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SEPTEMBER 2023 • Vol 55 • No 9

CE:

Respiratory illnesses: A growing opportunity for stewardship

Page 6

Virology testing post-COVID

Page 26

PLUS

A1c testing methodologies

Page 30

Understanding elevated cTn

Page 38

LAB INNOVATOR

Betty Woo, PhD
Vice President
and General Manager
of Cell and Gene Therapy
at Thermo Fisher Scientific

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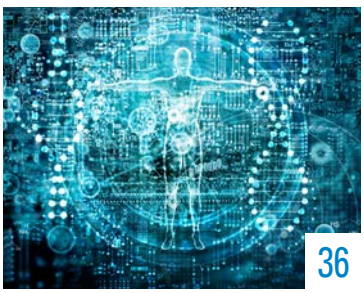

36

38

42

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ADLM 2023 Scientific Meeting & Clinical Lab Expo

By Christina Wichmann

Christina Wichmann
Editor in Chief

At the end of July, *MLO* staff attended the Association of Diagnostic and Laboratory Medicine (ADLM) conference in Anaheim, CA. It's a huge conference, and *MLO* was included in the over 900 exhibitors this year. We met with a number of the other exhibitors and learned about the latest innovations in laboratory diagnostics. There were also many educational plenary and scientific sessions offered.

One of the sessions I attended was called "Project Management in Laboratory Medicine: Principles and Applications in Large and Small Laboratories." The presenters described what project management is and why it is important in the laboratory, what project management in a large laboratory system looks like, and what project management in community hospital laboratories looks like. Three types of project management methodologies were explained: agile, waterfall, and hybrid. The agile methodology is an iterative approach to delivering a project that continuously incorporates customer feedback. The ability to adjust during each iteration promotes velocity and adaptability. The waterfall methodology has a clearly defined sequence for execution within project phases, which do not advance until a phase receives final approval. The hybrid approach combines the best of waterfall for planning and agile for execution.

According to the Project Management Institute, qualified and experienced project managers are skilled in the following areas:

1. Leadership and effective communication—project managers must effectively lead and communicate with their teams as well as stakeholders throughout the entire lifecycle of a project.
2. Organization and time management—project managers must handle the organization and delegation of tasks. They must also ensure that all project materials and deliverables are completed on time.
3. Creative problem solving and adaptability—project managers must understand how to resolve issues and adapt their projects creatively to avoid mishaps and losses.
4. Motivation and team management—project managers must ensure their stakeholders and team members stay motivated throughout a project's lifecycle. Moreover, they must be able to manage their team to ensure top-quality results and on-time completion of project deliverables.

Numerous tools that could be part of a project management toolbox were also shared. These tools ensure that initiatives keep moving even when a professional project manager cannot be assigned. These tools include those to help with data gathering such as a checklist, outline for organizing steps for a focus group, and a project mind mapping/brainstorming tool; tools that help with data analysis such as alternatives analysis, cost/benefit analysis, and qualitative risk analysis; tools that help with representing data such as responsibility assignment matrix, cause and effect fishbone diagram, and work breakdown tree; and tools that help with communication such as stakeholder and project communication and team roadmap. A variety of project management tools and templates are also available free through an online search.

Through my training in Lean and Six Sigma, I've seen firsthand the positive impact solid project management has on both large and small projects. It may seem like a lot of upfront work, but the results are clear goals, objectives, and responsibilities; improvements in effectively using staff and financial resources; and higher quality results. I encourage anyone interested to look into project management methodologies.

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

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Respiratory illnesses: A growing opportunity for stewardship

By Anooj Shah, PharmD, MBA, BCIDP; Marti Juanola Falgarona, PhD

Only the rare individual hasn't been sickened by a respiratory infection — either viral or bacterial. After all, these pathogens are among the most common causes of disease in human beings,[1] and a leading cause of death.[2] Properly diagnosing respiratory pathogens can be extremely difficult to do in the observational physician office setting, primarily because the symptoms of influenza, respiratory syncytial virus (RSV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and other respiratory infections are often indistinguishable.[3] Further complicating matters, the pandemic emergency caused shifting of assumed seasonal patterns, which have served as a "guide" for physicians' observational diagnoses.

Pandemic emergency measures such as social distancing and masking disrupted typical seasonal patterns of respiratory infections, including muting influenza for two years. When these measures ended and borders reopened, viral pathogens began to circulate again, but not on their usual schedule. A study of the 2022 flu season in Australia found that the incidence of flu peaked fully two months earlier than it had for the entire decade prior — in mid-June versus mid-August. Given that Australians typically receive their seasonal flu vaccine between March and May, the early start to the flu season meant that a smaller proportion of the population had received their annual flu shot.[4] The overlap of respiratory symptoms, along with the blurring of seasonal lines, reinforces the need for labs, and the doctors and public health officials who rely on them, to think in terms of syndromic diagnostics to help effectively manage patient and population health and monitor viral co-circulation.[5]

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LEARNING OBJECTIVES

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

1. Discuss the challenges that the healthcare industry faces with respiratory illness diagnosis.
2. Define syndromic testing and describe its benefits.
3. Describe the benefits of multiplex PCR testing and its utility in diagnosing respiratory illnesses.
4. Describe how diagnostic and antimicrobial stewardship work to improve antimicrobial resistance.

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Viruses or Bacteria
What's got you sick?

Antibiotics are often prescribed when they are not needed for respiratory infections. Antibiotics are only needed for treating certain infections caused by bacteria. Viral illnesses cannot be treated with antibiotics. When an antibiotic is not prescribed, ask your healthcare professional for tips on how to relieve symptoms and feel better.

Common Respiratory Infections	Common Cause			Are Antibiotics Needed?
	Virus	Virus or Bacteria	Bacteria	
Common cold/runny nose	✓			No
Sore throat (except strep)	✓			No
COVID-19	✓			No
Flu	✓			No
Bronchitis/chest cold (in otherwise healthy children and adults)*		✓		No*
Middle ear infection		✓		Maybe
Sinus infection		✓		Maybe
Strep throat			✓	Yes
Whooping cough			✓	Yes

* Studies show that in otherwise healthy children and adults, antibiotics for bronchitis won't help patients feel better.

BE ANTIBIOTICS AWARE
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To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.

CDC

CS328461-A

Figure 1.[17]

The COVID-19 pandemic accelerated the introduction of new methods to diagnose and treat viruses, and greatly heightened awareness of diagnostic stewardship programs. It also highlighted the clinical utility of multiplex polymerase chain reaction (PCR) assays, or syndromic diagnostic testing for infectious diseases. The ability to deliver a rapid and accurate diagnosis has significantly changed the way infectious disease clinicians and laboratorians manage patients and optimize workflow. Accurate, earlier diagnoses also enable more precise therapeutic decisions and infectious control measures.[6]

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Syndromic testing

A syndrome is a set of symptoms and signs that are correlated with each other and often with a specific disease. For example, a respiratory syndrome may include symptoms or signs such as fever, cough, muscle aches, elevated heart rate, or abnormal laboratory results (e.g., white blood cell count). Patients may experience just a few of these symptoms which can make it challenging for a clinician to identify a causative pathogen based on non-specific symptoms alone.

In addition, a patient's ability to recover from a respiratory infection varies widely.

Consider a patient with chronic obstructive pulmonary disease (COPD) or asthma, for example. These patients are more likely to become seriously ill from respiratory infections, as compared to a patient with no underlying lung or health conditions.[7] These and other factors that impact patient outcomes include the type of pathogen, its resistance to treatment, the patient's age and underlying health status, and importantly, the speed and accuracy of a diagnosis so proper treatment can begin promptly.

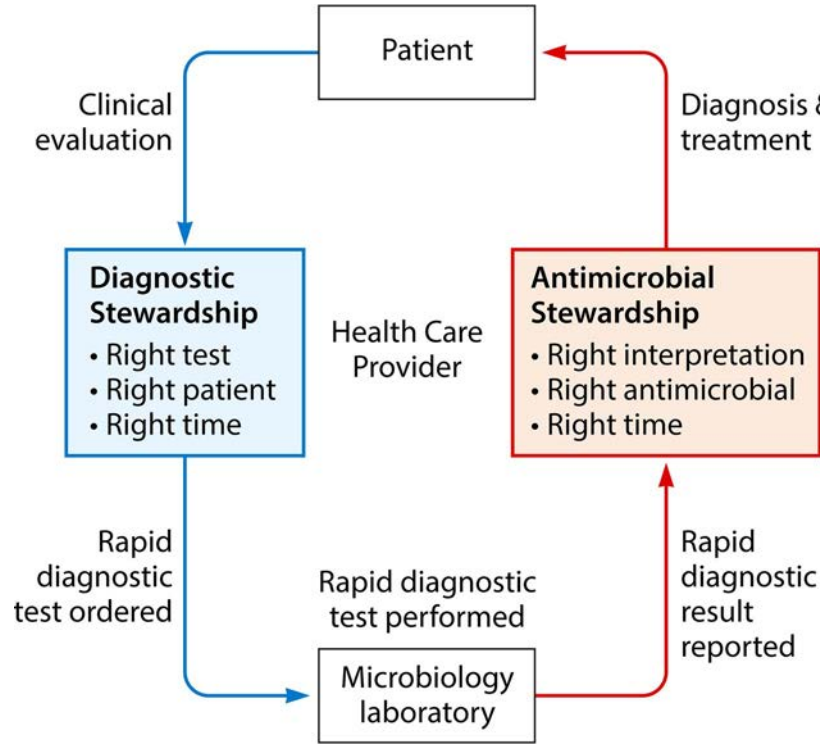

Figure 2. Roles of diagnostic and antimicrobial stewardship in the implementation of rapid molecular infectious disease diagnostics in the clinical setting.[23]

Misdiagnosis matters

At the point of care, physicians do not have the tools to differentiate among overlapping symptoms. In a study comparing the results of early identification in an office against the results of PCR and RNA sequencing of samples from the same patients, the study team found that skilled medical observation without laboratory testing identified only 37 percent of the study's patients with respiratory tract infections.[8] A brief retrospective analysis demonstrated that multiplex testing identified 59 percent positive targets and over 90 percent of co-infections not detected by low-plex testing.

Sensitive multiplex PCR panel testing is a fast and simple way to accurately diagnose patients when multiple respiratory pathogens are circulating. In fact, the Centers for Disease Control and Prevention and the Academy of Medical Sciences "strongly support multiplex testing" in this situation.[9,10] Syndromic testing with multiplex molecular panels offers clinical labs a way to quickly distinguish between a broad array of respiratory pathogens. Unlike traditional diagnostic methods, such as bacterial culture and microscopy, PCR tests can test for a host of pathogens and deliver accurate results in about an hour.

Without question, the coronavirus disease pandemic brought the utility of multiplex PCR assays into sharp focus. By combining common pathogens capable of causing a specific syndrome into one panel, multiplex testing can reduce the time needed to provide a diagnosis and a precise therapeutic decision.[11]

Many clinical publications show that syndromic testing can support antimicrobial stewardship programs, improve patient outcomes, and reduce overall healthcare costs, lessening the impact of misdiagnosis.

Diagnostic and antimicrobial stewardship

Many clinical publications show that syndromic testing can support antimicrobial stewardship programs, improve patient outcomes, and reduce overall healthcare costs, lessening the impact of misdiagnosis. Syndromic panels, if implemented thoughtfully and interpreted carefully, have the potential to improve antimicrobial use and patient outcomes through improved clinical decision making, optimized laboratory workflow, and enhanced antimicrobial and laboratory stewardship.[12] Diagnostic stewardship refers to the appropriate use of laboratory testing to guide patient management, optimize patient outcomes, and limit the spread of antimicrobial resistance. Partnership among clinical laboratories, pharmacists and infectious disease clinicians can ensure that the right tests are ordered for the right patients, and the information they provide is translated into appropriate treatment decisions.[13]

In turn, appropriate treatment decisions can advance antimicrobial stewardship. Antimicrobial resistance is considered an urgent global health threat.[14] In the United States, more than 2.8 million antimicrobial-resistant infections occur each year, and more than 35,000 people die as a result. The U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) includes a strategic goal to accelerate development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.[15] Syndromic testing can guide proper, evidence-based use of antibiotics[16] — which do not work on viral infections — and support global Antimicrobial Stewardship Programs (ASPs).

