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Features

8 Molecular Point-of-Care Testing in Clinical Laboratories
Laboratorians can lead a new era in rapid testing with expertise in quality control and result interpretation

16 COVID-19 Is a Catalyst for Remote Sampling and Telemedicine
Clinical laboratorians see the potential, and the limitations, in a push to move testing outside labs

22 Critical Value Change
Labs consider pros and cons of implementing new hypoglycemia target based on limited evidence

Departments
02 Federal Insider
04 Bench Matters
06 The Sample
26 Special Section: Lab Stewardship Focus
30 Regulatory Roundup
32 Industry Playbook
36 Ask the Expert

If a commercial clinical lab tests specimens from European citizens with LDTs, these LDTs are likely to be considered “distance sales” under the new regulations, meaning that the tests will require CE IVD marking.

p36
Federal Insider

HHS Still Working to Distribute Paycheck Protection Program Funds for Testing

The Department of Health and Human Services (HHS) announced several ways it will be using certain limited funds for COVID-19 laboratory testing from the Paycheck Protection Program and Health Care Enhancement Act passed by Congress in April.

Rural health clinics are a special focus. HHS, through the Health Resources and Services Administration (HRSA), is providing $225 million to rural health clinics for COVID-19 testing that will support some 4,500 clinics across the country. Rural health clinics are a special designation given to healthcare practices in underserved rural areas by the Centers for Medicare and Medicaid Services. Each clinic receives up to $50,000.

“The funding may be used for a wide range of COVID-19 testing and related expenses including planning for implementation of a COVID-19 testing program, procuring supplies to provide testing, training providers and staff on COVID-19 testing procedures, and reporting data to HHS on COVID-19 testing activities,” said HRSA Administrator Tom Engels. “Funds may also be used for building or construction of temporary structures, leasing of properties, and retrofitting facilities as necessary to support COVID-19 response.”

States receiving the greatest share of the funds include Texas, Missouri, Kentucky, and California.

HHS is also allocating $250 million for the hospital workforce and virtual healthcare. The money must go toward workforce training, expansion of telemedicine, and procurement of supplies and equipment. In addition to supporting healthcare capacity for COVID-19, the money also goes to the National Special Pathogen System to prepare for future pandemics.

AACC Calls for Integrated COVID-19 Testing Strategy

In a letter to Sens. Mitch McConnell and Chuck Schumer, AACC laid out a series of recommendations to increase testing capacity for COVID-19 and help prevent a second wave of infections. After the House of Representatives passed the $3 trillion HEROES Act on May 15, it’s now up to the Senate to begin negotiations on what could be the final large fiscal response to the coronavirus pandemic in the U.S.

AACC is asking senators to focus on a more integrated testing strategy that increases coordination across all levels of government. “Federal, state, and local agencies must employ shared terminology and have similar understandings of the problems that need to be addressed, specific goals for combating them, and the resources needed to succeed,” the letter says. The association is also underscoring the need for the federal government to ensure that supplies are manufactured and distributed to labs in a timely manner. The letter notes that laboratories and states still have to compete with one another for supplies.

Another issue government should tackle is the expansion of COVID-19 antibody testing, AACC says, as not all serology tests are of the same quality. AACC recommends that the federal government use its oversight authority to certify the quality of antibody tests and ensure adequate reimbursement to guarantee widespread patient access to appropriate testing.

Funding for the nation’s public health infrastructure and healthcare providers is also at the top of the list. The letter notes that federal expenditures for the Centers for Disease Control and Prevention (CDC) remain at fiscal year 2008 levels when adjusted for inflation. “It takes time to hire and train personnel, develop and implement response strategies, and identify and adopt useful reporting measures,” the letter says. “AACC urges additional funding be provided to the CDC to carry out its duties.”

Finally, Congress must act to safeguard the financial solvency of healthcare providers themselves. The association emphasizes that hospitals and commercial laboratories face significant losses of revenue due to the pandemic. While earlier coronavirus response bills gave some support, many providers still are struggling, and some hospitals have reduced the hours of or furloughed clinical laboratory professionals.

AACC calls for integrated COVID-19 testing strategy
New Aptima® assays are evolving the standard in vaginitis testing.

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References:
Effective quality assurance (QA) in point-of-care testing (POCT) requires a comprehensive, interdepartmental approach. Key elements for success include focusing clearly on quality indicators (QI), harnessing technology, training and recertifying current operators, and fostering proactive collaboration among users supported by trained POCT personnel.

POCT tracks with widespread and evolving patient care protocols. We have experienced this growth at University of Minnesota Medical Center, M Health Fairview, an integrated academic and research institution in Minneapolis that comprises three hospitals with a 1,057 bed capacity, free-standing and hospital-based clinics, inpatient and outpatient specialty hospital units, emergency departments, a surgery center, and research operations. Throughout these care sites, we offer 30 types of POCT, supporting approximately 4,000 healthcare providers.

My POCT colleagues and I have implemented an approach to ensuring POCT QA regulatory compliance that functions effectively in our large and diverse organization.

**MANAGING WHAT WE MEASURE**

The foundation of our plan rests on defining, monitoring, and assessing QI. We’ve created statistical measures across testing platforms to capture the performance of QI. Examples of measurable QI include labeling of reagent bottles with expiration dates, auditing the cleaning and disinfecting of POCT instruments, surveilling instrument errors in relationship to operator error and testing material wastage, and consistently documenting quality control (QC) of testing materials according to manufacturers’ instructions.

We also actively participate in our organization’s regulatory and standardization committees. Developing lines of communication through these committees has been essential in enabling us to provide technical advice. Our presence at these meetings also has helped us obtain senior nursing and medical leadership support in approving and enforcing POCT regulatory compliance.

Additionally, we thoroughly understand The Joint Commission’s and College of American Pathologists’ (CAP) governing guidelines and educate end users about appropriately using these regulations.

**SCHEDULING TASKS, REVIEWING PROCEDURES**

We create, monitor, and document completion of daily, weekly, monthly, biannual, and annual tasks related to regulatory compliance. We developed these tasks based on POCT manufacturers’ requirements for testing and in accordance with hospital accrediting agencies. For example, we perform QC on new lots and new shipments of testing materials, calibrate POCT instruments monthly, and certify operators annually.

Another aspect of our QA involves performing Gemba walks through hospital units and clinics. This element of Lean and Six Sigma consists of observing how POCT processes take place, requesting feedback from providers, and delivering answers and solutions to concerns or problems that might arise.

We maintain QA compliance by reviewing POCT procedures biennially or as needed to address important
changes, ensuring that we incorporate into our procedures the technical verbiage in CAP checklists.

We’ve taken several steps to ensure that POCT operators have comprehensive, upfront training and maintain their competency. We provide regulatory and technical support to M Health Fairview’s nursing core orientation, and we periodically audit and assess POCT-related training and procedures. We also identify proficient and reliable employees to function as preceptors who observe, evaluate, and certify users in correctly performing the annual testing process.

We couple upfront compliance expectations with a three-step process for warning POCT users that their competencies are overdue and privileges will be suspended if their competencies are not completed. The process starts with an email reminder to each user and his or her manager. If necessary, we send a second email to the user, his or her manager, and director. After the second warning, the user will be locked out from performing POCT. In some cases, a test might be stopped or removed from a unit until a process improvement plan is established to restore compliance.

**USING TECHNOLOGY**

Tracking compliance manually for approximately 4,000 users would simply be impossible. We use a learning module system (LMS) to assign certification lessons for waived and non-waived testing, respectively, and review LMS reports monthly to assess compliance. In the case of waived testing, we follow up with QC performance at least once each year. For non-waived testing, we schedule annual observations during skills fair day, through individual arrangements, or during monthly faculty meetings.

We also take full advantage of POCT instrumentation interfaces and software configurations to facilitate compliance monitoring. For example, we utilize a POCT middleware alert system designed with at least two elements of compliance to remind staff of their certification expiration dates and the need to review their annual learning module. We also deploy instrument lock-out settings to ensure end user compliance, use instrument interfaces to transmit results to medical records, and monitor QC through the Levey and Jennings function.

Another way we harness technology is by creating and implementing interactive, remotely accessed electronic QC logs. These handy metrics feature pop-up alerts and messages to end users to ensure QC and regulatory compliance.

A feasible, clear, and comprehensive action plan—effectively shared and implemented across the organization—is vital to sustaining POCT compliance. In a successful strategy, all processes performed are interconnected and interdependent in a synergistic relationship that ensures the efficacy of the approach.

