Flexible diagnostic panels for pathogen testing

Flu symptoms and the role of laboratory diagnostics

PCR-based testing in oncology

The LIS in today’s POL

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CMS’ proposed new fee schedule concerns lab community

On September 25, the Centers for Medicare and Medicaid Services published a news release “CMS Proposes New Medicare Clinical Diagnostic Laboratory Tests Fee Schedule.” The agency wrote:

“...the Centers for Medicare & Medicaid Services (CMS) today announced its next step in implementing the Protecting Access to Medicare Act of 2014 (PAMA), requiring clinical laboratories to report on private insurance payment amounts and volumes for lab tests. This data will be used to determine Medicare’s payment for lab tests beginning January 1, 2017. Under the proposed rule, certain laboratories would be required to report private payor rate and volume data if they receive at least $50,000 in Medicare revenues from laboratory services and more than 50 percent of their Medicare revenues from laboratory and physician services.

“Laboratories would collect private payor data from July 1, 2015 through December 31, 2015 and report it to CMS by March 31, 2016. CMS will post the new Medicare rates by November 1, 2016; these rates will be effective on January 1, 2017.”

CMS provided a link to the proposed rule (https://www.federalregister.gov/public-inspection) and indicated that a comment period will expire November 24, 2015. It rather summaized described the plan as “another example of our commitment to spending health care dollars more wisely” that “demonstrates CMS’ dedication to collaboration with private payors to improve the delivery system.”

Not everyone agrees.

The American Clinical Laboratory Association (ACLA), for instance, issued a statement that warns that CMS’ proposed coding and payment proposals will jeopardize the advancement of personalized medicine.

“CMS’ proposed payment determinations for new codes paid under the Clinical Laboratory Fee Schedule (CLFS) in CY2016 include severe cuts to the set of nine codes for advanced diagnostic laboratory tests that are currently covered and paid for by Medicare through their respective local contractors. These proposed cuts of 33 percent to as much as 91 percent, if finalized, are in direct conflict with the agency’s precedent for establishing rates for these type tests through the local contractors, and this proposed rate-setting methodology is inconsistent with the vast majority of stakeholder input and the recommendations of CMS’ own Advisory Panel on Clinical Diagnostic Laboratory Tests.”

Says Alan Mertz, ACLA president: “President Obama has highlighted the clear potential for precision medicine to improve healthcare for patients and continue the country’s progress as a world leader in medical innovation. Slashing payment of these tests—some up to ninety percent—will have a profound impact on the success we’ve achieved thus far, thanks to life-saving diagnostic discoveries.”

The National Independent Laboratory Association (NILA) states the proposed CMS regulation threatens competition and access to laboratory testing:

“Under the proposed regulation, laboratory reporting would be required between January 2016 and March 2016, though final CMS regulations would not be published until the end of December 2015, at the earliest. CMS would then quickly evaluate the anticipated billions of reported data sets to issue new proposed rates by November 2016, issuing final Clinical Laboratory Fee Schedule rates by January 1, 2017—providing just two months for laboratories to comprehend the impact adjustments will have on their business and their ability to provide ongoing services.”

Says Mark Birenbaum, PhD, NILA administrator. “The law itself is fundamental flawed, as it requires CMS to determine a weighted median of all the test rates/volumes reported in order to set new payment rates. Clearly, the largest players in the laboratory market—the two national publicly-traded laboratories—will drive the test volumes, and their rates will dominate CMS’s evaluation. The law does nothing to consider variances in the market and the impact that adjustments will ultimately have on community and regional laboratories.”

Industry sources have also expressed doubts. California-based CareDx and Veracyte, for example, have voiced concerns that established molecular diagnostic tests might be unduly impacted.

What are readers hearing and saying about the impact of the apparently imminent changes? We’d like to know your thoughts.
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Infectious Disease

CDC supports new WHO early release HIV treatment and PrEP guidelines. The CDC has endorsed the recent announcement by the World Health Organization (WHO) of new Early Release HIV Treatment and Pre-Exposure Prophylaxis (PrEP) guidelines that will significantly increase the number of people eligible for life-saving anti-retroviral treatment (ART) and expand access to a powerful tool for preventing HIV among those at greatest risk.

The new guidelines call for treatment for all individuals living with HIV, regardless of CD4 count. This is a shift from existing WHO guidelines that recommend ART for those with compromised immune systems (CD4 counts less than 500) and other vulnerable populations such as children, pregnant women, and people with TB. The new guidelines also recommend daily oral PrEP as an additional prevention choice for those at substantial risk for contracting HIV as part of a combination prevention approach.

Recent scientific breakthroughs show that early and effective treatment not only reduces HIV transmission but also significantly improves health outcomes for those living with HIV. PrEP has been shown in many studies and “real world” situations to reduce the risk of HIV infection by more than 90 percent among those who regularly take their meds.