To mitigate the misuse of antibiotics for viral respiratory infections, the CDC provides education resources to help patients and clinicians recognize if their symptoms may be caused by a bacteria or virus **(See Figure 1).**[17]

The coronavirus pandemic increased awareness of diagnostic stewardship programs that evaluated several testing platforms to ensure the right test was being ordered for the right patient. These programs also aimed to ensure that critical resources were being conserved and utilized appropriately. Since the pandemic has waned, diagnostic stewardship programs have continued to flourish and bring awareness to the relationship between diagnostic and antimicrobial stewardship to improve patient care **(See Figure 2).**[23]

Additional benefits of syndromic testing to address respiratory infections

Syndromic testing is the subject of a growing number of studies, and has been shown to offer benefits to patients, reduce certain healthcare costs, and improve lab efficiency. Particularly for at-risk patients, speed matters. Laboratories can cement relationships with ordering physicians and care providers by offering the improved sensitivity and specificity of multiplex PCR testing and deliver accurate results in as little as an hour, instead of 2 or 3 days.[18]

Across several studies, use of syndromic testing to diagnose and guide treatment for respiratory infections led to a 13 percent reduction in antibiotic therapy duration,[19] a 30 percent reduction in antibiotic prescriptions,[20] and one (1.0) fewer days in median antimicrobial duration in adult influenza patients.[21]

Mortality and length of stay in intensive care units (ICU) are both reduced by syndromic testing, with one study[3] reporting a three-day reduction in ICU days using multiplex syndromic tests as compared to batch testing and a 10 percent increase in survival when results were reported in less than seven hours.

Reinforcing the argument that quality, evidence-based care saves money, syndromic testing not only reduced ICU bed days, but delivered per patient ICU cost savings of over $9,000 with a positive respiratory pathogen and over $8,000 for a negative result.[3]

The benefits of syndromic testing for respiratory infections extends into the clinical laboratory, too. Among the significant benefits for labs, is the opportunity to streamline the workflow. One molecular test can provide multiple results so labs can reduce the number of low-plex, microscopy and culture tests ordered. Next, labs can optimize their operations. With less hands-on time and minimal training required, samples can be processed 24 hours a day, seven days a week, without waiting to batch samples. Also, labs were able to deliver a 30.4 hour reduction in turnaround time versus batch testing.[22]

Not all syndromic panels work the same way, but attractive features to look for include having all reagents preloaded into the cartridge, the ability to perform tests with a single-instrument solution, and cartridges that can be shipped and stored at room temperature.

Respiratory infections, caused by a wide range of pathogens, are likely to remain a significant source of illness among humans. As vaccines and treatments emerge to address viral respiratory pathogens, the role clinical laboratories can play is critical in differentiating what pathogen — bacterial or viral — has made a patient sick. Laboratories can drive the correct diagnosis and the correct treatment, meaning that diagnostic stewardship is a space that clinical laboratories are well positioned to define, underscoring the need for close partnership with front-line healthcare delivery providers, pharmacies, and public health agencies.

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Respiratory illnesses: A growing opportunity for stewardship

SEPTEMBER 2023 *[This form may be photocopied. It is no longer valid for CEUs after MARCH 31, 2025.]*

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TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: ○ X

1. _____ pathogens are the most common causes of disease in human beings.
   - A. GI
   - B. Urogenital
   - C. Respiratory
   - D. Skin
2. Diagnosing respiratory pathogens can be difficult in a physician's office setting because there are many respiratory viruses that are often indistinguishable from each other.
   - A. True
   - B. False
3. The SARS-CoV-2 pandemic muted influenza for
   - A. 5 months
   - B. 15 months
   - C. 2 years
   - D. 5 years
4. When viruses began to emerge at the end of the pandemic, flu seasons were shown to peak
   - A. 2 months earlier
   - B. 5 months earlier
   - C. 2 months later
   - D. 5 months later
5. The COVID-19 pandemic highlighted the clinical utility of _____ testing in order to deliver rapid and accurate diagnostics for respiratory illnesses.
   - A. Culture-based
   - B. Antibody
   - C. Microscopy
   - D. PCR
6. Which of the following factors impacts patient outcomes in the diagnosis and treatment of respiratory illnesses?
   - A. Health status and age of patient
   - B. Type of pathogen present
   - C. Speed and accuracy identified pathogen
   - D. All of the above
7. Studies have shown that without laboratory testing, _____ percent of the patients with respiratory infections were identified with skilled medical observation.
   - A. 8
   - B. 22
   - C. 37
   - D. 45
8. Multiplex testing studies have shown that this type of testing can identify over ____ percent of co-infections, which are not detected by low-plex testing.
   - A. 90
   - B. 93
   - C. 95
   - D. 98
9. The CDC does not currently support multiplex PCR testing when multiple respiratory symptoms are circulating in a patient.
   - A. True
   - B. False
10. Syndromic testing has shown to lessen the impacts of misdiagnosis by
    - A. Supporting antimicrobial stewardship programs and improving patient outcomes
    - B. Reducing overall healthcare costs
    - C. Both A. and B.
    - D. None of the above
11. _____ _____ refers to the appropriate use of laboratory testing to guide patient management, optimize patient outcomes, and limit the spread of antimicrobial resistance.
    - A. Diagnostic stewardship
    - B. Misdiagnosis stewardship
    - C. Antimicrobial stewardship
    - D. None of the above
12. Who is involved in a diagnostic stewardship program in which appropriate treatment decisions are made?
    - A. Pharmacists
    - B. Infectious disease clinicians
    - C. Clinical laboratories
    - D. All of the above
13. Appropriate treatment decisions will help to advance antimicrobial stewardship.
    - A. True
    - B. False
14. Which organization provides educational resources to mitigate the misuse of antibiotics for respiratory infections?
    - A. WHO
    - B. CDC
    - C. FDA
    - D. CARB
15. Across several studies, use of syndromic testing to diagnose and guide treatment for respiratory infections led to a ____ percent reduction in antibiotic therapy duration, a _____ percent reduction in antibiotic prescriptions, and one fewer days in median antimicrobial duration in adult influenza patients.
    - A. 10; 25; two
    - B. 13; 25; two
    - C. 13; 30; one
    - D. 30; 13; one
16. Syndromic testing showed per patient ICU cost saving of over $50,000.
    - A. True
    - B. False
17. Multiplex testing in the clinical laboratory has reduced the turnaround time by
    - A. 12.6 hours
    - B. 23.3 hours
    - C. 30.4 hours
    - D. 50.8 hours

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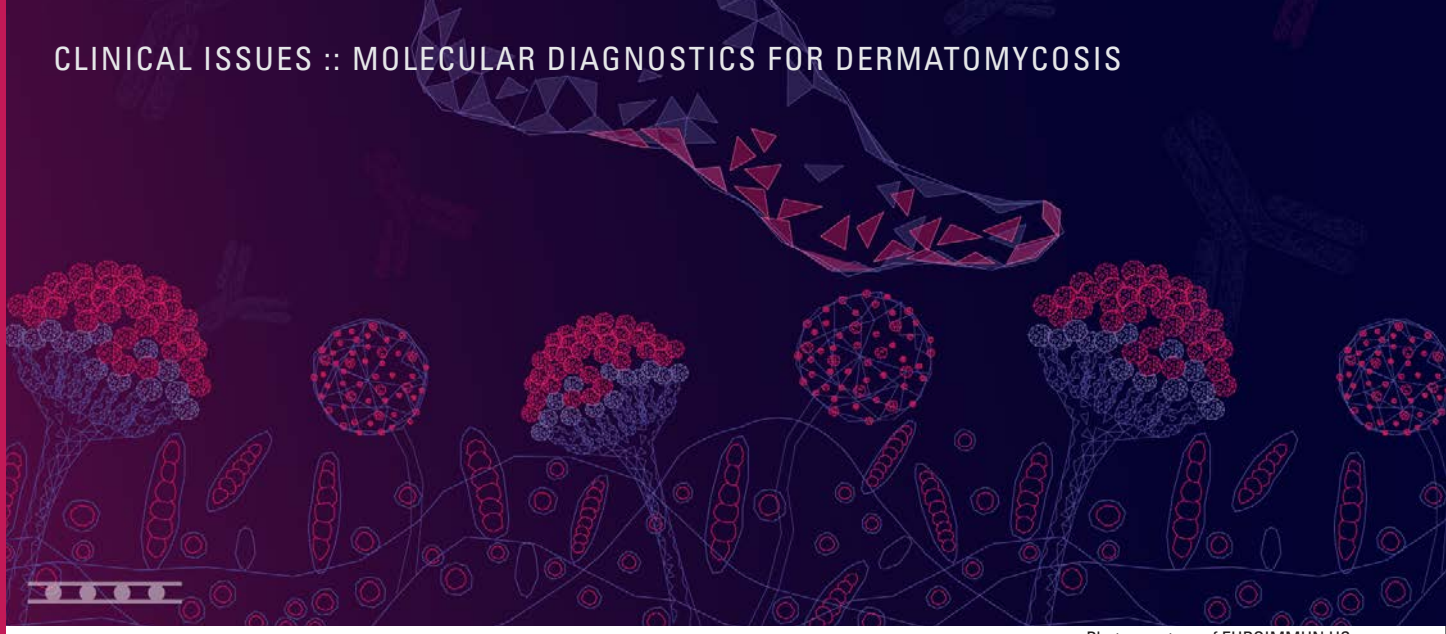

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Molecular diagnostics for sensitive detection of dermatomycosis species

By Jackie Weiss, PhD

Dermatomycosis of the hair, skin, or nails is one of the most prevalent fungal infections worldwide, affecting 20–25% of the global population.[1] The condition is caused by keratinolytic fungi called dermatophytes, in addition to molds and yeasts.[2] Dermatophytes are classified into six pathogenic genera: *Microsporum, Trichophyton, Epidermophyton, Nannizzia, Lophophyton*, and *Arthroderma*. Additionally, dermatophytes are categorized as anthropophilic, zoophilic, or geophilic according to their natural habitat.[3]

Clinical presentation varies depending on the site of infection, type of fungus, and immune response of a patient but frequently include rash, itchy skin, hair loss, or thickened nails.[3] Although antifungal medications are effective, dermatomycosis remains undertreated.[4] In addition to causing permanent damage to the affected area, dermatomycosis can progress to severe disease in elderly and immunocompromised patients if left untreated.[5-7] Furthermore, improper treatment will not only fail to clear the infection and prevent further spread but may also contribute to the development of antifungal resistance.[5] Importantly, healthcare providers must first identify the fungal species causing infection to prescribe the most effective treatment.

Dermatomycosis can be difficult to diagnose clinically, as symptoms may resemble other skin disorders.[8] Therefore, laboratory diagnostics are required for a definitive diagnosis. While traditional dermatomycosis diagnostics may take several weeks or are unable to identify dermatophyte species, molecular methods facilitate quick, species-specific determination.

Conventional diagnostics

Fungal Culture: Fungal culture using hair, skin, or nail specimens is a common method for detecting dermatomycosis and identifying fungal species.[9] Culture involves plating and incubating the patient sample for 4–6 weeks in sample media. Fungal species can then be visually identified based on morphological characteristics such as colony size, pigmentation, shape, and type of growth.[9] However, accurate species identification based on colony morphology requires well-trained mycology staff. While culture allows the identification of fungal species, the long incubation time delays species identification and subsequent treatment.

Additionally, fungal culture has limited sensitivity for detection of dermatomycosis. Some fungal species do not grow in culture, and recent systemic or topical use of antifungal treatments can prevent fungi from growing.[2] In these cases, a sample is at risk of being incorrectly identified as negative. False negative results may also stem from improper specimen collection or insufficient sample material, whereas false positives may result from contamination.[9]

Microscopy: Direct microscopy of hair, skin, and nail specimens is commonly performed to assess the presence or absence of pathogenic fungi. As with culture, technical expertise is required to differentiate between dermatophytes, molds, and yeasts.[9] While microscopy is less time-intensive than fungal culture, microscopy cannot be used to identify fungal species or indicate viability of the pathogen. Furthermore, microscopy has a high false negative rate of 35% for the diagnosis of dermatomycosis.[10]

Prior to microscopic evaluation, specimens are often digested in 10–20% potassium hydroxide (KOH), used as a clearing agent.[11] This technique facilitates the visualization of hyphae and spores by digesting the keratin surrounding the fungi. However, usage of KOH preparation may lead to false negative results in 5–15% of cases.[3] Additional stains, such as Calcofluor White (CW), can be used to improve sensitivity.[12] Periodic acid-Schiff (PAS) staining is another common method for detection of fungal pathogens. PAS staining reacts with aldehyde groups in fungal cell wells, allowing visualization of hyphae and yeast-forms of fungi. Previous work has shown that for diagnosis of onychomycosis (OM), nail plate biopsy with PAS stain is more sensitive than culture, KOH preparation, and CW stain.[13]

Molecular diagnostics

Molecular methods for dermatomycosis diagnosis include polymerase chain reaction (PCR), real-time PCR, DNA microarray, and next-generation sequencing (NGS). These techniques involve direct detection of genetic material and provide a faster, more accurate alternative to conventional diagnostics. Importantly, molecular methods enable rapid identification of fungal species, which allows patients to receive more expedient and appropriate treatments.

