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MEDICAL LABORATORY OBSERVER

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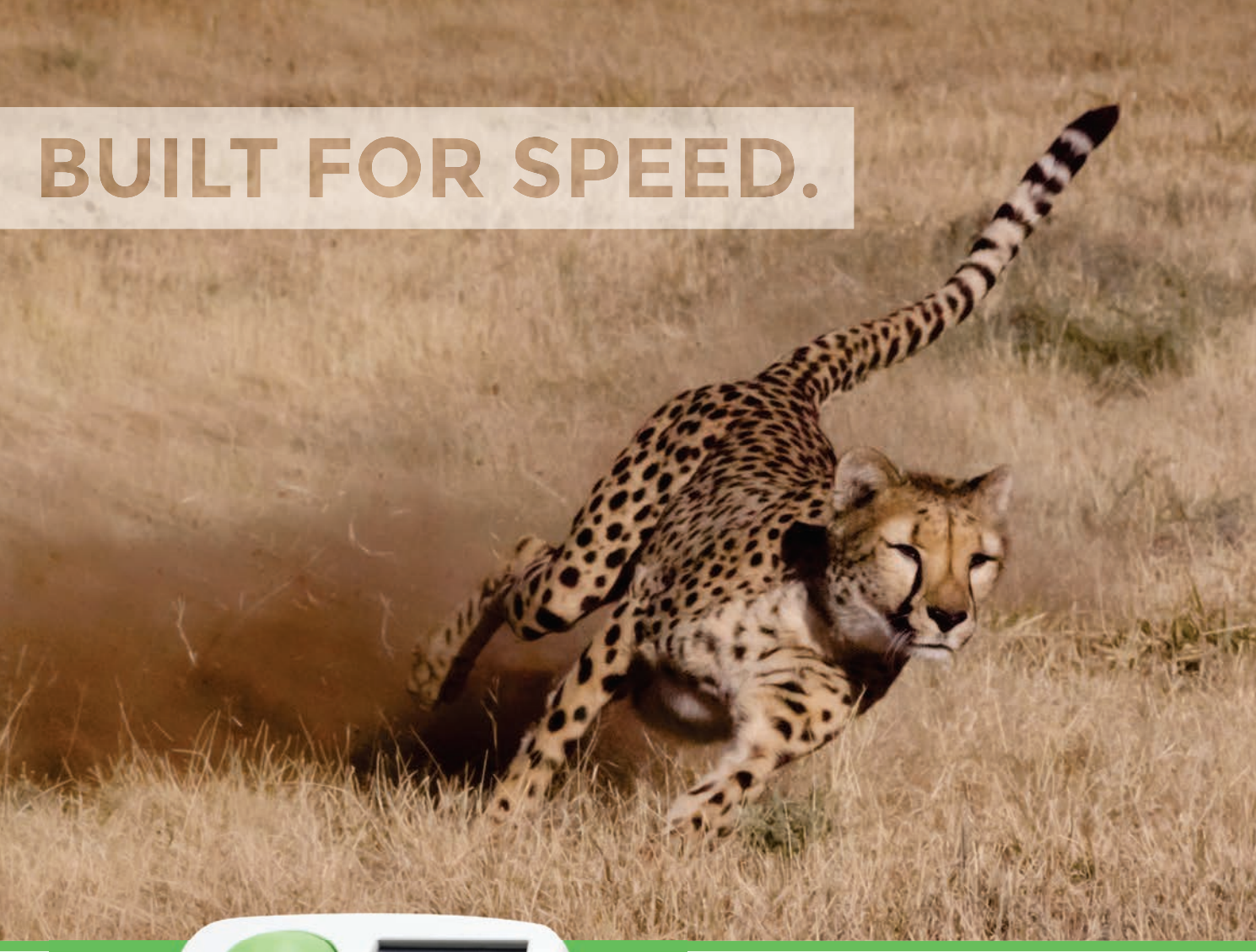

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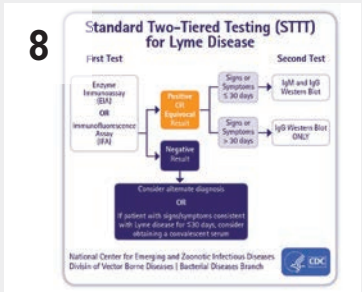

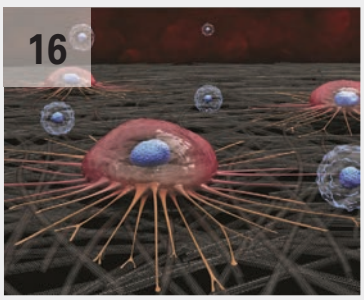

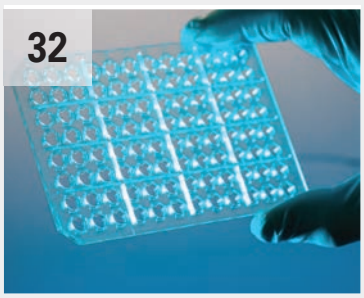

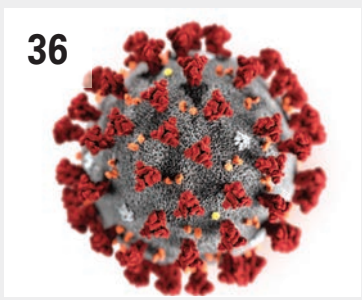

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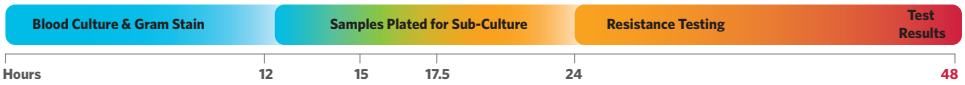

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KPC (carbapenemase)
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OXA (carbapenemase)
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The VERIGENE® System

1. Eur J Clin Microbiol Infect Dis. 2017 Oct;36(10):1879-87. doi: 10.1007/s10096-017-3008-6.
2. Box MJ, Sullivan EL, Ortwine KN, et al. Outcomes of rapid identification for Gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. Pharmacotherapy 2015; 35(3): 269-276.
3. Rivard KR, Athans V, Lam SW, et al. Impact of antimicrobial stewardship and rapid microarray testing on patients with Gram-negative bacteremia. Eur J Clin Microbiol Infect Dis. 2017 Oct;36(10):1879-87.

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Best practices and protocols for infectious disease outbreaks

By Brenda Silva
Senior Editor

As the lab industry watches the number of confirmed coronavirus cases increase, everyone connected to the disease – no matter how remotely – is getting an education in some way. Unfortunately for many people, this education has come with a high tuition that has cost lives around the world.

Beginning on December 31, the 2019 novel coronavirus (2019-nCoV) presented the clinical diagnostics industry with an emerging disease that forced lab professionals worldwide to pay attention to it, and what it's capable of in a short period of time. As the virus expanded its global reach, it claimed direct responsibility for over 40,000 confirmed cases and over 900 deaths (as of February 10). In this time, it also taught the industry that there was still a lot for us to learn about 2019-nCoV before it would no longer be a threat to the world at large.

Some of the most important lessons have been those learned by doctors in China who learned how to recognize and treat early signs of the disease, as well as scientists at agencies like the WHO, CDC and FDA who discovered similarities with past coronaviruses such as SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome).

Perhaps the most impressive side effect of 2019-nCoV has been the proactive response by over 20 diagnostics companies who are aggressively working on developing tests to detect coronavirus. In addition, numerous labs are purposely growing coronavirus in attempts to create a vaccine for it. These are the people whose motivation grows with every newly confirmed case or associated death, believing in the possibility of another coronavirus outbreak someday, and that education, prevention and early detection will make it more bearable throughout the world.

In this issue of *MLO*, we offer more information on 2019-nCoV in our special feature that looks at governments, diagnostic companies and providers and how they are responding to the coronavirus outbreak. In addition, we look at some of the best practices of RT-PCR use, including new applications in coronavirus detection.

When faced with a new or different strain of disease, scientists often revisit historical events to predict how a new disease could react in the future. Aside from an outbreak's location and symptoms, scientists consider climate and environmental factors that may also play a role in combating disease. As such, the key to managing future diseases remains constant communication between all parties concerned. With the global population always at risk of exposure, full disclosure of information educates everyone and lessens any disease impact. In this way, not only do we learn from each other, but we also become as prepared as possible for the next potential outbreak.

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

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Fast Facts

COVID-19*

Similar to MERS, SARS and the common cold, the novel coronavirus (COVID-19) was first detected in Wuhan, China, in December 2019, and has spread rapidly throughout China and the world.

3%

is the estimated mortality rate of COVID-19 infection

98%

of patients with COVID-19 infection presented with fever symptoms and later 55% of the patients developed dyspnea and 66% developed lymphopenia

76%

of patients presented with cough and 44% also had myalgia/fatigue with COVID-19 infection

2 days to 2 weeks

is the estimated incubation period after exposure according to the Centers for Disease Control and Prevention (CDC)

rRT-PCR

or Real-time reverse transcription polymerase chain reaction assay is the CDC prescribed test for labs to use for COVID-19 detection

774

is the number of deaths across the world from SARS; COVID-19 deaths have now exceeded that number with over 1,000**

$675 million

is the amount needed for new coronavirus preparedness and a global response plan covering the months of February through to April 2020 according to WHO International

- **Sources:**
- *https://www.who.int/news-room/detail/05-02-2020-us-675-million-needed-for-new-coronavirus-preparedness-and-response-global-plan*
- *https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html*

*Formerly 2019-nCoV
**As of February 11, 2020

Blood protein changes across lifespan

The bloodstream touches all the tissues in the body. It carries nutrients to tissues and takes waste products away. Tissues also release proteins into the bloodstream that can communicate with other parts of the body, help mount an immune response to disease, and much more.

Because of this constant flow of proteins through the body, some blood tests measure specific proteins to help diagnose diseases. Examples include diabetes, heart disease and kidney and liver problems. Scientists have been curious about whether blood proteins could be used to more broadly assess people's health and wellness.

To explore this idea further, researchers led by Drs. Benoit Lehallier and Tony Wyss-Coray from Stanford University collected blood plasma samples from more than 4,000 volunteers between the ages of 18 and 95. They compared the levels of nearly 3,000 proteins in blood between people of different ages as well as between men and women within those age groups. The work was funded in part by NIH's National Institute on Aging (NIA). Results were published in Nature Medicine.

Overall, about two-thirds of the proteins found to change with age differed between men and women. This supports the idea that men and women age differently—and highlights the need to include both sexes in clinical studies for a wide range of diseases.

The researchers identified a subset of 373 proteins that could accurately predict people's age within a range of a few years in both men and women. Participants who were predicted by their protein signature to be younger than they actually were performed better than their peers on cognitive and physical tests.

Unexpectedly, deeper analyses showed that most protein changes seen with aging did not occur in a linear fashion. Instead, they occurred in waves, with three large peaks of change around the ages of 34, 60 and 78. These waves largely consisted of changes in different proteins and were associated with different biological functions.

Some of the proteins found in these peaks had previously been associated with the development of age-related diseases. For example, proteins associated with cardiovascular disease and Alzheimer's disease were found in the peaks at 60 and 78 years of age.

"We've known for a long time that measuring certain proteins in the blood can give you information about a person's health status—lipoproteins for cardiovascular health, for example," says Wyss-Coray. "But it hasn't been appreciated that so many different proteins' levels—roughly a third of all the ones we looked at—change markedly with advancing age."

Vaping-associated lung injury

With research and understanding of electronic cigarettes or vaping product use-associated lung injury (EVALI) still evolving, a new *Radiology* review looks at the current state of the disease, diagnostics and the need for continued research.

Published online, "Radiologic Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use–associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions," is the newest research to tackle EVALI, a rapidly evolving public health crisis that has led to more than 2,500 hospitalizations since August, according to the Centers for Disease Control (CDC).

Recent research shows that most EVALI patients have smoked e-cigarettes that contained some mixture of marijuana and nicotine products, but study authors Seth Kligerman, M.D., and Mark Schiebler, M.D., say part of the problem is lack of regulation of vape pens and their contents.

In cases of EVALI reported to the CDC, 86 percent reported using products containing either nicotine or THC. The lack of regulation, black-market vape products and a young demographic of users all make researching the issue more complicated. The dramatic increase in vaping among middle school and high school students over the past year represents the largest increase in use of any illicit substance tracked by the National Institute of Drug Abuse over the last 44 years, according to the review.

"It all boils down to what is it that they are smoking? What they tell you they are smoking is not necessarily what they have been smoking. We have no idea what's in these cartridges and sometimes they don't know either, so there is a lot that's unknown," said Dr. Schiebler, professor of radiology at the University of Wisconsin School of Medicine and Public Health, Madison.

Other variabilities including the amount a patient inhales each time, length of inhalation, the volume of substance inside the vape pen and frequency of vaping can all make this research more challenging, said Dr. Kligerman, chief of cardiothoracic imaging and associate professor of radiology at UC San Diego Health.

Both doctors said that while the cases of EVALI seem to have slowed down after reaching a peak last fall, there is still

much doctors don't know about acute and long-term effects.

Originally touted as an alternative to traditional cigarettes, e-cigarettes still contain nicotine and have been marketed primarily to young adults with brightly colored packaging, advertising and flavoring.

Dr. Schiebler said the next phases of research will include epidemiology to trace particular outbreaks back to types of e-cigarettes and their contents, pathology to collect and study cases of EVALI and look for patterns, and research into particle size and how it affects the lungs over time.

The study reports that in most cases, both the imaging and pathologic findings of EVALI are that of organizing pneumonia and diffuse alveolar damage, although the disease can appear differently on scans for some people.

Researchers develop blood test to predict recurrence of gastric cancers

Researchers at the Johns Hopkins Kimmel Cancer Center in Baltimore, working with colleagues in the Netherlands, developed a blood test that can predict recurrence of gastric cancer in patients after surgery. A description of their test, which is still experimental, was published online in the journal *Nature Communications*.

Investigators analyzed blood samples from 50 patients with gastric cancer who participated in the CRITICS trial, a phase III, randomized controlled study of chemotherapy given at about the time of surgery. They performed deep sequencing of both circulating cell-free DNA (cfDNA) and of white blood cells to look for mutations. Subtracting the white blood cells' information from cfDNA yielded data investigators could use to predict cancer recurrence within nine weeks following preoperative treatment and surgery.

"We performed this study to see if we could predict whether gastric cancers would recur using noninvasive liquid biopsies. Using a deep sequencing approach of cell-free DNA and white blood cells, we found an outstanding prediction of whether the therapy was successful," says senior study author Victor Velculescu, M.D., PhD, professor of oncology, pathology and medicine. Velculescu also is co-director of the Kimmel Cancer Center's cancer genetics and epigenetics program, and associate director for precision medicine.