The WHO announcement aligns with two key U.S. recommendations. In 2012, the U.S. Department of Health and Human Services (HHS) issued treatment guidelines recommending ART for all patients diagnosed with HIV infection. In 2014, CDC issued clinical guidance recommending physicians consider advising the use of PrEP for gay and bisexual men, heterosexuals, and injection drug users at substantial risk for HIV infection.

Cancer

Researchers report genetic clue to breast cancer relapses. British scientists have discovered a genetic clue to why some breast cancers relapse, which could lead to better treatment. A research team from Welcome Trust Sanger Institute in Cambridge found that cancers that return were more likely to contain certain genes or combinations of genes. Targeting these genes with early treatments could be key. The study was presented at the recent European Cancer Congress in Vienna.

In approximately one in five people with breast cancer, the disease will return—either to the same place as the original tumor or another part of the body. Lucy Yates, MD, and her colleagues analyzed data from the tumors of 1,000 breast cancer patients, including 161 people whose cancer had recurred or spread. Comparing primary and secondary tumors, they found noticeable genetic differences, and several of the mutations that were present in the secondary cancers were relatively uncommon in cancers diagnosed for the first time.

Yates said the patterns they found suggested that the complement of cancer genes in some primary cancers may make them more likely to relapse in the future, while additional cancer genes acquired after diagnosis may drive the cancer relapse. She said doctors might be able to use this knowledge to identify patients at high risk of their cancer returning and pick the best treatment for targeting particular genetic mutations. This would mean taking regular samples of cancer tissue to track how the disease is progressing and changing.

Study shows K17 protein promotes cancer. Keratin 17 (K17), a protein previously believed to provide only mechanical support for cancer cells, appears to play a crucial role in degrading a key tumor suppressor protein in cancer cells called p27. This finding, published in Cancer Research, is based on the work of researchers in the Department of Pathology at Stony Brook University School of Medicine. They found that K17 has the ability to enter the nucleus of cancer cells, leading to the degradation of p27. The work illustrates that a keratin can function to promote the development of cancer. Furthermore, the researchers find that tumors with high levels of K17 are biologically more aggressive and have a worse prognosis than low K17 tumors.

The protein p27 is a master regulator of organized cell division and growth found in the nucleus of cells, and it is commonly inactivated in cancer cells. In the paper, “Keratin-17 Promotes p27K1P1 Nuclear Export and Degradation and Offers Potential Prognostic Utility,” lead author Luisa Escobar-Hoyos, a Molecular Pharmacology graduate student working on her PhD thesis project under the direction of Kenneth Shroyer, MD, PhD, Professor and Chair of the Department of Pathology, and colleagues, investigated if K17 interferes with p27 processes. Their findings validate previous observations from the Shroyer lab that reveal high K17 cervical cancer patients have a decreased chance of long-term survival when compared to patients who express little to no K17 in tumor tissue. In addition, it was discovered that K17 increases chemotherapy resistance in cancer cells.

This research suggests that K17 testing could provide valuable information that may be used to distinguish between “clinically identical” cancer patients, identifying cases with more aggressive tumors at the time of diagnosis, and potentially guiding personalized treatment based on individual K17 status.

Ebola

Portable, rapid DNA test can detect Ebola and other pathogens. Using technical advances not yet developed when the 2014 Ebola outbreak began, University of California San Francisco-led scientists completed a proof-of-principle study on a real-time blood test based on DNA sequencing that can be used to rapidly diagnose Ebola and other acute infections. The researchers say that the test can be used even where lab space and medical infrastructure are scarce.

Charles Chiu, MD, PhD, led a team that detected the genetic fingerprints of Ebola in stored blood samples from two African patients who had acute hemorrhagic fever, completing the diagnosis within five hours of opening the samples. The DNA sequencing took just 10 minutes.

Most commercially available or research-based genetic diagnostic tests target specific pathogens. But Chiu and colleagues have pioneered techniques that do not require suspected pathogens to be identified beforehand in order to detect their unique genetic fingerprints. This unbiased approach of analyzing all DNA in a clinical sample without knowing which species are present, which was used in the Ebola detection, is called “metagenomic” analysis.

To obtain such quick results, the researchers developed new analysis and visualization software and used it on a laptop computer to leverage an emerging DNA-sequencing technology called nanopore sequencing.