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The author gratefully acknowledges the participation of Ryan J. Strand, MLS (ASCP)CM, Sheree Humphries, MLS (ASCP)CM, Carmen L. Dorschner, MLT (ASCP), and Jessica Kopecky, MLS (ASCP)CM, in their daily POCT work and in writing and reviewing this article, with special thanks to Chris Senn, MLS (ASCP)CM.
Phosphate-Buffered Saline Reliable for Transporting SARS-CoV-2 Samples

Researchers at Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey, report that phosphate-buffered saline (PBS) is a “dependable transport medium for use with clinical samples” in detecting SARS-CoV-2 (J Mol Diagn 2020; doi.org/10.1016/j.jmoldx.2020.04.209). In comparing quantitative polymerase chain reaction (qPCR) results on 20 samples from two subjects, the investigators found a “strong correlation” between cycle threshold (Ct) values in samples transported in PBS or viral transport media (VTM), whether processed immediately or stored at room temperature and processed at intervals of up to 18 hours.

In light of continuing shortages of VTM during the COVID-19 pandemic, the investigators posited that PBS would be a viable transport medium and alternative to VTM for clinical qPCR testing. The Food and Drug Administration has authorized laboratories to consider testing alternative transport media for use with SARS-CoV-2 samples.

The investigators tested PBS- and VTM-transported samples in three experimental procedures using discarded respiratory secretions from 16 confirmed COVID-19 patients. In the first procedure, they collected eight samples from two patients at the same time, transported them in either PBS or VTM, and processed two samples from each patient immediately and after 2 hours at room temperature. The second procedure involved 20 samples each from two subjects, kept at room temperature and processed at 0, 2, 4, or 6 hours or overnight. The final procedure involved 24 samples from 12 patients, transported in either PBS or VTM and processed immediately.

The researchers compared Ct values for the SARS-CoV-2 nucleocapsid (N), open reading frame 1ab (ORF1ab), and spike protein (S) genes and used bacteriophage MS2 spiked into the samples as a positive control. Correlations between VTM- and PBS-transported samples were 0.93, 0.83, and 0.91 for the N, ORF1ab, and S genes, respectively. All were statistically significant, with P values <0.05.

This comparison involved samples from tracheal secretions of mechanically ventilated intensive care patients, so the researchers cautioned that their results might not extend to nasopharyngeal swabs, oropharyngeal swabs, or saliva samples.

Citing Lack of Evidence, Researchers Recommend Abandoning Use of Ammonia Levels in Managing Hepatic Encephalopathy

A study of 1,202 patients admitted for management of their hepatic encephalopathy (HE), a reversible neuropsychiatric complication of chronic liver disease, concluded that “there is no evidence that ammonia levels are important” in this clinical context (Am J Gastroenterol 2020;115:723-8). These results suggest that routine testing of ammonia levels either as an initial diagnostic for HE or to guide therapy “should be abandoned.”

An accompanying editorial concurred, noting that “there is a huge chasm between clinical practice and the evidence-based role for ammonia levels” (Am J Gastroenterol 2020;115:685-6). The investigators’ findings “so deeply devalue the clinical utility of ammonia that its widespread use now represents a clear unmet need for testing stewardship,” added the editorialists.

The researchers evaluated ammonia testing in HE patients admitted over a 10-year period to a single
In all, 46% of patients had ammonia levels analyzed; 60% of those tested had abnormal results >72 µmol/L. The study’s primary end point, total oral lactulose given in the first 48 hours of HE admission, was not statistically significant between patients who had ammonia testing and those who didn’t (167 mL versus 171 mL). Further, average lactulose levels were the same in patients with elevated ammonia levels and in those without.

In a propensity matched study cohort of 296 patients who had ammonia levels drawn and 296 who didn’t, the researchers found one statistically significant difference between the groups: 21% of patients who did not have levels drawn versus 11.5% of those who did had HE secondary to dehydration (P = 0.0013). All other secondary end points, including time to resolution of HE, overall length of stay, admission to intensive care, and mortality, were not statistically significant.

C-peptide levels in individuals at risk for type 1 diabetes do not change significantly until about 6 months before these patients are diagnosed with the disease, and they continue to decline at about the same rate for 6 months after clinical diagnosis (Diabetes Care 2010; doi.org/10.2337/dc19-2288). After being diagnosed with type 1 diabetes, patients’ C-peptide response to oral glucose tolerance testing (OGTT) and mixed-meal tolerance testing (MMTT) is not significantly different. These findings suggest that to preserve patients’ beta-cell function, disease-modifying therapies should start at or before the time their C-peptide levels decline.

Researchers conducted a longitudinal analysis of 80 individuals at risk for type 1 diabetes who participated in the Pathway to Prevention Protocol of the Type 1 Diabetes TrialNet, a network of clinical trials designed to intervene in the type 1 diabetes disease process at any stage of disease, with the aim of preserving beta-cell function. The study involved screening for autoantibodies in relatives of individuals with type 1 diabetes, and closely monitoring those who developed autoantibodies until they progressed to type 1 diabetes. The study also followed a cohort after they were diagnosed to assess C-peptide response to OGTT and MMTT.

The subjects’ median age was 14 years, and they underwent a median of nine prediagnosis and two post-diagnosis OGTTs. The change in participants’ C-peptide levels was about 0 until approximately 6 months before their diagnosis, after which the change continued at the same negative rate. Participants’ mean fasting and 2-hr glucose levels also started to increase 6 months before they were diagnosed. The researchers found “no real differences” in participants’ C-peptide response to OGTT versus MMTT.

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Point-of-Care Testing in Clinical Laboratories

BY PAIGE M.K. LARKIN, PHD, M(ASCP), AND OMAI B. GARNER, PHD, D(ABMM)
For those outside of the infectious diseases field, clinical microbiology might conjure an image of microbiologists manipulating petri plates full of bacteria. Although microbiologists still work on the bench with organisms, culture-only approaches have given way to molecular assays. In fact, most microbiology laboratories have decreased or discontinued using routine viral culture, a time-consuming and labor-intensive process.

Molecular microbiology has revolutionized the virology field in particular. These methods have cut down turnaround times (TAT) from weeks to mere hours, increased the sensitivity and specificity of viral detection, and allowed for quantification of viral load. Molecular assays have also improved diagnosis of enteric pathogens, including *C. difficile*, and organisms that are non-culturable using routine culture methods such as *Toxoplasma gondii*, *Bartonella*, and *Leishmania*.

Molecular microbiology approaches are based on detecting targeted portions of microbial genetic material, either DNA or RNA, that have been extracted directly from a patient sample. With molecular assays utilizing polymerase chain reactions (PCR), targeted genetic material is
Molecular assays have demonstrated IMPROVED SENSITIVITY compared to rapid antigen detection tests, eliminating the need for secondary confirmation of negative results.

(POCT) front—have spread this testing from molecular diagnostics laboratories into clinical microbiology laboratories—and now into general laboratories and even clinics and exam rooms (1).

Access to sensitive and rapid infectious disease diagnostic assays is essential for accurate diagnosis, effective treatment, and timely infection control, making POCT vital to reducing TAT. Although people think of POCT as near-patient diagnostic assays, POCT can be performed virtually anywhere that possesses a valid CLIA certificate of waiver.

A waived test is defined as a simple assay that has low risk for erroneous results. In using a POC test, the manufacturer’s protocol must be followed exactly. Any modification, whether a specimen source (such as nasal versus nasopharyngeal) or specimen handling (manually diluting a specimen before loading), changes the CLIA status from waived to non-waived and prohibits a test from being performed as a waived test. Waived testing can be performed in a moderate- or high-complexity lab environment. Laboratories must maintain training records for personnel performing the assay regardless of the complexity of the lab. Further, they must assess competency for all operators twice during the first year of performing the assay and then annually thereafter.

FROM ANTIGEN-BASED TO MOLECULAR PLATFORMS IN POCT

In the microbiology field, clinics have long used POCT that detects antigens or antibodies for infections such as influenza, mononucleosis, and group A Streptococcus (GAS) (2). These assays offer rapid, easy-to-use sample-to-answer options. Although their fast TAT enables patients to be treated promptly, these assays have lower sensitivity and specificity than their laboratory molecular counterparts. In the case of influenza, a molecular assay should be performed following a negative influenza antigen-based test due to false negatives occurring in high-prevalence populations.

Licensed technologists perform high-complexity molecular assays in molecular or microbiology laboratories. Although incredibly valuable, these assays suffer from increased TAT resulting from specimen transport delays, batch testing, complex multistep testing, or set performing schedules. Molecular POCT tests are now emerging that circumvent these obstacles. Molecular CLIA-waived POC tests are able to detect influenza, respiratory syncytial virus (RSV), GAS, and a group of respiratory pathogens.