PCR: Polymerase chain reaction (PCR)-based assays use primers to amplify fungi-specific DNA sequences in a sample.[14,15]

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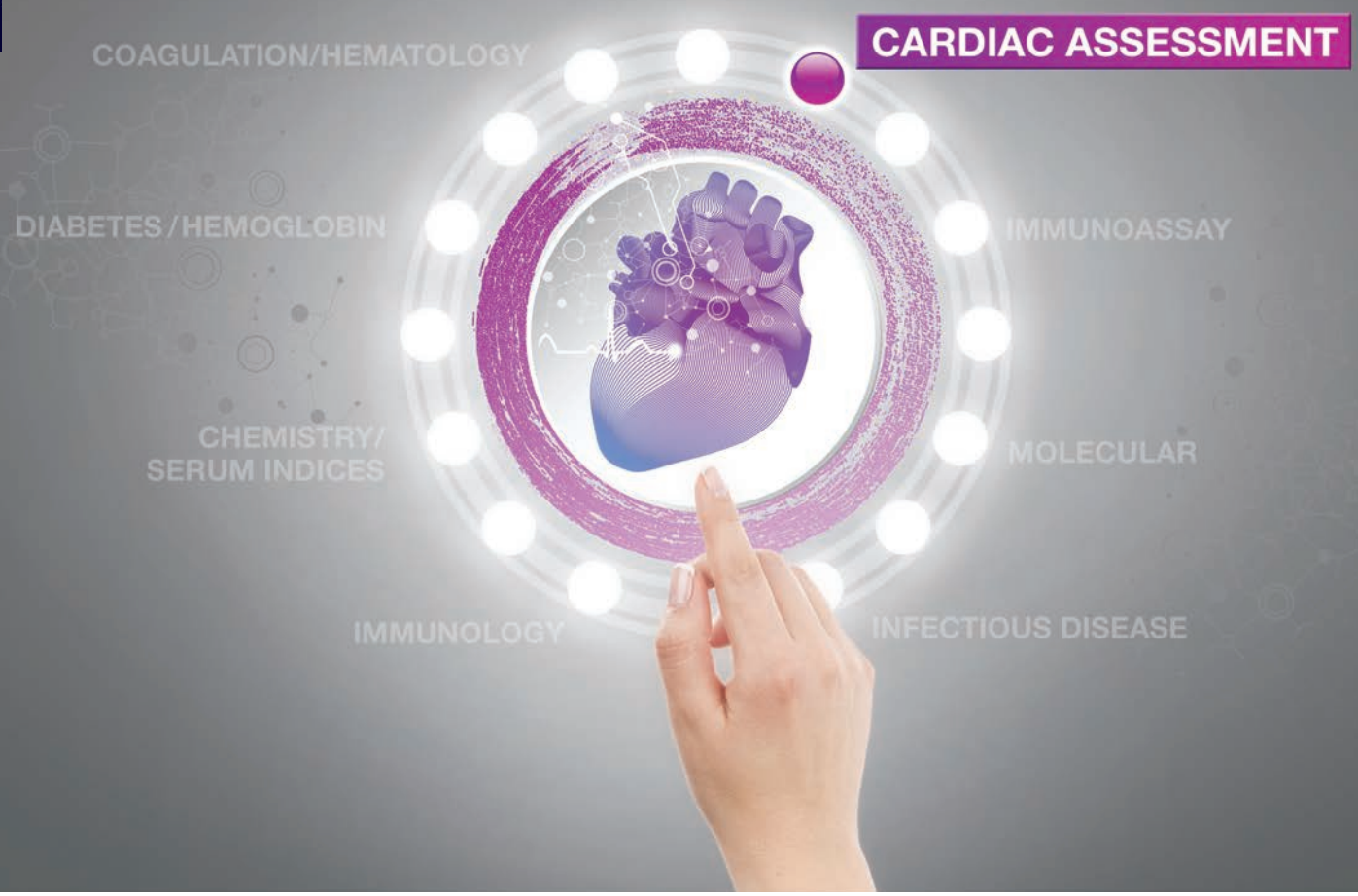

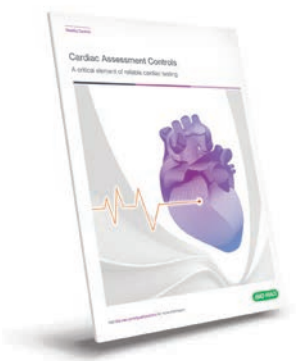

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Disadvantages	• High false-negative rate (30%) • False-positive results possible due to contaminations / artifacts • No species differentiation possible (only general fungi detection) • Manual / subjective analysis • Experienced laboratory staff needed	• Long growth time (at least 2 weeks) • False-negative results possible, since some fungal species do not grow - Often after therapy starts (e.g. with topic antimycotics) • Multiple infections will eventually / partially not be detected (fungal overgrowth) • Very experienced laboratory staff needed for microscopic and macroscopic evaluation • Manual / subjective analysis • When microscopic and macroscopic evaluation eventually not clear a biochemical differentiation necessary	• Specific equipment needed • Higher cost than conventional methods

Table 1. Laboratory diagnostic methods for Dermatomycosis[10,14,18,20,26]

Primers target components of a fungi's genome, including the nontranscribed spacer (NTS) regions, metalloprotease gene, chitin synthase (CHS) gene, tubulin gene, promoter region within ribosomal intergenic spacer, transcription elongation factor 1, actin gene, and calmodulin gene.[9] Notably, PCR is 20–30% more specific than culture and is capable of detecting dermatophytes that are difficult to grow in culture.[11]

Nested PCR aims to increase sensitivity or specificity by using two sets of primers in two sequential amplification reactions; the product from the first reaction serves as the template for the second run.[16] Prior work has found improved sensitivity for dermatophyte detection with nested PCR using CHS primers compared to conventional PCR.[17]

Real-time PCR: Real-time PCR provides rapid quantitative results for the identification of DNA or RNA, allowing estimation of a sample's fungal load.[18] Previous work has found that real-time PCR using a pan-dermatophyte primer targeting CHS is more sensitive (93%) than nested PCR (73.3%) targeting the same gene.[19] Additionally, real-time PCR demonstrated higher sensitivity and specificity compared to microscopy with KOH. Real-time PCR showed a sensitivity of 93.3% and specificity of 40%, whereas KOH microscopy had a sensitivity of 80% and specificity of 16%.[19]

DNA microarray direct detection: PCR-based detection by DNA microarray enables direct, species-specific detection of fungal pathogens. DNA microarray methodology allows for multiplexing, enabling simultaneous detection of different species. While traditional PCR usually identifies 1 to 6 fungal species at a time,[20] one commercially available PCR-based DNA microarray kit provides direct detection of 50 dermatophytes, with 23 species-specific dermatophytes in addition to six yeasts and molds within approximately three hours.[21]

Previous work comparing detection methods for OM and tinea pedis (TP) fungal infections found that the highest sensitivity among methodologies was PCR-based DNA microarray technology, with a sensitivity of 79% for OM and 91% for TP.[22] In contrast, direct microscopy showed sensitivities of 68% for OM and 37% for TP. Fungal culture had the lowest sensitivities, 29% for OM and 44% for TP.[22]

The same study found that combining conventional diagnostic methods with PCR-based DNA microarray yielded the higher sensitivities. While combination of culture and direct microscopy resulted in fairly low sensitivities of 79% and 59% for OM and TP respectively, the combination of culture and DNA microarray increased sensitivity to 87% for OM and 94% for TP. Additionally, combining direct microscopy and DNA microarray achieved sensitivity of 92% for OM and 96% for TP.[22] Overall, the combination of PCR-based DNA microarray methodology with direct microscopy yields sensitivity nearing 100% with the added benefits of species identification and a short turnaround time for results.

Next-generation sequencing: Next-generation sequencing (NGS) compares nucleotides in a sample against a catalogue library. NGS allows high throughput, rapid turnaround time, and accurate detection. Additionally, previous work has found that NGS is significantly more sensitive than culture for the detection of bacterial and fungal infections (95% versus 60%).[23] The genome sequences of several species are available, including *T. rubrum, Arthroderma vanbreuseghemii, A. benhamiae*, and *T. verrucosum*.[24,25] However, because NGS requires a genomic library, false negative results can occur if the library does not include the causative pathogen.

Advantages of molecular versus conventional methods

Species identification is crucial to appropriately treat patients with dermatomycosis. Differential diagnosis from noninfectious disorders is critical because they require different treatments.[26] Additionally, dermatophyte or non-dermatophyte species identification is also essential for determining the optimal treatment and its duration.[27,28] Providing an inappropriate treatment can lead to longer treatments with potential side effects. Furthermore, identification of the fungal species and antifungal susceptibility testing lowers the chance of resistance development.[27,29,30]

Direct detection with molecular methods enables rapid identification of fungal species, including those that are difficult to grow in culture. Molecular testing offers a faster turnaround time from collection to results, allowing for more expedient initiation of treatment.

Molecular methods also have the advantage of improved sensitivity compared to conventional diagnostics. A recent study by Pospischil, et al. 2022[26] examined specimens with a positive result by direct microscopy but a negative or contaminated

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culture. They showed that molecular methods were able to identify a fungal pathogen in 65% of these samples, emphasizing the importance of molecular testing for the diagnosis of dermatophyte and non-dermatophyte dermatomycosis when a culture yields a negative or contaminated result.[26]

Conclusion

Although dermatomycosis is the most prevalent fungal infection worldwide,[1] it remains undertreated.[4] While dermatomycosis generally has a low mortality rate and mild severity in healthy individuals, invasive dermatomycosis can cause severe disease in elderly and immunocompromised patients.[5-7] Fungal culture and microscopy are commonly used to diagnose dermatomycosis, but methodological limitations such as long incubation time, limited sensitivity, and inability to identify fungal species can prevent patients from receiving timely and accurate diagnoses and treatments. However, the use of molecular methods facilitates rapid, species-specific determination of causative pathogens. In addition, the combination of molecular methods and conventional diagnostics leads to improved sensitivity for detection of dermatomycosis. Notably, the use of PCR-based DNA microarray methodology combined with direct microscopy results in 100% sensitivity and rapid species identification, thereby enabling patients to receive prompt and accurate treatment.

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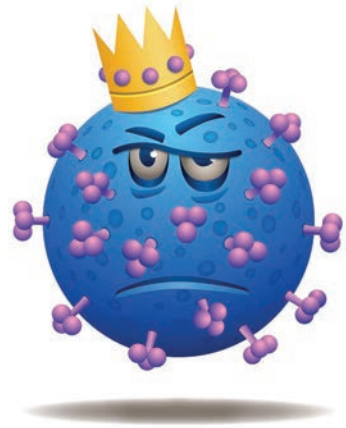

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Lab automation: Learnings and insights

By Nikola Baumann, PhD, DABCC; Paul J. Jannetto, PhD, FACC, MT(ASCP); Christopher T. Yoch, MA

The effort to lower costs, increase efficiency, and improve patient care continues to drive clinical laboratory automation. At Mayo Clinic, automation is embraced across our campuses, from the lab to the lawn and in other day-to-day routines including food service deliveries and supply chain. In the clinical lab, our laser focus on optimizing automation began more than 10 years ago and has continued as we leverage our own experience and technology developments. We envision that more and more areas within the Department of Laboratory Medicine and Pathology will benefit from automation as more automated analytics processes in mass spectrometry become reality, replacing costly, manual processes and supporting specialized expertise.

This article offers an overview of how two groups of clinical laboratories at our Mayo Clinic campus in Rochester, Minnesota, leverage automation to meet the increasing demand for timely, high-quality results in an environment of rapidly evolving technology. One group encompasses the Central Processing area, which receives and processes 12,000–15,000 patient specimens a day, and the Central Clinical Laboratory, with a volume of more than 6 million tests a year. The second group includes the Clinical Mass Spectrometry Laboratory, the Clinical and Forensic Toxicology Laboratory and the Metals Laboratory, with a combined volume of about 3.5 million tests a year. Both groups of labs serve local Mayo Clinic patients and Mayo Clinic Laboratory clients worldwide, with an estimated 15% of the patient testing volume coming from outside the United States.