Alessandro Leal, M.D., PhD, lead author of the paper on the study and former graduate student at the Johns Hopkins University School of Medicine says, "Patients who did not have mutations in the blood after surgery were all cured of cancer, while patients who had mutations in the blood typically recurred. We were able to predict patient outcome about nine months earlier through the blood test than we otherwise could have through clinical evaluation."

Physicians slow to use new antibiotics against superbugs

New, more effective antibiotics are being prescribed in only about a quarter of infections by carbapenem-resistant Enterobacteriaceae (CRE), a family of the world's most intractable drug-resistant bacteria, according to an analysis by infectious disease and pharmaceutical scientists at the University of Pittsburgh School of Medicine (UPMC) and published by the journal *Open Forum Infectious Diseases*.

This sluggish uptake of such high-priority antibiotics prompted the researchers to call for an examination of clinical and pharmaceutical stewardship practices across U.S. hospitals, as well as behavioral and economic factors, to see if the trend can be reversed before lackluster sales lead the pharmaceutical industry to stop developing much-needed antibiotics.

"The infectious diseases community spent the past decade saying, 'We need new antibiotics, this is a top priority,' and now we're at risk of sounding like the boy who cried wolf," said lead author Cornelius J. Clancy, MD, associate professor of medicine and director of the mycology program and XDR Pathogen Laboratory in Pitt's Division of Infectious Diseases. "We have a responsibility to learn why it takes so long for antibiotics to be adopted into practice and figure out what we need to do to ensure the best antibiotics quickly reach the patients who desperately need them."

The CDC has classified CRE as urgent threat pathogens and calls them the "nightmare bacteria." The WHO and Infectious Disease Society of America have designated CRE as highest priority pathogens for development of new antibiotics. At the time of those declarations, polymyxins were the first-line antibiotics against CRE, even though they failed to work in about half the cases and carried a significant risk of damaging the kidneys.

Since 2015, five antibiotics against CRE have gained FDA approval: ceftazidime-avibactam, meropenem-vaborbactam, plazomicin, eravacycline, and imipenem-relebactam. Studies, including those conducted at UPMC, have shown that the first three of these antibiotics are significantly more effective at fighting CRE and less toxic than polymyxins (eravacycline and imipenem-relebactam are still too new for conclusive data).

Clancy and his colleagues surveyed hospital-based pharmacists in the U.S. to gauge their knowledge of the new antibiotics and their willingness to use them. The drugs were classified as the "first-line" choice against CRE blood infections by 90 percent of the pharmacists, pneumonia by 87 percent, intra-abdominal infections by 83 percent and urinary tract infections by 56 percent.

"Clearly hospital-based pharmacists are aware of these antibiotics and believe they are the best choice for the vast majority of CRE infections," said Clancy.

But when the team estimated the number of CRE infections nationwide and used national prescription data to calculate the proportions of old vs. new antibiotics used to treat those infections, they found that from February 2018 through January 2019, the new antibiotics were used only about 23 percent of the time. Their use likely started to exceed that of polymyxins only in December 2018, nearly four years after the first of the new antibiotics was approved by the FDA. Even after accounting for CRE infections in which new antibiotics might not be first-choice agents, the team found that use was only about 35 percent of what was expected based on positioning by hospital-based pharmacists.

Allergan and The Medicines Company, developers of two of the new antibiotics, have sought to exit the antimicrobial field since introducing their drugs because of insufficient returns on investment. Achaogen declared bankruptcy months after attaining FDA approval for a third new antibiotic.

The researchers suggest several reasons for the slow uptake of the new antibiotics, starting with cost. A 14-day course of the new antibiotics costs between $13,230 and $15,070, compared to $305 to $784 for the old drugs.

"Cost is a limitation, but I'm not convinced it is the sole cause of our findings," said Clancy. "Clinicians may not be prescribing the new drugs due to concerns about accelerating antibiotic-resistance or because initial studies on their effectiveness were relatively small. We need to get at the root causes of the disconnect between what the doctors prescribe and what the pharmacists we surveyed believe they should be prescribing, and then find a solution" and that participants remain in the study for follow-up. The report noted there was no significant evidence of either decreased or increased infection rates with vaccination.

Improved detection of acute Lyme disease with MTTT

By Mark Kopnitsky, B.S., M.S.

Lyme disease is the most common vector-borne disease in the United States. In North America, it is transmitted to humans by the bite of an *Ixodes* spp. tick, which is harboring and subsequently passes the spirochete *Borrelia burgdorferi*. During the 10-year period of 2008-2018, the Centers for Disease Control and Prevention (CDC) reported an average of more than 26,000 confirmed cases annually of Lyme disease in the U.S. Within that same period, the CDC estimated that an average of greater than 9,000 probable cases of Lyme disease were not reported, bringing the number of total cases of Lyme disease in the U.S. to over 35,000 cases per year.[1]

While 35,000 cases per year is significant, this number is likely drastically underestimated. Using medical claims data to estimate the number of possible cases of Lyme disease, in 2015, the CDC estimated that greater than 300,000 cases of Lyme disease occur each year in the U.S.,[2] which is more than 10 times the number of cases reported. This all translates into more than 3.3 million laboratory tests for Lyme disease performed annually.[3]

Initial test options – IFA and ELISA

In 1982, when the causative agent of Lyme disease was determined, a whole host of tests were developed to aid in the diagnosis of Lyme disease. The first test approved by the FDA for commercial distribution was a *Borrelia burgdorferi* indirect fluorescent assay (IFA) that was cleared in 1987, which is still in use to this day.[5] The following year, a number of ELISA tests for measuring antibody to *Borrelia burgdorferi* became commercially available. ELISA tests were, and still are more widely used since they are easily automated and provide an objective result. Despite the simplicity and objectivity of those ELISA tests, the lack of agreement among commercial products prompted the need for guidance.

In 1994, several sponsors, including the Association of Public Health Laboratories (APHL), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) held a meeting in Dearborn, MI, called the *Second National Conference on Serologic Diagnosis of Lyme Disease*.[4] A portion of the conference was devoted to devising recommendations for serologic test performance and interpretation. The outcome was a two-test serologic approach for detecting active disease and for previous infection that has come to be known as the Standard Two-Tiered Testing (STTT) algorithm (The STTT paradigm is depicted in **Figure 1**).

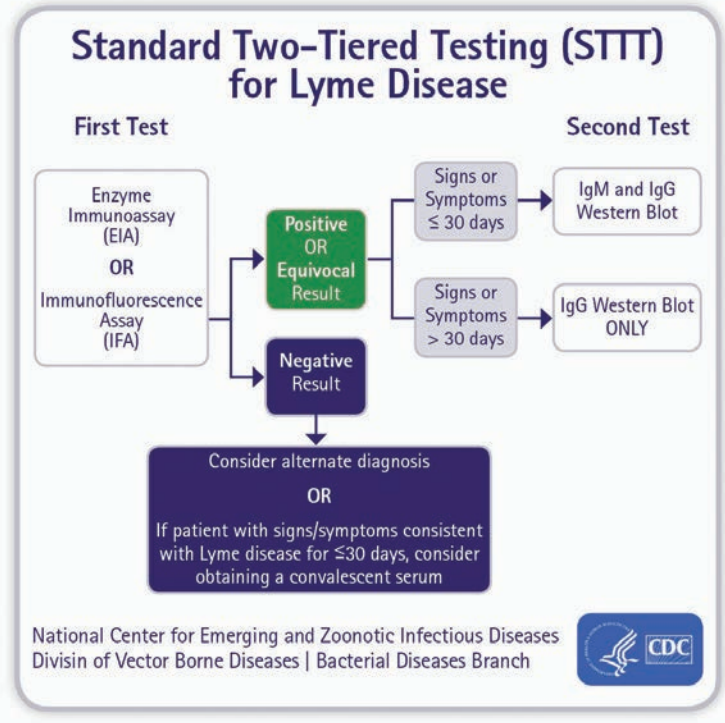

Figure 1. Standard Two-Tiered Testing Algorithm. Since 1994, this has been the standard for clinical serology testing for Lyme disease in the United States.

MTTT challenges the standard

The STTT algorithm typically incorporates an ELISA as the initial screening test. Any specimens that are positive or equivocal on that initial screen are subsequently tested by an IgG and/or an IgM immunoblot. For over two decades, the STTT algorithm has been the standard for Lyme disease serology despite documented shortcomings.[6,7,8] The most significant shortcomings are that many first-tier ELISA tests lacked specificity resulting in an excessive number of unnecessary second-tier immunoblots, which seemed to be even more problematic.

Most notably, the Western blots seemed to be less sensitive in early disease compared to the first-tier ELISA tests leading to possible STTT false negatives. The IgM Western blots had relatively poor specificity leading to potential STTT false positives. Finally, second-tier Western blots employed a subjective interpretation and were technically challenging to perform. With more than 3.3 million Lyme disease tests performed in the U.S. each year, a growing global prevalence of this elusive disease, and the STTT testing limitations noted above, there was a need for alternative diagnostic serology algorithms that could improve detection of early disease, while maintaining similar specificity to the STTT algorithm.

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LEARNING OBJECTIVES

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

1. Recall the causative agent of Lyme disease and estimated average of cases per year.
2. Describe the need and development of Lyme disease testing algorithms.
3. Discuss limitations of the STTT testing algorithm for the detection of Lyme disease.
4. Discuss the validation study findings of MTTT testing algorithms and their benefit to earlier developed algorithms.

In 2003, Bacon et al. demonstrated that the combination of certain second-generation ELISA tests – some commercial and some non-commercial – showed improved sensitivity in early disease as compared to STTT.[6] In a commentary letter related to that publication,[9] it was suggested that a combination of first-tier, commercial ELISA tests should be considered as an alternative for STTT. These were some of the early indicators that running specimens on a combination of first-tier screening tests might be more sensitive, yet equally specific as the STTT algorithm. Using a combination of commercially available, FDA-cleared *Borrelia* screening assays, it was demonstrated that using these sequential, first-tier screening assays showed superior sensitivity in early Lyme disease while keeping specificity constant.[10]

This study employed a *Borrelia* whole cell lysate ELISA followed by a VlsE1 and pepC10 multiplex immunoassay. This investigation revealed that replacing the Western blot with a multiplex immunoassay resulted in a 20.7 percent increase in sensitivity while maintaining specificity at 95.6 percent. Finally, Branda et al. showed that using a modified two-tiered testing (MTTT) algorithm comprised of two FDA-cleared, first-tier screening ELISA tests, resulted in significantly improved sensitivity for the detection of early disease while maintaining comparable specificity.[11] This laid the groundwork for a series of similar STTT versus MTTT studies that have been previously summarized.[12] All such studies seem to convey a common theme; two sequential first-tier ELISA tests have the potential to provide improved sensitivity in the detection of early Lyme disease, while providing comparable specificity (The MTTT algorithm is depicted in **Figure 2**).

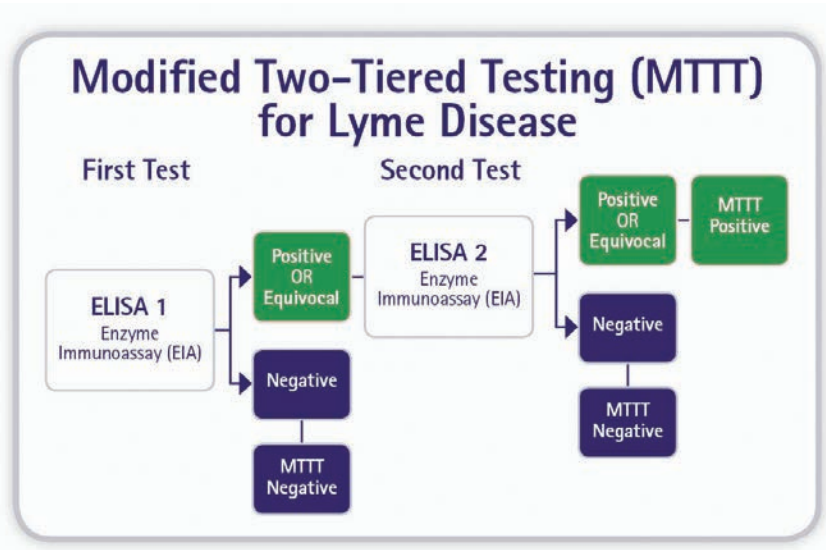

Figure 2. Modified Two-Tiered Testing (MTTT) Algorithm. The basic concept for the MTTT algorithm was to replace the second-tier Western blot with a second ELISA test or a second "first-tier" screening test. In general, first-tier screening tests tended to be more sensitive than the Western blot but lacked the specificity to be used as a stand-alone diagnostic test. Adding the second-tier blot improved the specificity of the combination but tended to decrease the overall sensitivity. By using two ELISA tests in the MTTT algorithm, it enables improved sensitivity yet comparable specificity as the STTT algorithm. This is because samples that contribute to specificity issues on any one ELISA rarely cause a specificity issue on both ELISA tests.

ELISA and the MTTT algorithm

Published studies clearly demonstrated the potential advantages of the MTTT algorithm, which are improved serodiagnosis of early cases of Lyme disease and the removal of the technically challenging and subjective immunoblots. The problem was that although the scientific community had adequately demonstrated over a period of many years that the "two ELISA" MTTT concept was clearly comparable, if not superior to the decades old STTT paradigm, without FDA clearance and CDC endorsement of the MTTT algorithm, there was little chance that clinical laboratories could take advantage of the MTTT concept. Likewise, without the lab's ability to fully adopt MTTT, it was inevitable that many infected patients with early Lyme disease who may actually be seropositive with the MTTT algorithm, may yield seronegative results with the STTT algorithm.

A new investigation to validate the MTTT algorithm was envisioned that incorporated four different FDA-cleared anti-*Borrelia* ELISA tests. If successful, this would allow for the MTTT concept to be used as an option for clinical labs. The four tests included one whole cell lysate ELISA that detected both IgG and IgM class antibodies, one whole cell lysate ELISA that detected IgG only, one whole cell lysate that detected IgM only and one second-generation IgG/IgM ELISA that incorporated a mixture of recombinant VlsE1 and synthetic pepC10 antigens.