One example of the shift from antigen-based to molecular diagnostics in the POCT setting involves detecting GAS, which is responsible for an estimated 15%–30% of sore throats in pediatric patients. While rapid antigen-based assays enable providers to make diagnoses in clinics, these assays lack sensitivity and specificity compared to conventional bacterial culture and have the added disadvantage of being subjective and difficult to interpret. More sensitive methods, including culture and molecular-based tests, are recommended when an antigen test yields a negative result because of the potential for this result to be a false negative. Molecular GAS POCT enables a clinician to provide, or exclude, a diagnosis and administer treatment while a patient is in a clinic. Moreover, molecular assays have demonstrated improved sensitivity compared to rapid antigen detection tests, eliminating the need for secondary confirmation of negative results.

THE ROLE OF MOLECULAR POCT FOR INFLUENZA AND RESPIRATORY ILLNESSES

Influenza, a seasonal respiratory virus, was responsible for an estimated 14 million to 21 million medical visits in the United States alone since October 1, 2019, according to the Centers for Disease Control and Prevention (CDC). Unlike the vast majority of respiratory pathogens, influenza has an approved antiviral treatment. Unfortunately, for maximal effectiveness, this antiviral must be administered within 48 hours of symptom onset, requiring a physician visit and
The Clinical Impact of Tight vs Standard Glycemic Control on COVID-19 Hospitalized Patients

Diabetes and stress hyperglycemia are two of the most common co-morbidities of COVID-19. Two recent multi-center studies of 8,500 COVID-19 hospitalized patients have found that type 2 diabetes (T2D) and poor glycemic control are risk factors for COVID-19 disease progression and adverse outcome. This webinar will review clinical characteristics and mortality of COVID-19 patients with pre-existing T2D, and possible avenues to improving their disease outcomes. Clinical evidence supporting tight glycemic management of T2D during COVID will be presented.

The webinar will also describe the growing interest in the antioxidant properties of ascorbic acid as an adjunctive therapy for COVID-19. For these critically ill patients, severe anemia is also a common underlying condition. This webinar examines the risk of inaccurate glucose meter results due to interference from ascorbic acid and anemia. A glucose meter that measures and corrects for these interferences will also be described.

Learning Objectives

- Frequency of T2D among a multi-center cohort of 8,500 COVID-19 hospitalized patients
- Risk of T2D patients developing more severe cases of COVID-19, including ARDS, septic shock and MODS
- Outcome of T2D patients with well controlled glycemic variability versus those with poorly controlled glycemic variability
- Use of adjunctive therapies such as ascorbic acid with COVID-19 patients
- Evidence based risk of glucose meter error due to ascorbic acid and anemia interferences
- Risk mitigation for hospitals in protecting their COVID-19 patients from erroneous bedside glucose tests

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- This program offers 1 hour of P.A.C.E. continuing education credit.
- This program has been approved by the American Association of Critical-Care Nurses (AACN), for 1.00 CERPs, Synergy CERP Category A, File Number 23205. Approval refers to recognition of continuing education only and does not imply AACN approval or endorsement of the content of this educational activity, or the products mentioned.

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diagnosis within that time frame. Often patients do not present to their physicians until symptoms have worsened, narrowing the available time to treatment. Moreover, due to symptom overlap with other seasonal respiratory viruses, influenza is difficult to diagnose based on clinical presentation alone. This makes influenza an ideal target for POCT.

As previously discussed, antigen-based influenza POCT is popular in outpatient and emergency department settings, but lacks sensitivity (50%–90%) compared to molecular methods. The first molecular influenza POCT test was approved in 2015, and since then several waived molecular POCT tests have entered the market. These include Alere i Influenza A&B, Accula Flu A/Flu B, BioFire FilmArray RP EZ, Xpert Xpress Flu, and cobas Liat Influenza A/B. These assays take 15 minutes to 1 hour to run, and aside from Xpert Xpress Flu, only process one sample at a time.

More influenza POCT tests now are incorporating RSV into their panels. Although RSV does not have a treatment, this virus is one of the leading causes of infant hospitalizations and also is problematic in the elderly, so identifying it is essential. Since RSV symptoms and seasonality overlap with influenza and other seasonal respiratory viruses, a molecular assay is necessary for diagnosing and managing this illness.

Molecular influenza testing has been shown to prevent unnecessary hospitalizations and antibiotic prescriptions, allow antivirals to be administered before patients are discharged, and directly guide isolation precautions (6). While the benefit to patients is evident, the advantages to medical staff, testing personnel, overall hospital function, and other patients are also significant.

CDC establishes guidelines for patient precautions based on the suspected infectious agent. Standard precautions are observed for all patients. For most seasonal respiratory viruses, including rhinovirus, healthcare professionals follow contact precautions, meaning that staff wear gloves when in contact with a patient, practice good hand hygiene, and wear gowns if they expect to come in contact with blood or bodily fluids.

For influenza, laboratories must follow droplet precautions. Patients must wear masks when not in their assigned rooms, and healthcare workers should don face masks when in the room of a patient with suspected or confirmed influenza. Based on current CDC recommendations, influenza positive patients should be placed in private rooms, and droplet precautions should be implemented for 7 days after illness onset or after a full 24 hours following resolution of symptoms.

Because respiratory viruses cannot be distinguished on the basis of symptoms, ruling out or confirming influenza as soon as possible is crucial. If a patient is negative for influenza, droplet precautions might not be necessary. This would reduce the strain on availability of individual rooms and usage of personal protective equipment (PPE). On the other hand, if a patient is positive for influenza, the ability to provide that diagnosis, appropriately treat, and discharge that patient as quickly as possible reduces the number of people exposed to this virus.

During influenza season a surge of patients visits urgent care, physician offices, and emergency departments. This leads to a shortage of space, healthcare workers, and PPE, for example. Thus, rapid diagnosis of any respiratory illness can allow for shorter wait times and visit times, reducing the burdens on hospitals.

**BEST PRACTICES AND QUALITY CONTROL**

Unlike viral culture, waived molecular testing poses minimal risks to the personnel performing the assay. In order for a test to be considered waived, a patient sample cannot be manipulated (diluted, centrifuged, etc.) in a way that is not specified by the manufacturer. This reduces the risk of aerosols, spills, or exposures. Furthermore, many of these assays are closed systems, meaning that the amplification and detection steps occur in a contained space. This prevents contamination of the environment with genetic material and organisms, further mitigating the risk. The greatest risk occurs during direct contact with a patient during specimen collection.

Test performing areas should be kept clean and organized to prevent cross contamination. Surfaces should be disinfected daily and also immediately disinfected following spills or visible contamination. As with any human specimen that would be processed in chemistry, hematology, or any clinical laboratory, all specimens should be handled using universal precautions and according to the notion that any sample might contain infectious pathogens. Testing personnel are required to wear appropriate PPE, including disposable gloves that should be changed between runs. In addition, test reagents must be stored and handled according to the manufacturer’s instructions.

The current CLIA-waived molecular POCT tests are qualitative assays, meaning that they only provide a positive or negative result. In some cases, an invalid result can occur because of an instrument, specimen, or reagent. Specimens producing an invalid result should be repeated.

Quality control (QC) confirms that an assay is functioning as expected by the manufacturer. According to CLIA regulations, QC must be performed according to the manufacturer’s instructions for waived testing. If the manufacturer does not define QC, the testing institution must define a policy that follows good laboratory practices. Best practices include running daily external positive and negative QC, even in a CLIA-waived setting. Documentation of controls and results is recommended. When QC fails, patient results should not be reported to avoid incorrect results. The problem should be identified and corrected before proceeding with patient samples.

QC metrics often include external and internal controls. An internal control is incorporated into each sample while an external control—which should include a positive and negative sample—is run as individual samples. The internal control can serve as a processing control or control for that test. The internal control in molecular-based tests is often a DNA extraction control, which indicates whether or not a patient sample was properly
extracted, a necessary step in order to receive a correct result. External controls evaluate whether an instrument provides correct results (for example, a positive external control is detected as positive) and should mimic patient specimens.

LIMITATIONS OF MOLECULAR POCT
Since both POCT and non-POCT molecular tests aren’t able to distinguish between live or dead organisms, they can’t be used as a test of cure and might produce false positives.

WHAT’S NEXT FOR POCT
Sexually transmitted infections (STI) have garnered attention in the molecular POCT field as rapid diagnostics allow for prompt treatment and consultations with patients, who might otherwise be lost to follow-up. Given the public health concerns associated with STI, these tests really need to be accurate. Development of and investigations into such assays are already underway worldwide including a molecular POC test for Trichomonas, Chlamydia trachomatis, and Neisseria gonorrhoeae (9).

When genetic changes occur the primer might no longer match the VIRAL GENETIC MATERIAL and that sequence will not be amplified, resulting in a false negative.

due to residual nucleic content from past infections. On the other hand, false negatives can occur due to viral genomic shifts and drifts, which is a limitation of all molecular assays. This was observed in 2014-2015 for clades of influenza A H3N2. Molecular assays use primers, which target specific areas of genetic material that are encoded by a virus or group of viruses. These primers are designed to match a conserved region of DNA or RNA, depending on the type of virus.

