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AUGUST 2020 ▪ Vol 52 ▪ No 8

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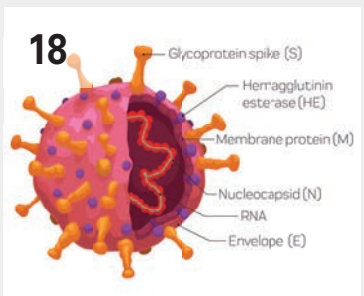

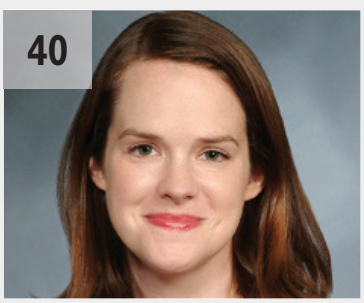

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Pooled testing may conserve costs and supplies

By Brenda Silva
Senior Editor

In an effort to reduce the time and costs associated with individual COVID-19 tests, as well as meet increased test demands, governmental agencies are looking into additional testing options that can provide more results and less cost at the same time. Currently, pooled testing, also called herd testing, is the test method being considered as one of the most promising options to detect exposure to COVID-19, which is caused by the SARS-CoV-2 virus strain. As one of the primary benefits of pooled/herd testing, scientists have the ability to test small groups of people at one time, versus being forced to test each individual person in a specific and/or suspected group that may have been exposed to COVID-19.

Another advantage of pooled testing lies in its convenience factor as it allows for multiple samples to be mixed together and run as one test. For example, if scientists need to test 100 people, they can divide the total into two much smaller groups of 50 and then have each groups' included members contribute samples. If the final amalgamated test result comes back negative, then all the people who contributed samples to that test run are assumed to have a negative result as well – which could effectively rule 50 people negative for exposure to COVID-19 at once.

However, if the combined sample evidences a positive result, then those sample contributors would be tested further to identify the person who may be asymptomatic but still infected with COVID-19. While positive-result pooled testing still requires additional tests, it still offers the option of being able to eliminate the time and costs related to staff and supplies for all the people who will not need to be retested because their samples contributed to the negative-result test run.

On the topic of pooled testing, Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases (NIAID), said "health officials are considering pooled testing for COVID-19 in response to the recent surge (of U.S. cases)." He said pooled testing may not be the best or most cost-effective testing option in every situation, as pooled testing works best with smaller groups that need testing. But as larger numbers of people will require a larger number of groups, this may create larger numbers of positive results and the potential for more people who need additional testing. All of this testing would defeat the time saving and cost-effectiveness of pooled testing as it is intended.

With millions of COVID-19 tests performed and cases diagnosed, at times it can still prove challenging to find a consensus of opinion on the best way to address best practice testing for the disease. There is no easy answer except to perform more testing, which includes existing testing methods that are used as strategic surveillance tools, as well as whatever testing options the clinical lab industry comes up with next to meet continued demand. Its only through accurate and reliable testing that we afford ourselves a better chance to get better prepared for the arrival of the next pandemic.

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

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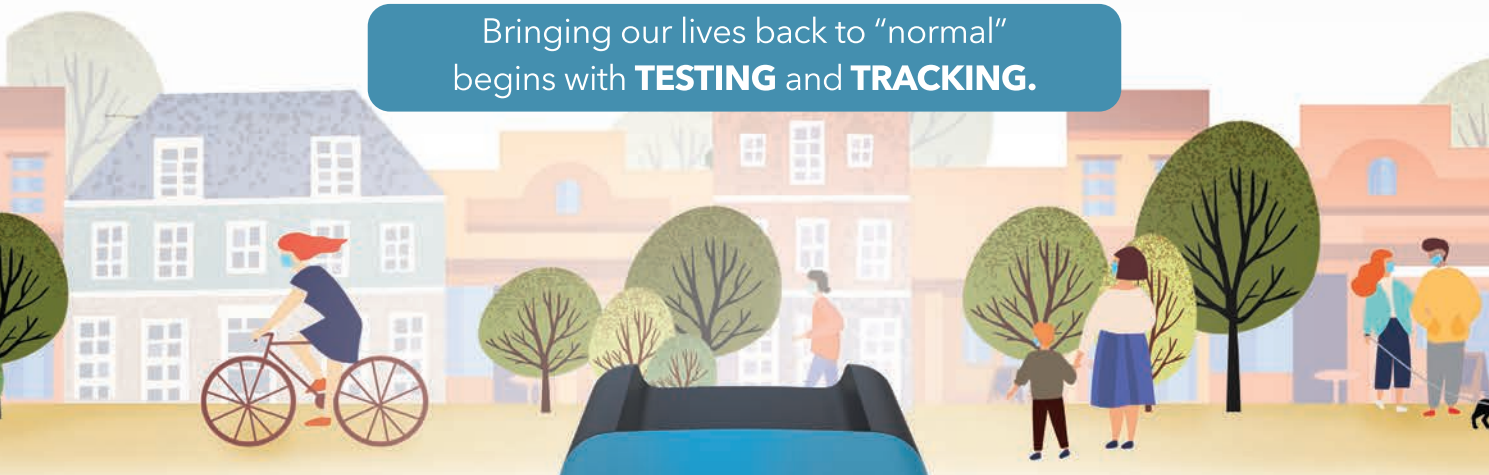

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Fast Facts COVID-19 Timeline

SARS-CoV-2 continues to spread throughout the world, causing disease, severe illness, and death, while exhausting the healthcare personnel who are scrambling to care for patients. The World Health Organization (WHO) posted a timeline of key dates, including those included here.

January 9, 2020

Chinese officials determine that a cluster of pneumonia cases are caused by a novel coronavirus.

January 20-21, 2020

WHO conducts first mission to China. U.S. reports its first case of the novel coronavirus.

February 11, 2020

The WHO announces that the disease caused by the novel coronavirus would be named COVID-19.

March 11, 2020

The WHO officially characterizes the COVID-19 outbreak as a pandemic.

March 21, 2020

The WHO publishes laboratory testing strategy recommendations for COVID-19.

May 15, 2020

WHO released a Scientific Brief on multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.

June 17, 2020

The WHO announces that the hydroxychloroquine arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped.

July 5, 2020

The WHO discontinues a clinical trial of hydroxychloroquine and lopinavir/ritonavir.

Sources:

- https://www.who.int/news-room/detail/29-06-2020-covidtimeline
- https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200705-covid-19-sitrep-167.pdf?sfvrsn=17e7e3df_4

Genes and blood type tied to risk of severe COVID-19

A recent genome-wide association (GWAS) study, published in the *New England Journal of Medicine (NEJM)*, finds that gene variants in two regions of the human genome are associated with severe COVID-19 and correspondingly carry a greater risk of COVID-19-related death.

The two stretches of DNA implicated as harboring risks for severe COVID-19 are known to carry some intriguing genes, including one that determines blood type and others that play various roles in the immune system. In fact, the findings suggest that people with blood type A face a 50 percent greater risk of needing oxygen support or a ventilator should they become infected with the novel coronavirus. In contrast, people with blood type O appear to have about a 50 percent reduced risk of severe COVID-19.

These new findings – the first to identify statistically significant susceptibility genes for the severity of COVID-19 – come from a large research effort led by Andre Franke, a scientist at Christian-Albrecht-University, Kiel, Germany, along with Tom Karlsen, Oslo University Hospital Rikshospitalet, Norway. Their study included 1,980 people undergoing treatment for severe COVID-19 and respiratory failure at seven medical centers in Italy and Spain.

In search of gene variants that might play a role in the severe illness, the team analyzed patient genome data for more than 8.5 million so-called single-nucleotide polymorphisms, or SNPs. The vast majority of these single "letter" nucleotide substitutions found all across the genome are of no health significance, but they can help to pinpoint the locations of gene variants that turn up more often in association with particular traits or conditions – in this case, COVID-19-related respiratory failure. To find them, the researchers compared SNPs in people with severe COVID-19 to those in more than 1,200 healthy blood donors from the same population groups.

The analysis identified two places that turned up significantly more often in the individuals with severe COVID-19 than in the healthy people. One of them is found on chromosome 3 and covers a cluster of six genes with potentially relevant functions. For instance, this portion of the genome encodes a transporter protein known to interact with angiotensin converting enzyme 2 (ACE2), the surface receptor that allows SARS-CoV-2, to bind to and infect human cells. It also encodes a collection of chemokine receptors, which play a role in the immune response in the airways of our lungs.

The other association signal popped up on chromosome 9, right over the area of the genome that determines blood type. The researchers did find evidence suggesting a relationship between blood type and COVID-19 risk. They noted that this area also includes a genetic variant associated with increased levels of interleukin-6, which plays a role in inflammation and may have implications for COVID-19 as well.

NIH group weighs role of human challenge studies for SARS-CoV-2 vaccine development

Large, randomized, controlled trials are the fastest and most effective way to establish the safety and efficacy of SARS-CoV-2 vaccine candidates. However, parallel development of controlled human infection models (CHIMS) may provide complementary tools to address additional questions, such as the duration of immunity and correlates of protection, if such studies can be conducted ethically, concluded a working group of the National Institutes of Health (NIH).

In a perspective for the *New England Journal of Medicin*e, members of the NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Working Group assess practical considerations and prerequisites for using controlled human infection models (CHIMs), which can be used for human challenge studies, to support SARS-CoV-2 vaccine development.

In the article, the authors determine that it could take one or two years to develop robust CHIMs that meet the essential criteria for limiting risk for study volunteers.

In a CHIM study, participants are intentionally exposed to an infectious agent to help scientists understand the virus or test interventions to prevent or treat infection. CHIMs use well-characterized microorganisms that either do not cause serious disease, are easily treated, or both. In addition, CHIM studies must take place in laboratories with rigorous isolation to ensure that the infection does not spread into the community.

The authors note that ethical evaluation of the risk to participants and the potential value to society are essential to future considerations of whether to conduct CHIM studies for COVID-19; currently there is no highly efficacious treatment for moderate or severe illness.

The authors propose that development of a SARS-CoV-2 GMP stock, preferably with attenuating mutations, should pro-

ceed along with preparation of facilities and procedures and engagement of a broad set of stakeholders. Additionally, the researchers recommend developing CHIMs for seasonal coronaviruses, which cause about 30 percent of cases of the common cold and can provide insights into more deadly coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2.

One mutation of SARS-CoV-2 dominates cases

In a new study, an international team of scientists show that the G614 variant of SARS-CoV-2 has come to dominate COVID-19 cases around the world. They report that this mutation does not make the virus more deadly, but it does help the virus copy itself, resulting in a higher viral load, or "titer," in patients.

The new study, led by scientists at Duke University, Los Alamos National Laboratory and La Jolla Institute (LJI), was published July 2, 2020 in *Cell.*

Back in March, two variants of SARS-CoV-2 were circulating. In addition to the G614, the other variant was the D614. The variants had just a small difference in their "spike" protein – the viral machinery that coronaviruses use to enter host cells, explained La Jolla Institute Professor Erica Ollmann Saphire, PhD, who leads the Bill & Melinda Gates Foundation-supported CoVIC at the institute.

Saphire said that viruses regularly acquire mutations to help them "escape" antibodies made by the human immune system. When a virus acquires many of these individual changes, it "drifts" away from the original virus. Researchers call this phenomenon "antigenic drift."

In the new study, researchers' tracking showed that while the G and D viruses both spread widely around the world, the G virus was "fixed" as the dominant variant by mid-March. They also determined that viruses carrying spike with the G mutation grew two to three times more efficiently, leading to a higher titer.

Saphire and her colleagues then used samples from six San Diego residents to test how human antibodies neutralized the D and G viruses. Would the fast-growing G virus be harder to fight?

Their experiments showed that the human immune response could neutralize the new G virus as well or better than the original D virus. This meant the immune system did not need to produce more antibodies or better antibodies against the G virus, even though this variant was more successful at spreading. This finding was in line with what doctors saw in COVID-19 patients.

High cortisol levels associated with greater risk of death from COVID-19

COVID-19 patients with very high levels of the stress hormone cortisol in their blood are more likely to deteriorate quickly and die, say researchers.

The study, led by NIHR Research Professor Waljit Dhillo from Imperial College London and Consultant Endocrinologist at Imperial College Healthcare NHS Trust, provides the first data to show that cortisol levels are a marker of the severity of the illness. The researchers suggest they can be used to identify those patients who are more likely to need intensive care.

Cortisol is produced by the body in response to stress such as illness, triggering changes in metabolism, heart function and the immune system to help our bodies cope. Our cortisol levels when healthy and resting are 100-200 nm/L and nearly zero when we sleep.

When ill patients have low levels of cortisol, it can be life threatening. Excessive levels of cortisol during illness can be equally dangerous, leading to increased risk of infection and poor outcomes. In the new observational study of 535 patients, of whom 403 were confirmed to have COVID-19, cortisol levels in patients with COVID-19 were significantly higher than in those without. The levels in the COVID-19 group ranged as high as 3241 – considerably higher even than after major surgery, when levels can top 1000.

Amongst the COVID-19 patients, those with a baseline cortisol level of 744 or less survived on average for 36 days. Patients with levels over 744 had an average survival of just 15 days.

Initial COVID-19 infection rate may be 80 times greater than originally reported

Many epidemiologists believe that the initial COVID-19 infection rate was undercounted due to testing issues, asymptomatic and alternatively symptomatic individuals, and a failure to identify early cases. A study from Penn State estimates that the number of early COVID-19 cases in the U.S. may have been more than 80 times greater and doubled nearly twice as fast as originally believed.