In the same set of experiments, the researchers were able to detect the Chikungunya virus just as quickly from a blood sample. In another example, detection of hepatitis C virus in blood from an infected patient, present at a much lower concentration than the other viruses, took just 40 minutes from the start of sequencing.
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The clinical and economic value of flexible diagnostic panels for respiratory pathogen testing

By Nathan Ledeboer, PhD

Significant strides have been made in the diagnosis of respiratory tract infections over the past decade. These improvements, in large part, are due to the greater availability, affordability, and increased pathogen coverage provided by molecular diagnostic tests for respiratory pathogens. While it has been a tremendous advantage to simply have diagnostic solutions that can provide rapid and accurate detection of a broad range of respiratory pathogens, the changing landscape of healthcare now requires clinical laboratories to provide more value and flexibility from the tests they choose to perform. Labs now have to be more conscious than ever of the needs of the providers and patients they serve.

A paradigm shift, marked by changing interactions among laboratorians, direct patient care providers, and patients is taking place within the field of clinical microbiology. This shift, in part, is due to the emergence of rapid diagnostic testing solutions and provider and patient awareness of the benefits of these tests. As more testing has become available closer to the patient or at the point of care, labs have had to alter the services they offer and, consequently, the manner in which they interact with clinicians and patients.

Infectious disease diagnostics: changing times

Specific to molecular biology, there are a number of different factors that are changing the field of infectious disease diagnostics. Clinical microbiology of the past was limited in impact and often viewed by many clinicians as confirmatory because of the long turnaround time associated with culture-based methods. Molecular diagnostics have emerged as the first viable replacement to culture-based diagnostics because these tests can deliver accurate results with a more clinically meaningful turnaround.

The most significant trends in molecular testing over the last decade have been the increase in the number of commercial molecular tests and the movement away from single PCR tests to disease-state testing. Clinicians now want to order tests based on a clinical diagnosis such as pneumonia or gastroenteritis, and they want the tests to be completed in a timeframe that allows their results to impact treatment decisions. The adoption of disease-state testing has increased significantly as more and more studies have demonstrated its ability to improve clinical and economic outcomes. This increased adoption has led to an increase in the number of diagnostic test manufacturers entering this space, which has led to a decrease in the cost associated with performing this type of testing. While there is now a plethora of multiplex molecular diagnostic options available for many infectious disease states, tests manufacturers will have to continue to adapt test designs to better complement the new pressures associated with the changing landscape of clinical microbiology.

Addressing the challenges of respiratory infections

There are a number of challenges specific to respiratory infections that can be addressed with different testing options provided by the laboratory. While symptoms of respiratory tract infection alone are not sufficient for clinicians to determine optimal patient management, clinicians do order testing based on medical and social history and underlying conditions. Clinician ordering patterns for respiratory pathogen testing are impacted by a number of different factors, including seasonality, positivity, patient demographics, and turnaround time. Clinicians are conscious of both the seasonality of respiratory pathogens (e.g., influenza) and the epidemiology of circulating pathogens; therefore, they prefer to order respiratory testing specific for what may be circulating at a given time.

Similarly, in terms of patient demographics, for patient populations primarily composed of outpatients, clinician ordering patterns reveal that influenza and respiratory syncytial virus (RSV) are the pathogens of greatest interest because detection of these viruses would impact patient management decisions, whereas detection of other viral pathogens may not. For inpatients, clinicians often order testing for a broader set of respiratory pathogens because positive identification of a pathogen could limit downstream testing, alter isolation precautions, and prevent unnecessary use of antibiotics.

In regard to the patient, the lab now also has to be focused on choosing a respiratory testing algorithm that is continued on page 10

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LEARNING OBJECTIVES

Upon completion of these articles, the reader will be able to:
1. Discuss the factors that are changing the field of diagnostic infectious disease testing.
2. Identify the challenges that laboratories face when choosing the best respiratory testing menu to offer to clinicians.
3. Discuss ways in which a flexible testing menu can be a benefit to both the laboratory and the ordering clinician.
4. Identify various diagnostic testing methods in the identification of influenza virus.
5. Describe the importance in viral culture testing of respiratory samples and the information that can be used as a result of this testing method.

continued on page 10
Syndromic molecular panels have revolutionized the way respiratory illness is diagnosed and managed. However, as labs strive to balance expanded testing capabilities with cost-effective patient care, one size doesn’t always fit all. Verigene RP Flex - now available on the sample-to-result Verigene System - is a comprehensive, yet flexible panel that enables labs to test for all 16 targets or any user-defined subset for each patient sample.

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cost-effective in order to minimize unnecessary cost to the patient. Labs are often put in a situation where they can only support one molecular platform because of resource and financial constraints, and this test may be too broad for a majority of the respiratory testing orders from their clinicians. In these situations, the laboratory is increasing the cost to the patient by performing unnecessary testing not requested by the clinician. This issue has become especially sensitive over the past few years, as there has been a substantial increase in the number of high-deductible healthcare plans that require the patients to pay for laboratory-based diagnostics, rather than insurance companies paying for this testing. Because of this, patients and clinicians are increasingly scrutinizing laboratory testing costs.