When the targeted genetic material is present, the primers bind to the DNA or RNA segment and that region is amplified and detected by the assay. However, when genetic changes occur, such as insertions or deletions, the primer might no longer match the viral genetic material. In this case, the primer cannot bind, and that sequence will not be amplified, resulting in a false negative due to lack of detection of that sequence. As such, new molecular POC tests will need to be developed to address novel viruses.

The increased sensitivity coupled with use by non-molecular laboratory personnel poses a risk of assay failure and environmental cross contamination. For instance, in clinics that administer influenza vaccine, contaminated instrumentation can produce false positives. However, multiple studies have demonstrated that failure rate and environmental contamination is low. One study found that the average failure rate for the Liat GAS assay was 6.6%, while environmental contamination was not detected after performing the assay on swabs on the instrumentation weekly (7). In another study where the cobas Liat system was intentionally contaminated with flu A/B-positive control material, this contamination was not found to affect any of the negative control tubes in runs immediately after assessing system contamination, thus showing that the contamination did not impact the integrity of results (8). Given the simplicity of the current molecular POCT with the sample-to-answer format, user variability, opportunities for contamination, and human errors are minimized if protocols are followed.

One potential source of human error involves results reporting. Although POCT instrumentation provides a clear positive, negative, or invalid result, the platforms are not usually interfaced to laboratory information systems, meaning that results must be manually entered. Care must be taken to avoid transcription or other data entry errors.

Space and cost limitations are also a concern. Molecular POC tests are more expensive than antigen-based tests, but have an increased sensitivity and specificity. Although molecular instruments are typically compact, many platforms can only run one sample at a time. In a large emergency department or urgent care clinic, several instruments would be required to meet the demand for influenza testing.

Although there are few approved analytes for molecular POCT in the U.S., the ability to rapidly test and respond with effective treatment, when applicable, makes POCT an attractive methodology for a variety of infectious diseases, including parasites, fungal infections, STI, and more.

Molecular POCT is increasingly advantageous in resource-limited settings, which typically have lengthy TAT and not enough trained technologists to perform high-complexity assays. Moreover, molecular testing closer to patient care, whether in generalized hospital laboratories or in emergency departments, mitigates the challenges faced with molecular testing in centralized clinical microbiology laboratories as previously discussed. With novel POCT on the horizon, future studies are warranted to determine cost savings, antimicrobial usage, TAT, patient impact, and how to best implement in non-microbiology clinical laboratories and clinics.

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COVID-19 Is a Catalyst for Remote Sampling and Telemedicine

Clinical laboratorians see the potential, and the limitations, in a push to move testing outside labs.

BY JEN A. MILLER

The COVID-19 pandemic is accelerating changes already underway in the practice of medicine, spurring both innovations and growing pains around technologies that allow patients to interact with the healthcare system virtually.

An April survey conducted by Sermo, a physician online community, reported that 85% of participants are seeing patients via video and phone. The survey also found that 68% of respondents believe this will have a lasting effect on how doctors see patients, and 77% support the shift to telemedicine. The telemedicine market is expected to be a $155 billion industry by 2027, according to Grand View Research.
This drive to see patients at home has also increased interest in at-home sample collection and testing, both for convenience and to avoid potential exposure to SARS-CoV-2, the virus that causes COVID-19 illness. “COVID-19 has accelerated this,” said Arielle Trzcinski, a senior analyst at Forrester, a market research company. She anticipates “a greater push on how we get to more convenient, cost-effective options for lab testing. Some vendors are already working on that, but it’s still an area that is further ripe for disruption and innovation.”

**PANDEMIC CONCERNS SPEED UP MARKET FOR HOME TESTING**

As the pandemic bore down on the healthcare system and the economy, companies began moving to bring direct-to-consumer (DTC) testing services online. Now, more steps of the testing process are entering patients’ homes, from test ordering to sample collection. Patients themselves might even perform certain tests.

On April 21, the Food and Drug Administration (FDA) authorized LabCorp’s Pixel for COVID-19, the first at-home sample kit for SARS-CoV-2 testing, specifically for LabCorp’s COVID-19 reverse transcriptase polymerase chain reaction test. The self-collection kit contains nasal swabs, saline, and an insulated package for sending the samples back to LabCorp.

Of course at-home testing isn’t new, especially when it comes to collecting cheek swabs and saliva. Consumers already have enthusiastically embraced kits marketed for allergies, vitamin D, food sensitivity, and DNA testing—for humans and pets. But most of these tests report genetic traits or conditions that “are not going to necessarily indicate a life or death situation,” said Trzcinski.

Telemedicine startups Vault Health and hims & hers, and DTC genetic testing company Vitagene, are now all selling home-collected saliva-based test kits. The actual testing for all three companies is performed by Rutgers University laboratory, called RUCDR Infinite Biologics, in partnership with Spectrum Solutions and Accurate Diagnostic Labs. FDA authorized the RUCDR test on May 7, and prices range from $116–$150.

Scanwell Health, a developer of smartphone-enabled, at-home diagnostics, has announced its work on a test kit ordered from and conducted at home. Scanwell has exclusive rights to license and distribute a SARS-CoV-2 rapid serology test from Chinese company Innovita. The test takes 15 minutes to complete using the Scanwell Health mobile app, and under the company’s plan, a doctor or nurse practitioner would reach out within hours to a patient with results and next steps. Scanwell is known for developing the first urinary tract infection test cleared by FDA for home use.

Most recently, DTC company LetsGetChecked received FDA authorization for its Sure-track test that includes at-home nasal swab sample collection and lab-based molecular testing for SARS-CoV-2. The company touts that it is the only DTC offering with an FDA emergency use authorization for at-home COVID-19 testing that owns all aspects of the testing service, including the collection kit manufacturing process, logistics, lab analysis, and physician approval.

Demand has also spiked for SARS-CoV-2 antibody and antigen tests that are easier to accomplish with small blood samples compared to the nasopharyngeal and nasal swabs used for lab-based molecular diagnostic assays.

In late April, Quest Diagnostics announced it would start selling a COVID-19 antibody test directly to consumers for $119. This test still requires a blood draw at one of the company’s patient service centers, and the utility of antibody tests remains unclear. This caveat hasn’t stopped consumers from purchasing the test (Quest said it had performed 975,000 antibody tests as of May 18), reflecting demand for ways to take blood samples without risking COVID-19 exposure and for a testing process anchored to consumer convenience.

**ADVANCES IN SAMPLE COLLECTION ARRIVE AT AN OPPORTUNE MOMENT**

Innovations in blood sample collection are proving their utility and validity just in time for the home-based medicine push. One such system is Neoteryx’s Mitra devices, which collect 20 mL of blood from a finger prick. Cathy Cordova, Neoteryx’s director of marketing, said Mitra is already used by organ donor transplant recipients, who need frequent blood tests to check their immunosuppression. Home testing lets them avoid coming into a healthcare setting repeatedly for blood
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A study recently published in The Journal of Applied Laboratory Medicine found that 82% of patients preferred using this microsampling device for therapeutic monitoring of tacrolimus and cyclosporine immunosuppressants following solid organ transplants (J Appl Lab Med.2020;5:516-30).

Neoteryx has also worked with “several large pharmaceutical companies that have looked to implement their phase I, II, and III clinical trials for drug development through what they’re calling virtual clinical trials,” Cordova said. These patients can participate while taking their own blood samples from home.

Mitra will also be used for a National Institutes of Health (NIH) COVID-19 serosurvey, a nationwide COVID-19 antibody survey that researchers hope will help determine how many adults without a confirmed history of COVID-19 virus infection already have antibodies. NIH plans to test as many as 10,000 volunteers, who will be shipped Mitra kits to take their own blood samples at home.

“For COVID-19 testing, AACC has asked FDA to ensure robust scientific evidence and transparency around home sample collection. Unique pre-analytical problems often surface with self-collection methods that can put patients at risk, the association emphasized in a letter to the agency.

“While home sample collection kits are designed to be simple, problems commonly occur with self-collection that can affect the quality of the sample and, therefore, the subsequent test result,” the letter said. Moreover, in the case of LabCorp’s Pixel test system, the experiments the company conducted showed stability of live virus that had been spiked onto swabs. “But no experiments were publicly shared that demonstrate equivalence between specimens collected by healthcare professionals and specimens collected by the patients themselves at home,” said AACC’s letter. LabCorp declined to comment for this story.

Laboratories themselves likely will face mounting challenges when asked to process samples taken from home kits. Last year, Kamisha Johnson-Davis, PhD, DABCC, FAACC, associate professor of pathology at the University of Utah and medical director for clinical toxicology at ARUP Laboratories in Salt Lake City, ran a feasibility study on the Mitra device. The research team specifically looked at using the device for immunosuppressant drug monitoring (J Appl Lab Med 2019;4:241-6).