In a paper published in *Science Translational Medicine,* researchers estimated the detection rate of symptomatic COVID-19 cases using the Centers for Disease Control and Prevention's (CDC) influenza-like illnesses (ILI) surveillance data over a three-week period in March 2020.

"We analyzed each state's ILI cases to estimate the number that could not be attributed to influenza and were in excess of seasonal baseline levels," said Justin Silverman, Assistant Professor in Penn State's College of Information Sciences and Technology and Department of Medicine. "When you subtract these out, you're left with what we're calling excess ILI – cases that can't be explained by either influenza or the typical seasonal variation of respiratory pathogens."

The researchers found that the excess ILI showed a nearly perfect correlation with the spread of COVID-19 around the country. Said Silverman, "This suggests that ILI data is capturing COVID cases, and there appears to be a much greater undiagnosed population than originally thought."

Remarkably, the size of the observed surge of excess ILI corresponds to more than 8.7 million new cases during the last three weeks of March, compared to the roughly 100,000 cases that were officially reported during the same time period.

New All of Us Research Program launches COVID-19 initiatives

The All of Us Research Program, part of the National Institutes of Health (NIH), announced plans to conduct research on COVID-19, according to a press release.

The program will gather data through three activities:

- Serology testing to detect the presence of IgG antibodies in participants to help assess rates of infections across regions and communities.
- An online survey, which will ask questions about how participants are coping with the pandemic. The 20- to 30-minute survey is designed both for participants who have been ill with COVID-19 and those who have not, and includes questions on COVID-19 symptoms, stress, social distancing and economic impacts.
- Standardization of information in participants' electronic health records related to COVID-19. The goal is to provide a resource to help researchers learn more about COVID-19 symptoms, associated health problems, and the effects of different medicines and treatments.

The NIH said the All of Us Research Program will make data gathered through these activities broadly accessible to approved researchers over time through future releases of its data platform, which is currently in beta testing.

The All of Us Research Program, which launched national enrollment in 2018, is building a research resource with data and biological samples shared by nearly 350,000 participants for use in thousands of studies, spanning many different aspects of health and disease.

New tools combat a complex antimicrobial resistance problem

By Diane Flayhart, MBA

Antimicrobial resistance (AMR) is among the greatest threats to the health and well-being of the world's population. If present trends continue, AMR will become a greater cause of mortality than heart disease or cancer by 2050.[1] As the bacteria that cause infections become increasingly drug resistant, even common medical procedures can become more life-threatening for patients.

This is not a theoretical future risk; it is already happening. In 2019, the U.S. Centers for Disease Control and Prevention (CDC) released updated estimates for the toll of drug-resistant infections in the United States, demonstrating that the risk is greater than previously believed, affecting more than 2.8 million patients annually and leading to more than 35,000 deaths.[2]

Antimicrobials are a mainstay of modern medicine but decades of outmoded prescribing practices and extensive use of antimicrobials in food production have driven a rise in organisms that are resistant to these life-saving drugs. The CDC has identified 18 antibiotic-resistant organisms, including Drug-resistant Salmonella Serotype Typhi, Drug-resistant Neisseria gonorrhoeae, Candida auris, ESBL-producing Enterobacteriaceae, and Erythromycin-resistant group A Streptococcus.[2]

The increased prevalence of drug-resistant organisms is impacting patients in both community and hospital settings. The World Health Organization (WHO) found widespread prevalence globally of patients with antibiotic-resistant infections, as well as wide variation in the rate of occurrence, depending on the country. For example, the WHO said 8 percent to 65 percent of urinary tract infections are not treatable with a regularly prescribed antibiotic. And among patients with bloodstream infections, the percentage with resistant infections ranged from zero to 82 percent.[3]

It is critical to understand the patient impact of drug-resistant infections to drive improved prescribing practices and behaviors. One example is the case of Tatiana Vargas,[4] a member of the Antimicrobial Resistance Fighter Coalition, which aims to drive behavioral change by elevating patient stories. In the case of Vargas, her story emphasizes that drug-resistant infections can happen when least expected. She was a healthy, recently married newlywed living in California. After returning home from her honeymoon, she began to feel unwell. She went to an emergency room and was misdiagnosed with a strep infection, treated with antibiotics, and sent home.

In no time, the infection moved to her lungs and Tatiana landed in the ICU. Different doctors then diagnosed her condition as methicillin-resistant S. aureus (MRSA), a very difficult staph infection for which the initial antibiotic no longer worked. After quarantine and many weeks of treatment, she was released. Tatiana now lives with a chronic cough and the reality that the infection might return.

While much of the focus on AMR has highlighted the need for a renewed pipeline of new antimicrobials, experts including the World Health Organization (WHO) and CDC recognize the need for a multi-pronged approach. In May 2015, the World Health Assembly (WHA) adopted a global action plan on antimicrobial resistance, which outlines five objectives:

- Improving awareness and understanding of antimicrobial resistance through effective communication, education, and training.

Earning CEUs

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LEARNING OBJECTIVES

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

1) Describe the causes of antimicrobial resistance.
2) Recall the five objectives of the global action plan on antimicrobial resistance.
3) Describe the role of diagnostic assays in providing information to help providers use antibiotics judiciously and effectively and cite an example of an assay.
4) Describe the three new programs launched this year to combat antimicrobial resistance.

- Strengthening the knowledge and evidence base through surveillance and research.
- Reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures.
- Optimizing the use of antimicrobial medicines in human and animal health.
- Developing the economic case for sustainable investment that considers the needs of all countries and increases investment in new medicines, diagnostic tools, vaccines and other interventions.

The main goal of the global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them.[5]

The same multi-pronged approach has been applied to combat SARS-CoV-2, the virus that causes COVID-19. The COVID-19 pandemic has reinforced the importance of effective measures to control the virus, which also help curb antimicrobial resistance, and these include:

- Improving education on the importance of hygiene in communities and infection prevention and control in healthcare facilities to contain spread of COVID-19.
- Accessing and utilizing surveillance data to identify and monitor infection outbreaks, spread and trends, both at a population level and within healthcare facilities and systems.
- Scaling-up COVID-19 diagnostic testing to identify and isolate people who are infected. Patients who are infected with COVID-19 and critically ill are vulnerable to secondary bacterial infections and drug resistance, and therefore, the importance of identifying a cause of infection – viral, bacterial, fungal, parasitic – is critical in order to optimize treatment.

While the urgent and immediate threat of the novel COVID-19 virus is the utmost priority for governments, health ministries, public health agencies and hospital systems, we also need to ensure that actions to curb and prevent AMR continue. The COVID-19 pandemic has been an acute shock to the world as the novel coronavirus has affected the health of millions and the lives and livelihood of billions. But the renewed focus on public health and the investments made to respond to the pandemic can have lasting impact to the long-term effort to address the untreatable infections caused by AMR.

By resetting efforts towards the five objectives outlined in the AMR Global Action Plan, we can ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines. The first objective is to improve awareness and understanding of antimicrobial resistance through effective communication, education and training. By deploying training and awareness programs, the remaining four objectives will be able to be achieved more effectively.

Over the past year, three new programs were launched focused on training and awareness building. These programs provide relevant information and training for healthcare and non-healthcare audiences, with effective training tools that enhance knowledge on ways to combat AMR within the United States and around the world.

Training for infection prevention

Preventing infections, particularly healthcare-associated infections (HAIs) that spread in hospitals, needs to be considered as the first line of defense against AMR. According to the CDC, resistant bacteria cause 18 percent of central line-associated bloodstream infections (CLABSIs), 15 percent of surgical site infections (SSIs) and 10 percent of catheter-associated urinary tract infections (CAUTIs) in U.S. hospitals.[6] Effective infection prevention and control programs can reduce the spread of HAIs, improve patient care and avoid costs that otherwise would be incurred through increased length of hospital stay and intensified treatment.[7]

Drug-resistant organisms on the rise between 2014 and 2019

Organism:	Cases:	Deaths:
Drug-resistant Salmonella Serotype Typhi	212,500	Less than 5
Drug-resistant Neisseria gonorrhoeae	550,000	Less than 5
Candida auris	323	N/A
ESBL-producing Enterobacteriaeae	197,400	600
Erythromycin-resistant group A Streptococcus	5,400	160

Source: CDC

The Society for Healthcare Epidemiology of America (SHEA) has developed and launched a new training course on best practices in infection prevention and control for hospital clinicians with direct patient care responsibilities. The online program, Prevention Course in HAI Knowledge and Control (Prevention CHKC), is supported by an educational grant from BD (Becton, Dickinson and Company) and was announced at SHEA's Spring Meeting in Boston (2019).[8]

"With many healthcare facilities stretched to or beyond their limits and others preparing to be, this course provides critical information and skills to keep frontline providers, their families and patients safe in this crisis," said Hilary Babcock, MD, MPH, chair of the SHEA Education and Research Foundation. "These prevention processes are not necessarily intuitive, and the need for refreshing these skills among healthcare workers is high in normal times and critical during this global pandemic."

While efforts to reduce healthcare-associated infections (HAIs) have been effective for certain infection types within specific care settings, HAIs still affect one in every 20 hospitalized patients, leading to morbidity, mortality, and excess healthcare costs.[9] One cause may be persistent gaps between recommended infection prevention and control strategies and what is practiced.

SHEA developed the Prevention CHKC program to address these knowledge gaps and improve the safety and quality of patient care provided by frontline healthcare personnel. The program includes 12 online, interactive modules authored by a program committee of multidisciplinary experts. Currently, they are focused on healthcare in acute care settings, such as hospitals, with the aim for the content to be adaptable for other care settings.

The training will help frontline personnel improve their understanding of their roles in HAI prevention. The program focuses on:

- Performing basic prevention strategies of hand hygiene and cleaning of the environment and equipment.
- Recognizing and managing outbreaks.
- Understanding strategies to prevent common HAIs, including central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections, ventilator-associated events, C. difficile infections, and methicillin-resistant S. aureus (MRSA).

Rapid Diagnostics Would Lead to Fewer Unnecessary Antibiotic Prescriptions	
40 million	People in the United States that are given antibiotics annually for respiratory issues
27 million	Of the 40 million, people who get antibiotics unnecessarily
13 million	Of the 40 million, people who get antibiotics appropriately

Source: amr-review.org

• Developing performance and accountability measures to assess infection prevention practices.

In the Diagnostic Stewardship and Antibiotic Stewardship module, participants learn about the impact of laboratory tests and how appropriate and inappropriate testing is reviewed. An inappropriate test can lead to the wrong diagnosis, which can result in unnecessary additional testing, patient harm due to testing or treatment, unnecessary treatment, and higher costs to the health system and to the patient. For example, a review of a typical urinary tract infection (UTI) timeline educates the learner about the timing of test orders, the role of chronic long-term urinary catheters, and the importance of understanding patient symptoms. The module concludes with case studies to demonstrate the value of using diagnostic test results to make informed antibiotic choices for the patient.

Prevention CHKC is intended for frontline healthcare personnel and is defined for the purposes of this course as individuals in healthcare facilities who are "responsible for direct patient care." This can include doctors, nurses, pharmacists, laboratory technicians, and others involved in supporting infection prevention and antimicrobial stewardship programs. The course offers practical resources to improve infection prevention, and can be used during planned training, e.g. new employee training or scheduled training events, as well as when a healthcare team needs a refresher on a specific topic. Prevention CHKC provides up to 6.75 AMA PRA Category 1 Credit, ABIM MOC Points, ACPE Pharmacy Credits, and Nursing Contact Hours. As of early June 2020, close to 600 participants have successfully completed the course.

While the course typically costs $25 for non-SHEA members, the organization is offering the course free to everyone through December 31, 2020.

Training to scale up diagnostics

Guiding appropriate use of antimicrobials relies on the accurate diagnosis of infection. Unfortunately, diagnostic tests are frequently unavailable or underutilized, resulting in antimicrobials being prescribed empirically and often inappropriately. Increasing awareness of the role of diagnostic testing can help laboratories to report timely, critical results to clinicians and antibiotic stewardship teams. The data generated from diagnostic testing also informs local, national, and global infectious disease surveillance systems. When combined with robust antimicrobial stewardship programs, rapid diagnostics have provided shorter times to optimal therapy, shorter hospital lengths of stay, and lower hospital costs.[10,11]

Director General of the World Health Organization Tedros Adhanom Ghebreyesus, PhD, has been quoted as saying, "An accurate diagnosis is the first step to getting effective treatment. No one should suffer or die because of a lack of diagnostic services, or because the right tests were not available."[12]

The London School of Hygiene and Tropical Medicine partnered with BD and global experts to develop a Massive Open Online Course (MOOC) to raise awareness, knowledge and to advocate for the role of diagnostics in the AMR response.[13] This partnership was formed in direct response to a call for public-private private partnerships in the global fight against AMR at the 2016 World Economic Forum in Davos, Switzerland. The MOOC aims to increase awareness of the role of diagnostics to guide the appropriate use of antibiotics in clinical medicine, screen for resistant infections in healthcare settings, and for surveillance to monitor AMR trends and the effectiveness of stewardship interventions.

An example of the depth that participants gain learning about each module is seen when Healthcare-Associated Infections (HAIs) are introduced in week three. HAIs are infections that patients acquire in healthcare settings, including hospitals and long-term care facilities. Organisms that cause HAIs such as MRSA (Methicillin-resistant S. aureus), CPO (Carbapenemase-producing organisms), VRE (Vancomycin-resistant Enterococci), and C. diff (Clostridoides difficile) can colonize in a patient or cause an infection in a patient. Based on the source of the clinical sample and the type of test completed, the diagnostic result will provide clear information about the possible colonization or infection. The role of diagnostic testing in identifying and facilitating the prevention and control of these HAIs is important.