With input from the FDA, an IRB-approved, investigational protocol was outlined that would empirically demonstrate if an all-ELISA, MTTT concept could serve as a substantially equivalent alternative to STTT. The general study design would test specimens with a first-tier ELISA test. Then, as per the STTT algorithm, any specimens that were positive or equivocal on the screen test would be

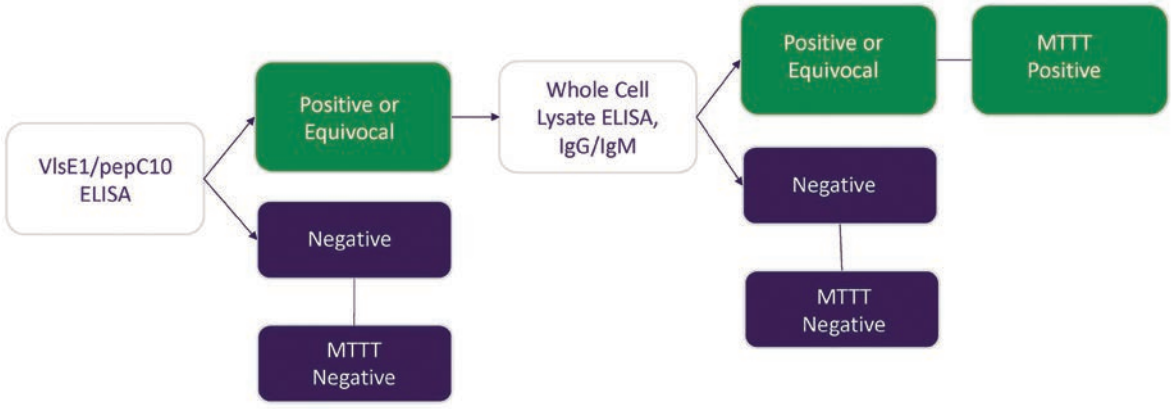

Figure 3. The *Borrelia* MTTT-1 concept submitted to FDA included screening patients' sera on the VlsE1/pepC10 IgG/IgM ELISA and reflexing those specimens that were positive or equivocal to a second ELISA; an ELISA test comprised of *Borrelia burgdorferi* whole cell lysate antigen and an IgG/IgM conjugate.

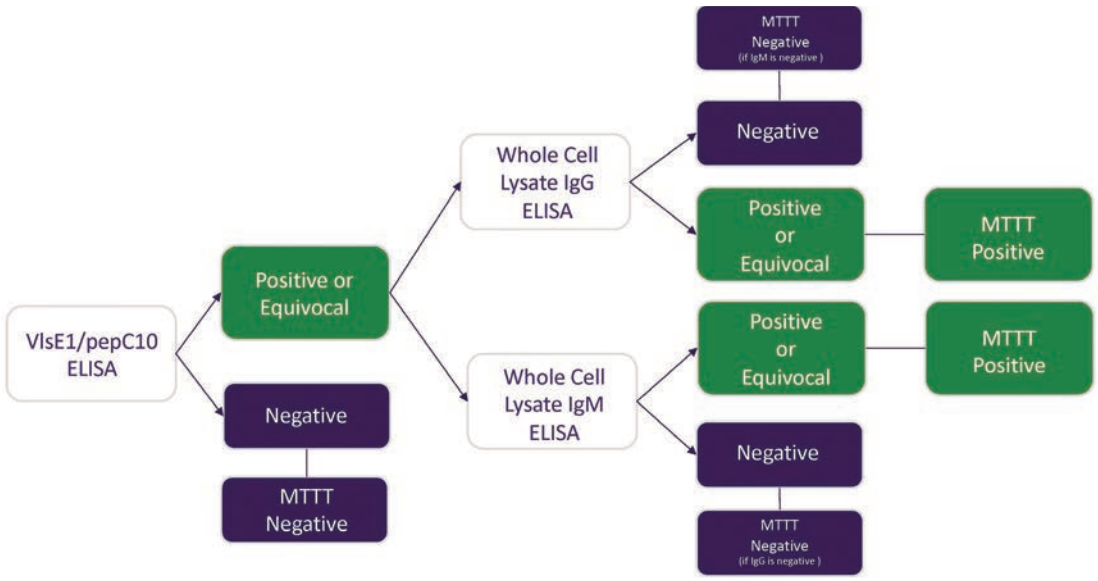

Figure 4. The *Borrelia* MTTT-2 concept submitted to FDA included screening patients' sera on the VlsE1/pepC10 IgG/IgM ELISA and reflexing those specimens that were positive or equivocal to two separate second-tier ELISA tests. One ELISA test comprised of *Borrelia burgdorferi* whole cell lysate antigen designed to measure IgG class antibody and a second ELISA test comprised of *Borrelia burgdorferi* whole cell lysate antigen designed to measure IgM class antibody.

reflexed to FDA-cleared Western blots. Those same samples were also tested on a second ELISA test. With that basic design, a direct comparison could be made with the Western blot as the confirmatory test versus the second ELISA as the confirmatory test.

It has been previously pointed out that the most widely published concept for MTTT was to initially screen with an ELISA test comprised of a whole cell lysate antigen, followed by an ELISA test comprised of a second-generation (recombinant and/or synthetic) antigen preparation.[7] However, it is also known that alternative scenarios have been validated and perform equally well. In this study, specimens were screened using the second-generation ELISA comprised of VlsE1/pepC10 antigen and confirmed using whole cell lysate ELISA(s). This scenario, coupled with three FDA-cleared whole cell lysate ELISA tests, enabled the investigators to envision two separate MTTT concepts (Those two MTTT concepts are depicted in **Figures 3 and 4**).

MTTT-1 and MTTT-2 algorithms

With the MTTT-1 algorithm, specimens negative on the VlsE1/pepC10 IgG/IgM ELISA were considered both STTT and MTTT-1 negative. Specimens positive or equivocal on the VlsE1/pepC10 IgG/IgM ELISA were reflexed to IgG and IgM Western blot and the *Borrelia* whole cell lysate IgG/IgM ELISA. With respect to STTT second-tier analysis, specimens positive by IgG and/or IgM Western blot as per the CDC guidelines for interpretation of Western blot[4] were scored as STTT positive. Specimens that were negative for both the IgG and IgM Western blot were scored as STTT negative. For the MTTT-1 second-tier analysis, specimens positive or equivocal for the *Borrelia* whole cell lysate IgG/IgM ELISA were scored as MTTT-1 positive, and those that were negative on the second-tier ELISA were scored as MTTT-1 negative.

The MTTT-2 algorithm was similar except that if the specimens were positive on the first-tier screen ELISA, in addition to being reflexed to IgG and IgM Western blot, they were reflexed to two separate second-tier ELISA tests; one was a *Borrelia* whole cell lysate IgG ELISA and the other was a whole cell lysate IgM ELISA. In this case, the MTTT second-tier ELISA tests were treated much like the conventional Western blot in the STTT protocol. If either of the second-tier ELISA tests were positive or equivocal, the specimen was considered MTTT-2 positive, and if both of the second-tier ELISA tests were negative, the specimen was scored as MTTT-2 negative (The STTT algorithm utilized is outlined in **Figure 5**).

This experimental design was used to evaluate two separate cohorts of specimens. One group of 356 clinically characterized specimens comprised of a mixture of patients diagnosed with Lyme disease as well as controls. More specifically, the cohort consisted of 166 cases of Lyme disease, 90 specimens from individuals with conditions other than Lyme disease and 100 healthy controls (50 from Lyme disease endemic areas and 50 from non-endemic areas). A second cohort of specimens was comprised of 2,932 specimens collected from three separate clinical labs that were located in three geographically distinct endemic regions. These represented specimens that were submitted to the clinical lab for routine *Borrelia* serology. The clinical information for these patients was largely unknown as is typical in many clinical laboratories.

With this experimental design, the FDA was provided with important data showing how MTTT compared to STTT using two specific patient cohorts; one comprised of extremely well-characterized clinical specimens and one comprised of prospectively collected, routine submits representative of samples typically analyzed by the average clinical lab. More specifically, the FDA was provided with data comparing MTTT-1 compared to STTT and MTTT-2 compared to STTT utilizing four different ELISA products which had been previously cleared for commercial use. These data enabled results to be shared relative to clinical outcome, as well as results relative to typical STTT performance.

For the prospective cohort, comparing MTTT-1 to STTT on the 2,932 specimens resulted in relative sensitivity, relative specificity and relative agreement of 99 percent, 98 percent and 98 percent respectively. When the same cohort was evaluated using the MTTT-2 algorithm compared to STTT, the relative sensitivity, relative specificity and relative agreement were 100 percent, 96 percent and 97 percent respectively. Both the MTTT-1 and MTTT-2 algorithms demonstrated a high degree of correlation relative to the existing STTT (depicted in Figure 5). These data are consistent with the many published studies comparing STTT to various MTTT algorithms.

Using the retrospectively collected, clinically characterized cohort allowed the FDA to review data summarizing clinical sensitivity and clinical specificity of all three algorithms: STTT, MTTT-1 and MTTT-2. In the non-Lyme disease control group, the clinical specificity of STTT,

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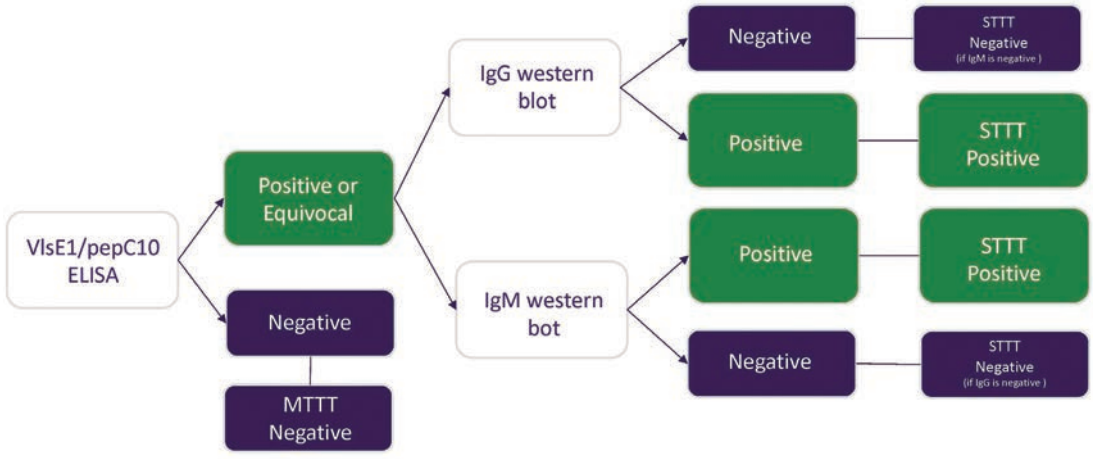

Figure 5. STTT algorithm used in this investigation is consistent with what was outlined by the CDC in 1994; however, in this case, the screening ELISA was the VlsE1/pepC10 IgG/IgM ELISA and all specimens positive or equivocal were reflexed to both the IgG and IgM Western blots.

MTTT-1 and MTTT-2 were 100 percent, 99 percent and 99 percent, respectively. In both MTTT scenarios, there were two patients diagnosed with mononucleosis that were MTTT positive and STTT negative.

In the clinically characterized, Lyme disease cases, the clinical sensitivity of STTT, MTTT-1 and MTTT-2 were 73 percent, 81 percent and 89 percent respectively. In both MTTT scenarios, the clinical sensitivity was significantly greater than the traditional STTT paradigm. As has been published previously, STTT and MTTT compared well in late, stage 3 Lyme disease; however, in early disease, especially acute stage 1 Lyme disease, the sensitivity of MTTT compared to STTT was significantly better. Specifically, in acute stage 1 Lyme disease, MTTT-2 detected 27 percent more cases of disease than STTT. While slightly fewer, MTTT-1 detected 23 percent more cases of early Lyme disease compared to STTT.

FDA clearance leads to paradigm shift

The FDA submission confirmed what nearly a decade of various scientific studies had documented; using multiple, sequential, tier-one *Borrelia* screening ELISA tests can significantly improve the detection of early Lyme disease compared to the 1994 STTT algorithm. In some cases, clinical sensitivity can be improved by as much as nearly 30 percent. Considering that the CDC estimates that there are approximately 300,000 cases of Lyme disease in the U.S. annually, there are likely tens of thousands of infected patients per year who have been tested for Lyme disease using the traditional STTT method and found to be seronegative; that would have been seropositive if tested by the MTTT-1 or MTTT-2 algorithms.

Considering the likelihood of improved patient outcomes, and the substantial equivalence that was demonstrated, the FDA cleared the two algorithms in July of 2019.[13] Shortly thereafter, the CDC subsequently modified their recommendations regarding *Borrelia* serology,[14,15] which represents a major paradigm shift as it relates to the 25-year-old STTT algorithm. A shift that will undoubtedly lead to greater operational efficiency in clinical laboratories and improved serodiagnosis of early Lyme disease.

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Improved detection of acute Lyme disease with MTTT

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TEST QUESTIONS

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

1. **How is Lyme disease transmitted to humans in the United States?**
   - a. mosquitoes
   - b. deer tick
   - c. Ixodes tick
   - d. droplet nuclei

2. **The CDC estimates that there are _____ times more cases of Lyme disease than of reported cases from 2008-2018.**
   - a. 2
   - b. 5
   - c. 10
   - d. 20

3. **In 2015, how many cases of Lyme disease did CDC estimate occur each year?**
   - a. 300,000
   - b. 89,000
   - c. 35,000
   - d. 26,000

4. **When was the first FDA-approved test for Lyme disease approved?**
   - a. 1980
   - b. 1982
   - c. 1987
   - d. 1990

5. **The first two tests that were used for Lyme disease testing in the late 1980's were**
   - a. Culture and IFA
   - b. Culture and ELISA
   - c. ELISA and IFA
   - d. ELISA and PCR

6. **ELISA tests that were initially developed showed a lack of agreement among commercial guidance.**
   - a. True
   - b. False

7. **The first devised recommendations for serologic test performance and interpretation of Lyme disease were devised by the Second National Conference on Serologic Diagnosis of Lyme Disease and were made up of the**
   - a. FDA
   - b. NIH
   - c. CDC
   - d. all of the above

8. **The Standard Two-Tiered Testing (STTT) algorithm was developed to determine**
   - a. active disease
   - b. previous infection
   - c. both a. and c.
   - c. none of the above

9. **In the STTT algorithm, what test is used as the initial screening test?**
   - a. Culture
   - b. ELISA
   - c. immunoblot
   - d. IFA

10. **What is the confirmatory test for all positive or equivocal tests in the STTT algorithm?**
    - a. Culture
    - b. ELISA
    - c. immunoblot
    - d. IFA

11. **The testing performance of the STTT algorithm showed missed diagnoses in those with _____ Lyme disease.**
    - a. early
    - b. late
    - c. no
    - d. none of the above

12. **Modified two-tiered testing (MTTT) studies have shown comparable sensitivity and superior specificity to the STTT algorithm for the detection of early Lyme disease.**
    - a. True
    - b. False

13. **The MTTT algorithm originally consisted of**
    - a. an ELISA test and an IFA test
    - b. four sequential first-tier ELISA tests
    - c. two sequential first-tier ELISA tests
    - d. none of the above

14. **The MTTT validation study compared _____ and _____ as the second tier of confirmatory testing.**
    - a. IFA and ELISA
    - b. IFA and Western blot
    - c. ELISA and culture
    - d. ELISA and Western blot