Johnson-Davis raised several issues about the device, including the potential to over- or under-saturate the Mitra tip. Her laboratory team also had to figure out how to fit the Mitra device into their workflow so that it could be tracked just like any other sample. The shape of the Mitra device also posed a complication, she said: The one they tested is clamshell-shaped, “which is totally different from the collection tubes that we use.”

Johnson-Davis also had concerns about the quality of the samples themselves. “As a medical director interested in these alternative ways of collecting specimens, it would be of interest to understand how this would work in practice in someone’s home,” she said. Laboratory directors would need to know how they can be sure of the sterility of the sample-taking environment, if patients are milking their fingers, and what happens to a sample between the time it’s taken and when it shows up at a laboratory.

“In practice, we just don’t know how patients are really going to transport samples,” said Johnson-Davis. “Let’s say it’s summertime and they forget they had it in their car but put it in the mail anyway. What’s going to happen to that specimen?”

Transportation logistics extend to laboratories too, she said. Maybe a laboratory doesn’t receive mail on Saturdays. Or a patient puts a sample in a mailbox on a Saturday afternoon but it isn’t picked up until Monday. “There are things we would need to work out in regard to specimen processing on-site and having it accommodate our track system,” she added. Plus, “we would need communication and videos on appropriate specimen collection and transport for the clients who would potentially be using these.”

In all of these remote sampling scenarios, clinical laboratory professionals have an opportunity to lead—from discovering how technologies and techniques work in the real world to developing the right quality systems that ensure high-quality results for patients, regardless of where sample collection takes place.

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32163 06/2020
In January 2019, the American Diabetes Association (ADA) in its annual standards of medical care in diabetes released new guidance, classifying level 2 hypoglycemia as a glucose value <54 mg/dL, the threshold at which “neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event” (Diabetes Care 2019;42(Suppl. 1):S61–70). This change, representing a new critical value, was based on a consensus report issued in 2017 by ADA and seven other organizations on standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes (Diabetes Care 2017;40:1622-30). Although the healthcare community generally hews closely to ADA standards, this move has been met with some doubt and disagreement among clinical laboratorians.

Conversation around the updated value perhaps has been more animated than other ADA recommendations because of the scant evidence behind it. The trail of references cited for the change eventually leads to a single 30-year-old study that involved only 10 people who did not have diabetes (Am J Physiol 1991;260:E67–74). For many in the field, that has called into question the need for a revised critical value, especially as making this change could create significant protocol pivots and shift workloads for laboratorians and providers alike, potentially straining already stressed resources.

Because monitoring patients’ glucose can play a critical role in many aspects of their medical care, clinical laboratorians are carefully considering whether to institute this new critical hypoglycemia value. With many factors involved, the decision will not be one-size-fits-all.

Labs consider pros and cons of implementing new hypoglycemia target based on limited evidence

TO CHANGE OR NOT TO CHANGE
Clinical laboratories and institutions will need to decide for themselves whether the new critical value is appropriate, said Steven Cotten, PhD, DABCC, NRCC, FAACC, co-director of clinical chemistry at UNC Hospitals in Chapel Hill, North Carolina. At UNC, adopting the new value helped avoid any future misunderstandings or miscommunications about patients’ care, according to Cotten.

“We ended up aligning our values with the ADA hypoglycemia protocols with the understanding that the change wasn’t based really on a study,” he explained. “But we felt it was best to eliminate confusion.”

The ADA update also fell in line with an existing policy at Bronson Methodist Hospital in Kalamazoo,
“Our laboratory leadership, including the director of clinical laboratories, wanted to know what other hospitals were doing,” he said. “When they heard the switch wouldn’t even be a change that would exceed the variability of glucose measurements on a glucometer, they lost a lot of enthusiasm for making the change.”

Adil Khan, MSc, PhD, director of point-of-care testing and clinical chemistry at Temple University Hospital and Temple University Episcopal Campus in Philadelphia, echoed Bertholf’s comments, adding that 54 mg/dL is more appropriate for clinical trials than patient care. In fact, he said, Temple uses a higher critical value, 60 mg/dL, because this threshold reduces the number of patients who experience negative outcomes, including fainting or a rapid, irregular heartbeat.

“A level of 54 mg/dL is more of a biochemically defined value where a patient would start to feel a lot of physiological issues. They develop an impaired mental status and many other symptoms,” he said. “After our endocrinologists spoke with their clinical colleagues, we felt we wanted our level to be higher.” Khan emphasized that any change to glucose critical values—regardless of the threshold chosen—should be made with improved patient care management in mind.

Other institutions arrived at different conclusions about making the change, Houston Methodist Hospital in Texas among them. Consultation with other organizations indicated that raising the hospital’s critical value from 50 mg/dL to 54 mg/dL would not serve a clinical need, according to Roger Bertholf, PhD, DABCC, FAACC, director of clinical chemistry.

“Michigan, said compliance and point-of-care coordinator Erika Deaton-Mohney, MT(ASCP). Bronson’s existing protocol for hypoglycemia was triggered above the critical value range, and a conversation had already begun about potentially changing the lab’s lower limit. Consequently, news of the ADA’s updated value accelerated the lab and clinical teams’ plan to switch from ≤42 mg/dL to ≤55 mg/dL.

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LAC+USC Medical Center in Los Angeles also has followed its own path on hypoglycemic critical values. Although the hospital flags as abnormal any glucose level <65 mg/dL, the organization’s critical value remains at <40 mg/dL, according to Allison Chambliss, PhD, DABCC, director of clinical chemistry and point-of-care testing.
The challenge is getting the education and knowledge out there about the change. You also need to make sure your instrumentation at the point-of-care can trigger and alert the operator on the main screen to any critical results with the patient.

— Erika Deaton-Mohney, MT(ASCP)

“I don’t want to discount the fact that a glucose below 54 is certainly very low, and we know patients can be asymptomatic and need intervention,” she said. “But for us, this discussion really came down to diagnosis or clinical classification, and that does not equal a critical value notification limit.”

THE JOURNEY TO A DECISION

Chambliss emphasized that deciding whether to switch a hypoglycemia critical value requires discussion and research. Any change also would call for methodical preparation because many parties, including both laboratory and point-of-care testing personnel, will be affected.

She also stressed the value in reaching out to peer institutions to see how they’ve approached this issue, including how they quantify and the reasoning behind their low glucose threshold. Bertholf seconded this recommendation, as the results of his poll of other organizations factored into Houston Methodist’s decision to maintain its current critical value.

Chambliss and her lab colleagues also gathered feedback from committees that involve providers who would receive the critical value calls. For instance, they collected input from the chairs of internal medicine not only at LAC+USC but also all USC hospitals, as well as from the health system’s ambulatory cases committee comprised of primary internal medicine providers and medical directors of outpatient clinics.

At Bronson Methodist, the patient safety and quality committee, as well as the medical process improvement and clinical care process improvement committees, contributed to the decision-making process, said Deaton-Mohney.

Back at UNC, Cotten recommended involving stakeholders from pharmacy and information technology to ensure the smoothest transition. “As a large health system, we tried to make the change globally, so it wasn’t just our laboratory that had to do this,” he explained. “It was every single other satellite location, ambulatory clinic, affiliated hospital. They all had to coordinate on a single date to make the switch.”

Deaton-Mohney recommended that labs provide knowledge-sharing documents filled with details about how to make the change. This can be a good way to ensure all providers—particularly nurses most directly involved in patient care—are aware of the new critical value and how to implement it.

“The challenge is getting the education and knowledge out there about the change,” she said. “You also need to make sure your instrumentation at the point-of-care can trigger and alert the operator on the main screen to any critical results with the patient.”

Another place to get the word out is in daily patient care huddles, added Deaton-Mohney. “It can be a hurdle to make sure all of your operators that aren’t in the main laboratory understand this change and know what the differences are from old to new,” she said. “It’s critical to have your nursing team work with you, making sure they follow their processes to train all their operators.”

Chambliss also cautioned labs to consider how any changes to glucose critical values might impact their workflows. “Examine your retrospective data from your labs so you know what those glucose results have looked like in the past,” she said. “Having the data and being able to play with the numbers will let you know how many more patients you would be making calls for so you can assess any impact on both the lab and on providers.”

It’s also important, she added, to know not only who will be responsible for making the calls about patients with low values but also who will be asked to receive this information. The switch to a higher critical value could become burdensome on both ends of the exchange—clinical laboratory staff and clinicians. Workflow reviews also would need to consider any adjustments needed in systems to document critical value calls for regulatory purposes.