The MOOC goes into detail on these tests and how the results impact individual patient management, healthcare system level surveillance, and global surveillance. For CPO, the MOOC describes the role of diagnostics for resistant organisms. They can be used to screen for carriers to enable infection prevention and control measures, to identify infected individuals to guide treatment or for active surveillance of resistant HAIs to enable alerts of outbreaks. CPOs can be detected using molecular testing, which has the benefit of fast time-to-results and can be more sensitive but more expensive. CPOs can also be detected using culture on plated media, which can take up to three days and may lack sensitivity, but it is less expensive than molecular testing. Once the samples are received in the laboratory, they can be processed and have a molecular assay completed. If tests – such as BD Phoenix CPO Detect, Carba NP, or modified Hodge test – are used, the patient sample needs to plated and incubated, with the testing completed on colony growth.

At the completion of the six-week course, participants are able to describe the top causes of AMR (linked to WHO and CDC priority list of pathogens) – such as Gram-negative bacterial pathogens causing urinary tract infections (UTI) and healthcare associated infections (HAIs), sepsis and gonorrhea – and explain the role of diagnostics for these conditions. They understand that everyone has a role to play in the fight against AMR – both for now and the future.

This course is intended for health professionals, such as clinicians, nurses, nurse-practitioners, pharmacists, lab managers, technicians, faculty, and students. The course is offered free of charge and is a flexible means of providing quality educational content from a community of experts to a global audience.

First offered in September 2019, the MOOC has reached more than 10,000 learners worldwide. "It is our vision that a world of knowledge and resources related to diagnostics and AMR be made available to healthcare workers all over the world with a simple click of a key on a computer. We believe that this knowledge will advance the ability to detect the emergence of resistance and take quick action." says Renuka Gadde, Vice President, BD Global Health.

Antimicrobial resistance threatens everyone. **All of us need to be resistance fighters.**

The ***Antimicrobial Resistance Fighter Coalition*** is a bold collective of like-minded organizations, leaders, and individuals united in their commitment to address the threat and burden of antimicrobial resistance.

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ANTIMICROBIAL RESISTANCE FIGHTER COALITION

Increased awareness of drug-resistant infections

To change behaviors and practices around antibiotic utilization, the risk of drug-resistant infections needs to be better understood by organizations and individuals. Antimicrobial resistance is a complex problem that involves human health, animal management and agriculture practices. A report published by Wellcome Trust[14] found that public understanding of antimicrobial resistance and its impact is currently limited. Some of reasons for the lack of understanding cited were the use of technical language and jargon, a lack of urgency in messaging, and a lack of understanding that AMR is a universal problem that affects everyone. Increasing awareness is the first objective of Global Action Plan and is a critical element in combatting AMR.

As mentioned earlier, the Antimicrobial Resistance Fighter Coalition was formed to address the need for greater awareness about the problem.[15] It is a collective of like-minded organizations, leaders, and individuals united in their commitment to address the threat and burden of antimicrobial resistance. With members from 44 countries, they share their work and commitments to inspire others. The global campaign works to substantially increase awareness of AMR and encourage action across a wide range of stakeholders, including policymakers, health agency officials, professional societies, clinicians, patients and family members.

The coalition focuses its educational efforts on the key elements needed to combat AMR, which include:

- Infection prevention, like vaccines and handwashing, to reduce the number of infections and the need to utilize antibiotics.
- Improved utilization of current diagnostic tests and new tests to provide rapid diagnosis of the causative agents.
- New treatments to provide targeted, effective management of infections.

As mentioned above, the Coalition also amplifies the voices of patients from around the world and reminds us that AMR can impact anyone at any time. Take, for example, the case of Lisa Smith,[16] a new mother from Arkansas who acquired a multidrug-resistant wound infection during childbirth. Lisa's drug-resistant infection required multiple readmissions, six weeks of antibiotic treatment and home healthcare treatment from an advanced wound center for 15 weeks. The emotional costs of spending her maternity leave fighting a drug-resistant infection instead of bonding with her newborn child were substantial.

The Antimicrobial Resistance Fighter Coalition features a website and social media channels that provide educational tools, current articles and publications, and current events focused on general AMR information, infection prevention diagnostic stewardship, and antibiotic stewardship. The website directly links to information provided by the coalition's partner organizations. It features an interactive map that allows viewers to identify and see messages of Antimicrobial Resistance Fighters from around the world. It is designed to be relevant and appealing both to people who are learning about AMR for the first time, as well as those who are already very knowledgeable about this threat.

In conclusion

Continued education to increase awareness of drug resistance infections will drive change in how we use our current antibiotics. Training on infection prevention and diagnostic stewardship will help mitigate the overuse of our current antibiotics. We are all living in a truly unique time when citizens throughout the world are now keenly awareness of the risks of untreatable infections and the effect they can have on the global community. The COVID-19 pandemic has changed how we all think about public health and will result in appreciation among policymakers for the importance of investing in robust public health and healthcare delivery systems. Among these to include substantially strengthened infectious disease prevention capabilities, and within the general public, the need to engage in safer hygienic practices.

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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. **Drug-resistant infections affect more than _____ patients annually.**
   - A. 1.4 million
   - B. 2.2 million
   - C. 2.8 million
   - D. 3.2 million

2. **_____ and_____ have driven a rise in organisms that are resistant to these lifesaving drugs.**
   - A. usage of unapproved antibiotics
   - B. excessive use of antimicrobials in food production
   - C. Outmoded prescribing practices
   - D. both B and C

3. **The U.S. Centers for Disease Control and Prevention has identified ___ antibiotic-resistant organisms.**
   - A. 8
   - B. 14
   - C. 18
   - D. 25

4. **The World Health Organization (WHO) found widespread prevalence globally of patients with antibiotic-resistant infections, but it did not find wide variations in the rate of occurrence, depending on the country.**
   - A. True
   - B. False

5. **The five objectives outlined in a global action plan on antimicrobial resistance by the World Health Assembly included the following:**
   - A. Improving awareness and understanding of antimicrobial resistance through effective communication, education and training.
   - B. Strengthening the knowledge and evidence base through surveillance and research.
   - C. Reducing the incidence of infection by using antibiotics less often to treat humans and animals.
   - D. Both A and B

6. **But the renewed focus on public health in the response to _____ can have a lasting impact on the long-term effort to address the untreatable infections caused by AMR.**
   - A. COVID-19
   - B. Influenza
   - C. Whooping Cough
   - D. AIDS

7. **Resistant bacteria cause __ percent of central line-associated bloodstream infections (CLABSIs) 15 percent of surgical site infections (SSIs) and __ percent catheter-associated urinary tract infections (CAUTIs) in U.S. hospitals.**
   - A. 10; 20
   - B. 18; 10
   - C. 14;10
   - D. 15;20

8. **The Society for Healthcare Epidemiology of America (SHEA) has developed and launched a new training course in best practices in infection prevention and control for hospital clinicians with direct patient care responsibilities.**
   - A. True
   - B. False

9. **HAIs still affect one in every __ hospitalized patients, leading to morbidity, mortality, and excess healthcare costs.**
   - A. 10
   - B. 15
   - C. 20
   - D. 25

10. **Prevention of CHKC focuses on:**
    - A. Performing basic prevention strategies of hand hygiene and cleaning of the environment and equipment; understanding appropriate prescribing practices.
    - B. Performing basic prevention strategies of hand hygiene and cleaning of the environment and equipment; recognizing and managing outbreaks.
    - C. Developing performance and accountability measures to assess infection-prevention practices and understanding appropriate prescribing practices.
    - D. Recognizing and managing outbreaks; understanding the financial costs of poor infection-prevention practices.

11. **An inappropriate test can lead to the wrong diagnosis, which can result in unnecessary _____, patient harm due to testing or treatment, unnecessary treatment, and _____ to the health system and to the patient.**
    - A. additional testing; higher costs
    - B. additional testing; lower costs
    - C. medications; higher costs
    - D. medications: lower costs

12. **What factors lead to antimicrobials being prescribed empirically and often inappropriately?**
    - A. Patients do not want to wait for their test results.
    - B. Physicians do not want to change patients' prescriptions from the original antibiotic they were given.
    - C. Uninsured patients cannot be tested for bacterial infections.
    - D. Diagnostic tests are frequently unavailable or underutilized.

13. **When combined with robust _____, rapid diagnostics have provided shorter time to optimal therapy, shorter hospital lengths of stay, and lower hospital costs.**
    - A. antimicrobial stewardship programs
    - B. provider involvement
    - C. patient monitoring
    - D. treatments

14. **The Massive Open Online Course (MOOC) aims to increase awareness of the role of _____ to guide the appropriate use of antibiotics in clinical medicine, screen for resistant infections in healthcare settings, and for surveillance to monitor AMR trends and the effectiveness of stewardship interventions.**
    - A. diagnostics
    - B. professional education
    - C. effective communications
    - D. A and B

15. **Based on the source of the clinical sample and the type of test completed, the diagnostic result will provide clear information about the possible ____ or infection.**
    - A. Disease
    - B. Colonization
    - C. Source
    - D. Bacteria

16. **For CPO, the MOOC describes the role of diagnostics for resistant organisms. They can be used to screen for carriers to enable infection prevention and control measures, to identify infected individuals to guide treatment, or for active surveillance of resistant HAIs to enable alerts of outbreaks.**
    - A. True
    - B. False

17. **CPOs can also be detected using culture on plated media, which can take up to three days and may lack sensitivity, but it is less expensive than ____ testing.**
    - A. Antigen
    - B. Serology
    - C. Molecular
    - D. DNA sequencing

18. **Antimicrobial resistance is a complex problem that involves human health, _____ management and agriculture practices.**
    - A) population
    - B) animal
    - C) hygiene
    - D) environmental

19. **A report published by Wellcome Trust found that public understanding of antimicrobial resistance and its impact _____.**
    - A. has been strengthened by the COVID-19 pandemic
    - B. is currently limited
    - C. has increased over the last few years
    - D. has not increased over the last few years

20. **The COVID-19 pandemic has changed how we all think about public health and will result in appreciation among policymakers on the importance of investing in robust public health and healthcare delivery systems, including substantially strengthened _____, and among the general public on the need to engage in safer hygienic practices.**
    - A. infectious-disease prevention capabilities
    - B. diagnostic capabilities
    - C. treatments
    - D. A and B

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1. **To what extent did the article focus on or clarify the objectives?** P ① ② ③ ④ ⑤ E
2. **To what extent was the article well-organized and readable?** P ① ② ③ ④ ⑤ E
3. **How will you use the CE units?** ☐ state license ☐ employment ☐ recertification ☐ other

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To cover all the bases, bring next-generation sequencing to the lab

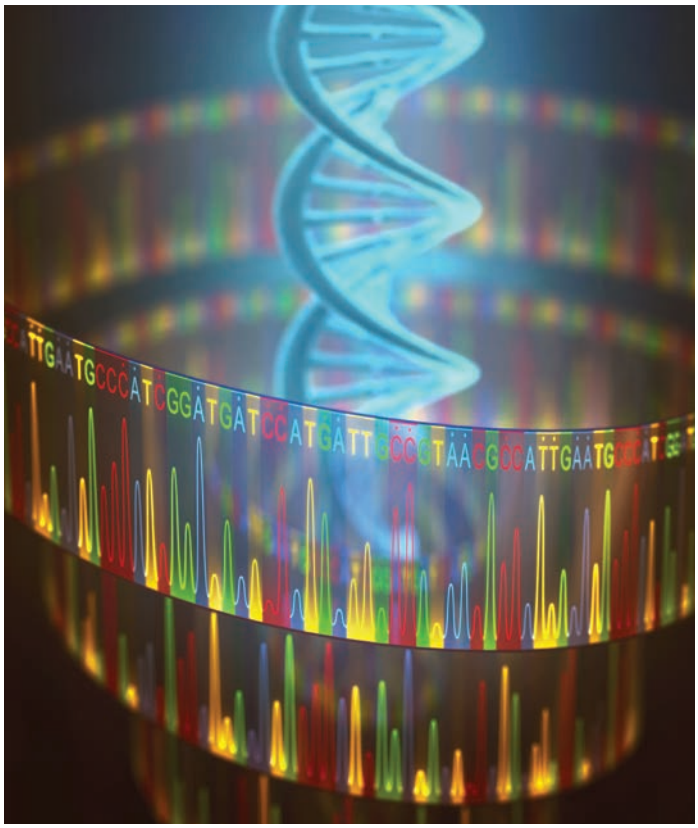
The last decade has seen an explosion in genomic medicine, which has revolutionized the diagnosis and care of individuals with genetic disorders, cancer, and infectious disease. Instead of waiting an average of eight years for a diagnosis, a patient with a rare genetic condition may wait only days or hours. Cancer patients who previously only had months to live, may survive a decade longer because of tailored and targeted interventions. The lives of individuals with enigmatic infections are routinely saved because of the rapid identification of a pathogen.

This is an exciting time for biological research. Meaningful discovery is churning at a pace unmatched throughout history. Thanks to the pioneering world of next-generation sequencing (NGS), the data we can derive from organisms is deeper and more insightful than ever imagined. NGS equipment, once reserved for the largest and busiest of research centers, is now accessible to enterprises of all sizes – unearthing new knowledge on cancer, microbiology, genetic disease, reproductive health, agriculture and forensics, and other emerging areas.