15. **The MTTT-2 algorithm reflexed positive first-tier specimen to be tested using**
    - a. two separate second-tier ELISA tests and Western blot
    - b. second-tier ELISA tests and Western blot
    - c. two separate second-tier ELISA tests only
    - d. Western blot only

16. **The findings in the validation study showing the clinical sensitivity of STTT, MTTT-1 and MTTT-2 were**
    - a. 70 percent, 80 percent and 88 percent
    - b. 73 percent, 81 percent and 89 percent
    - c. 63 percent, 71 percent and 99 percent
    - d. 75 percent, 84 percent and 87 percent

17. **MTTT-1 and MTTT-2 findings in the validation study showed that MTTT-2 detected more acute stage 1 Lyme disease cases than MTTT-1 did when compared to the STTT algorithm.**
    - a. True
    - b. False

18. **The FDA cleared the MTTT-1 and MTTT-2 algorithms in**
    - a. January 2017
    - b. July 2016
    - c. January 2019
    - d. July 2019

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SSC Hour-1 Bundle calls for early lactate measurement of tissue hypoperfusion

Surviving Sepsis Campaign (SSC) has introduced the 2018 Hour-1 Sepsis Bundle for early recognition and management of sepsis. The SSC Hour-1 Bundle includes obtaining blood for lactate measurement within the first hour of sepsis recognition and to remeasure lactate if the initial lactate is >2 mmol/L.[1] The campaign suggests guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.[1]

CMS SEP-1 quality metric includes early lactate measurement of tissue hypoperfusion

Consistent with the SSC Hour-1 bundle, US Centers for Medicare and Medicaid Services has introduced the Severe Sepsis and Septic Shock: SEP-1 Management Bundle to assess the quality of sepsis care in hospitals. The SEP-1 metric calls for lactate measurement to be completed within 3 hours of sepsis recognition.[2]

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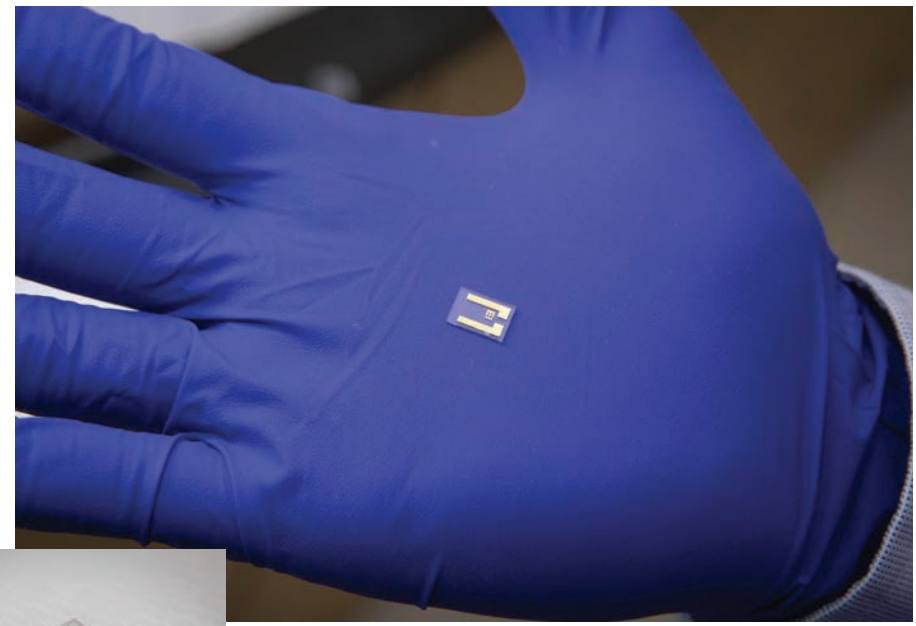
Liquid biopsy chip could detect early-stage cancer

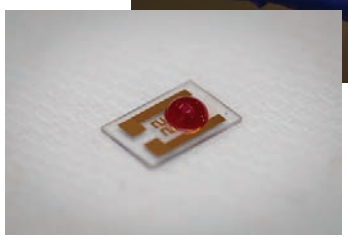
By WPI Staff

Researchers at Worcester Polytechnic Institute (WPI) have developed a chip made of carbon nanotubes that can capture circulating tumor cells (CTCs) of all sizes and types, and it can do so with far greater sensitivity than existing technologies. The unique design of the device makes it possible to easily identify and even culture the captured cells, which could make it possible to detect early-stage tumors, predict the course of a cancer and monitor the effects of therapy.

Details of the new technology are reported in the journal *Lab on a Chip* (Liquid biopsy using the nanotube-CTC-chip: capture of invasive CTCs with high purity using preferential adherence in breast cancer patients) by a team consisting of researchers at WPI, the Department of Neurological Surgery at the University of Massachusetts Medical School, and the James Graham Brown Cancer Center at the University of Louisville School of Medicine. Balaji Panchapakesan, professor of mechanical engineering at WPI, is the project lead.



WPI post-doctoral fellow Sadegh Mehdi Aghaei holds a single chip in his gloved hand.



A single drop of blood sits on the cancer-detecting chip developed.

The challenge of isolating CTCs

High cancer mortality rates are largely attributable to tumors developing undetected until they reach advanced or inoperable stages, and to metastasis (when tumor cells travel through the bloodstream and initiate new tumors in other organs). Scientists have long sought a method that can reliably snare tumor cells as they travel through the bloodstream. Such technology could make it possible to detect cancers at very early stages, when treatment is more likely to be successful, and to spot the genetic changes that tumor cells undergo when a cancer is beginning to metastasize.

"Isolating CTCs with high purity is a significant challenge, akin to finding a needle in a haystack," Panchapakesan said. "These cells comprise as few as one to 10 cells among a billion blood cells, and the shedding of CTCs from tumors is a highly discontinuous process."

A number of research labs and companies have created so-called liquid biopsy devices, but the devices currently available have important limitations, Panchapakesan said. These include low sensitivity; the inability to trap CTCs of all sizes and types or capture clusters of CTCs along with individual cells; difficulty in retrieving captured cells from the devices for laboratory analysis; and high manufacturing costs. In addition, contamination of captured CTCs by white blood cells, which are similar in size and can be mistaken for CTCs, is a problem for many liquid biopsy devices.

The device developed by Panchapakesan's team, described in the *Lab on a Chip* paper, has none of these limitations. The centerpiece of the device is a layer of carbon nanotubes that lines the bottom of a small well formed in a silicon/glass wafer. Panchapakesan says the chip design takes advantage of a natural tendency of CTCs to attach. "In order to travel to a distant site in the body and start a new tumor," he said, "CTCs need the ability to attach in an environment that is not conducive to attachment. In previous research, we have shown that they will attach preferentially to carbon nanotubes, but that white blood cells will not, by and large."

Fragility and behavior of CTCs

In addition, recent studies have shown that CTCs are far more fragile than previously believed and are subject to the environmental and mechanical stresses inherent in the bloodstream. "These cells won't survive unless you give them a rocklike matrix to attach to—a softer matrix requires too much energy from the cell," Panchapakesan said.

"It's a medical problem at the intersection of mechanical engineering and biology," he said. "An understanding

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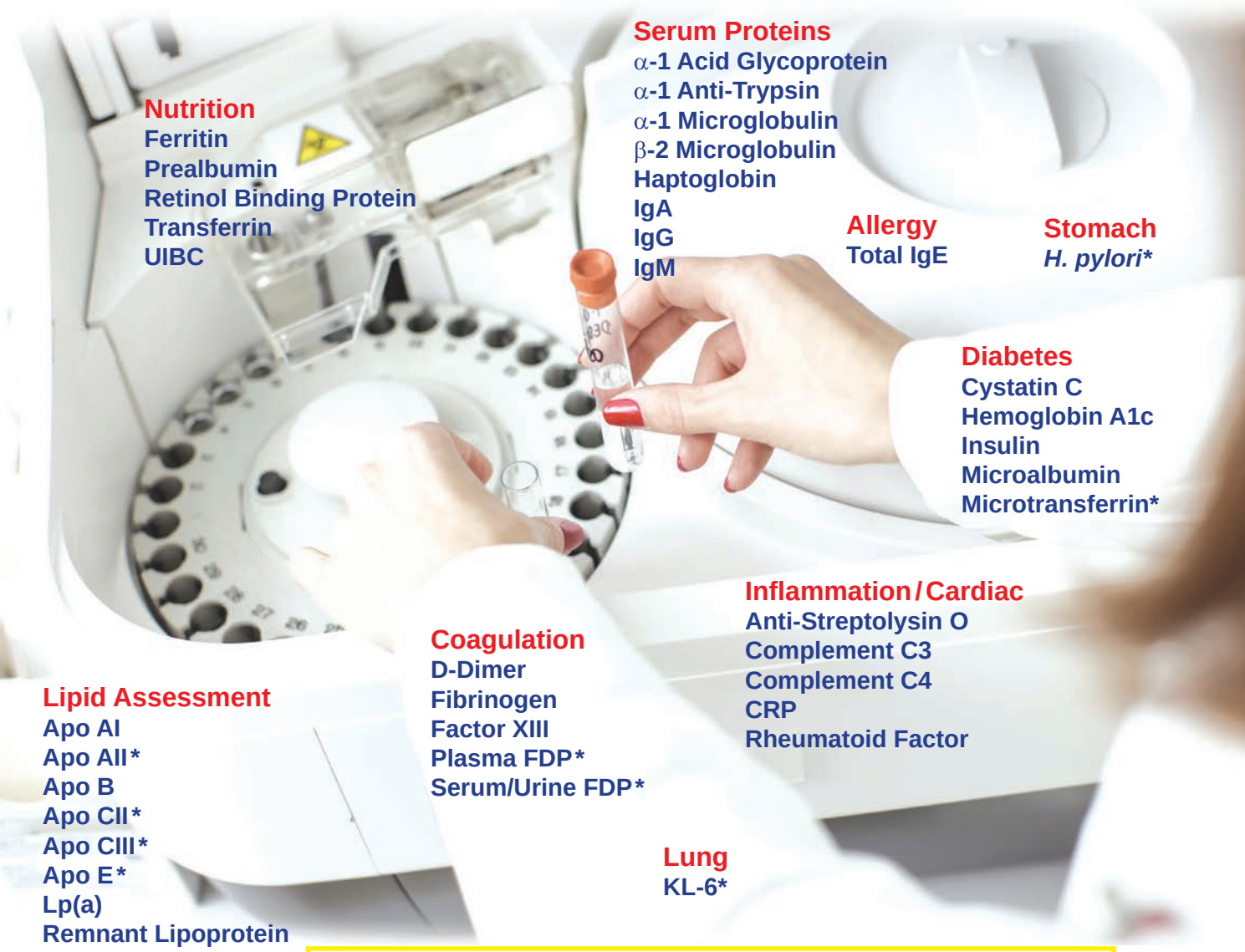

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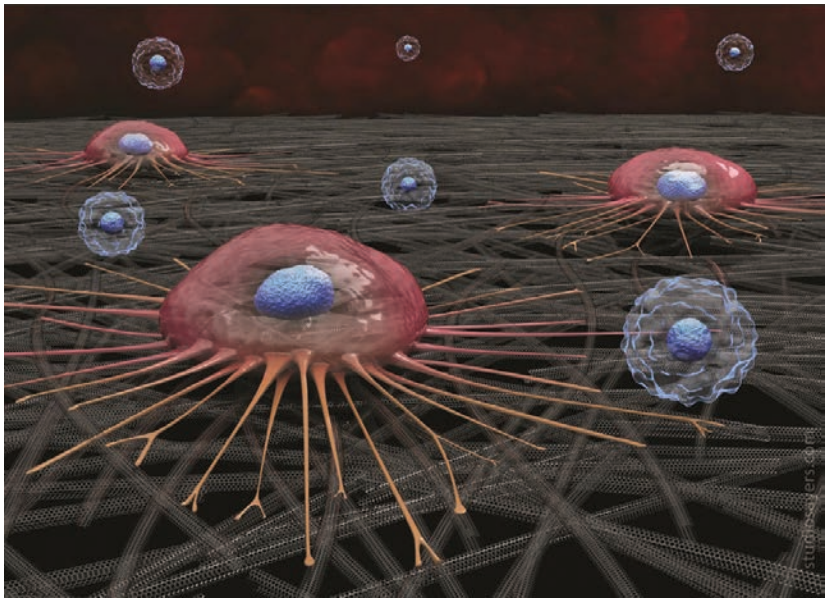
of the biology of cancer cells and how CTCs behave enabled us to design a mechanical engineering-based device."

The fact that white blood cells do not adhere to the nanotubes makes it possible to remove them from the chip, leaving the CTCs behind to be counted and identified. Red blood cells, which vastly outnumber the circulating tumor cells, also pose a problem. Since they tend to settle to the bottom of the chip, they could prevent CTCs from adhering to the nanotubes. The research team addressed this problem by lysing, or breaking up, the red blood cells before adding a blood sample to the chip. They found that the lysing process has no effect on the CTCs.

Test results and captured cells

Tests of the chip using blood spiked with a known number of cancer cells tagged with fluorescent dye showed that it has a high sensitivity, with between 89 and 100 percent of cells in the test samples being captured. (The sensitivity of the chip increased the longer the blood remained in contact with the nanotubes.) Tests were also run with blood samples from actual breast cancer patients (stages 1–4) and yielded 100 percent sensitivity for detecting CTCs. The CTCs were captured from all seven patient samples, while no tumor cells were captured from the samples from two healthy patients.



A circulating cancer cell (pink) attaches to carbon nanotube surface; white blood cells (blue) do not adhere and are later washed away.

What's more, the chip captured individual CTCs exhibiting multiple phenotypes from early- and late-stage cancer patients, another potential advantage of the device. While other methods used to capture cells in other devices exhibit biases that prevent them from capturing the full range of cancer cell phenotypes, the WPI carbon nanotube chip appears to have the potential to do so.

"These initial clinical studies," Panchapakesan said, "in which we were able to capture and identify individual CTCs of varying phenotypes, show that this device could become an important tool not only for tracking the progression of cancers and their response to radiation or chemotherapy, but also in making predictions about the likely course of the cancer, which could help physicians identity the most effective course of therapy."

The tests also showed that the carbon nanotube chip can capture cells regardless of their size and can also capture clusters of CTCs in addition to individual cells. (CTC clusters are rare, but they appear to have a greater ability to seed new tumors than individual CTCs) Because the cells settle gently onto the nanotubes and latch on with tendrils that extend from the cell body, they are not damaged.

While captured cells must be removed from other devices for analysis, which can be difficult with devices that use narrow microfluidic channels and often results in damage to the cells, the cells captured by the carbon nanotube chip remain viable and can even be cultured. In addition, because the chips are transparent, it is possible to stain and study captured cells without removing them.