**Imperfect choices for labs**

In addition to satisfying the needs of the provider and patient, the lab also has the pressure of finding a testing solution that provides the best performance at the lowest cost and with the lowest workflow burden. For many labs, there are two choices for respiratory pathogen testing: they must choose between selecting one abbreviated respiratory panel that does not provide the necessary coverage, and then sending the remaining respiratory orders to a reference laboratory; or running a one-size-fits-all panel for all respiratory testing orders, which may be too broad in some cases, yet not broad enough in others. Use of multiple platforms is too costly a solution for most laboratories, possibly requiring capital purchase of multiple instruments, additional medical laboratory professional training, extra quality control testing, and extra proficiency testing.

If labs choose one abbreviated respiratory panel for the primary respiratory pathogens of influenza and RSV, they are left with few alternatives when a clinician requires additional pathogen testing, which can result in sending out the sample to a reference laboratory. This respiratory testing algorithm is very expensive and is associated with turnaround times that are not clinically meaningful. Using a broad respiratory pathogen test often provides the necessary pathogen coverage; however, this approach can force clinicians to order a test with targets not necessary for the patient or force laboratories to view and report results that the clinician did not order. With an increasing downward pressure on reimbursement and the increase in high deductible healthcare plans, neither of these options offers a sustainable, long-term solution.

**The flexible test concept**

The newest challenge to manufacturers is to design tests that provide laboratories with the flexibility needed to satisfy both limited and broad testing requirements: ideally, a single respiratory pathogen test that could meet the needs of the provider, the patient, and the lab. This flexible test concept would be new to the clinical microbiology laboratory, but would not be a new concept within clinical laboratories. Serology is one example of a successful flexible testing model. With serology testing, multiple targets are tested for at one time, but results are only released based on individual orders by the clinician. A similar move to this flexible model in respiratory testing could allow for one diagnostic test to allow a narrow test to be ordered for outpatients and a broad test to be ordered for inpatients.

As with serology testing, if all respiratory pathogen targets could be run at one time and only a subset of these targets released to the clinician, a targeted testing with reflexing to broad testing-model could be achieved. This would ultimately minimize unnecessary cost to the patient and provide a testing algorithm favorable to many of the private payers. While this model can be achieved using multiple respiratory tests on multiple platforms, having this option on a single respiratory test would be favorable for many labs.

In the case of respiratory testing, flexible tests can be complementary to current respiratory testing algorithms in place at a hospital and address the weakest points of the algorithm. Often, labs will minimally have rapid, point-of-care testing available for flu and possibly RSV to satisfy the ED clinician’s request for a < 20 minute turnaround time so treatment decisions can be made when the patient is still in the hospital. Flexible respiratory tests could serve as a targeted reflex or confirmatory test for influenza and/or RSV or be the targeted testing choice for only the patients requiring broad viral pathogen work-ups or pertussis testing. Similarly, a flexible test could be used to provide an affordable stand-alone adenovirus test or human metapneumovirus test as an alternative to running a full respiratory panel and seeing results not ordered by the clinician or having to send out the testing to a reference lab, which is expensive and has a turnaround time that is often not clinically relevant. In other cases, flexible tests could provide the means for hospitals to provide targeted flu, flu and RSV, broad respiratory, and pertussis testing options all from one test on one platform. Since this could all be performed on one platform, more labs will be able to justify this responsible testing algorithm, as supporting multiple platforms for respiratory testing to achieve this same goal is not currently an option because of the resource drain that would put on the financial and personnel resources of the lab.

This flexible testing model could potentially drive the design of future infectious disease molecular tests, as it not only provides the accurate results necessary to be performed in the lab, but also provides laboratories with much more flexibility to be able to satisfy the changing needs of the clinicians and patients.

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**Nathan A. Ledeboer, PhD**, is an Associate Professor of Pathology at the Medical College of Wisconsin.
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Influenza symptoms and the role of laboratory diagnostics

By MLO staff

Here’s the latest from the Centers for Disease Control and Prevention (CDC) on influenza diagnostics, adapted from www.cdc.gov and abridged for space.

**Signs and symptoms**
Influenza illness can include any or all of these symptoms: fever, muscle ache, headache, lack of energy, dry cough, sore throat, and possibly runny nose. The fever and body aches can last three to five days, and cough and reduced energy may last for two weeks or more. Influenza can be difficult to diagnose based on clinical symptoms alone because the initial symptoms can be similar to those caused by other infectious agents including, but not limited to, *Mycoplasma pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and *Legionella* spp.

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. Early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, bacterial infections can occur as a complication of influenza.