NGS in lab space

With the advent of the first FDA-approved NGS instrument in late 2013, the technology is now gaining a stronger foothold in the clinical laboratory space for screening and diagnostic testing. Whether you are seeking to conduct research worthy of publication in a respected journal or looking for critical clues to the spread and evolution of disease, your work likely requires or would benefit from NGS technology. For this reason, labs that do not already own an NGS system are making a push to acquire equipment of their own. For many organizations, it's a matter of data privacy or a need for tight control over their projects and samples. For others, it's simply an issue of efficiency and time-saving. For all, it's seen as an investment in high-quality, reproducible data that leads to valuable biological insight.

If you are a principal investigator or manager for one of these labs, you have an important purchasing decision to make. The good news is that the market today offers plenty of choice. Next-generation systems range from ultra-flexible, high-output instruments that can read multiple samples in a single run, to desktop sequencers ideal for smaller-scale studies. This guide will walk you through the purchasing process by helping you evaluate your research goals and laboratory needs.



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First, let's tackle some of the most important questions that will define your product search: What types of NGS experiments do you plan to perform? And which applications will you use most? Think broadly here, considering your current needs as well as needs in the future. Purchasing NGS instrumentation is a commitment, and you want to be sure that your chosen instrument will provide the versatility and the power to accommodate your lab for years to come. For each application, consider your needs for these three areas:

Throughput per run

- Your needs in this area will largely dictate the type of sequencer that is best suited for you. Assess your projected sample numbers per month and year, and let this number guide your selection process. For example, if you plan to run large sample numbers for applications such as whole-genome or whole transcriptome sequencing, you are probably a good fit for a high-throughput system.

Read length

- Longer read lengths are very important for many applications, with de novo sequencing standing out as a prime example. Why? The longer the read, the better the coverage across the genome. And because de novo sequencing does not use a reference genome to align data, it is essential to produce long overlapping reads to complete the assembly. Applications such as microbial sequencing need long reads, as many viruses and other microorganisms have not been previously sequenced. Large structural chromosomal rearrangements in cancer genomes can also be difficult to detect without long reads, as the reads must span the chromosomal breakpoints in order to detect them.

Paired-end sequencing

- A broad range of applications can benefit from paired-end sequencing, which allows for maximum coverage across the entire genome. If you currently require or will require paired-end sequencing, be sure to investigate the solutions available for each of

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- This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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the instruments you are considering. It is important that the equipment supplier has established protocols and produces high-quality data with this technique. Easy sample preparation and data analysis tools are also valuable in this area, as a simple and integrated workflow will save you time and money.

Think about budget from DNA to data

Your budget can help you narrow your decision on the type of sequencer to purchase, but the issue of investment is not as clear-cut as you might think. There are many important factors to consider beyond the initial capital expenditure of the instrument itself, including the cost of ongoing operations, the quality of the data (ensuring the process won't have to be repeated at an additional cost) and the hands-on time required to get the job done right.

This is where it is critical to consider your research needs, as well as the labor required to prepare samples for sequencing and to analyze your results. What reagents will you need on an ongoing basis? How long will it take to interpret the data? How and where will you store the data? These are some of the most important issues to consider. Examine your budget per sample and make sure everything is included in that cost, including DNA extraction and informatics.

Operational expenses: cost per sample

Consumables are one of the biggest drivers of operational expenses, as they are required for both library preparation and sequencing. Library prep costs will vary depending on the study size, application, and vendor. Many third-party vendors sell library prep kits, but not all kits will work on every machine. That is why it's smart to select a sequencing technology for which various kits are sold. This ensures a larger range of options and, oftentimes, more competitive prices. When comparing operational costs, look at the cost per base or cost per sample. This figure is dictated by the amount of DNA that can be sequenced per run. For higher-output applications, economies of scale can help reduce cost. Tip: Sample indexing allows you to pack more samples into each sequencing run, lowering the cost per base. For labs running high sample numbers, the higher expense of a high-throughput sequencer is offset over time by the lower operating costs associated with each sample.

Hands-on labor: time is money

Another factor to consider with operational costs is the hands-on time required by lab technicians. The more time a lab tech must spend to carry out a given sequencing experiment, the less time that person has available for other important projects. It becomes an issue of both money and time. Consider the element of efficiency as you compare platforms. Tip: In addition to hands-on time, pay attention to the amount of user intervention needed per experiment. Even if hands-on time is minimal, you may have to return to the equipment often to intervene. This cuts into a user's ability to do other things in the lab, and, as a result, increases the operational costs.

Envision new workflow and informatics

You want your NGS system to foster the easiest workflow possible. Considering the scope of many DNA experiments, you should seek out any and all opportunities to save time and ensure accuracy. The quantity of data NGS produces can seem overwhelming at first. Next-generation sequencing data output has increased at a rate that surpasses Moore's law, more than doubling each year since it was invented. In 2007, a single sequencing run could produce a maximum of around one gigabase of data. Today, that rate exceeds a terabase of data in a single sequencing run — more than a 1,000x increase.

What does this mean for you? For starters, it means that you'll have to find a way to manage a very large amount of data. So, as you size up your NGS options, think about what each system will mean for your workflow, from sample preparation to informatics. How exactly will you turn that raw data into actionable information? Make sure you are comfortable with the workflow, not intimidated by it.

Sample and library preparation

Consider the types of experiments you do and how many samples they usually involve. When evaluating your NGS options, look specifically at how many days it will take to create the libraries. How much of that time is "hands-on" time? Does the equipment vendor offer a library solution? In general, sample preparation protocols for NGS are more rapid and straightforward than those for Sanger sequencing.

With NGS, you can start directly from a gDNA or cDNA library. The DNA fragments are then ligated to platform-specific oligonucleotide adapters to perform the sequencing biochemistry, requiring as little as 90 minutes to complete. When considering sample preparation, ask vendors about the versatility of their products: Do the sample prep solutions support a broad range of applications? Is it easy to purchase all of your needed solutions in one place and access support when questions arise?

Data analysis

Along with sample preparation, data analysis is an area that simply cannot be overlooked when comparing NGS equipment. A wide range of data-analysis algorithms are available that perform specific tasks related to a given application. Some applications require specialized assembly of sequencing reads.

Others require quantification of read counts to provide information about gene expression levels. While some of these data analysis applications are commercially available from software vendors, many are freely available opensource algorithms from academic institutions. Explore what types of analysis tools and protocols are available to users of a given platform and ask whether these tools are specialized in working with data from the equipment you are looking to purchase. Ease of workflow and data integrity are at stake. It is even better if some tools are open source because users and developers continually make improvements.

Conclusion

Revolutions in diagnostics, precision drug development, population health, forensics and environmental science have all been underpinned by NGS technology; and we are on the cusp of making genomic medicine a reality for hundreds of millions across the globe. In the span of just over 20 years, genomics has upended the paradigm of the slow introduction of new technologies into medicine and has the potential to further disrupt how the world thinks about their health care. As we look to the future, genome sequencing for every child at birth, every patient with rare disease or cancer and any individual with concerns about reproduction or long-term health risks is within reach.

(This article was created with the permission of Illumina, a provider of next-generation sequencing technology. For more information, visit www.illumina.com).

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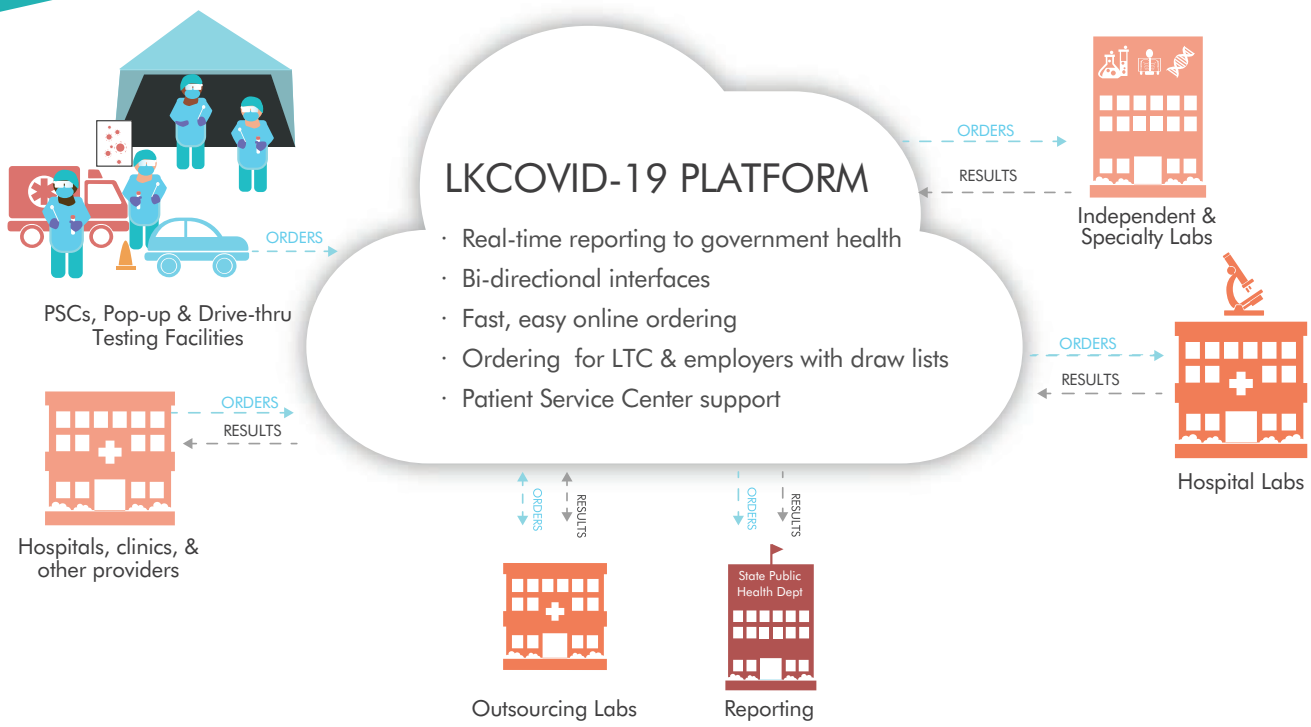

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Quality control for SARS-CoV-2 testing

By Peter Deman, PhD and Nico Vandepoele, BSc

To identify, treat, and contain SARS-CoV-2, the virus that causes COVID-19, clinicians worldwide rely on timely and accurate diagnoses. Because of the fast-paced development of test kits, it is important that laboratories maintain vigorous quality control (QC) practices to establish confidence in the reliability of test results. This article outlines some suggested best practices for good quality control when testing for SARS-CoV-2. Specific attention is given to practical approaches for utilizing quality control protocols for different testing methodologies.

Testing methodologies

There are currently three different test methodologies in practice to identify whether a patient has been exposed to the virus. Each methodology is either based on detecting the viral RNA or viral proteins (antigens) directly, or detecting the patient's antibodies, which are an immunological response to being exposed to the virus.

- Molecular tests are designed to detect the presence of viral RNA in a nasal or nasopharyngeal swab or wash/aspirate.
- Antigen tests are designed to detect the presence of viral proteins in a nasal or nasopharyngeal swab or wash/aspirate.
- Serology or antibody tests are designed to detect the presence of human immunoglobulins in blood.

Molecular testing

Molecular testing mainly relies on the analysis of nasal/nasopharyngeal or wash/aspirate samples by PCR methods. The identification of the virus is based upon detecting specific genes. Molecular tests use one or more of these genes to identify the virus.

When selecting a quality control material for your molecular test, you should ensure that the multiple gene targets used in the assay are also available in the control material. Reacting to testing supply shortages, some labs are validating and running multiple molecular assays so that if one system is down due to lack of supplies, testing can continue on another system. In these scenarios, inventory management can be streamlined by using a control containing all the gene targets covered by the laboratory's different molecular assays.

Commercially available control materials fit into three categories:

- Synthetic RNA: These materials, with one or more target genes, are designed by formulating synthetic RNA transcripts, which contain the unique genes. They are non-infectious and can be quantified at low positive concentrations.
- Inactivated or live virus: Viral particles can be chemically or heat-inactivated to be rendered non-infectious. Whole genome controls fit into this category.
- Plasmid DNA: Purified /intact bacterial cells containing a synthetic SARS-CoV-2 sequence. These also contain one or more target genes.

An important step in the testing process is the extraction or purification of the viral RNA from the biological sample. Patient samples are mixed with a lysing buffer to release the genetic material. The RNA is then separated from DNA and other proteins in the sample with specific extraction reagents. To test this extraction process, quality controls should contain human genetic material or a protein coat similar to the actual virus (armored control). A negative control material should contain human genomic DNA, which mimics the actual patient samples and allows laboratories to validate performance of the entire molecular assay process – including extraction, amplification, and detection.

Most control or reference materials are quantitative and have a concentration provided in the product insert. A well-characterized quantitative material can also be used for various aspects of the validation or verification process, such as establishing the limit of detection (the lowest analyte concentration that the test method can detect).

As with other test-method quality-control procedures, you should use independent, third-party quality control materials. Not only are these advantageous for efficiency by being able to be used across multiple platforms, they also offer an unbiased, independent performance check.

QC practices

To assist in the development of pragmatic operational QC practices, there are a number of resources offering guidance.