Automation: Where we are today

Automation was first implemented in our Central Processing area and Central Clinical Lab in 2009 and underwent a major update in 2019 to encompass greater functionality into our total lab automation (TLA) solution. Automation has been critical in enabling us to serve physicians and patients at Mayo Clinic by processing a large volume of specimens, including blood, urine and other body fluids. Two-thirds of patient blood specimens arriving in Central Processing are analyzed in the Central Clinical Lab, with a test menu that includes chemistry, immunochemistry, coagulation and hematology. **Figure 1** provides an overview of our total laboratory automation. The automation line covers pre-analytics and chemistry and immunoassay analyzers, as well as hematology and post-analytic refrigerated storage units. With post-analytic refrigeration and storage, we can eliminate the steps involved in manually archiving and retrieving specimens when additional testing is needed.

Our 2019 update was prompted by the availability of new technology, ever-increasing test volumes, staffing challenges and, to a lesser degree, a growing test menu. Key to this update was the consolidation of two automation lines into one, further streamlining workflow and improving efficiency. This included the integration of Roche cobas connection modules, cobas 8000 modular analyzers, Sysmex XN-9100, and cobas p701 post-analytic storage/retrieval.

Our second group of labs—including Clinical Mass Spectrometry, Clinical and Forensic Toxicology, and Metals—has a broad

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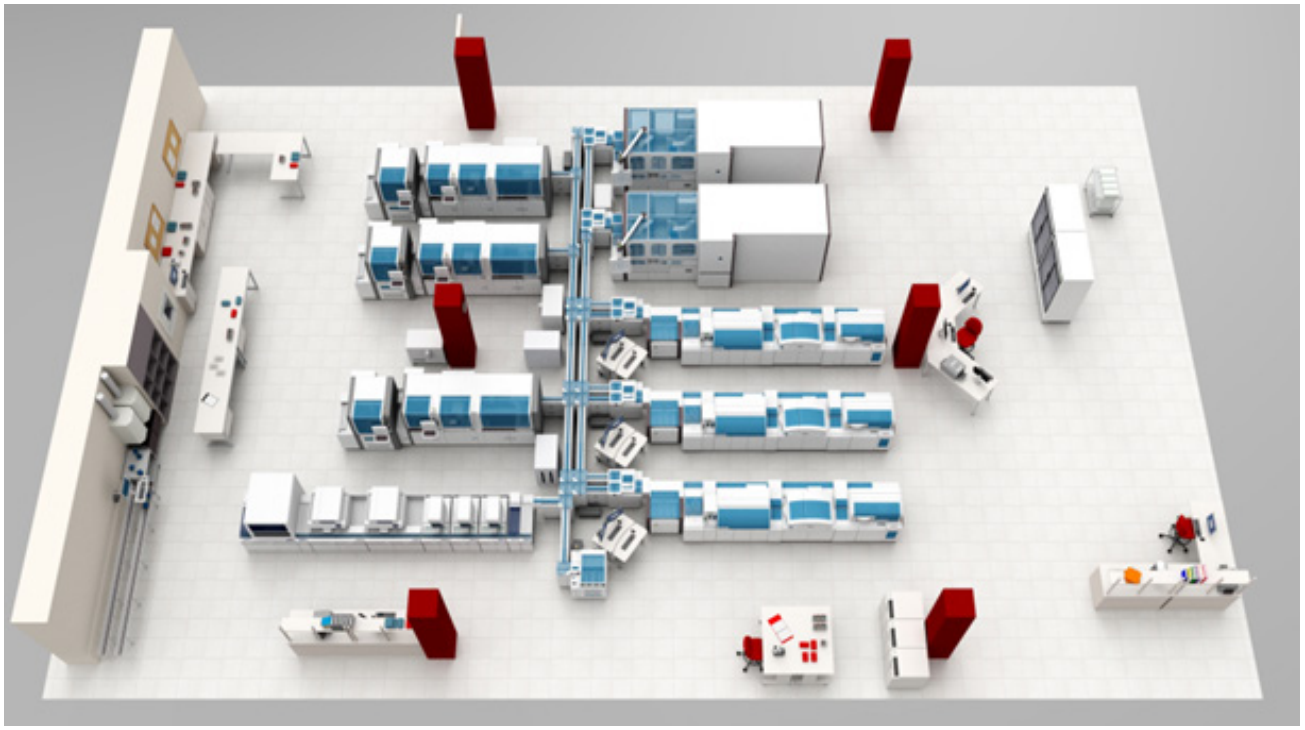

Figure 1. Mayo Clinic, Central Clinical Laboratory.

test menu that includes therapeutic drug monitoring (TDM), endocrine and hormone testing, vitamins, drugs of abuse, controlled substances, clinical toxicology, forensic toxicology, trace elements, and heavy metals. Mass spectrometry is a key methodology within Mayo Clinic and encompasses dozens of mass spectrometers coupled to high performance liquid chromatography and gas chromatography, along with Fourier-transform infrared spectroscopy (FT-IR), and inductively coupled plasma (ICP) mass spectrometry. Of note, the test menu includes more than 2,000 laboratory-developed tests (LDTs). Automation presently is focused on pre-analytics—from the primary tube all the way to the 96-well plates, a standard specimen entry point for mass spec and many other analyzer platforms. Pre-analytical automation, as set up in our labs, is important not only in addressing labor shortage and increasing throughput, but also in increasing accuracy and precision with robotic liquid handling. The valuable staff time freed up by automation is one contributing factor in supporting menu expansion as well as increased test volume.

Getting the most out of automation

Bringing total lab automation online is just the beginning. Our ongoing efforts strive to optimize our processes in order to achieve even greater efficiency. The following are key areas we focus on to reap the greatest benefit possible from our automation solutions.

Digital solutions: We rely heavily on data and analytics and use data to drive improvements. One example is rule-based logic for decisions such as whether a specimen needs to be further investigated, or a test result requires additional quality checks. This logic resides in cobas infinity, the customizable middleware solution we have used to create specific workflows based on our lab's needs, which reliably triggers intervention by the technologist when needed.

An example where Mayo has pushed care for patients forward for digital solutions is our AI-enabled kidney stone algorithm, as demonstrated in a recent initiative to apply AI in kidney stone FT-IR spectra analysis. Drawing on our database of more than 1 million kidney stones in our kidney stone FT-IR spectra library, AI algorithms were developed and validated, and their interpretations were compared with technologist interpretations. A comparison based on spectra data from >80,000 kidney stones showed an overall clinical concordance of 90% between technologist and algorithm. Importantly, the AI-augmented workflow allows the lab to "identify and correctly report kidney stone constituents at a higher rate, which is crucial for treatment and recurrence prevention in the stone-forming patient."[1]

Informatics: Customizing and fine-tuning workflows can result in operational benefits, but it is important to assess if the desired outcome is being achieved. Laboratories need tools that easily and reliably provide critical laboratory data such as test result turnaround times, specimen rejection rates, and other quality metrics. We are working with our colleagues in the Division of Computational Pathology and Artificial Intelligence to assess newer tools with broader capabilities, such as navify Analytics.

Next, we will take a close look at how this works in real time—i.e., assessing the frequency at which these rules are fired, and understanding the types of specimens and patterns of specimens that trigger the system to preempt auto-verification. These insights will allow us to adjust the underlying rules and optimize the process. Another example is taking a closer look at workflow—identifying windows where we are running at close to capacity, versus lulls—again looking for ways to streamline and optimize.

Specimen collection and handling: The ability of the new automation system to accept a multitude of different tube types has eliminated the need for manual presorting—saving staff time and time to results. Even more important is the ability of our automation line to handle a multitude of different specimen tube sizes. This enables us to collect only the amount of blood that is needed for the tests ordered, rather than the same specimen tube size for all patients, all tests. Because of the preanalytic automation's ability to handle multiple blood tube sizes, we have recently observed a 50% reduction in the volume of blood required for testing on the system. This is a

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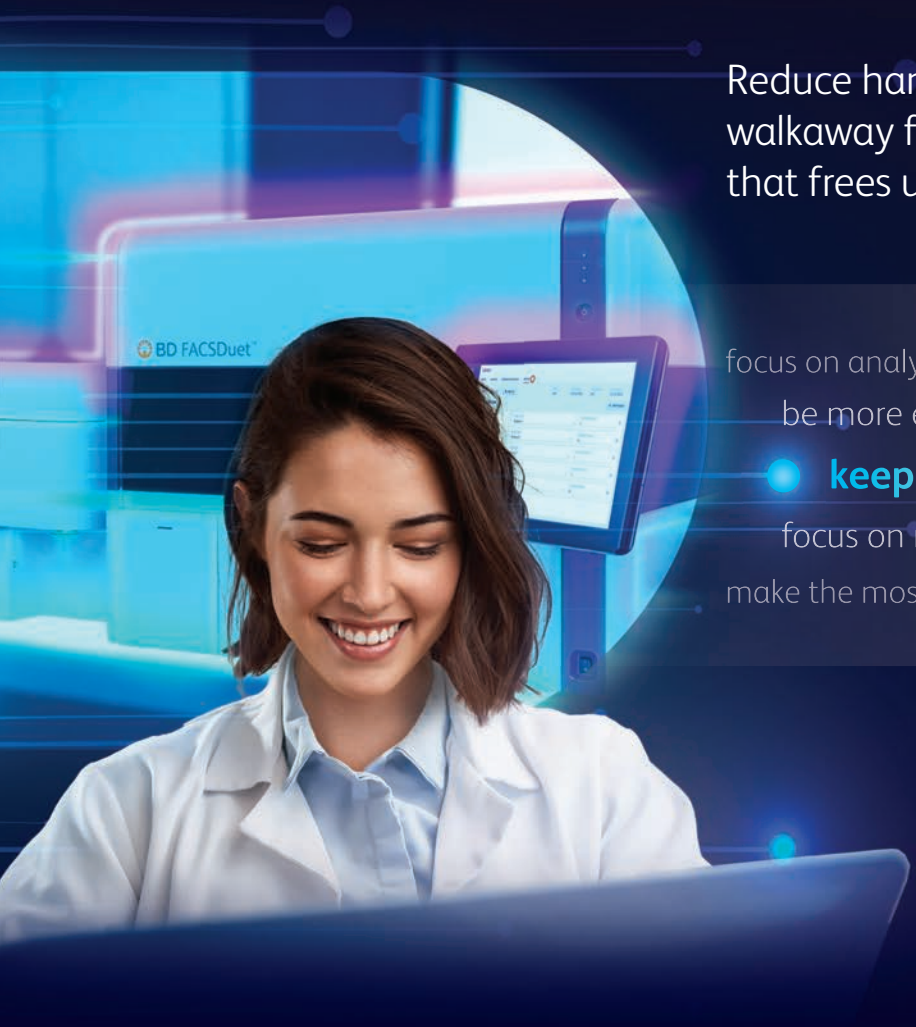

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Thoughtful change management

The transition toward total lab automation, like any change, can create uncertainty and perhaps concern among the staff as their roles are redefined. We have found it beneficial to have a concrete plan to prepare our team by sharing specifics about the upcoming transition toward automation, and how this will enable each individual's transition from manual tasks to more skilled and potentially more rewarding work—in decision making, troubleshooting, consulting. All of this can energize the team and pave the way to greater job satisfaction. Once we start laying the groundwork for change management, we can focus on training—familiarizing the staff with new technologies, how their workday may change, and best practices.

A perspective on quality

An important insight that we have gleaned from our experience is the elevated role of quality in a future of ever-increasing levels of automation. Automation is often associated with reduced human errors and the consistency and precision that robotics and computers can enable. But the high testing volume and the speed at which results are delivered also mean that problems can be rapidly multiplied, and along with that, the impact on patient care. The solution lies, in part, in making sure that processes are in place to detect issues quickly and enable just as rapid recovery from errors.

Partnership and collaboration

Our Central Clinic Lab has a collaborative relationship with a trusted vendor partner — Roche Diagnostics, which plays a key role in designing, configuring and installing the system; preparing, engaging, and training our team; and providing the ongoing technical and service support. Over the past 15 years, as our automation line has evolved, with more functionalities, interactivity, and complexity, our partnership has also evolved, and their field application specialists and field engineers have become familiar with our processes and therefore our needs as end users. In fact, we often think of their service engineers as honorary members of our lab.

Another key resource is our IT team, which has played and continues to play a critical role in approvals, validations, security, and all things IT. At our campus here, we are blessed with a team of information management specialists and coordinators many of whom, in addition to their specialized knowledge, began their careers in the laboratory and thus have insights from firsthand experience in a lab environment.