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. Influenza surveillance by state and local health departments and the CDC can provide information regarding the presence of influenza viruses in the community. Surveillance can also identify the predominant circulating types, influenza A subtypes, and strains of influenza.

**Diagnostic lab procedures**
A number of tests can help in the diagnosis of influenza (Table 1). However, tests do not need to be done on all patients. For individual patients, tests are most useful when they are likely to give a doctor results that will help with diagnosis and treatment decisions. During a respiratory illness outbreak in a closed setting (e.g., hospitals, nursing homes, cruise ships, boarding schools, summer camps) however, testing for influenza can be very helpful in determining whether influenza is in fact the cause of the outbreak.

<table>
<thead>
<tr>
<th>Method</th>
<th>Types Detected</th>
<th>Acceptable Specimens</th>
<th>Test Time</th>
<th>CLIA Waived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral cell culture (conventional)</td>
<td>A and B</td>
<td>NP4 swab, throat swab, NP2 or bronchialwash, nasal or endotracheal aspirate, spumum</td>
<td>3-10 days</td>
<td>No</td>
</tr>
<tr>
<td>Rapid cell culture (shell vials; cell mixtures)</td>
<td>A and B</td>
<td>As above</td>
<td>1-3 days</td>
<td>No</td>
</tr>
<tr>
<td>Immunofluorescence, Direct (DFA) or Indirect (IFA) Antibody Staining</td>
<td>A and B</td>
<td>NP4 swab or wash, bronchial wash, nasal or endotracheal aspirate</td>
<td>1-4 hours</td>
<td>No</td>
</tr>
<tr>
<td>RT-PCR (single-plex and multiplex; real-time and other RNA-based) and other molecular assays</td>
<td>A and B</td>
<td>NP4 swab or bronchial wash, nasal or endotracheal aspirate</td>
<td>Varied (generally 1-6 hours)</td>
<td>No</td>
</tr>
<tr>
<td>Rapid Influenza Diagnostic Tests (antigen)</td>
<td>A and B</td>
<td>NP4 swab, throat swab, nasal wash, nasal aspirate</td>
<td>&lt;30 min.</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

Table 1. Influenza virus testing methods; Source CDC.

Preferred respiratory samples for influenza testing include nasopharyngeal or nasal swab and nasal wash or aspirate, depending on which type of test is used (Table 2, page 14). Samples should be collected within the first four days of illness. Rapid influenza diagnostic tests provide results within 15 minutes or less; viral culture provides results in three to ten days. Most of the rapid influenza diagnostic tests that can be done in a physician’s office are 50 percent to 70 percent sensitive for detecting influenza and greater than 90 percent specific. Therefore, false negative results are more common than false positive results, especially during peak influenza activity.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), immunofluorescence assays, and rapid molecular assays. Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test, the type of test used, and the type of specimen tested. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens. As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic information available to healthcare providers.

**Viral culture**
Despite the availability of rapid influenza diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating strains and subtypes of influenza viruses. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus...
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Characteristics of rapid influenza diagnostic tests; Source CDC.

During outbreaks of respiratory illness when influenza is suspected, some respiratory samples should be tested by both rapid influenza diagnostic tests and by viral culture. The collection of some respiratory samples for viral culture is essential for determining the influenza A subtypes and influenza A and B strains causing illness, and for surveillance of new strains that may need to be included in the next year’s influenza vaccine. During outbreaks of influenza-like illness, viral culture also can help identify other causes of illness.

RIDTs

Commercial rapid influenza diagnostic tests (RIDTs) are available that can detect influenza viruses within 15 minutes. Some tests are approved for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These RIDTs differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B, and distinguish between the two.

None of the tests provides any information about influenza A subtypes. The types of specimens acceptable for use (i.e., throat, nasopharyngeal, nasal aspirates, swabs, or washes) also vary by test. The specificity and, in particular, the sensitivity of RIDTs are lower than for viral culture and vary by test. Because of the lower sensitivity of the RIDTs, and thus the possibility of false-negative rapid test results, physicians should consider confirming negative tests with viral culture or other means, especially during periods of peak community influenza activity.

In contrast, false-positive rapid test results are less likely, but they can occur during periods of low influenza activity. Therefore, when interpreting results of a rapid influenza diagnostic test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests.

Serologic testing

Routine serological testing for influenza requires paired acute and convalescent sera, does not provide results to help with clinical decision-making, is only available at a limited number of public health or research laboratories, and is not generally recommended, except for research and public health investigations. Serological testing results for human influenza on a single serum specimen is not interpretable and is not recommended.