For example, in terms of frequency, the WHO recommends that QC testing be performed with each run and has noted that, "each nucleic acid amplification test (NAAT) run should include both external and internal controls and laboratories are encouraged to participate in external quality assessment schemes when they become available."[1]

The College of American Pathologists (CAP) Microbiology checklist (MIC 65200) states that for (Daily QC - Molecular-based Testing), "molecular-based quantitative and qualitative tests, controls are run at least daily, or more frequently if specified in manufacturer's instructions, laboratory procedure, or the CAP Checklist, and when changes occur that may impact patient results."[2]

Clinical Laboratory Improvement Amendments (CLIA) has provided additional QC guidance for Emergency Use Authorization (EUA) COVID-19 testing, which in certain conditions allows for reduced QC without requiring an IQCP. CAP, Joint Commission, and other accrediting bodies have followed suit. However, given the sensitivity around this testing, reduced QC should not be taken lightly. For optimal results, however, it is recommended that labs adhere to the following CAP guidelines for QC of molecular testing:

- Quantitative tests: three controls at least daily, including a negative control, a low-positive control, and a high-positive control.
- Qualitative tests: daily positive and negative controls.[2]

While most of these molecular methods are reported qualitatively, many produce an underlying quantitative result as a Cycle Quantification (Cq) or Cycle Threshold (Ct), identifying the cycle number at which the sample's

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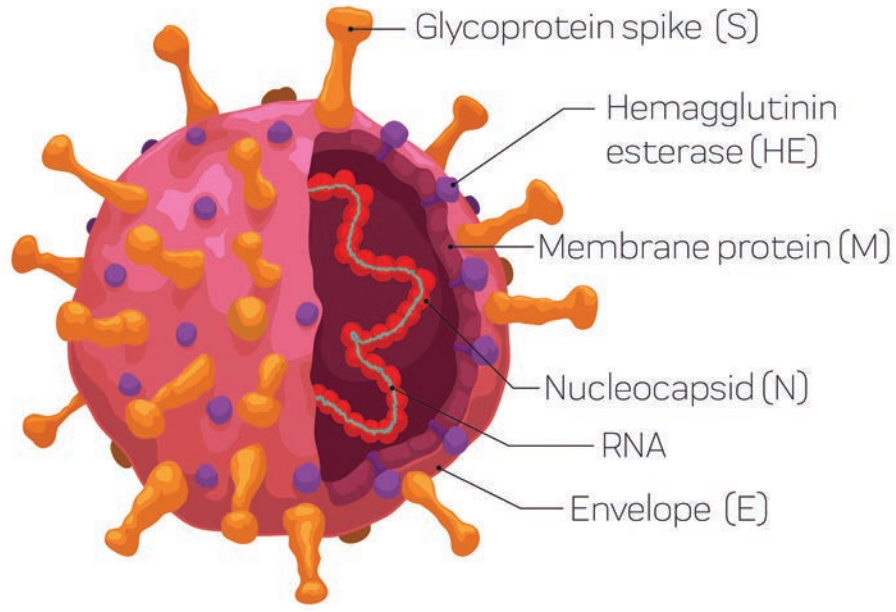
reaction curve intersects with the threshold line. That value is then translated into a qualitative result for purposes of test reporting. The resulting value can then be evaluated and used as a performance indicator for the test. Other quantitative methods can also produce additional quantitative values (ex: copies/uL).

When quantitative results are generated, laboratories can establish their own target means and ranges. Although the product inserts may provide target values, good QC practice dictates that the lab establish its own targets. This can easily be performed by running the control at least ten times over different days or runs.[3]

When setting an acceptable QC range, some labs have their own ranges defined based on experience or clinical use (for example +/- 3 Ct). However, as with traditional quantitative QC procedures, the lab can use an existing standard deviation (SD) or coefficient of variation (CV) from a previous control lot, or establish a new SD or CV by initially measuring 20 control results and then updating these estimates when more results are available.

Documenting the results in Levey-Jennings charts can help to identify trends and possible shifts in the test method performance. Further confidence is gained by participating in a peer-comparison program and proficiency testing program. These tools provide insights, not only for the lab itself, but also as to how a test method or reagent log is performing across many labs.



Schematic representation of the SARS-CoV-2 virus

Antigen testing

At the time of writing this article, there was only one test approved by the U.S. Food and Drug Administration (FDA). It is a cartridge-type rapid test utilizing a sandwich immunofluorescence technology to identify the SARS CoV-2 antigen.

As with many point-of-care (POC), lateral flow tests, this test provides a built-in procedural control, but also provides a positive and negative external quality control.

The quality control minimal requirements for point-of-care tests are often specified like this:

- Once for each new lot, or new shipment of kits, provided that each different lot received in the shipment is tested.
- In accordance with local, state, and federal regulations or accreditation requirements

Antibody testing

According to interim guidelines from the Centers for Disease Control and Prevention (CDC), there is currently no identified advantage of assays whether they test for IgG, IgM and IgA or total antibody.[4] Tests that detect binding antibodies can be classified via two broad categories:

- Laboratory tests that use ELISA (Enzyme-Linked Immunosorbent Assay) or CIA (Chemiluminescent Immunoassay) methods for antibody detection. Based on the reagents, IgG, IgM, and IgA can be detected separately or combined as a total antibody analysis.
- Rapid point-of-care tests generally are lateral flow devices that detect IgG; IgG and IgM; or total antibody presence in the sample.

QC practices

Depending on the methodology used and the types of antibody detected, different control materials are available. When running multiple assays in a lab, an advantage of a total antibody control (IgG, IgM and/or IgA) is that it can be used for both total antibody tests as well as specific antibody tests, which simplifies inventory management issues. As expected, individual antibody controls can only be used for the specific, designated antibody test.

Some kits might include their own control material (for example ELISA methods) that are required to verify that tests are performed according to procedures and/or are used to derive assay cutoff value. As ISO 15189:2012(E) sub-clause 5.6.2.2 references, "Use of independent third-party control materials should be considered, either instead of, or in addition to, any control materials supplied by the reagent or instrument manufacturer. The laboratory shall use quality control materials that react to the examining system in a manner as close as possible to patient samples."[5]

According to CLSI-C24-A4, "advantages for participating to an interlaboratory QC program are: Verifying that a laboratory is producing QC results that are consistent with other laboratories using the same measurement procedure, and thus demonstrating that the laboratory is using the measurement procedure correctly."[3]

Another aspect to take into consideration for both molecular and serology testing is the QC validation linked to"batch testing, where a direct correlation exists between the quality of a control material examination and the patient specimen examinations in the batch. With discreet testing, where each specimen is examined individually,

there is no longer a direct correlation between the quality of a control specimen and the quality of a subsequent patient specimen."[6] Bracketing patient samples with QC specimens is one of the most-used solutions for discrete testing platforms.

Conclusion

With the current climate of urgency and the emerging new tests and methods being approved through emergency use authorizations from the FDA, it is important to vigilantly control the performance of diagnostic and surveillance tests. With faster development and production, logic dictates that QC protocols should be bolstered to ensure performance issues are quickly identified and resolved. Standard good quality-control practices for molecular and serology methods certainly apply for the new SARS-CoV-2 tests.

When using different testing methodologies in the laboratory, selecting a quality control product that can work for multiple assays can be beneficial. Selecting independent third-party quality control materials with a matrix as close as possible to the sample material will also support a solid quality control design. As SARS-CoV-2 assays continue to evolve, so should quality control practices be strengthened to provide the best possible testing outcomes for the public during – and beyond – this pandemic.

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Nico Vandepoele, BSc, serves as Scientific and Professional Affairs Manager for Bio-Rad Laboratories Quality Systems Division. He works to promote an understanding of laboratory regulations and best practices as they pertain to QC and EQA/PT programs.

Employee-retention strategies, from boosting morale to promoting CE

By Linda Wilson

Today's lab managers are pursuing a wide range of employee-retention strategies, including initiatives to boost morale and develop careers.

Retaining existing staff members is regarded as less expensive than recruiting new employees. While not focused on laboratory professionals specifically, a widely cited 2004 study found that the average cost for hiring healthcare staff ranged from $276 for administrative assistants to $36,743 for attending physicians.[1]

Employee retention also promotes stability and is an important aspect of creating a positive work culture. "Focusing on creating, developing and sustaining a highly engaging environment is the best way to ensure appropriate staffing levels and provide a high quality of service and the best patient care," explained Tajana Turato MS, MLS (ASCP)cm, Laboratory Operations Manager, Clinical Pathology, Department of Pathology and Laboratory Medicine at Lenox Hill Hospital, New York, which was voted *Medical Laboratory Observer's* 2020 Lab of the Year.

Overcoming challenges

However, lab managers face daunting obstacles to sustaining adequate staffing levels. As Danielle Stroughton Duncan, Director of Education at COLA noted, "The medical laboratory industry has struggled to produce and maintain trained professionals for several years."

Image courtesy of Pixabay

An aging population is fueling demand for lab tests and, in turn, lab technologists and technicians. The Bureau of Labor Statistics (BLS) predicts that employment for clinical lab technologists and technicians will grow 11 percent, adding 35,100 positions from 2018 to 2028. There were 331,700 positions nationally in 2018.[2] The demand is even more robust for phlebotomists. The BLS expects demand for this position to climb 23 percent, adding 29,500 jobs from 2018-2028. There were 128,300 positions in 2018.[3]

At the same time, current shortages for key personnel exacerbate the situation. Vacancy rates in 2016 varied by department from 4.7 percent in atomic pathology to 10.98 percent for laboratory personnel focused on information systems, quality assurance and performance improvement, according to a survey conducted by the American Society for Clinical Pathology (ASCP). The vacancy rate for the core lab was 7.54 percent, and it was 8.11 percent in phlebotomy, 8.47 percent in hematology, and 5.93 percent in microbiology.[4]

There are several reasons for the vacancy rates. First, Duncan said that the number of academic programs has declined significantly. According to the ASCP, the number of training programs declined 30 percent from 659 programs in 1992 to 468 in 2002.[5]

On a positive note, Duncan said, "There has been an increase in the amount of online offerings with a combination of in-person rotations, which is a promising addition to the field of MLT and CLS/MT."

"In addition to declining training programs and graduates, the industry is also impacted by an aging workforce. Older laboratory professionals have outpaced younger professionals entering the market. Therefore, the industry experiences higher retirement rates," Duncan said.

ASCP data highlights this demographic issue. In 2016, the retirement rate was highest (28.3 percent) for LIS/QA/PI and lowest for phlebotomy (10.76 percent).[4]

Education as retention strategy

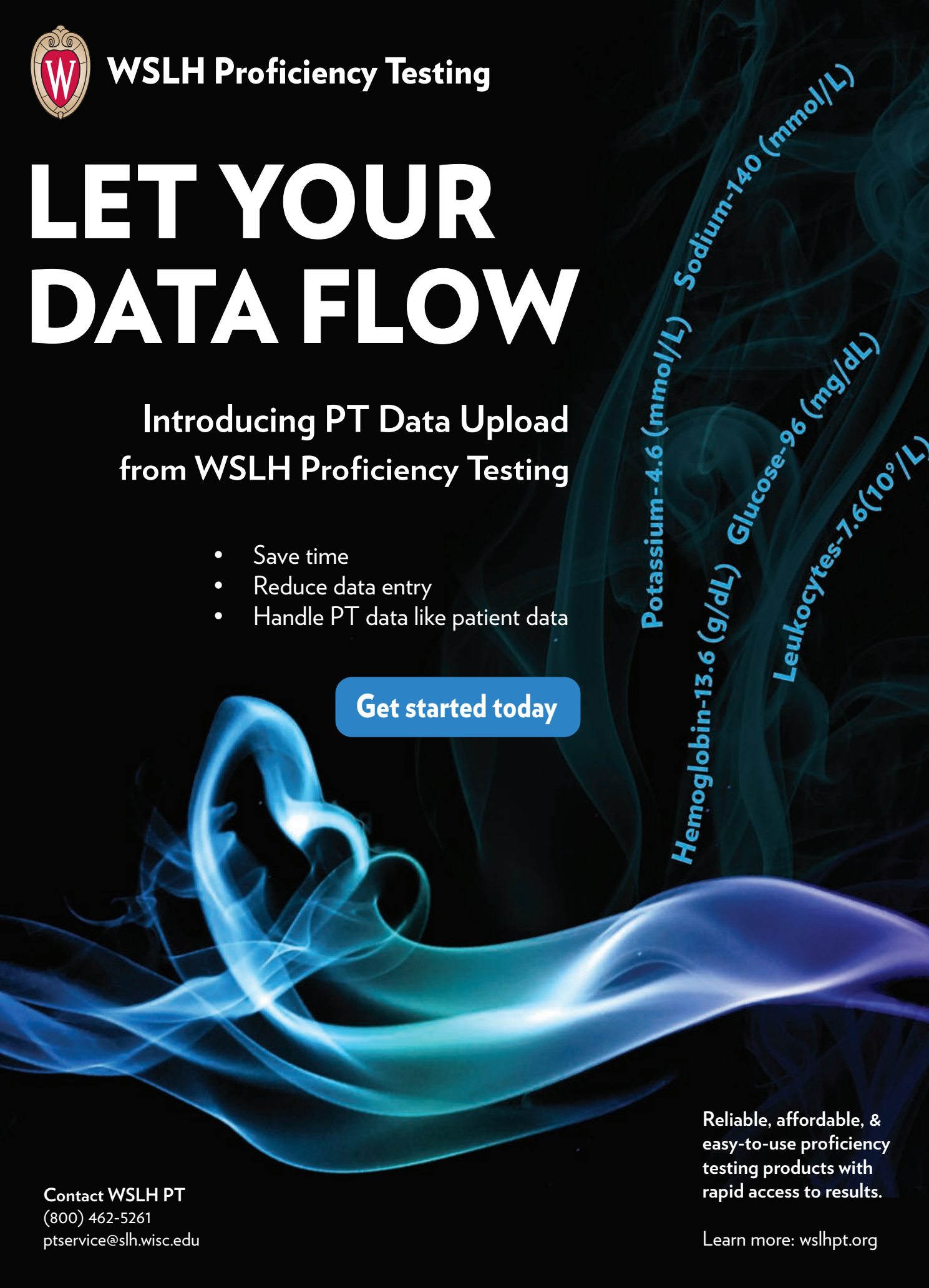
Against this backdrop, lab managers have adopted numerous strategies to retain staff.