Clinical trials and early detection

The chip described in the *Lab on a Chip* paper is the latest generation of a liquid biopsy chip that has been under development for several years in Panchapakesan's Small Systems Laboratory at WPI in collaboration with the University of Massachusetts Medical School and the University of Louisville.

The chips are made with materials and batch fabrication techniques similar to those used to make semiconductors. The current generation is a 76-element array of test wells on a glass and silicon wafer. In addition to making mass production possible, the multi-well design makes it easy to split a blood sample among multiple wells. The small volume of blood placed in each well makes it possible to more accurately count the attached CTCs.

Panchapakesan said he believes the latest generation of carbon nanotube liquid biopsy chip is ready for clinical trials. Toward that end, he is working with StrandSmart Inc., a Silicon-Valley start-up led by CEO Adrianna Davies. The team envisions testing a point of care (POC) device to detect cancer in the earliest stages globally.

"This potentially lifesaving technology could have multiple beneficial applications," Panchapakesan said. "It could help shed light on the complex biological and genetic processes at play in cancer. It could detect cancers at a very early stage by capturing the cells that nascent tumors shed into the blood. It could identify CTCs with metastatic potential before new tumors even begins, and it could help shape treatments customized to each person's cancer."

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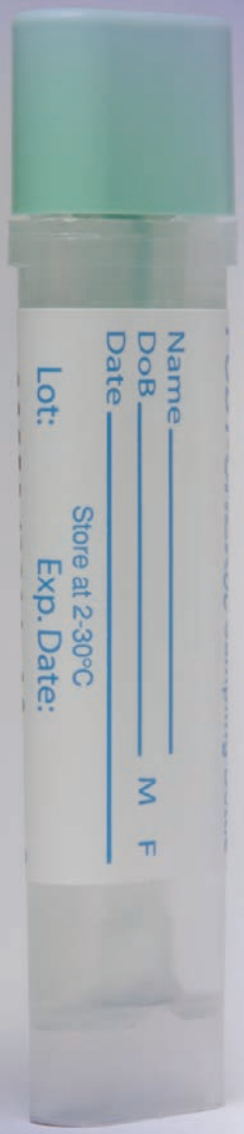

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Streamlining fertility treatment using clinical lab informatics solutions

By Katie Evans, M.S.

Sharing information quickly is essential for clinical laboratories to not only support decision-making by physicians, but also differentiate service offerings from competitors. The prompt delivery of test results can positively impact patient outcomes by expediting the initiation of a potentially life-changing treatment program or guiding a change in therapy. However, to assure patient safety, it is crucial to ensure information is shared in compliance with the latest industry standards around data integrity.

Despite the importance of rapid, highly accurate reporting, clinical laboratories still often rely on fragmented systems, such as paper-based records and offline spreadsheets, to manage data. With many of these documents stored in multiple locations and accessed by numerous technicians, this approach is notoriously prone to errors. Moreover, manually populating existing records is extremely laborious, taking up time that could be better spent on other business-critical functions such as improving existing tests.

To address the challenges associated with established methods of data entry and communication, many clinical laboratories are turning to the latest cloud-based laboratory informatics solutions. By promoting compliance with regulatory guidelines, these systems support the highest standards of data accuracy, consistency, and completeness, alongside improved turnaround times and throughput.

Overcoming the challenges around clinical data management

A sudden spike in laboratory workload prompted Examen – a diagnostics company based in Belfast, Northern Ireland, focused on transforming the diagnosis and treatment of male reproductive issues – to incorporate a new laboratory informatics solution into their workflow. This decision was driven primarily by growing demand for the company's sperm DNA fragmentation test (SpermComet), a method that provides a measure of DNA damage in sperm to aid prediction of fertility treatment success.

By coupling DNA fragmentation with semen analysis to provide a complete picture of sperm health, physicians rely on Examen's services to help clients make informed choices about *in vitro* fertilization (IVF) treatment. The process hinges on the prompt delivery of highly accurate DNA fragmentation test results to support clinical decision-making. However, with a rapidly expanding workload due to business growth, Examen's existing data management systems were under considerable strain.

A key limitation of Examen's established systems was that data processed in the laboratory was routinely stored in multiple locations. Following the lengthy procedure of sample registration and subsequent testing, extraction of information from disparate systems frequently made it impractical for technicians to generate reports on the same day. Moreover, at peak times, results reporting could be delayed until the next day or even to the end of the working week, risking data integrity by introducing the possibility that observations made during the testing process could be overlooked.

The problem of delayed reporting was compounded by the fact that data would often have to be manually transferred into reports from separate spreadsheets, adding time to workflows and significantly increasing the potential for error. With Examen pursuing ISO 9001 certification, it was essential to maintain the highest standards of data integrity, and it was apparent that the business demanded a more efficient data management solution to deliver on tight turnaround targets while meeting all regulatory requirements.

After considering multiple options, Examen chose to adopt a cloud-based laboratory informatics solution. With the promise of considerable time savings, especially during sample registration and results reporting, this represented an effective solution to increase productivity. Additionally, by freeing up researchers' time to further validate and improve the company's product offering, automated data management provided scope to extend the reach of the business.

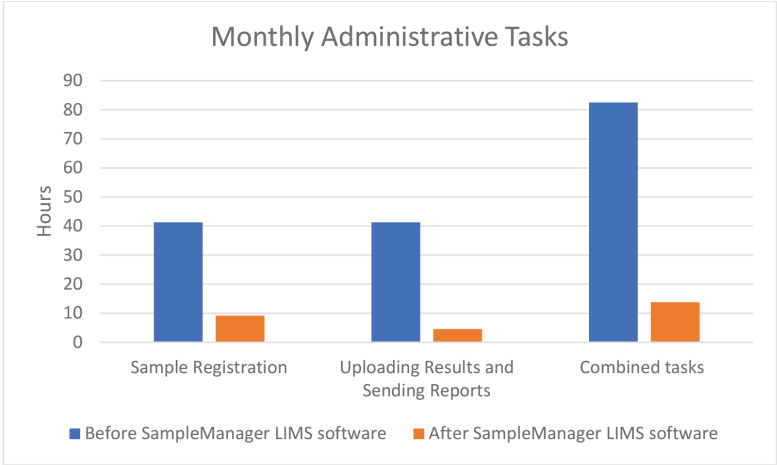

Figure 1. The time used each month for administrative tasks.

Boosting efficiency with cloud-based laboratory informatics solutions

Cloud-based laboratory informatics solutions are a highly effective method for managing data, resources and workflows within a single centralized system. With vast flexibility for configuration, these models provide end-users with in-built data integrity and security measures for compliance with worldwide regulatory requirements. Moreover, cloud-based architecture provides a scalable solution to enable future business growth.

By centralizing data management using a cloud-based laboratory informatics solution, Examen was able to significantly boost productivity and efficiency. A major factor in achieving this was the connection of the company's instrumentation to a single centralized system; by allowing raw data to be stored directly to the solution, the need for multiple, time-consuming manual data transfer steps was eliminated.

Figure 1 illustrates the time-savings made by Examen as a result of implementing a laboratory informatics solution. The time spent on administrative tasks was reduced from over 80 hours per month to under 15 hours, including an approximate four-fold decrease in sample processing times and a reduction in results reporting from over 40 hours per month to less than five hours. With improved turnaround times translating to same-day reporting as standard, the company has used the associated efficiency gains to focus on business development.

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A further benefit of centralized data management is that it allows for more efficient organization of resources, as exemplified by Examen's use of software to manage the liquid nitrogen canisters employed to transfer sperm samples to the laboratory. By tracking the calibration of these canisters digitally, rather than relying on established pen-and-paper methods, the risk of an error that could lead to a sample becoming unusable has been minimized.

Supporting data integrity and regulatory compliance

Examen sought to achieve the highest standards of data integrity, in accordance with ISO 9001 quality management requirements, prompting a switch from manual processing to a cloud-based laboratory informatics solution. By automating processes and eliminating manual data transfer steps, the potential for human error has been greatly reduced. Moreover, the implementation of a single centralized solution has allowed all user interactions with the system to be securely logged and easily searched, demonstrating compliance with ISO 9001 guidelines through a reliable audit trail.

As just one example of Examen's efficiency gains, direct connection of the cloud-based laboratory informatics solution to the company's microscopes has allowed raw data to be collected and parsed into a report within seconds, with the original measurements securely archived. Not only has this resulted in considerable time savings, it has also eliminated possible transcription errors and streamlined the location of data for audit purposes.

A flexible solution to support future growth

Following the successful implementation of a cloud-based laboratory informatics solution, Examen hopes to further capitalize on the benefits of centralized data storage by digitizing standard operating procedures (SOPs). For instance, by allowing protocols and parameters to be downloaded directly to instrumentation, or operators to be guided through SOPs on tablets, this approach promises to further lessen the potential for error while boosting productivity. To complement this measure, Examen is also considering the introduction of sample barcoding to improve sample traceability.

An additional advantage of centralizing data management is that customer portals can be enhanced in line with a specific business requirement: for example, enabling physicians to be automatically notified of reports as soon as they are ready. Underlying this capability is the flexibility and scalability offered by the cloud-based architecture, which permits rapid expansion of data management workflows without the need for substantial investment in internal IT resources.

Conclusion

Clinical laboratories are under increasing pressure to deliver against demanding turnaround times while maintaining compliance with the latest standards around data integrity. By streamlining data management using a cloud-based laboratory informatics solution, Examen was able to significantly boost operational efficiency and function to ISO 9001 guidelines. This new system will ensure smooth scale-up in line with growing demand for the company's services, enhancing Examen's position as a market leader in male infertility treatment.

Katie Evans, M.S., is a Senior Product Manager for the Digital Science business at **Thermo Fisher Scientific**. During her 22-year tenure, Katie has focused on product management and strategy development of Laboratory Information Management Systems (LIMS) software with an emphasis on the needs of laboratories serving regulated markets. Katie received her Master of Science degree from Exeter University, UK.

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Advances in oncology technology and free light chain testing

By Maureen Zetlmeisl

When we think of advancements in oncology, new and less toxic therapies are what we tend to focus on, for it is these new chemotherapies or drugs that extend and improve patient lives. But laboratory testing also plays a key role in oncology patient management. Without a means to detect biomarkers, pharmaceutical companies would have difficulty proving the efficacy of new drugs. As diagnostic testing improves and becomes more sensitive, pharmaceutical companies can create novel drugs that are more targeted to eliminate "bad" cells, deliver deeper responses than before, reduce toxicity, and extend life. At the same time, clinicians can use these diagnostic tests in patient management to improve diagnosis and monitoring of a patient's disease.

One cancer that has seen a drastic improvement in treatment outcomes over the last two decades is Multiple Myeloma, a cancer of the plasma cells. Patients with Myeloma often present first to their primary care physician with vague symptoms such as unexplained fatigue, bone pain and anemia. An acronym used to remember these non-specific symptoms is CRAB: C - Hypercalcemia, R – Renal involvement, A – Anemia and B- Bone lesions.

Identifying a Multiple Myeloma patient only after the onset of CRAB symptoms essentially means waiting for end-organ damage to take place, which is what produces these symptoms. Twenty years ago, doctors had to make a trade-off: wait for a patient to experience organ damage before treatment or subject the patient earlier to toxic chemotherapy regimens with questionable clinical benefits from early intervention. The advent of new diagnostic tests and techniques such as Free Light assays, flow cytometry and imaging have provided additional and more sensitive methods to measure the efficacy of new drug therapies for Myeloma.

What is Myeloma?

Multiple Myeloma is a malignant disease of plasma cells. The plasma cells reside in our bone marrow and are normally responsible for producing antibodies or immunoglobulins that fight against pathogens that enter our body. Antibody molecules are composed of two identical heavy chains and two identical light chains. There are five types of heavy chains: G, A, M, D and E and two types of light chains: kappa and lambda. As with most cancers, the cell grows and divides at an abnormal rate, creating a mass of cells that originate from one plasma cell. Patients who are diagnosed with Multiple Myeloma have their disease typed, e.g. IgA kappa Multiple Myeloma, or IgG lambda Multiple Myeloma.

Diagnostic testing for Multiple Myeloma

What tests should doctors order when they suspect Myeloma? Up until the beginning of this century, doctors would usually order Serum Protein Electrophoresis (SPE) to detect Myeloma and Immunofixation Electrophoresis (IFE) to type Myeloma. However, these tests are not very sensitive for detecting disease, and about 12 percent of patients with a malignant plasma cell disease are missed when only these two tests are performed.

This is where Free Light assays come in. These assays are very sensitive and specific tests that measure free antibody light chains in serum. Free Light Chain (FLC) serum assays allow performing of Free Light testing with SPE and IFE, which is part of the national and international guidelines for the initial diagnostic workup of Myeloma. This combination of tests increases the clinical sensitivity from 88 percent (for SPE alone) to 100 percent for diagnosing Myeloma.[1]

What are Free Light assays?

The serum Free Light Chain assays are a pair of automated tests that measure the concentration of antibody light chains in serum that are not bound to the heavy chains. The tests are run separately to detect free kappa and free lambda antibody light chains. Two numeric values are obtained, as well as a ratio of kappa/lambda. Each of the three values is important to clinicians.

Healthy plasma cells produce 40 percent more light chains than we need to make intact antibodies, thus even normal individuals have a small concentration of excess free light chains circulating in the bloodstream (i.e. serum). It is the ability to measure antibody free light chain concentrations not only at abnormal levels but also at normal levels that make assays valuable biomarkers for monitoring patients with malignant plasma cell disease. Free Light assays can provide clinicians with an indication of how the cancer is responding to therapy, if it is progressing or if it is in remission.

Evolution of Myeloma testing

Twenty years ago, when a patient was diagnosed with Myeloma the treatment options were so toxic that early detection was not advantageous. When Freelite* assays from Binding Site were FDA cleared in 2001, they were the first tests of their kind with improved sensitivity and specificity that traditional tests did not offer.

In 2009 the International Myeloma Working Group (IMWG) and National Comprehensive Cancer Network (NCCN) updated their guidelines to include serum Free Light Chain testing in the initial diagnostic workup of Myeloma.[2] The IMWG mentioned the assays by Binding Site by name in these guidelines.[3]

In 2014, a further update to the guidelines was made. This time CRAB symptoms were no longer required to make a Myeloma diagnosis if an individual had ≥10 percent clonal plasma cells detected in the bone marrow and at least one Myeloma Defining Event (MDE). An MDE was defined as an involved: uninvolved free light chain ratio ≥00 as defined by a Freelite test; evidence of end-stage organ damage that can be attributed to the underlying plasma cell disorder (i.e. CRAB symptoms); clonal bone marrow plasma cell percentage ≥60 percent; or >1 focal lesions on MRI studies.[4]

Also, with the recent advent of better and less toxic therapies, it became advantageous to pick up Myeloma earlier – before CRAB symptoms.[4] Now with much less toxic treatment options, early detection of Myeloma can improve outcomes of patients.