<table>
<thead>
<tr>
<th>Procedure (Manufacturer/Distributor)</th>
<th>Influenza Virus Types Detected</th>
<th>Approved Specimens</th>
<th>CLIA Waived</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M Rapid Detection Flu A+B Test (3M)</td>
<td>A and B</td>
<td>NP5 swab/aspirate Nasal wash/aspirate</td>
<td>No</td>
</tr>
<tr>
<td>Alere Influenza A &amp; B (Alere)</td>
<td>A and B</td>
<td>Nasal swab</td>
<td>Yes</td>
</tr>
<tr>
<td>BD Veritor System for Rapid Detection of Flu A+B (CLIA-waived) (Becton Dickinson)</td>
<td>A and B</td>
<td>NP5 swab/nasal swab</td>
<td>Yes</td>
</tr>
<tr>
<td>BD Veritor System for Rapid Detection of Flu A+B (Moderately Complex) (Becton Dickinson)</td>
<td>A and B</td>
<td>NP5 wash/aspirate/swab</td>
<td>No</td>
</tr>
<tr>
<td>BinaxNOW Influenza A&amp;B (Alere)</td>
<td>A and B</td>
<td>Nasal swab</td>
<td>Yes</td>
</tr>
<tr>
<td>BioSign Flu A+B (Princeton BioMedtech)</td>
<td>A and B</td>
<td>NP5 swab/aspirate/wash Nasal swab</td>
<td>No</td>
</tr>
<tr>
<td>Directigen EZ Flu A+B (Becton-Dickinson)</td>
<td>A and B</td>
<td>NP5 wash/aspirate/swab Throat swab</td>
<td>No</td>
</tr>
<tr>
<td>OSOM Influenza A&amp;B (Sekisui Diagnostics)</td>
<td>A and B</td>
<td>Nasal swab</td>
<td>No</td>
</tr>
<tr>
<td>QuickVue Influenza Test (Quidel)</td>
<td>A or B</td>
<td>Nasal wash/aspirate/swab</td>
<td>Yes</td>
</tr>
<tr>
<td>QuickVue Influenza A+B Test (Quidel)</td>
<td>A and B</td>
<td>NP5 swab Nasal wash/aspirate/swab</td>
<td>Yes</td>
</tr>
<tr>
<td>SAS FluAlert A&amp;B (SA Scientific)</td>
<td>A and B</td>
<td>Nasal wash/aspirate</td>
<td>No</td>
</tr>
<tr>
<td>SAS FluAlert A (SA Scientific)</td>
<td>A only</td>
<td>Nasal wash/aspirate</td>
<td>Yes</td>
</tr>
<tr>
<td>SAS FluAlert B (SA Scientific)</td>
<td>B only</td>
<td>Nasal wash/aspirate</td>
<td>Yes</td>
</tr>
<tr>
<td>Sofia Influenza A+B (Quidel)</td>
<td>A and B</td>
<td>NP5 aspirate/swab/wash Nasal wash</td>
<td>No</td>
</tr>
<tr>
<td>TRU FLU (Meridian Bioscience)</td>
<td>A and B</td>
<td>NP5 aspirate/swab Nasal wash</td>
<td>No</td>
</tr>
<tr>
<td>XPECT Flu A&amp;B (Remel/Thermofisher)</td>
<td>A and B</td>
<td>Nasal wash/swab Throat swab</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of rapid influenza diagnostic tests; Source CDC.
Changing Leaves, Cozy Sweaters, Pumpkin Spice and... Flu Season!

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10. A main purpose of surveillance of influenza by state and local health authorities is to identify the predominant circulating types, subtypes, and strains that are causing illness in the community.
   a. True
   b. False

11. The most common signs and symptoms of influenza do not include
   a. lack of energy.
   b. Sputum opacity.
   c. muscle aches.
   d. none of the above.

12. The duration of all collective influenza symptoms can last
   a. 1 to 2 days.
   b. 2 to 3 months.
   c. 3 days to 2 weeks, or more.
   d. 1 year or more.

13. The main advantage of testing for influenza in a closed setting is to gain knowledge about
   a. what type of antibiotics to prescribe.
   b. whether or not influenza is the cause of the outbreak.
   c. the number of patients contracting influenza.
   d. all of the above.

14. The preferred sample(s) for influenza testing include
   a. nasopharyngeal/nasal swab.
   b. nasal wash/aspirate.
   c. both a and b.
   d. neither a nor b.

15. When testing for influenza, specimens should be collected within the first four days of illness.
   a. True
   b. False

16. Which types of results from rapid diagnostic influenza testing will be seen more commonly during peak influenza activity?
   a. invalid results
   b. false positive results
   c. false negative results
   d. none of the above

17. Currently there is not a wide variety of diagnostic tests available on the market for influenza testing.
   a. True
   b. False

18. What type of respiratory specimen for viral isolation or rapid detection is most effective in regard to sensitivity/specificity?
   a. nasopharyngeal specimens
   b. throat swab
c. nasal swab
   d. neither a nor b

19. Viral culture of influenza is important for community health because the results can give information about
   a. who is contracting the illness.
   b. circulating strains and subtypes of influenza prevalent in the community.
   c. which type of drug regimen to prescribe to positive patients.
   d. none of the above.