A solid plan based on detailed information-gathering will guide labs in their decision-making on this issue, Bertholf suggested. “If you’re starting from ground zero to establish a program, and you want to know what sort of procedures you will implement, it is always helpful to have some sort of guideline document to which you can refer,” he suggested. “That gives you some sort of basis for choosing a particular threshold—otherwise, it can be an arbitrary threshold based solely on clinical judgment rather than evidence.”

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As the SARS-CoV-2 virus hit U.S. shores, the nation suddenly needed widescale, reliable diagnostic testing infrastructure in place—and fast. It turned out to be harder than non-laboratorians might think to manufacture out of thin air 5 million validated, accurate polymerase chain reaction (PCR)-based tests for a novel virus. The early quality control plan, which involved central testing available only at the Centers for Disease Control and Prevention (CDC), with no scope for laboratory-developed tests, proved to be woefully inadequate to meet demand, and the CDC’s tests were plagued with technical concerns (1).

In late January the U.S. declared a formal Public Health Emergency (2), freeing up some of the regulatory burden and allowing public and private laboratories to develop tests to meet demand. Normally, of course, we can’t use something in the care of actual human patients unless we show it works and is safe. That means a device, test, or drug has to be approved by the Food and Drug Administration (FDA)—a yearslong process in which the agency independently verifies that a test developer has correctly demonstrated that its assay works.

In an official Emergency—with-a-capital-E, though, FDA takes at face value the test and internal safety data that manufacturers submit; the agency then grants an emergency use authorization (EUA) and, with several disclaimers, the manufacturer can offer its test on the market. However, the EUA only lasts as long as the Emergency, after which it melts away like leprechaun gold, and we’re back to the “prove your data” standards.

During the early days of the COVID-19 pandemic, this process allowed a few high-quality diagnostic tests to trickle onto the market. Testing was somewhat regionally based (for example, an early testing program at the University of Washington), and market saturation was minimal. Supply was ravenously outstripped by demand. The lack of widescale diagnostic testing led to outrageous bottlenecks and, in many locations, a near-complete lack of information about the shape of the epidemic. Concomitantly, of course, researchers and commercial actors furiously attempted to develop serology tests for the virus—with the same problems.

Welcome to the Wild, Wild West

By March 16, FDA removed the brakes: All developers need to do is bring something to market and submit an EUA to FDA within 15 days. In the ensuing Wild, Wild West, unscrupulous vendors could a) misrepresent how good their test was, and no one would catch them; and b) they could offer their tests to the public—to human patients—without anyone checking to see if these tests worked.

FDA would start to apply the brakes again eventually, but the market was a free-for-all until then. Within a month, at least 90 serology tests were floating around in the U.S., with no fewer than 275 registered globally by the World Health Organization (3), many exhibiting the expected abysmal quality. For example, the city of Laredo, Texas, bought 20,000 rapid antibody tests for $500,000, only to discover that they were just 20% reliable—considerably worse than flipping a coin. The U.K. bought 17.5 million serology tests from China, but sent them back because they only detected antibodies at screamingly high titers (4). Pop-up drive-throughs in parking lots, operated by people who bought tests on the internet and who had no medical or laboratory qualifications, offered equally worthless finger prick tests.

Key Points to Consider for Serology Tests

- A commercial test comes with a package insert that contains all the information about how the manufacturer proved it works—the validation data.
- Evaluate a test’s sensitivity and specificity numbers articulated in the package insert. These detail how many true positives the test called positive, and how many true negatives it correctly called negative.
- Check out the test’s cross-reactivity data. Did the manufacturer specifically sample cross-reactivity to the other common cold coronaviruses? Some developers used large numbers of negative controls from before November 2019 (old banked serum), before SARS-CoV-2 appeared. Since about 90% of us have antibodies to the common cold coronaviruses, getting negative results here is a pretty good proxy for a lack of cross-reactivity. Less reliable SARS-CoV-2 antibody tests documented that there was no cross-reactivity to, say, hepatitis B virus, but neglected to run the alpha coronaviruses.
- FDA maintains a running list of all tests that have formally received an EUA (5).
Key Points to Consider for PCR Diagnostic Testing

- If there is viral RNA in the specimen, a conventional PCR test will find it. Sensitivity and specificity in the conventional sense are essentially perfect.
- While conventional PCR routinely detects very low amounts of RNA, on the order of 100 viral copies/mL, the least sensitive of the rapid tests (Abbott ID NOW) seems to perform only down to about 20,000 copies/mL (8), and other rapid tests down to 100-1,000 copies/mL (9). This means they will miss significant numbers of positive cases in which patients just don’t have that much virus.
- When providers suspect a patient has COVID based on clinical assessment, remember, a negative PCR result might simply mean the individual isn’t harboring virus in his or her nasopharynx. Sample other sites (if at all possible) deeper in the respiratory tree.
- When a test detects viral RNA, it might not be detecting infectious virus. This is particularly true of samples taken from the environment, like patient bedside tables or cruise ship bunkrooms.

Amid mounting concerns and near chaos, in late April the FDA tightened up the rules considerably, not all the way to pre-Emergency standards, but closer. Now serology testing can only be performed in an actual laboratory that holds a CLIA certificate for high-complexity testing, and manufacturers of serology assays must submit EUA requests to FDA within 10 days of launching a test. The agency also prioritized independently verifying the validation data submitted for all of the tests to which it had granted an EUA (5).

PCR Concerns

Diagnostic PCR testing fared much better in terms of test performance and reliability, but with two problems. The first involves a persistent rumor, based on an inaccurate understanding of a small case series from China (6), that “PCR tests have a 30% false negative rate.” This is incorrect. The clinical sensitivity of PCR tests is certainly variable since some patients simply don’t harbor virus in the nasopharynx, but these tests’ analytical sensitivity is essentially perfect.

The second issue is that some rapid tests are significantly less sensitive than the gold-standard PCR tests. In three separate studies, the Abbott ID NOW COVID-19 test missed 12%–48% of positives, showing diminished sensitivity even after optimizing sample collection and transport (7–9). Other, slightly less rapid tests from Cepheid and GenMark had substantially better, though not perfect, performance (8, 9). Rapid tests are quickly forming a cornerstone of perioperative care and workplace screening, which should trigger skepticism from the laboratory community.

City and national governments were not alone in feeling ill-equipped to navigate the new testing landscape. Our clinical colleagues are reflexively used to trusting, implicitly, the quality of the tests we offer them. Never in their lives did they stop and think when looking at a test result, “But is the serum sodium really 140? How can I know?” Suddenly, though, COVID-19 brought into sharp relief issues of testing quality, quality control, sensitivity, specificity, limit of detection, predictive values, and the like. We ourselves must select only reliable tests, and also explain in easy-to-grasp terms a quick method to address the quality and reliability of a particular assay.

Never before have clinical laboratories been so prominent, or so crucial. Never have all the countless hours we put into assuring reliable, high-quality, actionable results for our patients been so appreciated. This is the little rainbow in our COVID-19 thunderclouds.

References


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When Lab Testing Offered for Free Is Not Really Free

A free or reduced-rate test is a clinical test offered by a reference laboratory to some or all patients at no charge or at a reduced charge. A lab might have many reasons to not charge for a test, but the most common involves tests subsidized by a pharmaceutical company. In these cases, a pharmaceutical company pays a laboratory for the cost of performing a test, and the laboratory then passes on those savings to the collecting institution and to the patient. Other reasons include tests performed as research funded by other means (for example, grants) and new clinical tests for which the performing laboratory is trying to raise awareness and drive business.

Clinical laboratories offering free testing in such scenarios need to pay close attention to compliance considerations so that they don’t inadvertently induce providers. Moreover, laboratories should offer patients consistent, high-quality services, and offering free testing raises concerns about how to provide care equitably. For example, when a lab routinely sends a test to one preferred reference laboratory but sends the free/reduced-rate test to an alternate reference laboratory, the originating lab should critically evaluate test quality to support patients in accessing the highest value test—which in the end might not be the “free” test. Similarly, without careful oversight, patients needing the same test might be offered different routes for that testing depending on providers’ awareness of the options.

In truth, “free testing” is a misnomer, because as the adage goes, nothing is actually free. Both sending and receiving labs incur costs from collecting samples, processing, shipping, and managing results documentation. Dealing with billing also adds indirect costs. Healthcare workflows default to billing for a service, typically billing insurance first. Electronic medical record systems are derived from billing systems, and it’s actually rather difficult to not bill for a service. Free testing therefore adds a manual, nonstandard billing process that is cumbersome and inherently error-prone.

Free testing that requires using special kits adds another logistical challenge. Kit storage space, expiration dates, and transport for collecting and shipping samples are unnecessary barriers, particularly when these supplies and workflows are already part of a clinical laboratory’s standard work.

Managing Free Testing
As free testing becomes more available, how should clinical laboratories manage these requests consistently? How can we ensure we are selecting the highest-quality test regardless of cost, and ensure equitable access?