According to a State of the Industry survey from *Medical Laboratory Observer* released in April 2020, the most common tactic is supporting continuing education. Nearly two-thirds, or 60 percent, of respondents said they do this, with 39 percent of them rating continuing education with a four or five on an effectiveness scale in which one is the lowest ranking and five is the highest. [6]

Lenox Hill Hospital requires most lab employees – including all medical technologists – to earn 12 continuing education credits annually, so the department pays for relevant webinars.

"We use continuing education credit requirements as an opportunity for laboratory staff to create opportunities for engagement. Webinars offer an excellent occasion for the team to learn about relevant topics and discuss its implications in a laboratory group setting," Turato said.

Outside of webinars, lab managers create other opportunities for education. For example, the department hosts an annual Evening of Cytopathology event. The cytology team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"chooses a topic of interest and invites a nationally recognized speaker in the discipline to present a conference to the cytopathology community in the metropolitan area," Turato said.

Jon Harol, Founder of Lighthouse Lab Services, a management consulting firm that also operates a recruiting service, suggested that labs reimburse employees for the costs associated with sought-after certification programs – such as in blood banking or molecular biology – and then tie that investment to a commitment from the employee to stay at the institution for a specified number of years. "I think that is a great partnership opportunity because it benefits both of them," he said.

While paying for such a program might seem expensive, it may be cost effective in comparison to the expense of recruiting and potentially relocating a candidate from outside the organization. And lab managers may find themselves paying for a signing bonus as well, he said.

Turato said her lab does not pay for certification programs, but Lenox Hill Hospital's parent organization, Northwell Health, does offer reimbursement for traditional degree-seeking programs.

Other tactics lab managers use to retain staff include clinical ladders (33 percent), which allow staff to climb steps within a job title, such as from novice to expert, and daily huddles (40 percent), according to the *MLO* survey.[6]

Climbing career ladders

Career ladders are popular with staff because they provide employees with opportunities to advance in the profession. "A lot of people have been in the field a long time, and I think they get frustrated when there is one lab manager and two supervisors and everybody else is staff," Harol said.

"You are not able to create more lab directors, but you are able to create more levels," he said, such as level one, two and three for medical technologists. Harol suggested that labs create two tracks in the career ladder: one for managerial skills and a second for technical knowledge.

A study involving 23 clinical laboratories, which was conducted by the American College of Pathologists (ACP), suggested that career paths and continuing education were associated with lower turnover rates. The three-year turnover rate for all lab staff was 3.3 percent lower for labs that develop career paths and 3.6 percent lower for labs that provide funding for external continuing education, compared with labs that did not implement these strategies.[7]

Staff huddles

Staff huddles are another recruitment option. At Lenox Hill Hospital, "our weekly 'Let's Connect' meetings are short, 15-minute departmental huddles, which offer a chance to reignite our passion for laboratory science while learning how to connect with our patients and customers and celebrate team members' outstanding contribution to these causes," Turato said.

Giving people an opportunity to lead projects is another way to promote career advancement within the lab, Harol said.

Turato said, "We routinely involve our team members in performance-improvement projects, quality initiatives and workflow design, which ensures that any solutions implemented are built from the ideas and input of the users."

Harol recounted an anecdote about a lab manager who surveyed the laboratory scientists on her staff to find out what kinds of activities they would like as a reward. What she found is that staff members had different ideas about the type of activities that motivate them. For example, some staff members liked the idea of going out on a sales call to a potential outreach client, while others liked the idea of working on the laboratory information system (LIS).

"I don't think most managers have gone to that level of understanding, so they end up hurting morale because they are making the person who doesn't want to go on a sales call go on one, and they are making someone else who doesn't want to work on the LIS system be part of that. If they align people and what motivates them with the task that needs to be done, everybody would be happy. That is a realistic solution," Harol said.

Managers at the Minnesota Public Health Lab also work to develop career opportunities for staff members, according to an article in a 2019 issue of *Public Health Reports*. The public health lab encourages staff to create an individualized career development plan, which allows "staff members to maximize job duties that play to their strengths, prioritize learning objectives, and identify leadership opportunities," the authors wrote.[8]

In a 2018 survey of 122 employees, the Minnesota Department of Health found that career-growth assignments, such as short-term projects or mentoring opportunities, impacted job satisfaction in a positive way.[8]

Continuing education, staff huddles, and career-advancement strategies also help nurture a positive culture within the lab, making it a more appealing place to work. "I don't find medical lab scientists to be super money-motivated. If we call a scientist and are able to offer $1 or $2 more an hour to go to the lab across the street and they are happy where they are, they are not going to move for that," Harol said.

Harol said negative cultures fester when managers favor certain employees over others, such as when developing shifts and schedules and sharing important information. Instead, Harol urged managers to treat everyone fairly and communicate openly.

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Myths and misconceptions about male menopause

Certain disorders have a stigma in many societies for no legitimate reason other than they are not considered "polite" topics of conversation – examples include hyperhidrosis, or excessive sweating; psoriasis, which causes cracked, scaly skin; and male menopause, during which men can experience a range of symptoms and changes as they grow older.

Male menopause and another term, andropause, are used to describe decreasing levels of the male hormone testosterone that come with aging. The group of symptoms associated with age-related changes in male hormone levels are also known as testosterone deficiency, androgen deficiency, and late-onset hypogonadism.

Not just fighting a stigma

Not only is there an unwarranted stigma against discussing male menopause that physicians and those working in the healthcare industry have to fight against, some question whether the condition really exists at all. The name itself is misleading. Relating the process to female menopause is not accurate: the condition affects only some males, while menopause is a natural part of female sexual development. The hormone change happens suddenly and dramatically in women, while in men, the change is gradual.

While only a small percentage of men are affected by male menopause, it is important that men feel comfortable discussing all aspects of their health with their care providers. The first step in fighting any kind of misinformation and/or stigma is education. After all, the more you know, the more power you hold.

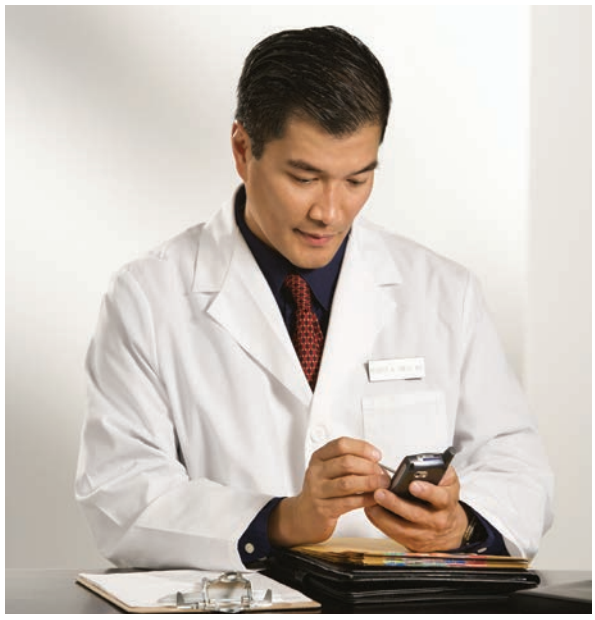
A murky picture

Male menopause causes several physical, sexual, and psychological problems that worsen as men age. (See Table 1) While some of these symptoms are similar to what women experience as they go through menopause, there are additional reasons why the term male menopause can be misrepresentative. Testosterone and other male hormones decrease slowly and gradually. The symptoms of female menopause are linked to estrogen levels, but the cause of symptoms in men is unclear, and some men with relatively high levels of testosterone still experience symptoms.

Common symptoms of male menopause	
Low energy	Gynecomastia, or development of breasts
Depression or sadness	Decreased bone density
Decreased motivation	Erectile Dysfunction
Lowered self-confidence	Reduced libido
Difficulty concentrating	Infertility
Insomnia or difficulty sleeping	Swollen or tender breasts
Increased body fat	Decreased testicle size
Reduced muscle mass	Loss of body hair
Feelings of physical weakness	Hot flashes

Table 1. Common symptoms of male menopause (Content courtesy of Sekisui Diagnostics).

To muddy the water further, experts do not believe that normal, age-related decline of testosterone levels triggers male menopause symptoms. If so, every man would experience them. Doctors do know that symptoms tend to occur in older males with heart disease, obesity, high blood pressure, and type 2 diabetes. Several underlying lifestyle problems are also risk factors, including lack of exercise, smoking, alcohol consumption, stress, anxiety, and sleep deprivation.



Dreamstime

Diagnosis and treatment

Any man who experiences symptoms should make an appointment with his doctor, and this is the major hurdle for most men. Doctors can try to overcome this by talking with patients about male menopause during annual physicals. Once a patient visits his doctor, a series of blood tests can easily diagnose whether low testosterone is the cause.

Once diagnosed, treatment can include testosterone replacement therapy or prescription medication, but less drastic steps may also help. The side effects of testosterone therapy can include acne or oily skin, fluid retention, stimulation of prostate tissue, breast enlargement, worsening of sleep apnea, and decreased testicular size.

Healthier lifestyle choices, such as diet changes, more sleep, exercise, and treatment for depression or anxiety can help alleviate symptoms. For many men, the symptoms of a decline in testosterone levels are manageable without treatment, but the first step should always be meeting with a healthcare provider without worrying about public perceptions.

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Assure Tech	http://www.diareagent.com/news_details_45.html	Assure COVID-19 IgG/IgM Rapid Test Device	IgG/IgM Rapid Test Device	IgG/IgM Rapid Test Device	15 minutes
Autobio Diagnostics	https://catalog.hardydiagnostics.com/cp_prod/product/rta0203-anti-sars-cov-2-rapid-test-covid-19-50-tests-per-kit-by-autobio-diagnostics-rapid-id-test-kits	Anti-SARS-CoV-2 Rapid Test	IgM and IgG, Lateral Flow Immunoassay	N/A	15 minutes
BD	https://www.bd.com/en-us/offerings/capabilities/microbiology-solutions/point-of-care-testing/bd-veritor-sars-cov-2	BD Veritor System	Immunoassay	BD Veritor Plus Analyzer Instrument	15 minutes
Beckman Coulter	https://www.beckmancoulter.com/products/immunoassay/access-sars-cov-2-igg-antibody-test#/overview	Access SARS-CoV-2 IgG assay	IgG Antibody Test	Access 2, DxI 600, DxI 800	25 minutes
Biohit Healthcare	http://www.biohit.cn/en/info_97.aspx?itemid=506	Biohit SARS-CoV-2 IgM/IgG Antibody Test Kit	IgM and IgG Lateral Flow	N/A	15-20 minutes
Bio-Rad Laboratories	https://www.bio-rad.com/en-us/sku/72710-platelia-sars-cov-2-total-ab-assay?ID=72710	Platelia SARS-CoV-2 Total Ab Assay	Total Antibody, FMIA	N/A	30 minutes
DiaSorin	https://www.diasorin.com/sites/default/files/allegati/liaisonr_sars-cov-2_s1s2_igg_brochure.pdf.pdf	LIAISON SARS-CoV-2 S1/S2 IgG	IgG, CLIA	LIAISON XL analyzer	35 minutes
Emory Medical Laboratories	https://www.fda.gov/media/139052/download	SARS-CoV-2 RBD IgG Test	IgG, ELISA	N/A	N/A
EUROIMMUN	https://www.coronavirus-diagnostics.com/antibody-detection-tests-for-covid-19.html	Anti-SARS-CoV-2 ELISA (IgG)	IgG, ELISA	N/A	1 hour
Hangzhou Biotest Biotech	http://en.biotests.com.cn/product/278199748	RightSign COVID-19 IgG/IgM Rapid Test Cassette	IgM and IgG Lateral Flow	N/A	10 minutes
Healgen Scientific	https://www.healgen.com/if-respiratory-covid-19	COVID-19 IgG/IgM Rapid Test Cassette	IgM and IgG Lateral Flow	N/A	10 minutes
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Mount Sinai Laboratory	https://www.fda.gov/media/137029/download	COVID-19 ELISA IgG Antibody Test	IgG, ELISA	N/A	N/A
Ortho-Clinical Diagnostics	https://www.orthoclinicaldiagnostics.com/en-us/home/ortho-covid-19-answer	VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack	IgG, CLIA	Used in combination with the VITROS Immunodiagnostic Products Anti-SARSCoV-2 IgG Calibrator on the VITROS ECi/ECiQ/3600 Immunodiagnostic System and the VITROS 5600/XT 7600 Integrated Systems	N/A
Roche Diagnostics	https://diagnostics.roche.com/us/en/products/params/elecsys-anti-sars-cov-2.html	Elecsys Anti-SARS-CoV-2	Total Antibody, ECLIA	cobas e 411, cobas e 601, cobas e 602, or cobas e 801 analyzers	18 minutes
Siemens Healthineers	https://www.siemens-healthineers.com/en-us/products-services	ADVIA Centaur SARS-CoV-2 Total (COV2T)	Total Antibody, CLIA	ADVIA Centaur XP and ADVIA Centaur XPT systems	14 minutes
Siemens Healthineers	https://www.siemens-healthineers.com/en-id/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/cov2t-assay	Atellica IM SARS-CoV-2 Total (COV2T)	Total Antibody, CLIA	Atellica IM Analyzer	10 minutes
Siemens Healthineers	https://www.fda.gov/media/138754/download	Dimension EXL SARS-CoV-2 Total Antibody Assay (CV2T)	Total Antibody, CLIA	Dimension EXL integrated chemistry system with LOCI Module	16 minutes
Siemens Healthineers	https://www.siemens-healthineers.com/en-id/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/cov2t-assay	Dimension Vista SARS-CoV-2 Total Antibody Assay (COV2T)	Total Antibody, CLIA	Dimension Vista System	N/A
Vibrant America Clinical Labs	https://www.vibrant-america.com/covid-19/	Vibrant COVID-19 Ab Assay	IgM and IgG, CLIA	N/A	N/A

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Metagenomics – a current snapshot and future forecast

By John Brunstein, PhD

Metagenomics is the term for applying untargeted next-generation sequencing (NGS) to specimens – sometimes from unlikely sources, such as swabs of cell phones or bus seats, as well as more traditional clinical sample types – with a goal to identify and enumerate to a species level all of the different organisms present.

