relatively young science — have been on the fast track in basic and translational research and are emerging as a powerful diagnostic tool. Importantly, they also are gaining ground in companion diagnostics for personalized medicine, helping doctors to stratify patients for suited therapies and to understand a patient's response to those therapies. Their ability to derive information from throughout the body, rather than a single site tissue sample, is making them increasingly critical diagnostic aids to discover residual and even reoccurring disease. For this reason, they hold significant potential for broadscale screening tests for cancer and other diseases.

From a patient's perspective, they are a winner. The collection of simple blood, urine, or even saliva samples are far less invasive, easier to collect, and less risky than more invasive, traditional tissue samples, particularly where lesions are difficult to access or present risk of hemorrhage or other complications. To be clear, it is unlikely that extracted tumor tissue or tissue biopsies will be unseated from their primacy in molecular and other pathology tests and technologies such as staining and immunohistochemistry for diagnostic and prognostic purposes. Nevertheless, liquid biopsies have become a strong complementary or alternate tool in patient care.

For example, tissue samples of a tumor remain important to grade and stage a tumor, but prior to and after both surgery and other treatment, liquid biopsies can deliver important information about remaining undetected metastasis, the tumor's response to therapy, and whether additional or alternate treatments are necessary. Liquid biopsies also offer clear utility in post-surgical patient surveillance for discovering tumor relapses, finding minimal residual disease (MRD), and earlier recognition of new metastases.

The method gives treating oncologists (and their patients) a proven method to understand treatment decisions in their battle with many forms of cancer.

Expanded use relies on sensitivity, specificity

Understanding, treating, and monitoring other diseases and conditions is a rapidly developing area for liquid biopsies. Much like any other evolving technology for diagnostics, liquid biopsies require more development to realize their full potential in additional applications. Sensitivity, specificity, and accuracy, among other test characteristics are paramount. Today, the race is on to achieve these goals and enable expanded adoption in clinical practice, particularly in patient stratification required for personalized medicine, early cancer screening, and the screening and detection of other diseases.

Liquid biopsies derive improved sensitivity from a specified, verified, and validated diagnostic workflow — from sample collection, to the dedicated analytical diagnostic test, to treatment insight. Liquid biopsy-based diagnostics, therefore, rely on the integrity and precision of the processes around them. Hence, it is crucial to choose the right state-of-the-art platform, including instruments, chemistries, software, bioinformatics, and all workflow components for the application targeted.

Another driver in the broad effort to improve sensitivity is the potential offered by the combining of tests for the different components of a liquid biopsy sample. Such multimodal approaches would offer a much sharper picture of the patient's system including circulating cell-free DNA (ccfDNA), including methylated DNA, RNA in extracellular vesicles (such as exosomes), and molecular profiles of circulating tumor cells. Combining liquid biopsy insights from different specimens from the same patient, such as parallel analysis from blood and urine, can further broaden this approach. The multimodal capability offers tremendous insight for the patient profile and a roadmap for future application.

Sensitivity relies on the absolute integrity of the entire workflow

An entire diagnostic workflow takes place at different locations. It starts with patient preparation at home for professional specimen collection. It continues at a hospital or doctor's office with the specimen collection itself, including analytes stabilization for preventing post-collection changes. Next comes specimen storage and transport to the medical laboratory where the carrier's workflow is critical (e.g., temperature, duration). The next stages of the workflow are within the purview of the laboratory where the isolation of the required analytes, such as ccfDNA, occurs.

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The analytical test itself is conducted along with bioinformatic analysis, and then the post-analytical steps such as the creation of the test report for the physician and patient are completed.

The validity of that report is only as strong as the weakest link in the workflow chain — be it an unsuited specimen collection device, unsterile catch or blood draw, mislabeling of a sample, out-of-specification temperature variance during sample transport, a nucleic acid isolation that causes bias in the targeted analyte profile, varying analytical test technology and so on.

It cannot be overstated that liquid biopsies are highly dependent on the strength and integrity of the entire workflow. During the development of a diagnostic test, it is critical to assess risk and specify, verify, and validate all workflow steps.

Strengthening every link in the chain

Several studies have demonstrated that the largest contribution to diagnostic errors comes from the pre-analytical workflow steps. The molecular profile of clinical samples can change drastically during the pre-analytical workflow, which involves all steps from specimen collection to the isolation of the target analytes, such as nucleic acids.