Commitment to continuous improvement and innovation

Total lab automation has benefited our Central Processing Lab in cost containment, efficiency improvement, and, most importantly, quality patient care. Currently, pre-analytic automation is utilized in our Clinical Mass Spectrometry Laboratory, but we see opportunities for greater automation of key or routine assays in the near future. This increased level of automation would be especially beneficial given mass spectrometry's powerful analytic processes, as reflected in the higher sensitivity and specificity compared with immunoassays. However, it is significantly more complex and mainly associated with larger labs with complex instrumentation and specially trained personnel using primarily LDTs. Mass spec automation will especially benefit high-volume tests such as TDM and tests that require rapid turnaround times, and perhaps near-patient testing. As we look to the future of total lab automation across our Mayo Clinic campus, we are reminded of our primary value: *The needs of the patient come first.* And this primary value continues to motivate us to leverage technological innovations for automation and, ultimately, the highest quality patient care.

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The plasma volume status of a patient is one of the top priorities in evaluating and treating critical illness including CHF, ARDS, AKI, Surgery, and Sepsis.[3-5]

Test Menu

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Our pandemic response enhanced in-house capabilities in virology testing and beyond

By Sonia Benhamed, PharmD, SMB(ASCP); Michael Mihalov, MD

Reflecting on the start of the COVID-19 pandemic, the memories are painful—the desperate need for clinical testing when none was available; quickly developing novel molecular COVID tests with the majority being imperfect; establishing and maintaining safe practices for handling COVID samples in the lab. Through teamwork and innovation, we persevered, eventually ramping up to perform 2,000 tests per day and, after three years, over 900,000 COVID molecular assays in total.[1] This feat was achieved thanks in no small part to our industry partners, who maximized their expertise in developing some of the best nucleic acid amplification tests (NAAT) available—with sophisticated technology such as transcription mediated amplification (TMA) and polymerase chain reaction (PCR) to provide clinical labs with highly sensitive, reproducible, easy-to-use assays for SARS CoV2.

Overcoming the challenges of the pandemic made us a better lab. Our lab has been utilizing NAATs based on TMA technology for years, chosen for their excellent performance as well as the reduced likelihood of inhibition and contamination. Now, equipped with automated, easy-to-use molecular testing platforms and an expanded menu of in-house assays, we are becoming more effective advisors to our patients' healthcare teams, and at the same time, training our staff in new skills like viral load (VL) assays to meet the dynamic clinical testing needs of the future. The diagnostic testing system we rely on today is easy to obtain and master, and we can now address clinical needs like human immunodeficiency virus (HIV) and hepatitis C virus (HCV) as a natural extension of the women's health and sexually transmitted infection (STI) testing we have provided for years. The ways in which we have learned to maximize on our COVID-era investments are strategies that any hospital or community lab can apply, regardless of size, workforce, and testing volume.

Leveraging lessons learned at the local labs to control HIV and HCV

The healthcare community has made significant progress in caring for and treating people living with HIV. Over 50% of U.S. HIV-positive patients were older than 50 by 2016, and that population is expected to be ~70% by 2030.[2] The cumulative effects of a larger population being monitored for HIV, plus that population living longer, forecasts a more acute need for

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individualized attention to test results as clinicians confront novel effects of aging with HIV as well as drug therapies taken for several decades. Even with successful viral suppression and barring side-effects, HIV infection is associated with accelerated aging and increased rates of cardiovascular, renal, neurocognitive, oncological, and osteoporotic disease.[2] Yet, viral suppression is also critical to avoid transmission and new infections.

National efforts to limit the transmission of HIV include ambitious new programs such as the Ending HIV Epidemic (EHE), which sets the goal at fewer than 3,000 new infections per year beginning in 2030.[3] Antiretroviral treatment has proven highly effective in maintaining non-transmissible VL for HIV-infected individuals and pre-exposure prophylaxis (PrEP) has shown exceptional results in preventing infection among at-risk patients.[4] To achieve the ambitious EHE objectives, the Centers for Disease Control and Prevention (CDC) recommends substantially increasing both antiretroviral treatment and administration of PrEP.[5] Local laboratories more intimately involved with patients are the ideal venues to provide regular testing, diagnosis, and VL monitoring with highly sensitive and reliable assays, and in turn ensure patients are quickly linked to the appropriate care for prevention or intervention.

In an effort to combat an increase in new HCV infections, the CDC Division of Viral Hepatitis, in cooperation with the Association of Public Health Laboratories (APHL), provided grants to support laboratories in at least 12 states seeking to add or expand HCV testing.[6] Left untreated, HCV infection can become chronic in approximately 50% of patients, and nearly a fifth of those patients will develop serious morbidities including progressive liver fibrosis, cirrhosis, and liver cancer.[7]

Fortunately, HCV infection is curable in more than 90% of patients who receive timely treatment,[7] which again places laboratory testing at the forefront—especially because both new and chronic HCV may be asymptomatic. The ideal candidate to coordinate these efforts is the local hospital laboratory where testing can be performed closer to the patient, where test results can be available in hours instead of days, and where clinicians can consult with pathologist colleagues to guide the often nuanced treatment decisions. For instance, because HCV shares corresponding risk factors with HIV, concurrent screening may be recommended, and many emergency departments around the country automatically screen for both infections unless the patient opts out.[8] The local laboratory that can run these assays with a single sample, return accurate results quickly, and consult directly with clinicians will foster a better patient experience and better care.

HIV and HCV present unique challenges as life-threatening viral infections that many at-risk people avoid confronting due to persistent stigmas throughout various segments of society. We stand a greater chance at achieving the national infection reduction targets when patients feel supported by their healthcare team. Keeping testing local with in-house capabilities can play a significant role in the lives of people living with HIV. Reliable laboratory test results keep patients informed on their viral suppression and CD4 count, minimize follow-up visits, and reduce the anxiety caused by extensive turnaround times.

VL testing is an essential skillset worth developing

Within the laboratory, we are also very excited about making the most of our new capabilities to further develop the knowledge of our highly skilled staff. In the past, when we could not hire off the market, we created our own histology school as a one-year program, and many bright, motivated candidates who started as unlicensed lab aids, became full-time, licensed histology techs.

> Clinical laboratories faced unprecedented challenges throughout the pandemic, but it is time to make good use of these past experiences and move on to new challenges.

Now, we envision similar success as we move all VL testing from the molecular virology lab to cytology, where personnel already have experience running HPV, chlamydia, gonorrhea, and trichomoniasis assays.

Many of our techs, already familiar with similar instrumentation, are in the perfect position to acquire the expertise necessary to become bona fide molecular techs—which in our lab means learning to troubleshoot quantitative assays. As these techs advance and become key advisors to clinicians, the rewards for their career, our lab, and ultimately for patients, will be very gratifying to see.

Conclusion

Clinical laboratories faced unprecedented challenges throughout the pandemic, but it is time to make good use of these past experiences and move on to new challenges. The lessons learned and technologies acquired can be used to seamlessly transition to address current and growing clinical needs—fulfilling the mandate to curtail HIV and HCV transmission and disease; engaging bright talent in the 21st century pathology laboratory; and continuing to cultivate in-house testing and local hospital resources to benefit our patients and to improve healthcare worldwide.

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A practical approach for your lab's A1c testing & why your methodology matters

By Matthew C. Wagner, PhD

Although a hemoglobin A1c (HbA1c) measurement for evaluating patient glycemic control is well established for diagnosis and monitoring in patients with normal hemoglobin, this does not speak to the sizeable minority (~7% worldwide[1]) of patients with *abnormal* hemoglobin, for whom the HbA1c test may not be appropriate. These patients possess hemoglobinopathies; genetic mutations affecting the structure (hemoglobin variants), and/or production (thalassemias) of hemoglobin A, resulting in assay interference, altered glycation dynamics, and/or changes to red blood cell (RBC) lifespan that result in a different relationship between the patient's glycemic status and the measured HbA1c. Some patients with multiple mutations even lack any normal hemoglobin A (Hb A) and, hence, produce no HbA1c.

The 2018 American Diabetes Association update to the *Standards of Medical Care in Diabetes* first broached this topic with new recommendations, stating that recent evidence "describe[ed] potential limitations in A1c measurements due to hemoglobin variants, assay interference, and conditions associated with red blood cell turnover…"[2] This update addresses the laboratory phenomenon of occasional patient samples giving no A1c result, non-physiologic results, or clinically discordant values.

However, these recommendations can be seen to place the laboratory in an unfortunate position: the lab may either routinely perform additional hemoglobinopathy testing on all A1c screening samples or produce results that may be incorrect for a portion of their patients, risking a diabetes misdiagnosis that significantly impacts these patients' health. Here we will explore the impact of these recommendations, the reasoning behind them, and show how labs can mitigate the risk of invalid testing through careful A1c methodology choice.

The intrinsic nature of Hb A in HbA1c formation makes it unsurprising that structural variants may interfere with detection and measurement of the glycated form, either analytically (in methods unable to distinguish/separate the variant) or clinically (altering the formation or retention of the glycated hemoglobin) as noted in a previous issue of this publication.[3] Very often manufacturers, supported by the NGSP,[4] indicate no analytical interference from common variants for their methods, but this does not speak to the clinical interference caused by the systemic effects of the variant. In explaining their new recommendations, the ADA noted a study in which Hb S trait (heterozygous Hb S) patients have a systemically lower HbA1c value by 0.3%,[5] even despite the noted higher A1c value found in African American populations[6] where the variant is common. A subsequent study found a similar shift in Hb E trait patients.[7,8] While these shifts are relatively small, possibly only impacting cases on the borderline of diagnostic cutoff, there

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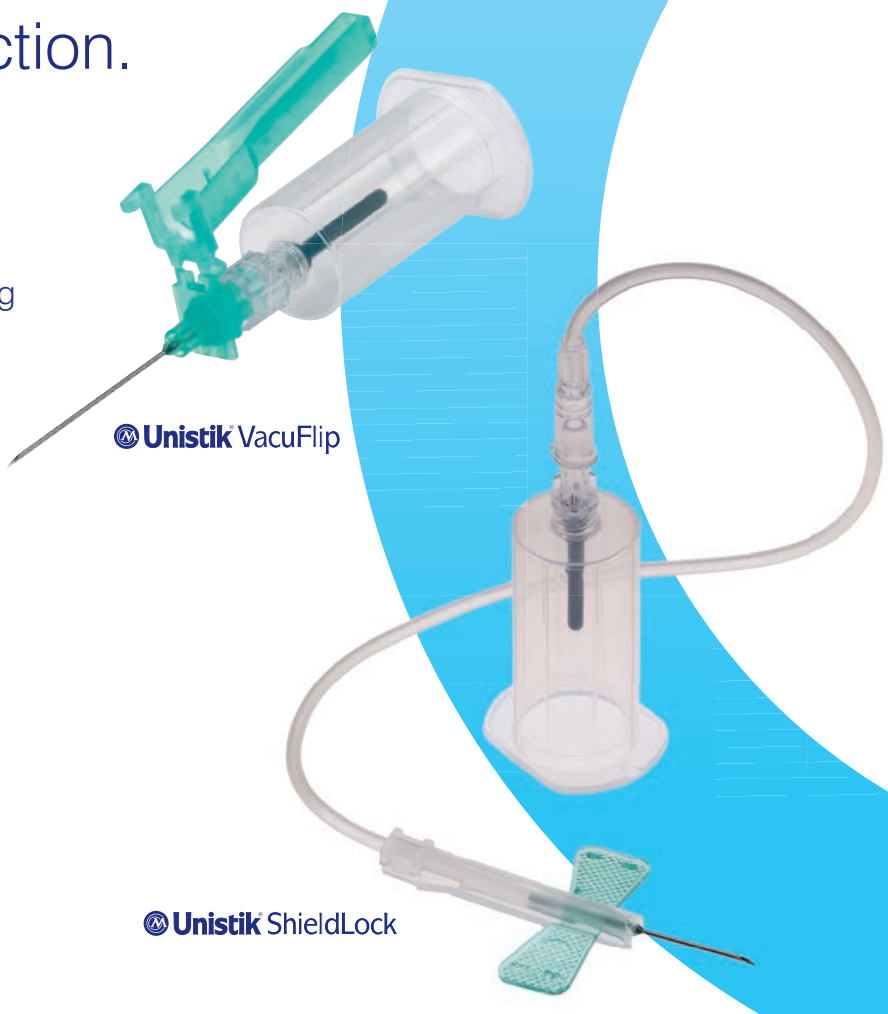

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are also extreme cases such as sickle cell disease, where the RBC turnover is significantly impacted. Homozygous Hb S[9] or Hb S in combination with some other variants (Hb C, D-Los Angeles, O-Arab) results in rapid RBC turnover and cause low glycated hemoglobin fractions. To address this, manufacturer package inserts note that the assay should not be employed "in the absence of Hb A." Further, some *rare* hemoglobin variants can cause profound analytical interferences even in trait form.[10-14] Proven interferences such as these motivated the ADA to recommend the following:

"Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1c assay interference due to hemoglobin variants (i.e., hemoglobinopathies) and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes."