This space has looked at this topic before in its use as a targeted means to probe for novel pathogen(s) in association with conditions of unknown etiology, but the uses of metagenomics go beyond this and are in some cases informing a much deeper understanding of previously unguessed human-microorganism interactions. In this episode of The Primer, we will touch on what some of these are and where this may lead in the future.

Metagenomics – the method

First, a very brief refresher on how the process works. A sample is obtained; DNA is extracted; depending on platform, some form of untargeted library preparation is done; NGS is performed on the library; and data is sent to a bioinformatics pipeline. Simplistically, this usually involves removal of all human-derived sequences, and then testing each remaining read against databases, such as Genbank, for identity with, well, anything non-human. Depending on sample type, this can include all sorts of environmental contact DNA (which can be interesting and likely has uses in applications such as forensics), but for more mundane clinical sample types, the majority of non-human DNA of interest is microbial.

Each read is either unassignable (no definitive homology found), or else is tallied as coming from a particular organism. Organisms that are high abundance in the sample tally up more "hits" than ones in low abundance (loosely; genome size has an impact here, too, but can be corrected). The end is a list of what organisms – and on a relative ratio, how much of each – were present in the input material. In a microbial context, this concept is referred to as the microbiome of the sample.

Technical variations sidebar

Metagenomics as described above, based on "shotgun sequencing" (random sampling and sequencing of all nucleic acids) by its nature, can provide the most widespread and comprehensive image of the microbiome, including bacteria, fungi, and (DNA) viral components (bear in mind this, for example, could include things such as bacteriophages, which can indirectly impact the human source, by modifying bacterial virulence).

If only bacteria, strictly, are of interest, then degenerate primers to a commonly shared but variable region, such as the 16S rRNA gene, can be used to PCR amplify a presumably not too badly biased library of fragments suitable for analysis. While narrower in focus, aspects of library preparation may be easier in this approach and truly miniscule sample inputs are required. In general, the applications of either method are similar, and we will not distinguish between these approaches further.

Gut feelings – more than just a term?

One of the most fascinating applications of metagenomics has been in the analysis of gut microbiomes, and what it has turned up. It's easy to imagine how this might impact issues such as food tolerance, as microbial activity can produce secondary metabolites, which can be absorbed by the host and have biological activities (positive or negative, and with that distinction likely having some variation from host genetic factors). What might come as more of a surprise, however, is the now-overwhelming evidence that gut microbiome can have significant implications for neurological functions – what is known as the "gut-brain axis."The list of neurological conditions which have demonstrated potentially causal correlates to variation in gut microbiota include Parkinson's Disease, schizophrenia, autism spectrum disorders (ASD), and anxiety.

Some of this may be attributable to direct microbial impacts on serotonin metabolism. An important neurotransmitter, serotonin (aka 5-hydroxytryptamine or 5-HT) is primarily known for its induction of feelings of well-being or happiness. Perhaps unexpectedly, the majority of serotonin (estimated at ~95 percent) is produced by neurons in the gut, not the brain, and their synthetic activity for this compound is influenced by microbiome composition. Intriguingly, mouse models of depression have shown positive responses to increased Lactobacillus levels in the gut.

That this might translate to a basis for treatment of mood disorders in humans has not gone unnoticed, with some trials having been made with both prebiotic dietary supplements (food components which can bias gut microbiome composition by selectively supporting growth of some microbial types over others) and probiotics (basically, edible cultures of actively reproducing, presumed beneficial intestinal flora such as Lactobacillus and Bifidobacteria species), which can help to increase the number of these species in the microbiota.

Results of these trials are not completely clear-cut as multiple conditions (and perhaps even multiple underlying etiologies within those) have been examined, but at least some (e.g. generalized depression, but not schizophrenia) have shown statistically relevant improvements above both baseline or traditional antidepressive drug therapy.

A second mechanism whereby abnormal intestinal microbiota composition (dysbiosis) can influence neurological condition is by triggering chronic inflammatory responses. Cytokines produced locally in response to this circulate systemically, and either directly cross the blood-brain barrier, cross in the form of activated and secreting circulating immune cells, or otherwise indirectly influence inflammatory responses in the central nervous system (CNS).

Evidence suggests this can have adverse effects on memory and cognitive abilities, as well as being linked with specific diseases. For example,

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current hypotheses suggest that gut dysbiosis may be a key triggering event in Parkinson's disease, and there is evidence that routine use of non-steroidal anti-inflammatory agents (NSAIDs such as acetylsalicylic acid "Aspirin" or ibuprofen) correlates with reduced progression of Alzheimer's disease.

On the surface

Another major site for human/microbiome interaction should come as no surprise – the skin. What is perhaps less expected though is that the skin microbiome differs across the body (for a fascinating figure depicting this, and a broader discussion in context, see [1]). Variations between individuals is also quite broad, although Staphylococcus, Propionibacterium, and Corynebacterium species generally make up the major constituents of most locations on most individuals; variability is primarily observed in distribution of less-common constituent organisms. Aspects including geographic locale, occupation and related environmental exposure, age, and perhaps even time of year might be expected to also play a role in this. Many of these organisms may be considered commensal, as they either act to out-compete and displace more potentially harmful microorganisms or directly influence the chemical microenvironment of skin in ways beneficial to the human host.

From a dermatological disease perspective, P. acnes subspecies present (but not total number) are associated with severe acne; increased number and subspecies diversity of Staphylococcus has been found in atopic dermatitis; and dysbiosis (although exactly of what form, or whether it's related to a single pattern of dysbiosis or just dysbiosis in general is unclear) appears to be a component of psoriasis. More broadly, there is evidence for bidirectional interaction between the human immune system and skin microbiota, with immune system deficits shown linked to alternate and more diverse microbiota profiles. Conversely, skin microbiota, either directly or through the activity of released metabolites, have been found to modulate inflammation and immunity in ways thought to be beneficial.

As with all correlations, drawing assumptions of causal links in absence of Koch's Postulate being fulfilled is unwise, but at least worthy of consideration as a possibility in lack of contradictory evidence. With this in mind, it's notable that as with gut microbiomes above, intentional manipulation of skin microbiome through application of both pre- and probiotics continues to be examined as a means to treat various conditions. More exotic applications for manipulation of skin microbiota, such as doing so with an aim to repel insect disease vectors, have also been postulated.

Back to diagnostics

So where does all of this impact the clinical molecular lab? Right now, probably only on the bleeding edge of research. As such research starts to produce supported correlates of microbiome composition to prophylaxis, diagnoses, or actionable medical interventions, however, it will likely start to become more common and perhaps even part of a routine clinical workup in some settings. That such methods can have clinical utility has long ago been shown in a context predating NGS: analysis of airway microbial composition in cystic fibrosis (CF) patients by traditional culture has long been a part of routine care. Supplanting culture with NGS just allows for a vastly more detailed picture to emerge than that available by culture.

The likelihood of increased clinical future application of metagenomics is supported by the technical side considerations that microbiome metagenomics can be done very cheaply in comparison to other NGS applications. Massive read depth is absolutely not needed in a microbiome – as opposed to specific pathogen detection context – because it's unlikely a species present at 0.01 percent of the population is very important. Samples from multiple patients can be readily multiplexed on a single instrument run; during each library preparation, a sample-specific "barcode" in the form of a short unique DNA sequence is appended to each captured random-template DNA.

Samples on a shared instrument run spread out the reagents, consumables, and labor costs, and may be demultiplexed bioinformatically post-run (reads are grouped by shared barcode). Subsequent bioinformatics workflow – identification and classification of microbiome constituents – is about as close to turnkey for the non-bioinformatics specialist as is possible, making meaningful downstream analysis potentially accessible to a wide range of laboratorians and clinicians. Finally, these processes are readily viable across all NGS platforms of either long- or short-read technology; whatever instrument(s) are available to your lab can be put to use for this. A combination of utility plus low barriers to implementation bodes well for increased use in the near future.

What such application would look like remains to be seen, but in broad strokes, it would likely consist of a surveillance microbiome taken from a relevant sample; a comparison of its composition in terms of relative microbial species, abundance, and diversity against a composite "normal" microbiome for the sample, based on population studies; and interpretation of any observed dysbiosis based, again, on preexisting associative study 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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Cleaning protocols for COVID-19 prevention

By Brenda Silva

Since the arrival of the SARS-CoV-2 virus, many regular routines that take place in the clinical lab have been directly affected, with daily cleaning and disinfecting practices at the top of the list. Established and existing protocols set in place by individual facilities and/or government agencies have been enhanced because of the seriousness of COVID-19, the disease caused by the SARS-CoV-2 virus, and its potential for infection, severe illness, and death. To date, there are over 13 million reported global cases of COVID-19 – a number that demands lab cleaning and disinfecting practices become a top priority in an effort to prevent as little further increase as possible.

Infection prevention and PPE

Two areas considered key to infection prevention among both lab and medical staff have always been the frequency of cleaning practices combined with the use of disposable personal protection equipment (PPE). With the devastating effects of COVID-19 already apparent on a worldwide scale, requirements for both PPE and cleaning frequency protocols have been increased to prevent new infections from occurring. However, one major challenge created by COVID-19 is the lack of readily available, single-use PPE, which has forced wearers to find secondary solutions for disinfection of daily-use items.

Increased frequency of lab cleaning and disinfection has become top priority in prevention of new COVID-19 infections.

Dan Scungio, MT (ASCP), SLS, CQA (ASQ), better known as Dan The Lab Safety Man, pointed out, "With national shortages of PPE, such as isolation gowns, surgical masks, and N95 respirators, many organizations have had to move to methods which both prolong the use of such items and disinfect them – something that was not previously done with disposable or single-use products."

He continued, "Processes like UV light sterilization and hydrogen peroxide mist treatments were tested and implemented in many organizations across the country. This brought forth the need for quality checks like respirator fit-testing and the use of biological indicators to ensure complete disinfection."

Adding to Scungio's comments, Kedar Patel, Senior Product Manager at Contec, noted, "The shortage of PPE (masks, gloves, gowns, etc.) has created many new temporary procedures. As an example, for Sterile Compounding Pharmacies, the FDA (U.S. Food & Drug Administration) issues guidance stating that in the event of PPE shortages, the facility should increase the frequency of cleaning and disinfecting – they also recommended the 'judicious' use of sporicidal disinfectants."

Patel added, "The CDC (Centers for Disease Control and Prevention) issued a similar guidance for acute healthcare settings but added that 'as PPE availability returns to normal, healthcare facilities should promptly resume standard practices.'"(Source: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html)

In addition to PPE disinfection, new protocols also address the increased frequency of daily cleaning and disinfecting of "high-touch" surfaces. Patel defines high-touch, or frequently touched areas, as "common surfaces that multiple people can touch within a short period of time like door handles, lab refrigerator handles, phones, armchairs, etc."

Kaumudi Kulkarni, MS, MSc, Senior Manager of Research and Development at Healthmark Industries, said, "Our R&D Laboratories are now getting cleaned and disinfected more frequently than before. Shared equipment is wiped with isopropyl alcohol after each use. During the middle of every workday, all high-touch surfaces in the labs get disinfected by wiping with isopropyl alcohol, and at the end of the workday, all work surfaces, equipment and lab tools are disinfected by the laboratory personnel. The facilities team then comes in and wipes the floors, blinds and top of the cabinets with a bleach solution."

Changes to existing PPE protocols

One of the most common and important responsibilities for laboratory personnel is knowing when PPE protocols must be followed, and the duration of time that the PPE must be worn during any procedure or practice. With the heightened awareness of COVID-19's rapid rate of infection, a higher emphasis has subsequently been placed on the wearing of PPE at all times by lab personnel. This change has left some lab managers and staff looking for guidance on what qualifies as PPE and what does not.

Kulkarni reported, "All laboratory personnel now wear face masks all the time in the labs and in the offices. All employees get a mandatory wellness screening before entering the premises. New face masks are required to be used every day, and face shields are made available to be used if needed."