Today's opportunities for improved patient care

Myeloma can present with non-specific symptoms such as unexplained back or bone pain, anemia, fatigue, or recurring infections, which make it difficult to diagnose early. Patients typically visit their primary care or internal medicine clinicians when they experience such symptoms. Running Free Light assays with SPE and IFE will pick up 100 percent of Myeloma diagnoses,[1] and help ensure that

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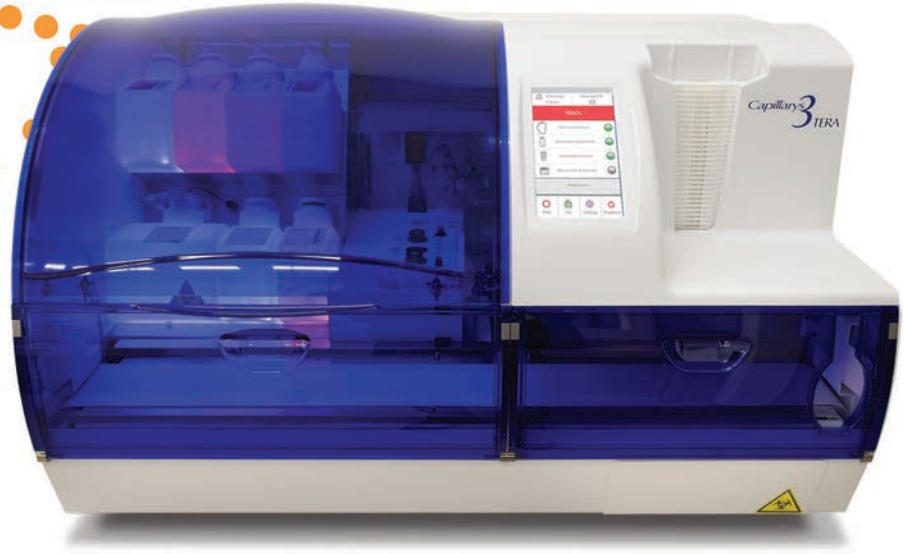

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However, in 2018, Genzen et al. published a study that showed only 6 percent of the initial diagnostic workups for monoclonal gammopathies followed the NCCN guidelines.[5] When the appropriate tests are not run upfront, it can take six months or longer for patients to be diagnosed; by this time, patients are usually experiencing more severe symptoms such as kidney issues or bone fractures. Laboratories can take a leadership role in improving patient care by educating clinicians on which tests to order to be compliant with existing guidelines.

The future of testing for Multiple Myeloma

As Myeloma patients go into deeper remissions from the use of improved therapies, they need to continue to be monitored to ensure that the cancer does not come back. It is important that diagnostic tests with improved sensitivity be available to detect even small levels of minimal residual disease (MRD). As diagnostic testing continues to advance and as new technology becomes available, this depth of response can be measured more accurately.

Binding Site is developing novel tests to improve the identification and accurate measurement of monoclonal proteins using mass spectrometry. The new assay is designed to allow the monitoring of monoclonal proteins with increased sensitivity and to enable clinicians to monitor their patients' depth of response even more closely. It is these types of innovations that will continue to extend patient lives.

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Maureen Zetlmeisl, is the Senior Marketing Manager at **Binding Site, Inc**.

New requirements and technologies improve sepsis management and outcomes

By Mauricio A. Berdugo, MD, MPH

Sepsis is a life-threatening dysregulated host response to infection that may lead to organ failure and even death. Years ago, sepsis was a life or death medical condition and it remains so today, even as advances in patient care and medicine continue to evolve. Faster recognition of the signs and symptoms of sepsis is vitally important to help ensure patients receive treatment as early and as quickly as possible to help improve a patient's odds for survival. As hospitals spend more than $27 billion on sepsis each year in terms of extended length of stay, high readmission rates and antibiotics costs,[1] new requirements and new technologies now available are welcome additions to aid physicians in modernizing and strengthening sepsis best practices.

As sepsis is secondary to preceding conditions like pneumonia, increased vigilance during notable periods such as flu season is warranted. The signs and symptoms of sepsis are very dramatic and can include but are not limited to high fever, lethargy, lack of appetite, extreme fatigue and shortness of breath. For patients, the challenge is to recognize these indications as sepsis symptoms and seek medical attention immediately.

For medical professionals, the challenge is to correctly identify a patient's infection and name it so the proper treatment can begin without delay. It is important for physicians to continue increasing awareness and communicating the telltale warning signs and indications of sepsis among the general population. A persistent fever coupled with extreme lethargy and vomiting should trigger patients and their families to seek medical attention at their nearest Emergency Department facility.

As many as 80 percent of sepsis deaths could be prevented with rapid diagnostics and appropriate treatment.[2] Time is the most critical factor in determining survival, which is why a best practice approach to managing septic patients is essential. Treating patients during the first hour of hypotension onset gives patients the best odds for survival. However, a patient's mortality rate increases for each hour appropriate antimicrobial therapy is delayed.[2] The survival rate with antibiotics at hours five to six post documented hypotension is 42 percent, and plummets to just 25.4 percent at hours nine to 12.[3]

Diagnosis of Suspected Infection

The qSOFA score is a bedside prompt that may identify patients with suspected infection who are at greater risk for a poor outcome outside the intensive care unit (ICU). It uses three criteria, assigning one point for low blood pressure (SBP≤100 mmHg), high respiratory rate (≥22 breaths per min) or altered mentation (Glasgow coma scale<15). With scores ranging from zero to three points, two or more qSOFA points near the onset of infection are not only associated with a greater risk of death or prolonged ICU stay but also with patients who may be septic. This is why the Third International Consensus Definitions for Sepsis recommends qSOFA as a simple prompt to identify infected patients outside the ICU who are likely to be septic.

In addition to qSOFA and a physical examination, the most important aspect of properly and quickly diagnosing sepsis is through the use of diagnostic tests. Blood work, urine tests, white blood cell counts, lactate, C-reactive protein (CRP) and procalcitonin (PCT) tests enable physicians to accurately determine the presence or absence of a bacterial infection. Following these measures with blood cultures, diagnostic testing and imaging allows physicians to identify the microorganism causing the infection and gain a bigger picture of what the patient is experiencing.

When it comes to designing sepsis protocols, physicians have a few successful best practices to reference. In addition to the Surviving Sepsis Campaign treatment bundle, medical professionals can look to the group at the University of Nebraska which adds a procalcitonin-guided protocol to enable physicians to quickly identify if an infection is bacterial or viral, as well as help them quickly deescalate the use of antibiotics.

In February 2017, the FDA cleared the expanded use of the VIDAS B•R•A•H•M•S PCT assay to help healthcare providers determine if antibiotic treatment should be started or stopped in patients with lower respiratory tract infections, such as community-acquired pneumonia, and when to stop antibiotics in patients with sepsis. As a result of FDA's decision, more hospitals are aware of this new technological tool that can be used not only in sepsis protocols but in Antimicrobial Stewardship Programs (ASP) as well to strengthen such initiatives.

ASP and Sepsis Protocols

From a best practice perspective, a sepsis protocol could be seamlessly integrated with an institution's ASP. As CMS has mandated U.S. hospitals to have ASPs in place by March 30, 2020, to meet reimbursement guidelines, ASP committees could examine a sepsis protocol from a multidisciplinary approach. If it makes sense for an institution to do so, aligning the two would be an excellent idea. As ASPs focus on curtailing any overuse or misuse of antimicrobials

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to help curb the spread of antimicrobial-resistant infections, ceasing the use of powerful antimicrobials in a patient with sepsis as soon as possible helps patients experience better outcomes while lowering their risk of resistant infections. PCT testing supports the goals of both sepsis protocols and ASPs by determining if an infection is bacterial or viral, as well as indicating when antimicrobials can be scaled back.

Another technological advancement that may help strengthen hospitals' sepsis protocols is the availability of data analytics tools in healthcare. Data analytics platforms like AGILIST consolidate multiple test results across disparate platforms to give physicians access to rich data in real-time for more informed decision-making. Having a holistic view of infectious disease management through data analytics could allow medical professionals to customize treatment protocols to sepsis patients' individual needs, maximizing the limited time window for sepsis treatment, and it may also allow for physicians to benchmark their own performance in antibiotic use.

Within the past few years, the medical community has been able to identify sepsis much sooner and manage it much faster. This is vitally important as every minute counts with sepsis, because the longer it takes to administer the antibiotic, the harder it becomes to achieve recovery. In septic shock, mortality increases 7 percent for every hour delay in initiation of antibiotics, so early recognition of sepsis and initiation of appropriate antibiotics can improve the chances for survival.[3]

As medical technology continues to advance, it is vital to continuously modernize sepsis protocols. To do so, look at the technology utilized in your institution and compare it to what is newly available, such as diagnostic tests that quicken the determination of sepsis and the underlying infection or data analytics tools that empower physicians with real-time information for more targeted treatment decisions. Incorporate qSOFA score measurements and imaging along with the success protocols of others, such as University of Nebraska's inclusion of procalcitonin-guided therapy. Also establish a multidisciplinary team, similar to an ASP team, comprised of a laboratory director, hospital pharmacist and an ICU physician to best manage sepsis patients' care. Through continuous improvement of sepsis protocols, medical professionals can improve sepsis patients' odds and outcomes.

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RT-PCR usage expands as preferred method of infection detection

By Brenda Silva

Within clinical labs, rapid reverse transcription polymerase chain reaction (RT-PCR) tests have become standard protocol due to their speed and sensitivity in diagnosing cases of infection such as influenza and Strep. More recently, however, the same test features are being relied upon for a different best practice application – detecting cases of global infections, which have seen the tests' usage increase on par with diagnosed patients.

Traditional clinical use

Since its introduction to the clinical lab industry, RT-PCR (also known as qPCR – quantitative polymerase chain reaction) found its place as a reliable and reproducible method of infection detection. Looking at its top applications, John Osiecki, PhD, Director, Medical and Scientific Affairs, Molecular Diagnostics at Roche Diagnostics Corporation, said, "PCR has a diverse array of applications. With the capability of detecting single copies of the genetic signature of pathogens in human samples, it has been a critical tool in clinical diagnostics for infections such as influenza, Group A Streptococcus, Chlamydia and Gonorrhoeae."

He added, "Due to its ability to accurately quantify the presence of pathogens in blood, PCR technology has provided physicians with confidence to manage patients across different therapeutic regimens for chronic infections such as HIV and Hepatitis C, and even alert physicians to rising amounts of Human Cytomegalovirus in patients following transplant."

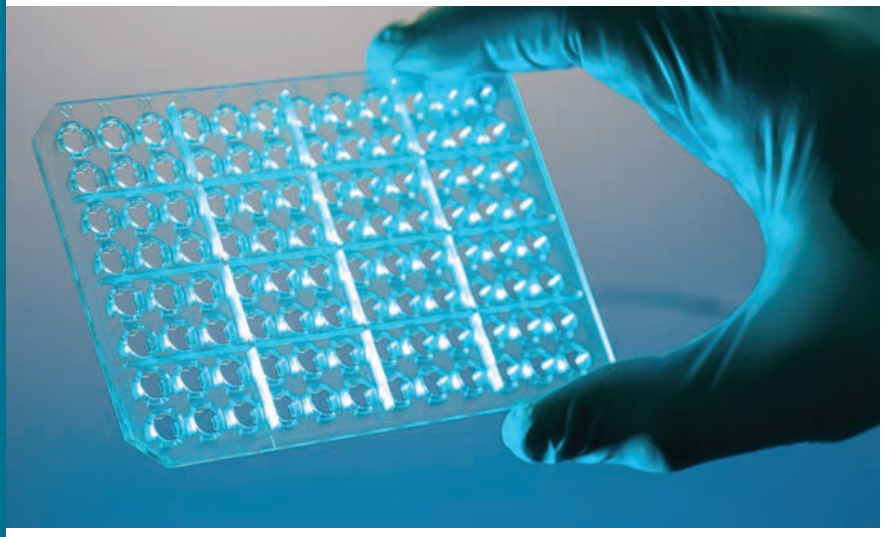
When asked about some of the industry trends in PCR usage, and why it's preferred, Osiecki replied, "PCR is exquisitely sensitive and very specific, which promotes confidence as a 'go to' tool for the laboratory. The industry is shifting toward adoption of PCR protocols with a dual-target approach, allowing a level of redundant coverage by detecting two different genes in a specific bacterium or virus. As these pathogens evolve due to error-prone processing of their own genetic material, or selective pressure from a variety of therapeutic treatments, the PCR diagnostic tools maintain excellent performance."

As the use of RT-PCR increases, market researchers predict an aggressive growth rate. According to research firm MarketsandMarkets, "the global dPCR (digital PCR) and qPCR market is projected to reach USD 6.3 billion by 2024 from USD 4.1 billion in 2019, at a CAGR of 8.8 percent from 2019 to 2024." Cited as the primary driving force for the growth of this market is the "rising incidences of target diseases and genetic disorders, increasing use of biomarker profiling for disease diagnostics and continuous technological advancements in PCR technologies," among other factors.[1]

Best choice options

Looking at the advantages and any apparent limitations of using RT-PCR versus other clinical options, Osiecki pointed out, "Sensitivity, specificity and confidence in reporting are the real strengths of PCR technology. Most applications include internal controls that are processed simultaneously with the target, helping us to know a true sample was present and the process worked as it should."

He continued,"Every method has limitations, and one of the primary concerns in the early days of PCR was the risk of contamination. The process involves amplifying tremendous amounts of target sequence of interest, and open systems could spread this amplicon to the laboratory environment, potentially generating false positives for new samples that were exposed. Design features such as closed systems where the amplification is detected through the wall of a completely sealed reservoir have minimized this risk. Also, the addition of enzymes that selectively degrade any residual amplicon from previous PCR runs, such as uracil N-glycosylase, has been shown to be effective."



A 96-well plate for PCR processing in a microbiology lab

RT-PCR as cost-effective choice

When it comes to fast and accurate infection detection, RT-PCR seems the logical choice for clinicians, but at what cost? MarketsandMarkets points out that "a typical PCR analysis conducted through dPCR instruments involves several scientific technologies (PCR, microfluidics, and nanofabrication) integrated to achieve the desired process outcome. These instruments are small and boast reduced cycle times. However, the development of such instruments requires large capital investments and extensive scientific validation on a nanoscale level."[1]

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Adding to the capital investment is that because "dPCR is a relatively new technology; as a result, most manufacturers often price their state-of-art dPCR instruments at a premium (~USD 120,000) compared to qPCR instruments (~USD 50,000). For instance, as of January 2016, the average price of a dPCR instrument is reported to be USD 55,000–120,000, according to their device architecture and target application area in the U.S."[1]

But for people like Osiecki, the benefits far outweigh any associated costs of using RT-PCR tests. "Traditionally, bacterial and viral culture for identification of pathogens was labor intensive and could take days. PCR technology has improved the turnaround time dramatically, and newer applications include fully automated sample processing, amplification and detection. Taken together, PCR applications can improve lab efficiency by allowing our highly skilled laboratory professionals to focus on other tasks," he said.