It is further recommended that "In conditions associated with increased red blood cell turnover, such as sickle cell disease… only plasma blood glucose criteria should be used to diagnose diabetes."[15]

When identified, a clinician could consider a hemoglobinopathy in conjunction with the A1c result; common trait variants could be disregarded (except in borderline cases, calling for more careful assessment), while severe interferences (compound hemoglobinopathies, or no Hb A) would warrant reflex to an alternate tests or analytes (fructosamine, glycated albumin, fasting blood glucose) as mentioned by the ADA. However, the practical considerations of the laboratory aren't addressed; how does the lab know which patients have interfering hemoglobinopathies? Interference here is detected after the fact: an A1c result is discordant from the rest of the patient clinical profile, suggesting a variant or altered RBC turnover. While effective in cases of obvious discordance, it presumes access to additional results not always available to the lab, placing the impetus for interference detection on the clinician, a burdensome and roundabout approach to result validation. It further ignores the reality of results less obviously discordant, such as the noted Hb S trait and Hb E trait influencing the A1c value.

> Testing methodologies incapable of detecting hemoglobinopathies include those employing antisera (immunoassay) or enzymatic digestion.

This context surrounding HbA1c testing implies a preference for HbA1c techniques capable of incidental hemoglobinopathy discovery. If detected at the time of the A1c testing, then appropriate notice of minor interferences can be provided to the clinician, and extreme discordance (Hb A absence, sickling disease) identified by the lab can be blocked before release. This stratifies the current A1c testing methodologies; those able and those unable to visualize variants and thalassemias.

Testing methodologies incapable of detecting hemoglobinopathies include those employing antisera (immunoassay) or enzymatic digestion. These techniques, using highly specific antisera or enzymes, excel in finding the recognition sequence at the glycated N-terminal beta chains, but their limited scope means they can't discern further distant mutations, "seeing" only the amino acids within their target region. Variants with mutations outside of this window are included in A1c calculations and may significantly influence the reported value. The boronate affinity method similarly fails to detect variants, as it back-calculates A1c from measurements of all hemoglobins and glycated hemoglobins within the sample, regardless of mutations. The blinded nature of these methods' results is true even in the extreme cases where no Hb A is present.

> Many labs resort to the expediency of running non-separation, low-resolution techniques and simply "send out" samples with questionable results, hoping reference labs will solve the problem for them.

Methods capable of detecting hemoglobinopathies (variants and some thalassemias) include HPLC and capillary electrophoresis (CE). A more detailed profile of the patient's hemoglobins is integral to these methods, as the different fractions are separated by either electrophoretic mobility or affinity to an anion exchange column, isolating the Hb A and HbA1c for measurement. As hemoglobin variants are, by their very nature, structurally different from Hb A or HbA1c, they typically migrate or elute differently on these "separation" techniques, generating distinct and obvious peaks or distortions. This indicates patients who have hemoglobinopathies for closer analysis, while normal patients will pass without note. All the common variants (and many rare variants) are distinctly visualized, and using a separation methodology significantly minimizes the chance of an undetected variant interfering with A1c measurement.

This presents a seemingly obvious choice: the laboratory can employ either a "separation" technique, or a technique where hemoglobinopathies are undetected, leaving them uncertain of their result without additional testing. However, practical considerations of lab testing may not allow for the obvious choice. Many labs resort to the expediency of running non-separation, low-resolution techniques and simply "send out" samples with questionable results, hoping reference labs will solve the problem for them. Unfortunately, reference lab may not be employing the separation techniques either. Labs may assume that separation techniques have lower throughput, and result review may seem an intensive, specialized job, especially as staffing shortfalls are common in the modern laboratory. There simply are not technologists available to review every A1c result in even the moderate-volume laboratories. Fortunately, workflow improvements solve these challenges; for example, the capillary systems employ an auto-flagging software that detects and flags abnormal profiles. Normal profiles require no further review, with their results sent automatically to the LIS. The remaining samples, representing the significant but small minority of patients with hemoglobinopathies, can be retained for review, representing a more reasonable workload. Those samples exhibiting non-analytically interfering variants are reportable, and appropriate notice to the clinician could be provided. The remaining few, where A1c results are inappropriate for diabetes diagnosis, could be referred for alternate analyte testing.

Further streamlining could rely on the genetic nature of hemoglobinopathies; a hemoglobin variant or thalassemia will not "suddenly develop" in a patient. Separation techniques could therefore be used for an initial screen and those patients exhibiting no indication of hemoglobinopathies would be transferred for future monitoring on "non-separation"

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techniques without concern for an unknown interference and undetected misreporting of results. Those patients with incidental hemoglobinopathies detected would have their clinicians notified and be flagged for future monitoring by a separation technique or by an alternate analyte, as appropriate. This approach could be viewed as a modification of approaches suggested elsewhere[16,17] especially for screening populations with high hemoglobinopathy incidence.

Despite decades of use for the diagnosis and monitoring of diabetes, laboratory standards have only recently addressed how HbA1c testing should account for the presence of hemoglobinopathies that could potentially interfere, both analytically and clinically, with the result. The use of a separation technique for HbA1c measurement allows for the detection of hemoglobin variants and thalassemia without the associated cost of additional testing. Recent advances in result review and workflow have mitigated the throughput, complexity, and labor intensity surrounding the use of these higher-resolution techniques and will enable labs to release timely A1c results with confidence.

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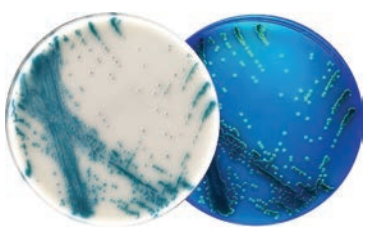

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The critical role of testing for transplant donors and recipients

By Robert S. Jones, DO, MS, FACP, FIDSA, CPE

In the fall of 2022, the United States reached a historic and critical milestone — its organ donation system surpassed 1 million organ transplants, more than any other country in the world.[1] Each of these 1 million organs represents an individual living with a condition that requires exceptional care. These patients must endure ongoing post-transplant monitoring, anti-rejection medications, and other therapies. Post-transplant, patients can require anywhere between 10 and 20 years of monitoring, on average, and will need as many as 500 diagnostic tests throughout their lives.[2] Making this process as convenient as possible, and eliminating barriers to receiving this testing, is essential for transplant patients to achieve the best health outcomes. Yet, this is only one piece of the larger transplant patient journey.

The rising trend of living donation for transplant patients

In the United States, the most transplanted organs are the kidney, liver, heart, lungs, pancreas, and intestines. Some of these, like the heart, can only be transplanted from cadavers, or deceased donors. Others, like the kidney, can come from a living donor — a procedure that is often associated with more favorable outcomes, including lower risk of complications. Living donation is also associated with shorter hospital stays and related cost savings post-surgery. While most patients receive organs from cadavers, in 2021, over 6,500 transplants were performed from living donors — an increase of 14.2 percent over 2020.[3]

Furthermore, if a person is able to secure a living donor, it reduces their need to wait for a cadaver, saving not only their life, but potentially the lives of other patients who may be waiting with them for the next available organ. Though living donation is most common in the case of kidney transplants, recent years have seen a rise in living donation for partial liver transplants, which are also associated with better outcomes as the less time a harvested liver is artificially preserved, the better.[4]

These trends have been made possible by the emergence of new guidelines and further advancements in testing. As one example, providers now have improved methods to test donors and patients to determine match compatibility. This has helped match patients with HIV with donors who also have HIV, enabling care for people who previously had limited access. Yet, this is only one piece of how providers can work together to improve ability to access services.[5]

Broadening convenient access to transplant services and eliminating barriers to testing

Access to fast and convenient transplant testing services is vital for transplant donors and recipients. Testing provides invaluable insights to identify infectious diseases in donors and recipients, determine match compatibility, monitor transplant therapy response, and identify rejection. Given certain transplant therapies may suppress the immune system, testing is also crucial to identify pathogens to help prevent transmission from a donor.

While patient compliance in testing is critical, several factors can impede a patient's ability to receive testing, which can ultimately contribute to poor outcomes, such as late acute rejection.

As an example, long travel times and inflexible scheduling can worsen a patient's access, ultimately lowering the likelihood of compliance. It is important, therefore, to meet transplant patients where they are, and invest in their care. By offering a mobile testing option, both transplant recipients and living donors can complete specimen collection at a time and place convenient for them, especially when they may be at suboptimal health. It is important for providers to continue to find ways to remove barriers to care and increase access to testing.

Additionally, a hospital or transplant center can work with a collaborator to improve logistics access by offering specimen collection through a nationwide network of patient access points. This is particularly critical in cases where a living donor or recipient lives far from the institution that will or has performed the transplant procedure. By working with a testing provider, patients may cut down on otherwise excessive travel times and see benefits related to scheduling and walk-in appointment availability.

As one example, when we heard from clients that our transplant offering needed improvements, we made efforts to streamline patient education, help phlebotomists fast-track specimens, decrease turnaround times, and increase access to at-home testing through our ExamOne mobile phlebotomy business. Yale New Haven Hospital in Connecticut, which piloted the improved transplant offering we debuted earlier this year, has said that working with us has helped expand access for patients who previously would have had to visit a transplant center to receive testing — in many cases, one that was extremely far from a patient's home. Other clients have reported the same, and that reducing patient noncompliance has eased strain from overloaded health system workers who lacked the time needed for follow-up.

Exploring advancements in transplant testing: How genetic testing can impact patients

Beyond the traditional battery of tests associated with transplantation, advanced genetic tests may also provide invaluable insights for donors and recipients.

Genetic testing is traditionally used to identify differences in a person's DNA that can influence the way their cells function. Examining these DNA variants is often useful for both identifying a person's risk of disease development and the likelihood that a certain disease might respond to a specific therapy. Different types of genetic tests look for different kinds of DNA variants, and sometimes different combinations of genetic variations.

There are many different technologies that can help detect genetic variations. For transplant patients, these tests are most often utilized when assessing kidney recipients or donors. Specifically, the National Institute of Health cites three main applications of genetic testing in clinical kidney transplantation: (1) the risk assessment of donors, (2) disease characterization of recipients, and (3) improving drug selection and dosing for recipients using pharmacogenomic data.[6]

One such test, Apolipoprotein L1 (APOL1) renal risk variant genotyping, is an advanced genetic test to help evaluate kidney disease risk for donors. The test identifies those who have a "high-risk genotype," and increased susceptibility to certain types of non-diabetic kidney disease, compared to individuals with a"low-risk genotype."Data shows the APOL1 status of the donor can impact post-donation renal function in the donor and recipient.[7]

It is worthwhile to explore whether genetics affect donor suitability, particularly for those with a family history of cystic kidney disease. As living donations become more popular, genetic testing may also see an uptick in utilization. Its assessments can be valuable in both determining match favorability and understanding risks for both donors and recipients, so that when working with a physician, the appropriate actions can be taken.

Genetic testing is traditionally used to identify differences in a person's DNA that can influence the way their cells function.

Conclusion: Improving testing availability remains a priority for providers

As the number of yearly transplants increases nationwide, and as younger patients receive more transplants, the need for more testing and monitoring over a longer period will also continue to increase.

Health systems and healthcare professionals caring for these vulnerable patients need to consider not just quality of testing but also location in order to optimize patient compliance. When the health of the patient is centered in all care decisions, the best outcomes for all parties can be achieved.