Specifically, transporting, storing, or archiving a specimen, or isolating the molecules carried in the sample, can change analytical target profiles, such as circulating cell-free nucleic acid profiles including circulating cell-free tumor DNA (ctDNA) and circulating tumor cells (CTCs), upon which most liquid biopsies rely. Absent a rigorously guided workflow, the tests bear a high risk that the diagnostic analytical test cannot measure the analyte profile as it was in the patient body. Instead, the test studies artificial levels that were generated post collection during the pre-analytical workflow, thus risking a wrong or unreliable diagnostic result. For most liquid biopsy applications, it is therefore key to preserve the analytical target profiles in liquid biopsies by using specimen collection devices with stabilizers for ensuring that such critical changes, such as those caused by post-collection cellular changes or chemical modifications, do not occur.

Circulating cell-free DNA (ccfDNA) offers a good example. This analyte provides real-time mutational information that can be used to detect and monitor biomarkers of cancer and other diseases in a simple blood test. Circulating ccfDNA is often found in low concentrations with rare mutations or in a fragmented condition that can undergo critical post-collection changes as white blood cells die after removal from their natural environment in the body. In this process, white blood cells release huge amounts of additional DNA that can significantly reduce the analytical test sensitivity, leading to false negative results. Reliable tools offer confidence in the signal detected (or not) from a sample.

If the entire diagnostic workflow including its pre-analytical steps is not specified, verified, and thus standardized for the dedicated diagnostic test by developers and manufacturers and then managed by users according to the diagnostic product's instructions for use, the research and diagnostic results can be invalid or unreliable. Preserving every possible target analyte profile through a well-managed workflow — and analyzing them with equal rigor — offers the most profound basis for obtaining correct and reliable information for diagnostics and treatment consideration.

Developing verified workflows

The importance of workflow integrity as a prerequisite for the continued use and expanding future of high-quality liquid biopsies, is widely appreciated. As a result, steps in the process are being verified and standardized.

Diagnostic companies and diagnostic laboratories are increasingly focused on specified and verified generic pre-analytical workflows for different specimen types and analytical targets. These verifications can include tools such as the specimen collection devices with analyte stabilizers and nucleic acid isolation kits; links to state-of-the-art, well-designed, specified, and verified analytical test technologies including related instrument platforms (such as NGS [next generation sequencing], qPCR [quantitative polymerase chain reaction], and dPCR [digital polymerase chain reaction]) with verified software; and integrated post-analytical steps such as bioinformatics for data analysis and interpretation. All are increasingly becoming the building blocks and basis for the development of new, safe, and reliable analytical tests.

Automation has become more crucial than ever, especially with increased throughput capabilities. Standardization of target analyte isolation and analysis can be achieved by integrated, automated instruments for sample processing including nucleic acid extraction as well as for analytical, including multimodal testing. The automation requires reliable hardware and software as well as optimized chemistry to ensure maintenance of required sensitivity and specificity.

Developing evidence-based standards for pre-analytical, analytical, and post-analytical workflows for routine in-vitro diagnostics is critical work being done in Europe and in the United States. Based on scientific evidence, new standards are mostly developed via the International Organization for Standardization (ISO) Committee "Clinical laboratory testing and in vitro diagnostic test systems" for the global markets or European Committee for Standardization (CEN) Committee "In vitro diagnostic medical devices" for the European markets if global standards are not available. QIAGEN and sample workflow specialist PreAnalytiX were drivers of consortia for the first large pre-analytical standards projects in this field. Guidance documents also are published by other professional institutions such as the U.S. Food and Drug Administration and Clinical & Laboratory Standards Institute (CLSI).

Conclusion

Liquid biopsies offer genuinely exciting potential for understanding disease and treating patients across the entire continuum of care. With stronger specified, verified, validated, and complete diagnostic workflows, liquid biopsy diagnostics will shed any lingering doubt on the quality of results, benefitting researchers who will have more and faster reproducible data to drive the discovery and development of new biomarkers. And new biomarkers will allow care providers to expand the clinical use of minimally invasive biopsies as part of a new generation of patient care.

Dr. Uwe Oelmueller is **QIAGEN's** Vice President, Head of the Molecular Diagnostics Technology Center for Sample Technologies. He is an award-winning expert in the standardization and improvement of pre-analytical workflows for in-vitro diagnostics. In addition to his work assuring QIAGEN products and workflows deliver high-quality insights, Dr. Oelmueller has been widely recognized for his work with the ISO, CEN and other organizations developing standards for quality management in medical laboratories. Dr. Oelmueller also is QIAGEN's management committee co-chair at PreAnalytiX, a joint venture between QIAGEN and BD, focusing on specimen collection, preservation and processing.