When considering the actual cost of RT-PCR tests, a simple internet search shows figures as low as $15-25 per test to amounts in the hundreds for more detailed and extensive tests. However, these amounts are often overlooked when compared with the higher costs associated with tests that are not as fast or reliable, do not offer early detection and have the patient suffer much longer than necessary.

Future usage grows

Looking to the future of RT-PCR clinical lab usage as additional options for DNA/RNA analyses become available, Osiecki said, "There are many new applications for PCR technology that will benefit the clinical community in the years to come. For example, new diagnostic tests are being developed for applications in transplant for monitoring the presence of EBV and BK Viruses, where FDA-approved solutions were not available in the past."

He added, "New systems are being introduced that provide laboratory-quality results with PCR technology in 20 minutes or less with a point-of-care (POC) device. Digital PCR, a method that captures nucleic acids and separates them into tiny wells for individual PCR reactions, can provide unprecedented accuracy in absolute quantification, monitoring of cancer by evaluating liquid biopsies, and rare mutation detection of one in 200,000 of wild type background."

According to forecasted statistics from MarketsandMarkets, North America is expected to account for a large amount of RT-PCR growth during the 2019-2024 time period. In addition, a recent global event has created the need for a significant increase in RT-PCR test usage in Asia-Pacific countries, unfortunately.[1]

Global best practices

While the clinical lab industry has busied itself with infection detection within the lab environment, another best practice use for RT-PCR testing was created when a new virus emerged in Wuhan, China, in December 2019. The novel coronavirus, referred to as 2019-nCoV, has demonstrated the efficiency and efficacy of using RT-PCR testing by way of thousands of suspected cases of the deadly virus.

When 2019-nCoV emerged, scientists at the U.S. Centers for Disease Control and Prevention (CDC) studied the virus and its common characteristics with the former SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) outbreaks, which are in the same virus family as the new 2019-nCoV coronavirus. The CDC was quick to develop its own RT-PCR test that offered the speed, sensitivity, reproducibility and reduced risk of contamination they were looking for as they faced a global concern that was expanding every day with more confirmed cases and deaths.

The CDC test was initially designed for use at the CDC only. Patient specimens from suspected cases of 2019-nCoV were to be sent to them for analysis and infection confirmation results while the patient in question was detained in quarantine with others awaiting their own results. But as the new virus spread to almost 30 additional countries with over 40,000 confirmed cases and approximately 1,000 deaths* (*figures as of 2-11-20), the demand for patient results became too much for the CDC to process alone.

Because of the growing amount of suspected cases that needed review, the U.S Food and Drug Administration (FDA) "issued an emergency use authorization (EUA) to enable emergency use of the Centers for Disease Control and Prevention's (CDC) 2019-nCoV Real-Time RT-PCR Diagnostic Panel. Initially, this test was limited to use at CDC laboratories, but the EUA now allows the use of the test at any CDC-qualified lab across the country."

With additional results-processing assistance throughout the country, the CDC – along with other agencies such as the FDA and the World Health Organization (WHO) – can focus on creating a vaccine and/or solution to slow down the rate of infection of the virus. With no cure available now, over 20 diagnostics companies have opted to create tests, many of them PCR-based, designed to identify virus exposure and infection in the future.

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Governments, diagnostic companies and providers respond to coronavirus outbreak

By Linda Wilson

As the number of novel coronavirus cases continually increase throughout the world, laboratorians and hospitals need to ensure they are prepared to diagnose and treat infected patients.

When Chinese officials first released information about the 2019 novel coronavirus (2019-nCoV) on December 31, 2019, they described the illness as pneumonia with an unknown cause.

Just one week later, on January 7, 2020, Chinese officials identified a new coronavirus, sharing the genetic sequence publicly on January 12.

Despite relatively quick scientific legwork and discovery, the disease has spread rapidly throughout China, leading to a lockdown of at least 50 cities. Other countries have followed suit with travel restrictions, quarantines and other containment measures.

In late January, the World Health Organization (WHO) declared a public health emergency of international concern, designed to help countries coordinate resources, contain the spread of the disease, and minimize the impact on travel and the global economy.

Like MERS (Middle East respiratory syndrome) and SARS (severe acute respiratory syndrome), the virus is a betacoronavirus, which primarily originates in bats, according to the Centers for Disease Control and Prevention (CDC). "The sequences from U.S. patients are similar to the one that China initially posted, suggesting a likely single, recent emergence of this virus from an animal reservoir," CDC officials posted on the agency's website.

Government agencies have responded by updating procedures for handling and testing potentially infectious specimens, while researchers and diagnostics companies have begun to develop tests and vaccines.

Meanwhile, laboratorians and hospital executives around the country brace themselves for the possibility that an infected patient will walk into their facility. To help them prepare, *Medical Laboratory Observer (MLO)* gathered pertinent information in this special report.

CDC Test Kits

In early February, the Food and Drug Administration (FDA) approved an Emergency Use Authorization (EUA) filed by the CDC for a real-time reverse transcriptase polymerase chain reaction test—the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel.

The Emergency Use Authorization expedites the usual regulatory process for the use of potentially life-saving medical or diagnostic products during a public health emergency. In this case, the FDA's approval means that any CDC-qualified lab that is certified to perform high complexity tests can use the CDC's diagnostic panel, the FDA said in an announcement.

The test detects the coronavirus from respiratory secretions, such as nasal or oral swabs. However, "negative results do not preclude 2019-nCoV infection and should not be used as the sole basis for treatment or other patient management decisions. Negative results must be combined with clinical observations, patient history and epidemiological information," the FDA said in a statement announcing the decision to approve the CDC's test.

"This will greatly enhance our national capacity to test for this virus," National Center for Immunization and Respiratory Diseases (NCIRD) Director Nancy Messonnier said during a press briefing in February. "In preparation for that approval, CDC has shipped the test to the International Reagent Resource, so that states and international partners can begin ordering the test for their use."

The FDA is encouraging commercial enterprises to also use its Emergency Use Authorization process to shepherd any diagnostic tests they develop through the regulatory process.

Several organizations have already announced plans to develop tests.

One of those is altona Diagnostics, based in Hamburg, Germany, which is developing a molecular diagnostic assay for the detection of the new coronavirus by collaborating with major reference institutes for emerging diseases. The real-time RT-PCR-based assay will be designed for the qualitative detection of 2019-nCoV specific RNA in respiratory samples.

Co-Diagnostics, based in Salt Lake City, UT, is also developing a PCR screening test for the new coronavirus.

Meanwhile, IDbyDNA, based in San Francisco, CA, has announced that its Explify Respiratory test, a currently available laboratory developed test (LDT), can detect 2019-nCoV.

Since the publication of the 2019-nCoV genome, IDbyDNA's Salt Lake City lab has analyzed in-silico generated samples and validated computationally that Explify Respiratory test can detect the novel coronavirus, the company said in a news release.

In the meantime, Chinese laboratories are using existing products—such as mixes and enzymes from Meridian Bioscience in Nashville, TN—in molecular assays to diagnose infected patients.

During an earnings call in January, Roche said it developed tests for diagnosing the coronavirus for use by researchers, according to Kalorama Information, an Arlington, VA-based market research firm specializing in biotechnology, diagnostics, medical devices and pharmaceuticals.

CDC sample-collection procedures

The CDC has posted guidelines on its website about how labs should collect, handle and test specimens from people who might be infected with the novel coronavirus.

Generally, the CDC is "testing respiratory samples, but we are also testing blood, and we are currently working to expand the kind of diagnostics we can do, but the focus right now with the real-time PCR is respiratory specimens and sometimes blood," Messonnier said at a press conference.

The CDC recommends collecting and testing multiple specimens from different sites, including both lower respiratory and upper respiratory tracts.

CDC officials want healthcare providers to notify their local or state health department about patients with fever and lower respiratory illness who might be infected with the novel coronavirus. Public health staff will then decide if patients meet the criteria for a patient under investigation (PUI) and coordinate work with the CDC's Emergency Operations Center.

The CDC, which also has posted safety guidelines for handling specimens, says laboratory workers should wear personal protective equipment when handling potentially infectious specimens. The agency also says that any procedure with the potential to generate fine-particulate aerosols be performed in an enclosed and ventilated laboratory space, or class II biological safety cabinet, using physical containment devices.

Supply Chain Issues

Another concern for laboratory and hospital officials is access to the supplies they need to test and treat infected patients while also protecting employees.

Concerns about potential shortages of key supplies are driven, in part, by several recent developments.

The first issue is Cardinal Health's recent recall of more than 9 million Level 3 gowns, which are used during surgical procedures or to provide barrier protection.

Cardinal Health decided to initiate the recall after learning in December 2019 that one of its FDA-approved suppliers in China, Siyang Holymed, had shifted production of some gowns to unapproved sites, with uncontrolled environments, meaning that Cardinal Health could not be sure that the gowns are sterile. Since then, Cardinal Health has terminated its relationship with Siyang Holymed.

To help bridge the supply gap, Cardinal Health is increasing production of similar products, sourcing alternative suppliers of gowns for its customers, and offering customers protective Level 4 gowns.

Cardinal Health is certainly not the only organization manufacturing medical products in China. As the outbreak spreads and China places more locations into lockdown, disruptions to the global medical supply chain are becoming increasingly worrisome.

Resilinc, a vendor of supply chain risk and resiliency software, believes there is a high risk of disruptions to the supply chain, based on global containment measures. Bindiya Vakil, founder and CEO of Resilinc, noted during a webinar presentation that businesses should expect supply chain disruptions for three to six months.

To help head off potential shortages of personal protective equipment, the World Health Organization (WHO) in January launched a private-public collaboration called "The Pandemic Supply Chain Network," which is an effort to gather information about market capacity and risk assessment. It had hoped to complete the assessment by February.

Wuhan, the epicenter of the outbreak, is a manufacturing hub in China, including production of biotechnology products and the active ingredients, or APIs, used in pharmaceuticals, according to Resilinc. The city also is home to China's largest inland port, which handles ocean-going ships, Resilinc adds.

Given the potential for supply chain issues, the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response has been "assessing the level of preparedness" of pharmaceuticals and medical supplies within the Strategic National Stockpile, which can be used in the diagnosis and treatment of people infected with the novel coronavirus, HHS Secretary Alex Azar said in a news briefing in January.

Vakil recommends that organizations develop supply-chain preparedness plans based on likely scenarios, set clear triggers for action, and communicate information widely. The planning process also should include collaborating with suppliers, she added.

In a statement, Roche said it donated diagnostic tests, medical supplies and financial resources to the government, local health officials and hospitals in the Hubei Province.

Treatments and Vaccines

The WHO launched a clinical database platform, allowing countries to contribute clinical data in a standardized way, so global officials have the information they need to develop medical treatment protocols and public health measures.

As there is currently no known effective antiviral therapy for the novel coronavirus, the WHO also is conducting a systematic review of potential therapeutics and developing master clinical protocols to speed development of treatments globally.

For its part, the CDC uploaded the entire genome of the virus from the first and second cases reported in the United States in January.

The CDC also has isolated the cells in cultures and sent them to the National Institutes of Health (NIH) BEI Resources Repository, which is a NIH resource that supplies organisms and reagents to microbiology and infectious disease researchers.

The next steps will be the development of monoclonal antibody–based therapies for treating the virus and a Phase 1 clinical trial of a potential vaccine, National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony Fauci said at a press conference in January.

Working toward the goal of developing therapies, the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) expanded an existing collaboration with Regeneron Pharmaceuticals, Tarrytown, NY.

The Biomedical Advanced Research and Development Authority within ASPR and Regeneron plan to develop multiple monoclonal antibodies that, individually or in combination, could be used to treat the coronavirus, HHS said in a press release.

Fauci also said that China was currently using both the antiviral remdesivir and the antiretroviral drug Kaletra (lopinavir and ritonavir) on a compassionate basis on some coronavirus patients. Both treatments, used against Ebola and HIV, respectively, are unproven against the novel coronavirus.

	Novel Coronavirus	SARS	MERS
Year(s)	12-2019 to 2-2020	2003	2012 to 2019
Total Cases	43,000+	8,403	2,494
Total Deaths	1.000+	774	858
Number of Countries	27	29	27
Epicenter	Wuhan, China	Hanoi, Vietnam	Saudi Arabia

Sources: Johns Hopkins University, World Health Organization

Meanwhile, commercial diagnostic companies and academic researchers have begun developing potential vaccines and treatments.

For example, Purdue University scientists Andrew Mesecar, Purdue's Walther Professor in Cancer Structural Biology and head of the Department of Biochemistry, and Arun Ghosh, the Ian P. Rothwell Distinguished Professor of Chemistry, have been working to develop both oral medicines and vaccines to fight coronavirus. The molecules Mesecar and Ghosh have developed block two of the coronavirus enzymes (proteases), stopping the coronavirus from replicating.

Johnson & Johnson also has begun development of a vaccine for the novel coronavirus through its subsidiary, Janssen Pharmaceutical Companies, according to a press release.

The Coalition for Epidemic Preparedness Innovations (CEPI), based in Oslo, Norway, says it plans to coordinate the development of potential vaccines against the novel coronavirus. CEPI will coordinate vaccine development through partnerships with Inovio, based in Plymouth Meeting, PA; the University of Queensland in Brisbane, Australia; Moderna, based in Cambridge, MA; and the National Institute of Allergy and Infectious Diseases.

CEPI, a partnership between public, private, philanthropic, and civil organizations, was founded in 2017 to develop vaccines against diseases such as novel coronavirus, Ebola, MARS, and others.

However, the coronavirus vaccines may not be developed quickly enough to help curtail the current spread of disease.

For example, Vas Narasimhan, CEO of Novartis, told CNBC in a recent interview that he expects development of a vaccine to take more than a year.

And as NIAID's Fauci noted at a press conference, the U.S. never launched a Phase 2 trial with a vaccine for SARS because the outbreak dissipated before that step became necessary.

Nonetheless, Fauci said the United States is "proceeding as if we will have to deploy a vaccine" for the novel coronavirus.

Molecular Testing of Lung Cancers - A Summary of What, Why and How

By John Brunstein, PhD

Worldwide, lung cancers represent the single most common cancer type in men and third most common in women with age standardized incidence rates in 2018 as high as 0.078 percent (Hungarian males).[1,2] It's a heterogenous catchall term, with the primary stratification from both histological and behavioral considerations being between small cell lung cancer (SLLC; primarily smoking associated) and non-small-cell lung cancer (NSCLC). NSCLCs are the more common group at roughly 80 percent of presentations, of which most can be immediately further stratified into adenocarcinomas, large cell carcinomas, and squamous cell carcinomas.