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The ongoing troponin conundrum: Understanding an elevated troponin

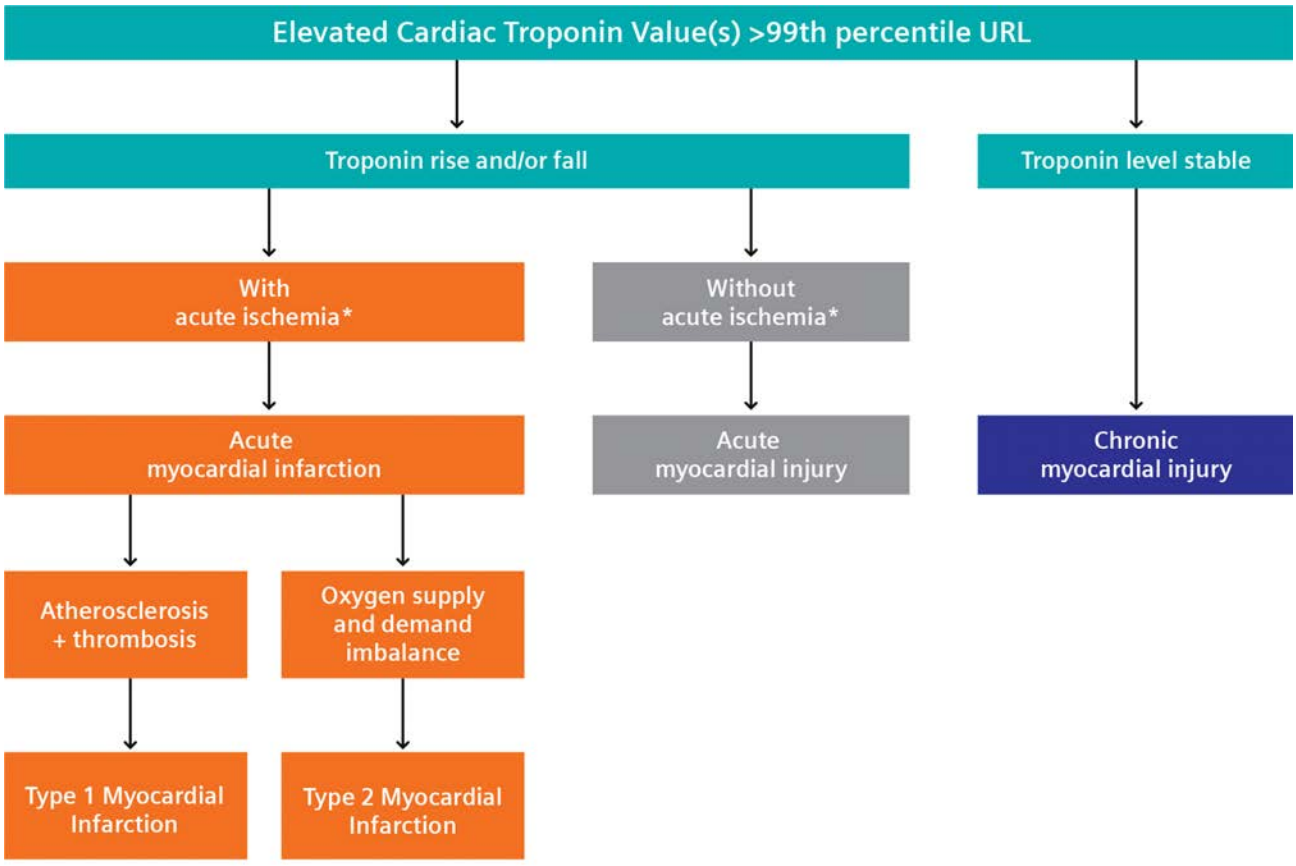
By Kalen Nissen, PhD, DABCC, FAACC

As laboratory assays have evolved with improved performance, the clinical use of cardiac troponin (cTn) has also evolved beyond the context of myocardial infarction (MI). The release of high sensitivity (hs) cTn assays has led to even more changes in clinical and laboratory guidelines for cTn use and expanding data on additional clinical uses. As defined in the Fourth Universal Definition of Myocardial Infarction,[1] "the clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia."The preferred biomarkers for myocardial injury evaluation are cTnI and cTnT, with hs-cTn assays recommended for routine clinical use.[1,2] Myocardial injury is defined by an elevated cTn value, with at least one value above the upper reference limit (URL), as defined by the 99th percentile of a health population. Therefore, MI is a type of myocardial injury, but not every myocardial injury is an MI.

With the advent of hs-cTn assays, as required to qualify an assay as being highly sensitive, now more than 50% of healthy individuals (>80% for some assays) will have a detectable troponin. Gone are the days when any detectable troponin was an indicator of a potential evolving health emergency or poor prognosis. Now, clinicians must be able to assess a troponin result in consideration of the many causes of troponin elevation and patterns over time. Clinical decisions for interpretating hs-cTn elevations, including potential use of rule-in/rule-out algorithms, make it critical to have accurate cTn results and to interpret the results in the context of the patient's presentation, clinical history, and other assessments (e.g., ECG results). This high sensitivity in more healthy individuals brings a challenge of accommodating the differential diagnosis for different types of myocardial infarction and injury that release troponin into the blood, so as not to contribute to unnecessary work-ups and procedures. Data on risk stratification using cTn, including when below the 99th percentile URL, is being studied, to elucidate appropriate cutoffs and interpretation.

Across the continuum of myocardial injury

Serial testing of cTn in patients needing testing has grown in importance with the shift to hs-cTn assays, to help identify presence of an acute (rising and/or falling pattern) versus chronic elevation of cTn (see later section "Biological-related cardiac troponin elevations"). Additionally, there is an increased need to understand different clinical classifications of MI beyond the ST-segment elevation (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina paradigm. More nuanced classifications describe various types of MI, based on their pathological, clinical, and prognostic differences along with associated differences in treatment strategy. The criteria for type 1 MI includes a rise and/or fall of cTn values with at least one value above the 99th percentile, and at least one related appropriate sign of artherothrombotic coronary artery disease **(Figure 1)**.[1] This "traditional" type of MI must be distinguished from another group of diseases that cause acute myocardial ischemia but due to another reason. Type 2 MI involves ischemic myocardial injury caused by an oxygen supply and demand mismatch, also requiring similar cTn criteria as type I with evidence of the mismatch from symptoms, imaging, or ECG changes. Some examples of type 2 MI include coronary embolism, hypotension or shock, and respiratory failure.



URL = upper reference limit.
**Ischemia denotes signs and/or symptoms of clinical myocardial ischemia.*

Figure 1. Assessment of elevated cardiac troponin using serial pattern and signs of ischemia. *Adapted from Thygesen et al.*[1]

In the presence of a cTn above the 99th percentile URL, the serial troponin pattern helps distinguish acute versus chronic myocardial injury, and the presence or absence of signs and/or symptoms of clinical myocardial ischemia help further distinguish acute myocardial injury from acute myocardial infarction (type 1 versus type 2 MI; **Figure 1**). MI types 3, 4, and 5 involve cardiac death and coronary procedure–related ischemia, and more information can be found within the referenced publications.[1]

Defining and interpreting an elevated troponin

Two overarching groups of elevated cTn in the absence of MI include causes related to 1) biological factors, including other disease states that can cause acute or chronic myocardial injury, and 2) assay factors, including interferences and pre-analytical influences. A contributing effect may begin with a choice made prior to even beginning use of a cTn assay, when making the choice of the 99th percentile URL to utilize. It is recommended to utilize sex-specific 99th percentile URLs, as women have lower levels of cTn compared to men.[1,3] Use of an overall 99th percentile (which falls below the male-specific 99th percentile, and above the female-specific 99th percentile) in a male patient with a result near this threshold may lead to interpretation of the result as greater than the 99th percentile, when with use of a male-specific 99th percentile URL the result would be less than this threshold. The probability of this scenario is somewhat low, however, given the likelihood of cTn results that may be expected to occur close to the 99th percentile.

Biological-related cardiac troponin elevations

One of the first factors to consider when interpreting an elevated troponin result in the differential diagnosis of acute MI is a cause where the troponin is truly elevated, but due to disease other than acute MI, to assure the proper diagnosis and treatment are identified. Referring back to **Figure 1**, these mechanisms of myocardial cell injury may be acute non-ischemic (no cTn rise and/or fall) or may be chronic (cTn stable). These diseases can largely be grouped into two categories: 1) cardiac causes and 2) non-cardiac or systemic causes **(Figure 2)**. Examples of cardiac diseases that may cause an elevated cTn include atrial fibrillation, myocarditis, and acute heart failure.[1,4] Some cardiac disorders would have overlapping signs or symptoms with acute MI, such as shortness of breath, weakness, and even chest pain, meaning that the differential diagnosis must be carefully evaluated. Examples of non-cardiac or systemic disorders that may cause myocardial injury and elevated cTn include chronic kidney disease, pulmonary hypertension, stroke, and sepsis.[1,4] For some cTnT assays, one source of elevation that has been published on consistently in the non-cardiac disorder group is skeletal muscle disease, which has been hypothesized to be due to re-expression of cTnT in the skeletal muscle.[5,6] Another more recently discovered cause of increased cTn is COVID-19. A variety of cardiac or non-cardiac sources may cause a cTn increase in the clinical context of COVID-19, some of which may be non-ischemic but also ischemic, and the observed cTn concentration reflects a combination of what may be pre-existing cardiac disease and acute myocardial injury.[7]

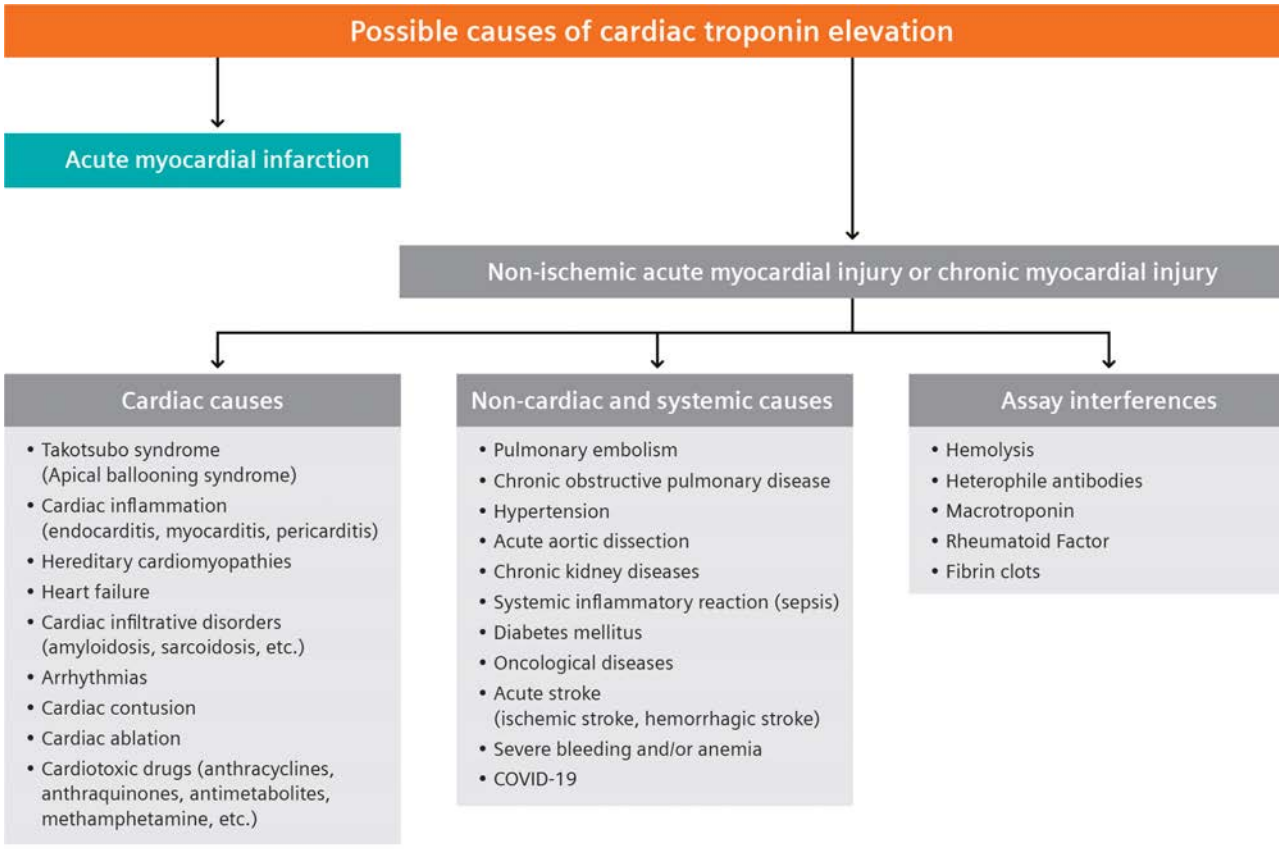


Figure 2. Possible causes of elevated cardiac troponin. *Adapted from Chaulin.*[4]

Assay-related cardiac troponin elevations

As with many laboratory assays, interferences may exert effects that assay design cannot mitigate or at least fully mitigate. Some of these interferences affect all assays, and some may affect only certain assays. Three common interferences that are regularly tested make up the HIL index, or hemolysis (hemoglobin), icterus (bilirubin) and lipemia (triglycerides/Intralipid; also called turbidity). As hemolysis increases, hs-cTnI and hs-cTnT results have been reported to increase (or decrease) for susceptible assays.[8-10] Laboratories should seek out the assay Instructions for Use (IFU) from their manufacturer to understand the HIL interference criteria and limits for their assay.