Offering more detail, Scungio explained, "Much has evolved in the past few months regarding PPE protocols in hospitals, and there has been a great deal of confusion for managers and lab staff as a result. Some facilities have

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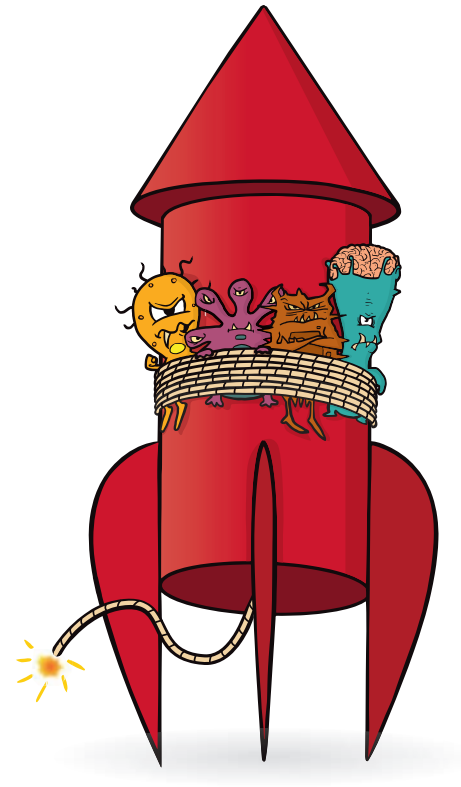

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moved to requiring staff to change clothes before leaving work if they have direct patient contact. In addition to usual PPE (lab coats, gloves, etc.), lab staff have moved to wearing face masks (N95 respirators in some hospitals) and goggles or face shields at all times. While it was considered normal to need face protection when a risk for splash existed, what was new was using face masks and face or eye protection at all times – even when leaving the lab in some locations."

He continued, "Some facilities decided that cloth or homemade masks were not sufficient in areas where staff work closely together, so only surgical masks were permitted. Other facilities began to require masks for all staff whenever inside any part of the facility, even in clean areas such as cafeterias and hallways. In normal circumstances, OSHA (Occupational Safety and Health Administration) does not allow PPE used inside the lab to be taken out of the department. Under the new guidelines, are masks considered PPE? Can goggles or face shields be worn outside of the department? These are issues that have had to be addressed in many facilities."

New normal for labs

In much the same way that COVID-19 shows no signs of stopping anytime soon, so do the new and enhanced lab protocols that are now being considered the new normal going forward, regardless of the finality of COVID-19 on a global basis.

Scungio asserts, "Most of the changes occurred due to shortages of disinfectant products and PPE. As some supplies slowly become more available, many organizations are reverting back to standard use and disinfection processes. When the next virus spike occurs, it is possible there will be another run on such products, but hopefully businesses will have a better handle on supply chain management going forward."

Patel sums up, "These uncharted times have only heightened the vulnerability of facilities for disaster preparedness. Practices, protocols, and contingency plans are being developed, stressed, and challenged to ensure best chance for success. Based on adoption and procurement of consumables, we may be well on our way to a new 'normal,' and that much wiser for the next potential hurdle to be faced."

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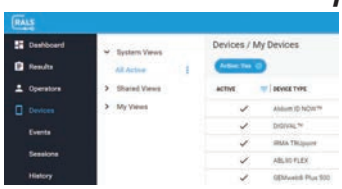

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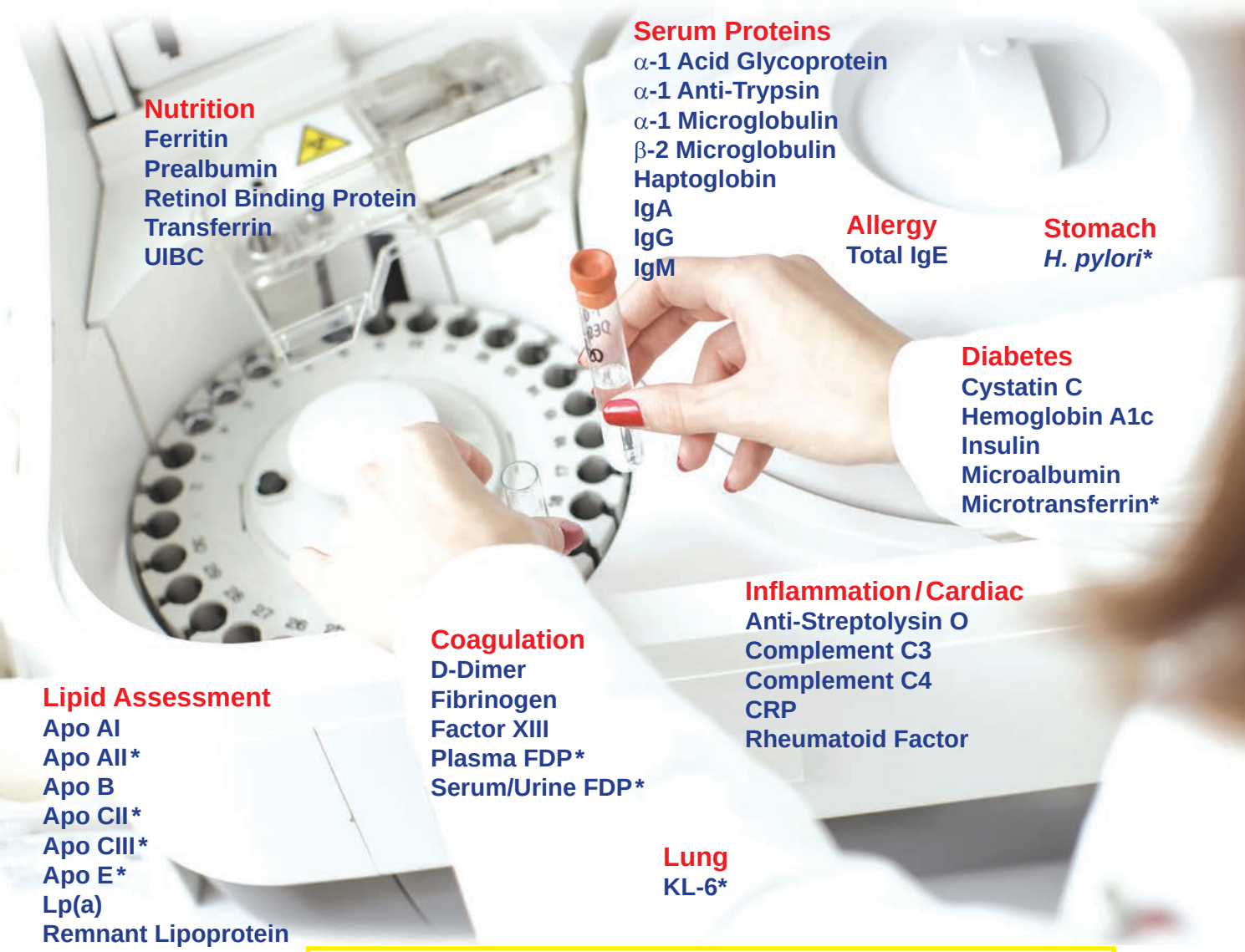

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Pediatric testing protocols prepare for next pandemic

By Brenda Silva

Rebecca M. Harris, MD, is the Director of the Infectious Disease Diagnostics Laboratory at Children's Hospital of Philadelphia. Board-certified in Clinical Pathology and Medical Microbiology, she received her MD from the Medical University of South Carolina, Charleston.

Based on your professional experience and focus on clinical pathology and medical microbiology, what led you to your current position at Children's Hospital of Philadelphia?

Children's Hospital of Philadelphia (CHOP) is a stellar institution. The Infectious Disease Diagnostics Lab, as well as the division at large, are full of passionate, talented people. It was also clear that CHOP is willing to put resources toward clinical innovation in the lab. I was practicing general clinical pathology in my previous role, but microbiology has always been my first love. So, I jumped at this opportunity when it became available to me.

How do test development protocols differ when intended for pediatric versus adult patients/medicine?

I believe innovation and more extensive validations of commercial products are often a necessity for labs in children's hospitals. There may not be a commercial test available to meet a pediatric testing need, or manufacturers may not have evaluated the tests for a pediatric population. I believe children's hospitals have been leaders in lab-developed molecular testing for that reason; for example, in the use of lab-developed respiratory viral panels before the availability of commercial respiratory viral panels (RVPs).

What do you see as potentially the "new normal" in pediatric testing with regard to infectious diseases, and do you think influenza and COVID-19 can coexist if necessary as we go into the second half of the year?

While hoping for the best, we are preparing our lab for the potential of an unprecedented viral season that includes both flu and COVID. We are planning to add the SARS-CoV-2 assay to our RVP, and we are looking critically at our ability to provide sufficient rapid testing (for flu, as well as for the coronavirus) if commercial rapid tests remain in short supply.

With many diagnostic companies looking to partner in developing rapid tests to detect SARS-CoV-2 (the virus that causes COVID-19), why did CHOP decide to develop their own test?

We chose to develop our assay because it was the only option. Only the CDC (Centers for Disease Control and Prevention) and public health laboratories had authorization for testing when we began development, and no commercial test had received an FDA (U.S. Food and Drug Administration) Emergency Use Authorization (EUA). We knew we would want to test in-house since access to testing was limited. We hoped the FDA would loosen the initially stringent requirements for test authorization, which is what fortunately happened. We have continued using our LDT (lab-developed test) because we are happy with its performance, and we experienced very few problems in the supply chain for test materials.

What were some of the biggest challenges in developing your molecular lab-developed test (LDT) for detecting COVID-19 (SARS-CoV-2 RT-PCR test) and getting an Emergency Use Authorization (EUA) from the FDA?

There was tremendous pressure to develop a test, and we were racing against the spread of the virus. We completed most of the validation in a little over a month. We threw everything we had toward the project and, fortunately, had skilled technologists well-versed in molecular test development. The entire lab chipped in to complete the validation process in a short amount of time. The FDA initially had specific requirements for the validation studies to obtain an EUA, which differed significantly from what we would usually do for validation, more akin to what a manufacturer would do to obtain FDA approval to sell a product. The FDA eventually relaxed those requirements.

The recommendations for testing – like using paired nasopharyngeal and oropharyngeal swabs – and the requirements for the test itself – like having multiple targets – seemed to change almost daily. So, we made a number of modifications during the validation process. It was difficult to obtain the type of positive reference material required by the FDA for validation studies because almost no one in the U.S. had positive samples. January of 2020 feels like a different world. So far, we have been fortunate to meet our testing needs with our LDT, but we will need thoughtful management of our resources and further innovation as we contend with this ongoing pandemic going forward.

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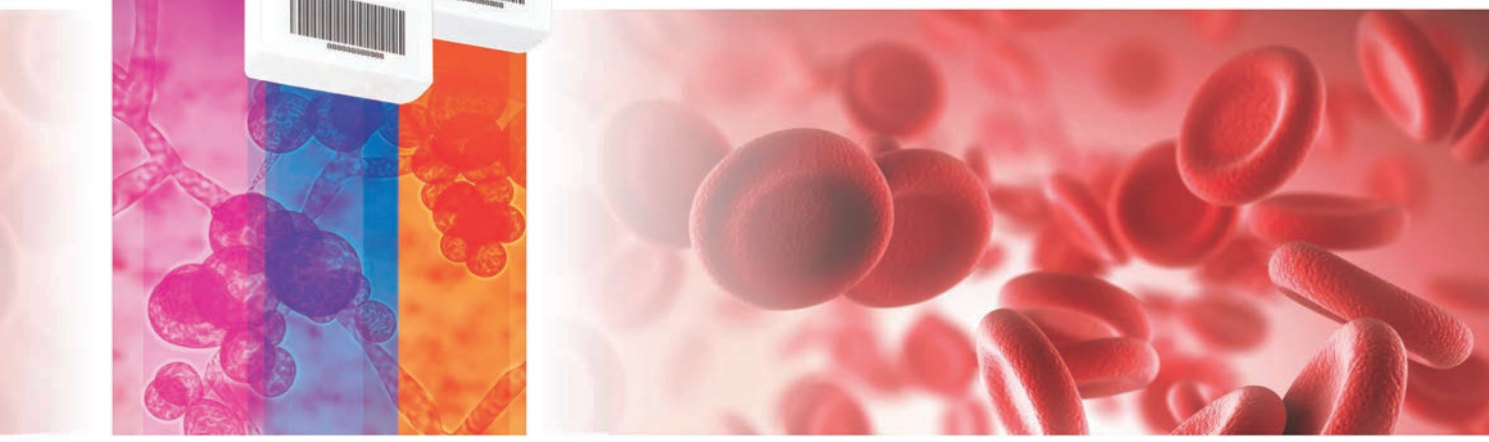

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[1]Timbrook, et al. (2017) **The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis.** Clin Infect Dis. 64(1):15-23

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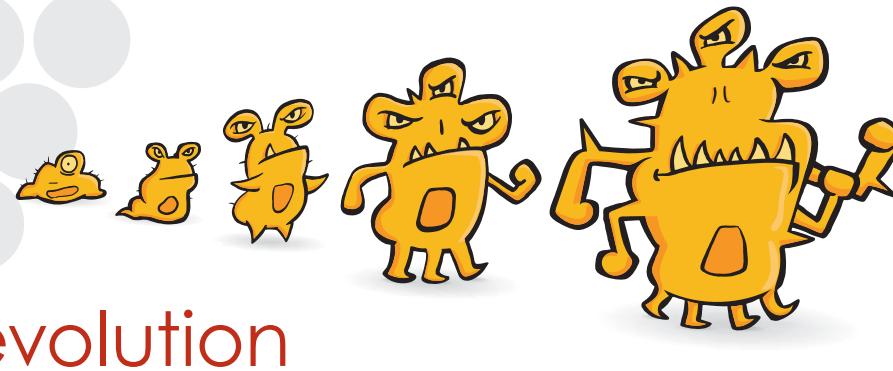

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