Among these three NSCLC subclasses, a relatively small pool of genetic mutations including point mutations, indels, rearrangements and copy number variations are associated or mechanistically contributing (even foundational) to the cancer at high frequency. Where these mutations impact key specific cellular pathways to induce cancer (so called "driver mutations"), there can be opportunities for narrowly targeted, specific drug therapies. Compared to generic broad-spectrum antineoplastic agents, which tend to target all rapidly dividing cell populations with inherent side effects, these targeted therapies can be highly effective and target selective – but only when they are correctly matched to a cancer. Use in the wrong context is ineffectual, economically unwise (expensive therapy without benefit), and worst of all, might displace timely application of a more effective therapy. For these reasons, molecular testing of lung cancers is standard of care and key to improving medical outcomes through appropriate treatment selection.

Such testing begins with collection of test sample, an action which can influence what molecular test modalities are applicable. For primary tumor biopsy samples with histologically identifiable high preponderance (>50 percent) of cancer cells, direct whole genome sequencing by next-generation sequencing (NGS) is the most informative (and the most costly, and time consuming) approach – but with no inherent expectation bias, it can provide information on both known mutations and novel ones of potential relevance. For samples with smaller fraction of cancer cells – down to about 1 percent in practical terms – an alternate approach is direct real-time PCR with allele specific primers for particular known mutations; this is rapid, sensitive, and inexpensive to perform but can only look for what it's designed to find.

In between these extremes falls an "NGS panel" approach where PCR amplification of key pathway genes where relevant mutations are known, followed by sequencing; while this only examines preselected gene regions, it can find novel mutations. In the case of novel mutations – either here or in the whole genome context – relevance must of course be demonstrated, although in the case of some types of mutations such as gene fusions, significant indels, or nonsense mutations, a high probability of causal relevance to the cancer may be immediately apparent.

Practical sample types

Almost any sample type as available – fresh, frozen, or formalin-fixed paraffin-embedded (FFPE) (best if it's prepared with downstream molecular testing in mind, meaning not overfixed) – obtained by needle aspirate, bronchial wash or (insert your method of choice) – can be suitable for at least one form of the testing overviewed here, although note the caveat above about minimal tumor cell content for direct sequencing approaches.

Sampling and analysis of metastatic sites can be useful as well, although this assumes that oncogenic mutations developed early in progression and are thus common to all tumor sites; not necessarily true but observational data suggests in this context it's often a valid assumption. One class of sample which current publications do not suggest are great here is circulating tumor cells (CTCs). While these show promise in some oncology contexts and may be relevant in lung cancer where positive results (tumor cells and associated data are detected), high false negative results have been noted and more direct tissue biopsy is preferable.[3]

Gene Examples

Before we proceed let's provide some examples of genes, mutation targets and associated targeted therapies considered in lung cancer cases (see Table 1). It should be stressed this is an incomplete list, highlighting only some common mutations and therapy implications for illustrative purposes; factors out of scope for this brief article come into play in deciding best therapies in actual cases.

Application of data

While incomplete, we can see from Table 1 how molecular knowledge of a lung cancer can be applied to making informed therapy decisions. If a sample is detected as having known activating mutations in EGFR but not having the T790M mutation, then something like Gefitinib might be a good choice (again, also influenced on factors beyond our scope). If, however, the T790M mutation was simultaneously present, we'd already know Gefitinib would not work and Osimertinib would be our best choice. If instead our tumor was detected as having a rearrangement in ROS1 but unmutated in ALK, EGFR or KRAS, then neither Gefitinib nor Osimertinib would be likely of much benefit and we'd want to use something from the Crizotinib, Ceritinib, Lorlatinib, Entrectinib list.

All three of these cases could occur in something correctly identified as an NSCLC adenocarcinoma by

Gene	Mutation / comments	Therapy implications
EGFR (Epidermal growth factor receptor)	Activating mutations in this gene observed in nearly half of NSCLC adenocarcinoma Frequent: Deletion Exon 19; L858R missense	Responsive to Osimertinib, Erlotinib, Afatinib, Gefitinib, Dacomitinib
	Above, plus T790M missense	Not responsive to Erlotinib, Afatinib, Gefitinib, Dacomitinib Responsive to Osimertinib
ALK (anaplastic lymphoma kinase)	Gene rearrangements found in ~5 percent NSCLC, primarily adenocarcinoma subtype	Responsive to Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib
ROS1 (c-ros)	Rearranged in 1-2 percent NSCLC, primarily in adenocarcinoma cases without ALK, EGFR, or KRAS mutations.	Responsive to Crizotinib, Ceritinib, Lorlatinib, Entrectinib
BRAF (b-raf)	Involved in up to ~4 percent adenocarcinoma NSCLC. Multiple known activating mutations, most commonly V600E. Activated BRAF activates MEK	BRAF V600E directly responsive to Dabrafenib, Vemurafenib MEK inhibited by Trametinib
MET	Exon 14 skipping present in 3-4 percent NSCLC adenocarcinoma	Responsive to Crizotinib
HER-2	Involved in 1-2 percent NSCLC adenocarcinoma; most commonly exon 20 in-frame insertion	Responsive to Trastuzumab, Afatinib

Table 1: Selected examples of gene targets, associated mutations and therapeutic implications in lung cancers.

classical pathology examination. Add in the possibility BRAF, MET, or HER-2 mutations could also be involved, each with their own best drug strategies, and the impracticality of trying to select best matched therapy by some trial and error process with its inherent cost, time and attendant disease progression before the correct match is made provide the compelling argument for molecular testing in this context.

Possible future evolution?

The utility of molecular testing in this context has been driven by the relatively small number of specific known mutations, and the pairing of these to tailored therapeutic agents. In turn, small numbers of defined targets lend themselves well to rapid, relatively low cost and complexity test modalities like allele specific PCR. As the number of gene targets and the number of known mutations per target with significance for therapeutic decision-making both increase these single target tests will become less practical. A simultaneous ongoing decrease in cost, size, and complexity of use for NGS methods is occurring.

The conclusion would seem that NGS panels combining the ability to be amplification based (that is, requiring low content both numerically and in percentage) of cancer cells in sample, plus the ability to identify both known and novel alterations in key genes of relevance, will be the method of choice for balancing cost versus completeness of data in this application. For cases where this approach does not prove fruitful, a costlier direct sequencing approach utilizing a sample enriched in tumor cells would be a second line.

Information on novel driver mutations uncovered either way may still direct therapy choices based on knowledge of signalling pathways. Consider for example Table 1, and the hypothetical detection of a suspected causal mutation in BRAF causing not just pathway activation but leaving the mutant BRAF unresponsive to agents directly binding the altered protein. Knowing BRAF signals on through MEK would suggest that Trametinib to block or reduce MEK signalling would be a likely successful intervention.

Finally, these methods – regardless of exact sample and technical approach used – will all improve over time as more and more less common significant mutations are detected, cataloged and their significance with regard to therapy choices and outcomes are known. Less Variants of Unknown Significance – VUS – mean faster, better interpretation of patient data.

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John Brunstein, PhD, serves as an Editorial Advisory Board member for MLO. John is also President and CEO for British Columbia-based **PathoID, Inc.**, which provides consulting for development and validation of molecular assays.

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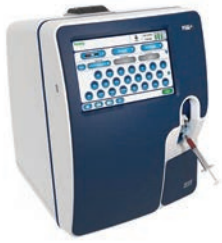

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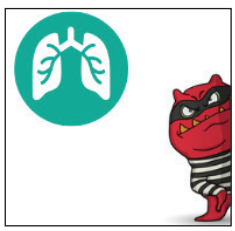

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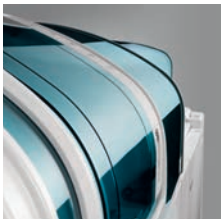

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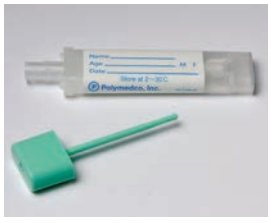

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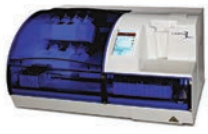

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LABORATORY INNOVATOR

Tim Bickley on developing a clear vision of clinical data

Tim Bickley is Vice President of Sales at Visiun. Tim has held roles as Administrative Laboratory Director, QA/QC Section Chief, and Regional Sales Manager and Strategic Account Executive for major LIS and laboratory diagnostic suppliers.

You are a certified MT (ASCP) and (CPHIMS) Certified Professional in Health Information and Management Systems, with a long history in Clinical and LIS systems and operations. How did that experience transition into your current role that shows labs how they can connect their operations with clinical IT tools?

At my first job out of MLT School, I worked the midnight shift, mostly by myself. After one year, I entered the MCV/VCU Medical Technology program and obtained my BS in Medical Technology in 1988. I worked many years as a bench tech and supervisor, and later held management roles in the lab. When LIS's were first introduced, I immediately took an interest in its features and benefits for the lab. I had an opportunity to join a leading "Best of Breed" LIS vendor in 1996, and learned how the LIS works with instruments and connectivity to the EMR and other systems. With the advancements of automation and IT, including lab analytics software, lab managers are being asked to produce data constantly and getting to that data is usually a challenge. Lab analytics can help identify trends and show areas in the lab that need attention. Ultimately, I was asked to head up sales at a leading laboratory analytics company, Visiun, and joined in 2014. We are a medical technology-led company, our CEO is a Med Tech, I'm a Med Tech, and all our support and implementation team members are Medical Technologists. I believe our combined years of lab experience and our analytics software provide leadership with the answers needed for today and for the future.

At the MLO Laboratory Leadership Summit in December 2019, you spoke about the importance of improving quality, efficiency and test utilization. What have been some of the biggest changes you've seen in being able to gather and use that information?

We've seen lab reimbursements decline, and there is a shift away from fee-for-service. This led to increased emphasis on the quality and value of the services provided by clinical labs. With fixed reimbursement models no longer compensating for additional hospital clinical lab testing, and increased patient length of stays due to additional lab testing, we've seen test utilization become one of the greatest opportunities for health systems to cut costs while improving patient outcomes. When the lab works with physicians to eliminate unnecessary tests or duplicate test orders, the cost savings are immediate. We have seen hospital labs save an average of $230k/year (based on a hospital performing one million billable laboratory tests) after installing our software.

What are the advantages of linking LIS with EMR and are there any IT-related advances on the horizon in the lab that are forecast to become the next trend or asset to the healthcare industry?

There are certainly advantages to linking EMR data and LIS. In terms of forecast trends and assets, I think Artificial Intelligence (AI) and Machine Learning (ML) will have greater roles to play in the lab. Predictive analytics for workload is a huge opportunity and when this is accomplished, we'll see improvements in turnaround times (TATs), patient satisfaction, time savings, etc.

At the Summit, you addressed the value of being able to compare your lab results to other lab peer groups that give visibility into turnaround times for various tests. Why is that so important?

We have seen significant improvements in performance and reduction in outliers, both in-lab and pre-lab, when labs are able to compare their performance to that of peer groups. When key performance indicators reveal areas that are underperforming in comparison to a peer group of similar institution type, lab type, or test volume, lab managers can make the changes needed to lead their teams towards those levels of best practice. External peer comparison is also extremely important as long as the peer group is significant, large in number, and matches your scope of operations. With external peer comparisons, you can quickly identify areas in the lab where you should focus on improving and whether you are underperforming or overperforming in comparison to your peer.

What are the biggest challenges currently faced by labs, and what tools are available to help?

There are several issues lab management must tackle daily from requests for data, to staffing or maintaining a competitive edge as a lab service. Lab managers are being pressured to reduce costs, trim budgets and document any savings they can find, and analytics can help the lab manager see areas where they can improve service and productivity. Another area that I hear frequently is staffing issues. By automating lab analytic report generation and analysis, you free up time for managers who previously compiled reports manually. Lab analytics should touch on every area important to the lab manager.

Currently, Visiun connects real-time test results with LIS. One of the greatest challenges across all healthcare IT is achieving interoperable systems that actually store and provide patient data in a way that is beneficial to patient care.

With lab analytics you can add so much value and do things like manage your lab quality, help physicians with lab stewardship and guide them to order the correct tests, and focus on risk management and population health with care gap analyses. The result we're seeing is that analytics are empowering the lab to become a hospital-wide partner and asset, while improving patient safety and satisfaction.

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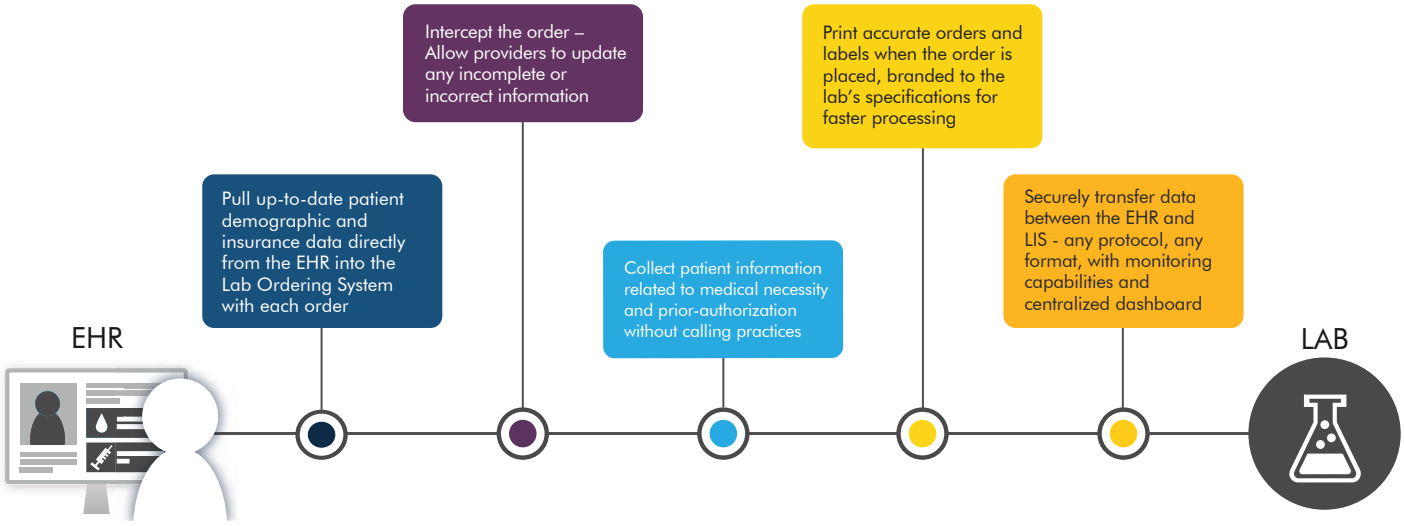

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  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*
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