Dr. Nedal Safwat is **QIAGEN's** Vice President of Sales for North America Molecular Diagnostics. He is focused on delivering to customers leading technologies, workflows and supporting systems to accurately identify the building blocks of life in every patient sample. He brings significant experience in the IVD market and the life science industry through a variety of roles including leading a business franchise, global marketing, product management, and commercial positions. Dr. Safwat earned his doctoral and undergrad degrees in biochemistry from North Carolina State University.

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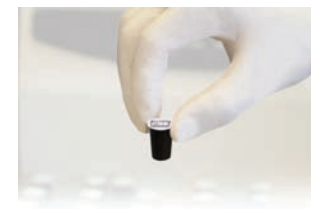

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LABORATORY INNOVATOR

Keenly focused on the future of pathology

by Christina Wichmann

Piotr Borkowski, MD, is Managing and Medical Director of AmeriPath Central Florida and Director of the Center of Excellence for Digital and AI-Empowered Pathology at **Quest Diagnostics.** Dr. Borkowski is board-certified in anatomic and clinical pathology, as well as clinical informatics. With over 25 years of experience, Dr. Borkowski specializes in digital pathology powered by artificial intelligence and attended both the Medical University of Gdansk, Poland and the University of Maryland School of Medicine before competing his residency at Mount Sinai Medical Center in Miami Beach, Florida.

An energetic Tampa Bay resident, Dr. Borkowski loves soccer, the great outdoors, and staying active in the area. He also speaks five languages and enjoys drawing and painting.

In your observation, what impact has COVID-19 had on the diagnosis of cancer?

I believe that, when we review a biopsy under a microscope, every pathologist's greatest hope is to find no cancer, or to be able to make a very early cancer diagnosis. We know that early detection of cancer often leads to the best treatment outcomes. However, the COVID-19 pandemic created and fostered an environment where the diagnosis and treatment of cancer were both delayed. A Quest Diagnostics Health Trends study by some of my colleagues found even after two years, cancer diagnosis has not returned to pre-pandemic rates for breast and prostate, two of the most common cancers. We are likely to see the impacts of the pandemic for years to come.

What advice do you have to improve the pathologist—clinician collaboration?

Effective collaboration between the clinician and the pathologist leads to the best patient care. Both must be willing to work together and have clear and direct lines of communication. The increased use of virtual technologies like Zoom over the last few years has assisted this and helped both parties talk directly as much as possible — literally face to face. I have been doing this myself for a few years now and believe it makes me a more well-rounded physician. There is information both clinicians and pathologists can learn from each other, making both parties medically 'bilingual.' As an example, it is important for pathologists to learn as much as possible about the clinical aspect of the disease such as any advances in treatments or clinical trials, and it is equally as important for clinicians to learn about diagnostic aspects from pathologists.

How are AI-based approaches expanding the treatment of cancer?

This is a very exciting time to be in the field of pathology. We are currently integrating artificial intelligence (AI) into the diagnosis of some cancer types at Quest Diagnostics, which I find very interesting. I believe in the near future AI will be integrated into the pathologist's workflow, and I am honored and energized to be part of the team leading that cause at Quest Diagnostics. Specifically, AI has the potential to assist in tumor detection, tumor grading, and classification. It is also expected to play a role in the prediction of mutations, survival, and therapy response solely based on H&E-derived computational data. Integrating AI into the diagnosis of cancer, and then using AI to assist in determining the most optimal treatment, is a groundbreaking advancement. This can – and I believe will – save many lives by directing clinicians to the best treatment, for the best outcome, from the start of a patient's cancer journey. We also have used AI in cytotechnology to significantly hasten our results reporting for some applications, namely the chromosome analysis procedure, which is known to be a highly manual process. By using AI to make this step more efficient and analyze chromosomes faster, we were able to eliminate backlogs and improve consistency of turnaround times.

What do you think the future holds for personalized medicine in the next 5–10 years?

The last few years have led to some large changes in the field of pathology. Many have experienced this twice before, through the introduction of immunohistochemistry and genomics. I believe we are experiencing a third revolution in pathology with the introduction of digital and AI-empowered pathology. Though I have been in this field for over twenty years, this is the most exciting time of my career, creating big changes that bring with them big opportunities. The opportunity to improve and optimize care via personalized medicine is before us, and it is my belief that we will continue to see important developments and advancements in how the patient interacts and receives information and care from his or her physician. With these new advancements, patients can expect improved care — leading to better outcomes and improved health.

What challenges do you face in your everyday work?