In our experience at a large pediatric tertiary care facility, we have seen a dramatic increase in free and reduced-rate testing requests, largely in the category of pharmaceutical subsidized tests. We requested guidance from our hospital laboratory stewardship committee, which in turn recommended that we collaborate with legal counsel to develop a hospital-wide policy. This policy encompasses scenarios in which free testing is prohibited (such as inducements) and cases outside the scope of the policy (such as quality assurance testing to evaluate an analytical/quality question and compliant research testing addressed by other policies).

The main criteria our policy considers for allowable free and reduced-rate testing include that the testing must be standard of care, performed in a CLIA environment (same as if the test were charged), and offered equitably.

For example, the policy permits pharmaceutical companies to subsidize testing with specific criteria applied such that all patients who meet criteria receive the same test. Importantly, the testing is not completely free—we include a nominal fee to account for our laboratory’s costs and to support best laboratory stewardship practices. Defining these tests in patients’ medical records with a nominal fee, allows us to keep track of these requests in the overall lab budget and include them in laboratory metrics we report up to hospital administrators. If we do work that can’t be measured, it impacts our ability to grow and provide all lab services.

Case Examples

Spending More for Free
A provider requested a “free” pharmaceutically sponsored biomarker test for a rare genetic condition. At first glance, this request was reasonable—we have the same test defined in our system for charge, and it was sponsored in a way that did not raise compliance concerns.
However, a complicated kit using a patented cooling system was required to qualify for the free test. Storing and managing the test kits complicated logistics that had been routine when the exact same test was ordered and charged at the same lab. We evaluated prior test charges for our patients, and not one paid out of pocket as this is a covered insurance benefit. So, in this case “free” wouldn’t help us or the patient—we’d spend more money and time trying to avoid the cost of the inexpensive test. We did not implement this free test.

Accounting for Free
Our gastroenterology clinicians requested that our lab define a “free” pharmaceutically sponsored gene sequencing panel that included specific inclusion criteria, a signed consent, and a requisition. We partnered with the specialists to ensure standard use of this panel. We built the test as a defined orderable in our electronic medical record, which prompts standardized resulting workflows and automatic billing of a nominal processing fee. We built links to the required forms and used our standard shipping/processing devices. We found this test feasible to manage and apply equitably because of the limited scope of providers who order it.

Sending Out a Test Offered In-House
A provider ordered a “free” pharmaceutically sponsored test performed at a reference lab after we had collaborated with clinician stakeholders to develop a very similar test in-house. While the provider was frustrated initially by not being able to avoid charges for one family, he ultimately conceded that sending out this test was undermining our ability to recuperate test development costs, support our lab’s infrastructure, and provide ongoing expert support to our clinicians more broadly.

Disguising Research as a Clinical Test
A reference lab identified a variant of uncertain clinical significance (VUS) in a gene. This lab offered to perform “free” mRNA sequencing to investigate the VUS. Further vetting uncovered that the lab did not offer mRNA sequencing as a clinical test and it was unclear how the result would be reported. We decided to send the test to a different lab that offered it as a clinical test, but we paid for the test using lab quality assurance funds instead of billing insurance because the clinical utility was being evaluated.

Inducing Providers
A provider ordered a new clinical test after a reference lab offered her “the first five tests for free.” This was deemed an inducement to earn the provider’s business. When a reference lab inequitably offers some patients free testing, this leads to distributing charges unfairly to other patients. We sent this test to another reference laboratory with compliant billing practices.

Being Prepared
Even with a policy and review process, we still feel like we are playing a game of whack-a-mole. We’d like to get ahead of these free test requests when possible. To improve the process, we recently implemented a standard test request form to provide a structured way to compile information and assess a request in collaboration with the requesting provider. We’ve also found it helpful to meet with laboratory sales representatives to explain our policy when they visit—too often they contribute to the hype around offering free testing for patients, which misleads our providers.

By being good stewards, we can better ensure high-quality testing and standard care for all our patients and consistent support for our providers.
FDA Continues to Fine-Tune Regulation of SARS-CoV-2 Serology Tests

On May 21, the Food and Drug Administration (FDA) created a public list of SARS-CoV-2 serology tests that the agency has removed from its so-called notification list for SARS-CoV-2 tests. This means that these tests can no longer be marketed under the terms of the agency’s current policy for authorizing tests intended to aid in managing the COVID-19 public health emergency.

At the start of the COVID-19 outbreak, FDA responded to concerns that its regulations were hampering testing by allowing in vitro diagnostic companies to develop and market SARS-CoV-2 serology tests without applying for emergency use authorization (EUA). However, this led to a flood of serology tests hitting the market that were of dubious quality. FDA therefore revised its guidance for SARS-CoV-2 serology tests in early May so that manufacturers must now submit an EUA within 10 business days after the date they notify FDA of their test validation or the date that FDA published the revised policy, whichever is later.

The new removal list includes tests that manufacturers have voluntarily withdrawn in the wake of FDA’s revised serology test guidance, as well as those tests for which manufacturers did not submit EUA requests within the 10-day window. In a public statement, FDA said that it expects manufacturers to stop distributing tests on the removal list, and that it will continue updating the list as needed.

Regulatory Roundup

FOUNDATION MEDICINE, MYRIAD GET MULTIPLE CO-DIAGNOSTIC APPROVALS FROM FDA

The Food and Drug Administration (FDA) has approved Foundation Medicine’s next-generation sequencing-based FoundationOne CDx test to aid in identifying patients with non-small cell lung cancer (NSCLC) for whom treatment with Tabrecta (capmatinib) might be appropriate. Tabrecta, which was developed by Novartis, is currently the only FDA-approved therapy for patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping, which occurs in 3% to 4% of NSCLC cases.

FDA has also approved both FoundationOne CDx and Myriad Genetics’ BRACAnalysis CDx for use as companion diagnostics for Lynparza (olaparib), which received simultaneous approval for use in patients who have deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer and who have progressed following prior treatment with enzalutamide or abiraterone. This is the seventh regulatory approval Myriad has received for BRACAnalysis CDx in support of Lynparza, a novel poly ADP ribose polymerase (PARP) inhibitor jointly developed by AstraZeneca and Merck.

Additionally, Myriad’s myChoice CDx has received FDA approval to aid in identifying advanced ovarian cancer patients with positive homologous recombination deficiency (HRD) status who are eligible or might become eligible for first-line maintenance treatment with Lynparza in combination with bevacizumab. MyChoice CDx is a comprehensive HRD test that identifies people with tumors that have lost the ability to repair double-stranded DNA breaks, resulting in increased susceptibility to PARP inhibitors.

FDA CLEARS CANCER GENOMIC PROFILING TEST FROM PERSONAL GENOME DIAGNOSTICS

Personal Genome Diagnostics, a company established by researchers from Johns Hopkins University specializing in cancer genome sequencing and liquid biopsy technologies, has earned Food and Drug Administration clearance for PGDx elio tissue complete. This diagnostic kit is designed to enable molecular laboratories to perform genomic profiling of cancer in a more efficient manner. PGDx elio tissue complete detects single nucleotide variants and small insertions and deletions in more than 500 genes, select amplifications and translocations, and genomic signatures including microsatellite instability and tumor mutation burden. The assay includes biomarkers to help inform the use of targeted cancer therapies and immunotherapies and to help oncologists identify patients for
clinical trial participation. It also includes software that automates the data analysis process. Personal Genome Diagnostics supported the 510(k) submission for this test with accuracy data across all genetic variant classes in clinical samples from 35 tumor types.

**Binx POC Test for Chlamydia, Gonorrhea Gets FDA OK for Use on Male Urine Specimens**

The Food and Drug Administration (FDA) has given a second 510(k) clearance to binx health’s molecular point-of-care (POC) platform, the binx io, which will enable healthcare professionals to use this test to detect chlamydia and gonorrhea in male urine specimens. Previously in 2019, FDA also cleared the binx io for use with clinician and self-collected vaginal swab specimens. The binx io platform couples polymerase chain reaction amplification with proprietary electrochemical detection technology to produce chlamydia and gonorrhea test results in about 30 minutes. To evaluate the platform’s performance, binx performed a multi-center clinical trial involving 10 evaluation sites across the U.S. and samples collected from 922 male symptomatic and asymptomatic patients. Non-laboratorians in POC settings processed 94% of all patient samples. The study compared results for male urine specimens run on the binx io with results from three FDA-cleared laboratory tests, and found that the binx io showed a 92.5% sensitivity and 99.3% specificity for chlamydia and 97.3% sensitivity and 100% specificity for gonorrhea.