Various types of endogenous antibodies may also affect cTn results, including heterophile antibodies, autoantibodies, and macrotroponin. Anti-troponin autoantibodies likely cause a falsely low result, and therefore are less concerning from the perspective of elevated cTn in the differential diagnosis of acute MI. Heterophile antibodies and macrotroponin, on the other hand, may cause falsely elevated (or falsely depressed) results. Heterophile antibodies are produced against poorly defined immunoglobulins, and have weak avidity to multi-specific antigens, generated from any number of environmental sources, certain infections, or some treatments. Prevalence estimates vary widely. When present in a patient sample, heterophile antibodies can cause falsely elevated results by cross-linking of the heterophile antibodies with the cTn antibodies used in the assay architecture. As has been reported since the late 1990s, this may cause a falsely elevated result, which has been reported in multiple case studies and reviewed.[11,12]

Macrotroponin interference can occur when autoantibodies bind cTn to make a complex. These large immunoglobulin-troponin complexes have reduced clearance and can affect assays differently and inconsistently. In other words, a particular assay may be affected by macrotroponin in one sample, but not be affected by macrotroponin in another sample.[13] The results are often elevated above the 99th percentile, and sometimes very elevated, as demonstrated in a recent case study.[14] Prevalence of macrotroponin has been suggested to be 5% or less,[15] but our knowledge of prevalence, causes, and other aspects is currently limited.

Another potential cause of elevated cTn results is rheumatoid factor (RF), an interferent that may affect various analytes on immunoassay analyzers. Rheumatoid factor may be elevated in autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus, especially when the disease is active, such that the elevation is significant enough to cause an interference and false positive cTn. RF can cause significantly elevated results high above the 99th percentile URL.[16]

In addition to those interfering factors covered here, other factors that may cause falsely elevated cTn results should be considered when interpreting or investigating cTn elevations, including fibrin clots, sample type, time of day of blood draw (which has been reported to affect cTnT), and transportation of specimens.[17-20]

Conclusion

The proper interpretation of cTn elevations in the context of acute myocardial ischemia/infarction requires careful consideration of potential preanalytical and clinical causes of cTn elevation. In addition to many types of preanalytical factors, there may be analytical and clinical causes of troponin elevations, which

may be from acute non-ischemic disease, or chronic disease that causes myocardial injury. The consideration for acute MI versus other cardiac or non-cardiac and systemic diseases, and communication with the laboratory if an analytical-related influence is suspected, will help ensure the patient receives the most accurate diagnosis and treatment plan.

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INDEX OF ADVERTISERS

LABORATORY INNOVATOR

A focus on collaborations

By Christina Wichmann

Elizabeth Woo, PhD (Betty) serves as the Vice President of Cell, Gene and Advanced Therapies at **Thermo Fisher Scientific.** In her current role, Betty leads a business focused on fit-for-purpose solutions for cell and gene therapy (CGT) innovators, by integrating CGT products and services across Thermo Fisher. Prior to her current role, Betty led a corporate team focused on strategic collaborations with Thermo Fisher global customers. Betty has held business, technical, and commercial leadership positions at Thermo Fisher over the past 20 years, with a common thread of providing enabling technology to serve customers.

Prior to joining Thermo Fisher, Betty served in various leadership roles at Cellomics, a biotechnology start-up, spanning product management to business development and strategic marketing. Betty started her professional career on the faculty of University of Pittsburgh Medical School in the Department of Pharmacology, where she also completed her post-doctoral studies. Betty obtained her doctorate in pharmacology from the George Washington University School of Medicine and Health Sciences.

Betty serves on several advisory boards including the Standards Coordinating Body, the International Society for Cell & Gene Therapy, Carnegie Museum of Natural History, and the Pittsburgh Life Sciences Greenhouse.

For laboratorians not currently working in advanced therapies, would you provide a summary (i.e., elevator speech) on cell and gene therapies?

Of course – the cell and gene therapy (CGT) industry is regularly making headlines, and for very good reason. There's a lot of excitement right now around this emerging class of therapeutics, particularly in areas like cancer and inherited disorders like sickle cell anemia where patients have limited treatment options. What's unique about CGT is these therapies hold the potential to not just prevent and treat diseases, but to potentially cure them. This is because these therapies work by addressing the root cause of diseases, which can be found at the level of the patient's DNA. In brief, gene therapies work by introducing genetic material into the patient to inactivate, modify, or replace the gene(s) associated with the disease. Alternatively, a patient's cells can be removed from their body and the genetic modifications can be made in a laboratory, then returned to the patient's body, and this is known as gene-modified cell therapy.

Though CGT holds incredible promise, the actual number of commercially available therapies is currently just over 20 in the U.S. That said, there is a robust clinical pipeline of thousands of candidates, and CGT remains an active area for science and technology development. The demand is there, and the pressure is on to bring these therapies to market faster and more affordably.

What are Thermo Fisher's primary strategies when it comes to helping advance cell and gene therapies?

To help advance cell and gene therapies, we've integrated our broad portfolio of fit-for-purpose products into flexible workflow solutions to help CGT developers confidently move their CGT assets from R&D through clinical development, and then scale to commercial manufacturing. Our differentiating value lies in supporting both build and buy strategies for our CGT customers, including quality and regulatory expertise, leading supply chain capabilities, and a customer-centric focus.

While internal collaboration drives better solutions and customer experience, external collaboration is a key driver of our innovation strategy. We listen closely to what our customers need and design our products and workflow offerings based on our learnings. Our strategies work best when we partner with CGT developers early. As an example of the benefits of early collaboration, we have an ongoing strategic partnership with Arsenal Biosciences, Inc., a clinical-stage company developing programmable, autologous T-cells to treat solid tumors. Our collaboration has thrived, not only due to early access to technology, but by cultivating a close working relationship, transparency, and importantly, a shared vision. This vision is to advance and optimize their manufacturing workflows with urgency to get into the clinic faster and with the confidence that the processes will hold up to CMC and regulatory scrutiny.

Earlier in the year we celebrated the opening of our cGMP cell therapy manufacturing facility housed at the University of California, San Francisco's Medical Center's Mission Bay campus. Being at the center of this CGT ecosystem, we engage with world-class researchers, clinicians, and ultimately, patients, providing early access to our technologies and our team's expertise. The feedback we receive informs our innovation strategy and together, we can help developers overcome many of the CGT manufacturing challenges that must be addressed to bring new treatments to market at scale.

The U.S. Food and Drug Administration has approved numerous gene therapies the past couple years for diseases such as bladder cancer and Duchenne muscular dystrophy. What upcoming approvals do you foresee in the next five years for gene therapies?

With over 2,000 clinical trials for cell and gene therapies underway, the next five years will bring further growth and several key approvals. Recently, the focus has been on the innovative companies developing gene editing treatments for sickle cell, with approval(s) expected later this year. Sickle cell is a rare disease with limited treatment options, so a potential gene editing cure would be a major milestone for patients. Furthermore, one of the treatments being developed by Vertex and CRISPR Therapeutics would be the first gene editing treatment based on CRISPR-Cas9, if approved.

While it is difficult to predict exactly which diseases will see approvals in the next five years, I expect that many more treatments will emerge and be approved

for a range of rare and orphan diseases, which continue to be an important area of investment for CGT. However, cell and gene therapies for broader indications like diabetes and solid tumors is where the industry is going. Addressing larger patient populations, possibly with single dose therapies, brings enormous benefits to affected patients; however, healthcare provider and payer systems are not currently set up for this new treatment paradigm.

How are biotechnology companies addressing cell and gene therapies manufacturing capacity constraints?

A fundamental and unique challenge faced in CGT manufacturing is the highly manual, aseptic, and complex nature of the manufacturing process itself. There are also challenges associated with scaling lab-developed processes so these therapies can be produced outside the lab at therapeutically relevant doses.

Our biotech partners turn to us at Thermo Fisher to help them automate and standardize approaches so they can achieve scale and avoid potential failures further down the road. While our partners are working on developing cutting edge treatments, our focus is on continually innovating to help drive cost down and shorten timelines so once these treatments are approved, they can be made accessible to patients.

What advice do you have for women aspiring to leadership roles in the life sciences?

More than a role, leadership is a set of qualities and behaviors that can be cultivated. Though more natural to some, I've seen excellent examples of leadership at all organizational levels, the common denominator being an ability to inspire and drive people toward a common goal. The path for getting to a formal leadership position is as varied as the leadership styles themselves. For me, I leaned in on the technical side, pursuing a PhD in pharmacology, carving a path from bench scientist to product manager, business development to marketing and sales roles. The critical learnings on the way for me was to anchor on my core beliefs, know my strengths and blind spots, and be willing to take calculated risks that pushed me out of my comfort zone. Now with Thermo Fisher for nearly 20 years, I've grown with the company, serving in a variety of technical, commercial, and business leadership roles at the divisional and corporate levels.

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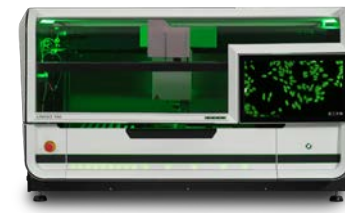

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KRONUS

Compact, semi-automated benchtop analyzer

The Evidence Investigator integrates immunoassay and molecular diagnostics using Biochip Technology for accurate results with CVs <10%. Performing up to 2376 tests/hour with 44 analytes/biochip, requiring only 7-25uL sample volume, preserving enough for confirmatory testing. Store up to 20,000 sample results and 500,000 sample test results. Perfect for medium-throughput laboratories.

Randox

Syphilis testing

ASI Evolution Automated RPR Syphilis Analyzer Nontreponemal RPR platform for diagnostic, blood donor screening and cadaveric tissue screening.

Features:

- 190 samples/hour
- Provides highest endpoint titers for automated RPR testing
- Reduce hands on time by 92%
- Intelligent ASI Smart Rack (available soon)
- Analyze, archive and retrieve results
- Standardized objective results

Arlington Scientific, Inc.

We have you covered

The dIFine 30 System is a powerful partnership which pairs the ZEUS dIFine digital immunofluorescence system with the new ZEUS SP30 slide processor! The SP30 is our easy-to-use and efficient walk-away benchtop instrument for IFA slide processing, designed to improve laboratory workflow and ensure high quality results… including cover slipping!

ZEUS Scientific

AlinIQ
PRE-ANALYTICS, POWERED BY INDEXOR

DIGITAL HEALTH SOLUTIONS

Avoid lost samples by digitizing your pre-analytical tracking with Indexor

DID YOU KNOW: ONE IN 1400 SAMPLES GO MISSING.[1]

Managing samples through tracking, transport, lab reception and accessioning of samples to ensure they are in the right place at the right time is a critical indicator of a lab's performance. Missing and delayed samples can result in extra work for the lab, recall for the patient, or missed reporting for physicians who rely on same-day results.

With AlinIQ Pre-Analytics, powered by Indexor, you can eliminate many of the manual steps needed to keep tabs on your samples. By reducing the number of touch points, you lower the risk of lost specimens – which makes for a better experience for everyone involved.

INDEXOR CAN HELP YOU:

TRACE SAMPLES FROM PATIENT DRAW TO ARRIVAL IN THE LAB

MONITOR KEY QUALITY INDICATORS

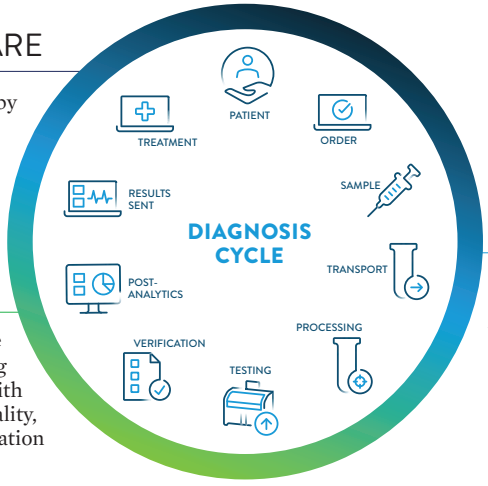
AUTOMATE TO SAVE TIME AND IMPROVE SERVICE LEVELS

EMPOWER PATIENT CARE

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

ELEVATE DIAGNOSTICS

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



OPTIMIZE WORKFLOW

Drive better outcomes by optimizing your pre-analytical and IVD workflows with new understandings and insights

SEE HOW INDEXOR STREAMLINES AND AUTOMATES SAMPLE TRACKING FOR BETTER RESULTS.

1. Wiwanitkit, V. Types and frequency of preanalytical mistakes in the first Thai ISO 9002:1994 certified clinical laboratory, a 6 – month monitoring. BMC Clin Pathol 1, 5 (2001).

Abbott

QuidelOrtho™

Sofia® 2
Vitros®
QuickVue®
Triage®
Solana®

Meet the family

Combining Quidel Corporation and Ortho Clinical Diagnostics allows us to deliver over 80 years of expertise, clarity, and insights across the full healthcare continuum. While devices in our portfolio might not look or act alike, they all share common family traits of reliability, speed and accuracy.

Welcome home. **QuidelOrtho.com**