20. Commercial rapid influenza diagnostic tests can detect Influenza A and B viruses; however, they cannot identify different subtypes of Influenza A.
   a. True
   b. False
1 test. 14 pathogens. All in about an hour.

A fast diagnosis of meningitis is essential, but difficult due to overlapping symptoms. The new FDA-cleared Meningitis/Encephalitis Panel helps with this medical emergency by detecting bacterial, viral or fungal infectious agents in about one hour. This can influence better patient management, leading to reduced healthcare costs and improved outcomes.

Learn more about the FilmArray Meningitis/Encephalitis (ME) Panel and BioFire’s leading syndromic panels at [FilmArray.com](http://FilmArray.com).
The polymerase chain reaction (PCR) in its many forms has become a routine clinical and academic laboratory assay during the past 20 years. Assays range from microbial detection in soil for oil exploration,1 to food analysis,2—to mutation analysis in cancer diagnostics.3 The basis of all PCR assays is the biochemical interaction between key components of the reaction (template, primers, nucleotide, and polymerase) during repeated cycles of denaturation, priming, and extension (thermocycling) to rapidly and reliably copy DNA.

The sensitivity of PCR is excellent, even from minute DNA samples, and this sensitivity is achieved by the exponential amplification of as little as one copy of a DNA fragment. However, this sensitivity is not suited to all situations; for example, it is not suited to the detection of a few mutated DNA copies in a great excess of normal (wild type) DNA. In this instance, pre-selection of mutated DNA copies would be required, and this can now be achieved through PCR-based DNA enrichment. Notably, this new technique is opening up new possibilities in cancer diagnosis and treatment monitoring, particularly when combined with liquid biopsies.

PCR-based DNA enrichment relies on a modification of PCR principles to enrich a mixed DNA template for rare sequences. Such rare sequences, or mutations, are typically associated with resistance or sensitivity to certain drug types in cancer treatment. Due to tumor heterogeneity, cancer biopsy samples typically contain a low abundance of mutated DNA in a high background of wild type DNA. Even with the exponential amplification of a PCR reaction, the mutated sequence is often present at such low levels that the wild type DNA prevails in the reaction and subsequent downstream sequence analysis.

Identification of rare single nucleotide polymorphisms (SNPs, i.e., mutations) in a DNA sequence that alter the function of the encoded protein is becoming increasingly important in cancer treatment pathways to monitor disease and treatment progression. Examples of these SNPs include BRAF V600E in melanoma, EGFR T790M and L858R in lung cancer, and various mutations in codons 12, 13, and 61 of KRAS found in colorectal cancer.4-10 In these instances, PCR-based DNA enrichment can provide a valuable tool to increase the detection of a mutated sequence in a cancer biopsy, be it a solid tumor sample or a blood/plasma sample.

PCR-based enrichment methodology

PCR-based DNA enrichment uses modifications to the principles of PCR such that wild type DNA amplification is suppressed and mutant/SNP DNA is exponentially amplified. The method requires the design of two primer sets, one pair specific for the wild type DNA at the potential site of the SNP (these are the enriching primers) and a second set upstream of the mutation site (these are the amplifying primers). See Figure 1.

The enriching primers contain a blocking moiety (typically a DNA analogue) that is incorporated into wild type PCR reactions, which prevents exponential amplification of wild type sequences and hinders the amplifying primers from extending through the blocked site. When an SNP is present in the DNA sample, the enriching primers have a 5’ mismatch and fail to anneal efficiently; this allows annealed amplifying primers to extend and displace the enriching primers and run on through the mutation site. Products of this reaction are available for further rounds of the PCR, and thus exponential amplification continues. Continued on page 20.

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**Figure 1.** PCR-based DNA enrichment methodology

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**Figure 1.** PCR-based DNA enrichment methodology

**Step 1 & 2:**

**Wild Type.** Enriching primers containing blocking moiety complementary to the wild type sequence anneal to wild type DNA sequence and extend.

**Amplifying primers** prime at sites flanking the sequence of interest but are blocked from extension by the extended enriching primers.

**Variant.** Enriching primers do not efficiently anneal and extend due to mismatch at the 3’ end and stringency of PCR conditions. Amplifying primers therefore extend right through the region of interest, without hindrance.

**Step 3:**

**Wild Type.** Lack of priming sites for either set of primers ensures only linear replication of template.

**Variant.** Exponential amplification of PCR products is possible.
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amplification of the mutation of interest is permitted. The blocking of wild type amplification allows for development of very sensitive assays suitable for use in the emerging field of cancer liquid biopsy.