The integration of artificial intelligence (AI) and digital pathology software into the workflow is a current challenge that I find very intriguing. My approach is to take my experience as a pathologist and tweak the digital software so that the workflow becomes seamless, thereby creating an environment where adoption by the pathologists I work with is made easy. I look forward to the ways this technology will continue to evolve and present new, unique, and interesting challenges to my work.

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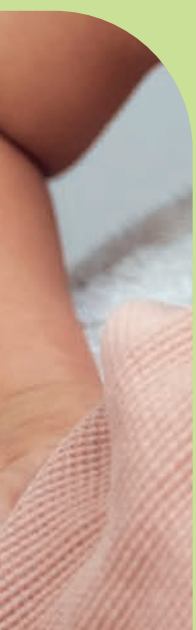

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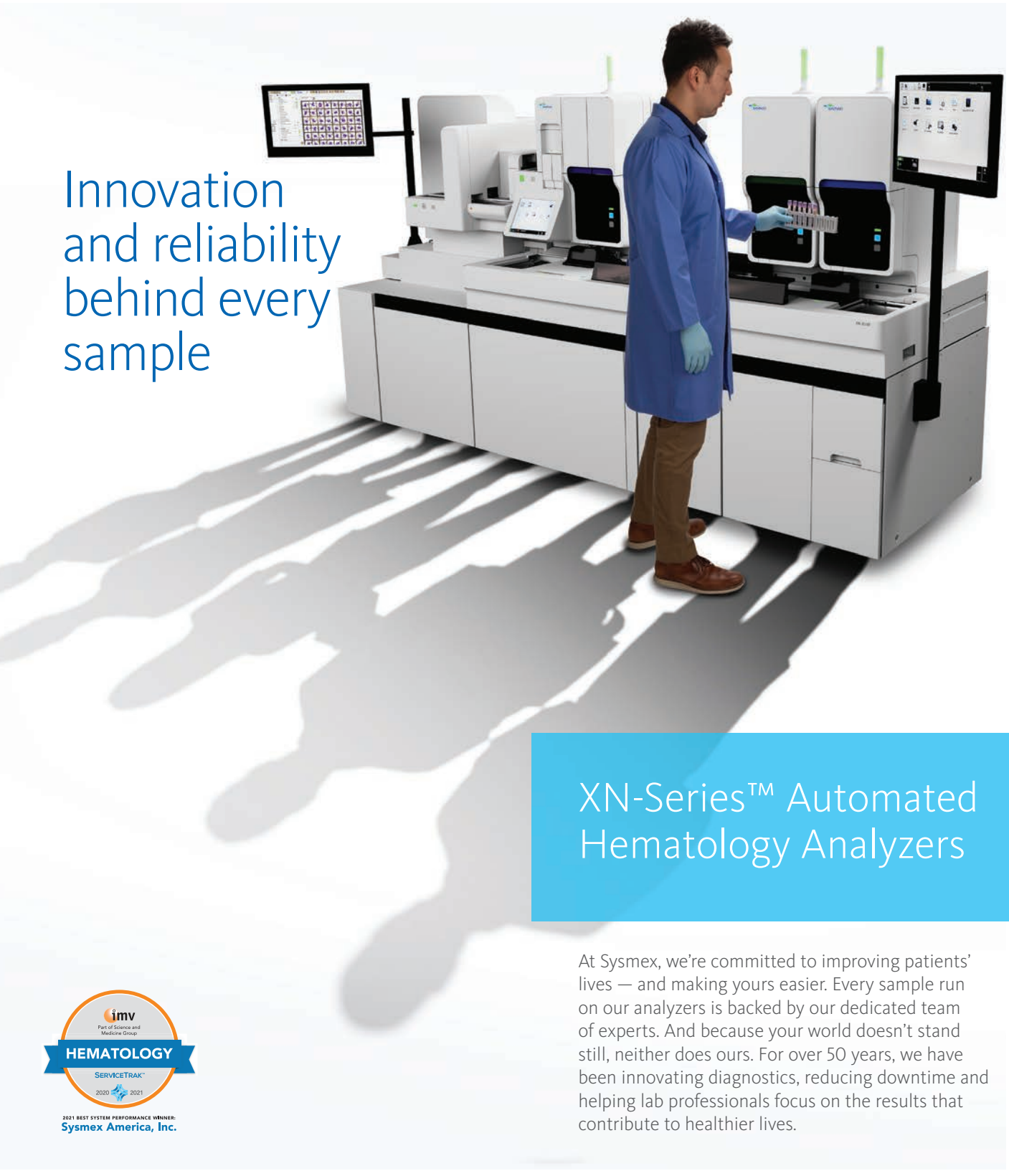

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