**CE Mark Granted to Advanced Biological Laboratories for HIV Drug Resistance Tests**

Advanced Biological Laboratories (ABL) has received the CE mark for its two DeepChek-HIV drug resistance assays, which use capillary electrophoresis and next-generation sequencing (NGS) to genotype HIV-1 group M viruses. The first assay covers the protease and reverse transcriptase regions of the virus while the second assay covers the integrase region. Both tests are performed using RNA extracted from plasma, serum, or whole blood samples, and they have been validated to process clinical samples with viral loads as low as 1,000 copies/mL. According to ABL, the DeepChek-HIV assays exhibit 100% agreement on analytical reproducibility and repeatability, 100% clinical reproducibility, and 99% clinical sensitivity for all three HIV genomic regions. The tests can also be used in a broad range of laboratory settings running either Sanger or NGS workflows, and they have been validated together with the DeepChek Library Preparation assays on several NGS platforms from Illumina, including the iSeq100 instrument.
Renalytix AI, Mount Sinai Launch COVID-19 Kidney Disease Study

Renalytix AI and Mount Sinai Health System will collaborate on a study of COVID-19 patients and their risk of acute and chronic kidney disease. Researchers at Mount Sinai will utilize Renalytix AI’s KidneyIntelX platform to monitor patients’ kidney disease risk as COVID-19 progresses.

Evidence has shown that 20% of patients have developed acute kidney injury (AKI) after being diagnosed with COVID-19, the illness caused by the SARS-CoV-2 virus. Further research shows that AKI causes higher mortality rates in those same patients. A recent study in China also revealed that SARS-CoV-2 has the potential to travel into kidney tissue, leading to further health issues in COVID-19 patients.

The study, Prediction of Major Adverse Kidney Events and Recovery (Pred-MAKER), will use the KidneyIntelX to analyze plasma and urine biomarkers in admitted patients. Researchers hope the findings will provide evidence of which patients are at a high risk of kidney diseases.

In addition, Renalytix AI and Mount Sinai have formed a joint venture, Kantaro Biosciences, to increase antibody testing for SARS-CoV-2. Kantaro has entered into a deal with Bio-Techne Corporation to develop testing kits designed to measure the presence or absence of anti-SARS-CoV-2 antibodies in addition to measuring the number of antibodies a person has produced. Both companies have a goal of performing over 10 million tests a month beginning in midsummer.

Thermo Fisher Scientific has acquired a contract from the U.S. government to ramp up its supply of viral transport media (VTM) for COVID-19 sample collection. As the U.S. races to provide sufficient testing for SARS-CoV-2, laboratory medicine professionals have continued to face shortages of VTM, which plays a vital role in ensuring the integrity of patient samples and the accuracy of test results.

Currently, Thermo Fisher’s site in Lenexa, Kansas, is the only one of the company’s locations that provides the necessary environment for dispensing VTM into transport tubes. The government contract will support Thermo Fisher’s plans to expand the Lenexa site. The company has already begun to increase VTM distribution from 50,000 tubes to more than 1 million tubes per week, and with a newly built $40 million facility dedicated solely to VTM production, the company hopes to manufacture over 8 million transport tubes per week.

“We have a proven blueprint for high-quality VTM production in Lenexa and look forward to bringing significant new capacity on line as quickly as possible to continue the necessary ramp-up in the U.S.,” said Marc N. Casper, chairman, president, and CEO of Thermo Fisher Scientific.
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The company aims to open the new facility in the coming months and expects this to create approximately 300 new job opportunities.

COMPANIES TEAM ON MOLECULAR BIOSENSOR CHIPS TO DETECT SARS-CoV-2

Roswell Biotechnologies and Imec have announced they will work together to develop what could be the first molecular biosensor chip that tests for SARS-CoV-2. Roswell, a long-time developer of molecular electronic sensor chips, plans to use Imec’s research in nanoelectronics and digital technology to advance detection of infectious diseases.

The companies’ plan calls for developing a hand-held molecular electronic sensor chip that will integrate single molecules as electrical sensor elements on standard silicon chips. The company will also incorporate Roswell’s Electronic Nano-Device Sequencing System, which can sequence an entire human genome in just minutes.

“The Roswell molecular electronic platform will transform the way infectious diseases are detected, with powerful new capabilities that enable rapid screening of many infectious diseases at once, or many viral strains, with portable or hand-held devices,” said Paul Mola, CEO of Roswell.

Both partners hope that the molecular electronic sensor chip could be a breakthrough to screen for the COVID-19 virus, antigens, and antibodies rapidly, accurately, and at a low cost. Currently, the companies are finalizing development and aim to commercialize the chip in 2021.

OLINK ACQUIRES AGRISERA FOR PROTEIN RESEARCH

After several years of collaboration, Olink Proteomics has acquired Agrisera to enhance Olink’s portfolio of protein assays available for its Proximity Extension Assay (PEA) technology. The PEA technology features multiple immunoassays that measure 92 proteins across 96 samples simultaneously. Olink plans to use Agrisera’s assortment of antibodies to develop additional protein assay services.

Olink’s specialization in protein research has allowed the company to advance in the field of precision medicine. Through the acquisition, Olink aims to analyze additional proteins that could be disease biomarkers. The acquisition also will provide Agrisera a new network of clients and potential for further partnerships.

“This is a great opportunity for Agrisera and we are very happy to be part of the Olink team, facilitating the Olink mission with our world class high-throughput antibody development capabilities. We are sure that Agrisera, as well as our partners and current customer base, will benefit from the strength of our new owner,” said Erika Gelfgren, CEO of Agrisera.
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How Europe’s New IVD Regulations Will Impact Labs

EXPERT
Natalie J. Kennel, RAC, FRAPS, ASQ CQE, CQMgr

What are Europe’s new in vitro diagnostic (IVD) regulations?
A: The IVD Medical Device Regulation (IVDR) European Union (EU) 2017/746 was published on May 5, 2017, starting a 5-year transition period until its implementation. This new regulation is significantly more extensive and far ranging than the current EU IVD Directive, and now that it’s 2 years away from kicking in, IVD companies are scrambling to meet the product requirements of the new standard. Meanwhile, however, the clinical laboratory community has barely noticed this impending change.

What do these new regulations have to do with clinical laboratories?
If they are even aware of the impending regulations, most clinical laboratories think that this is an IVD-company issue that won’t affect them. However, the IVDR actually will have a significant impact on clinical laboratories, too. If a commercial clinical laboratory tests specimens from European citizens with laboratory-developed tests (LDT), these LDTs are likely to be considered “distance sales” under the new regulations, meaning that the tests will require CE IVD marking—regardless of whether the lab is or isn’t located in the EU.

Aren’t there exemptions for LDTs under the IVDR?
Yes, the IVDR includes an in-house exemption that allows healthcare institutions to manufacture, modify, and use LDTs on a nonindustrial scale to meet the specific needs of target patient groups if an equivalent device available on the market cannot already meet these needs at the appropriate level of performance. However, this exemption will only apply to a small subset of LDTs and associated labs that are part of healthcare institutions established in the EU. Most commercial laboratories will therefore be required to CE mark their LDTs. And even for the subset of labs that meet the in-house exemption, the IVDR will require them to meet several new standards, including compliance with the IVDR’s Annex I “General Safety and Performance Requirements” and quality management system framework.

Could the COVID-19 pandemic delay the implementation of these new regulations?
The European Union Medical Device Regulation was published on the same date as the IVDR with a planned 3-year transition through May 26, 2020, and it has been delayed by 1 year due to the COVID-19 pandemic. However, as of this writing, the IVDR’s date of application remains May 26, 2022, which is the end of the current 5-year transition period, and no delay of this effective date has been proposed. Furthermore, the pandemic has increased the public’s awareness of IVD testing and laboratories, which may reduce the likelihood of the IVDR’s application date being delayed at a later point in time.

What should clinical laboratories do to prepare?
Regardless of their location, all clinical laboratories that test specimens from European citizens using LDTs should become familiar with the IVDR and carefully review its definitions and in-house exemption. As most clinical laboratories will not meet the in-house exemption, the next step is for labs to classify their LDTs according to Annex VIII of the regulations. All labs should perform a gap analysis of their existing LDTs’ clinical evidence, particularly against Annex 1 “General Safety and Performance Requirements,” and they should also conduct a thorough assessment of their quality management system against the IVDR requirements to identify gaps and areas in need of improvement. Based on these analyses, labs should then develop and begin executing a plan to meet the IVDR requirements. Time is short and it is imperative that laboratories not delay action.

Ms. Kennel will discuss this topic during two roundtable talks (session numbers 43112 and 53212) at the 2020 AACC Annual Scientific Meeting on December 15 at McCormick Place, Chicago.

Natalie J. Kennel, RAC, FRAPS, ASQ CQE, CQMgr, is the founder and president of NJK & Associates, which helps companies with U.S. and international regulatory submissions and quality system implementations and improvements.

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