Cancer diagnostics and monitoring

It has become apparent that sensitive molecular biology techniques such as PCR-based DNA enrichment could open new possibilities in cancer diagnosis and treatment monitoring when combined with liquid biopsies. This is because groups of cells within the same tumor can be genetically different and, following metastasis, they can be more different still. Relying on a single tissue biopsy can, therefore, give an incomplete picture of a patient’s disease. Liquid biopsies, using patient body fluids such as whole blood and plasma, could overcome this problem while also avoiding the costly and dangerous invasive surgery associated with obtaining a solid tumor biopsy.

Liquid biopsies are based on the biological phenomena that tumors shed both cells and tumor DNA into the circulation. Known as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) respectively, they are found in whole blood and plasma. The obvious benefit of a liquid biopsy is that samples are easier to obtain, but they can also be taken on multiple occasions to routinely monitor the state of the tumor and follow any genomic changes that are occurring with minimum discomfort to the patient. This serial sampling enables analysis of tumor genomic changes in real time, allowing clinicians to ensure that the therapy they have selected, based on a particular molecular target, remains relevant.

Case studies

DNA enrichment techniques have recently been used in studies using CTCs and ctDNA as the target.

KRAS mutations are found in many cancers but most notably in 40 to 50 percent of colorectal cancer (CRC) cases. These KRAS mutations are predictive of a very poor response to some monoclonal antibody therapies. In a study using CTCs isolated from an in vivo cannula, it was shown that cells expressing mutated KRAS genes could be isolated from the circulation of lung cancer patients. Certain samples showed wild type in the primary tumor but KRAS mutations in the CTC sample, demonstrating the utility of liquid biopsy as an early detection for mutations.

The epidermal growth factor receptor (EGFR) is the drug target for small molecule tyrosine kinase inhibitors, which have proved efficacious in non-small cell lung cancer (NSCLC) patients. These KRAS mutations are predictive of a very poor response to some monoclonal antibody therapies. In a study using CTCs isolated from an in vivo cannula, it was shown that cells expressing mutated KRAS genes could be isolated from the circulation of lung cancer patients. Certain samples showed wild type in the primary tumor but KRAS mutations in the CTC sample, demonstrating the utility of liquid biopsy as an early detection for mutations.

Liquid biopsies as a diagnostic tool

Studies such as this demonstrate that analyzing tumor DNA from liquid biopsies (whether isolated CTCs or ctDNA) using PCR-based DNA enrichment can reveal not only a patient’s current cancer status, but also provide the opportunity for ongoing monitoring. This is vital for a diagnostic, particularly in the field of oncology, where the availability of the tumor biopsy may be limited and a liquid biopsy is the preferred option. The ability of DNA enrichment to facilitate mutant DNA analysis from a blood-based sample without the need for further biopsy has thus been established to be working at the levels required for it to be a usable system to follow the course of a patient’s treatment, once the appropriate regimen has been determined.

REFERENCES

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The evolution of routine PCR testing: insights from the core lab model

By John W. Longshore, PhD, FACMG

Clinical laboratories face significant challenges today including decreased reimbursement, a shift from volume-based to value-based healthcare, and labor shortages in the face of increased demand for testing. Molecular labs, in particular, are being asked to increase productivity while decreasing costs, and to demonstrate their value and contribution to institutional success.

But the more things change, as the saying goes, the more they stay the same—in a way. These challenges are strikingly similar to the ones that core chemistry and hematology labs faced a decade ago. While substantive differences exist in test methodologies and complexity, some molecular labs are beginning to look at the evolution of the core lab model and ask if a similar paradigm shift may be one of the keys to long-term success for the molecular lab—especially in the area of routine or high-volume polymerase chain reaction (PCR) testing.

Barriers to efficiency and productivity

There are several components of the conventional molecular testing model that inherently limit the lab’s ability to achieve the types of efficiency, productivity and LEAN operations that are commonplace in today’s core chemistry lab. These limitations also hinder its ability to provide increased value to the healthcare institution or integrated health network it serves.

Decentralized structure and platforms. In sharp contrast to the concept of a centralized core lab, most molecular testing today is highly fragmented—e.g., genetic testing performed in a genetic lab, infectious disease testing in a microbiology lab, STI testing in cytology, etc. In many cases, this silo effect is intensified by physical or geographic separation of the labs. In addition, much routine molecular testing is performed on standalone platforms that are dedicated to a single test and/or are limited in their ability to accommodate mixed runs or consolidated test menus—capabilities that are common in core chemistry labs.

Cross-training staff. In a molecular pathology lab that incorporates testing for genetics, virology, microbiology, women’s health, and oncology markers, there is great value in having laboratorians be cross-trained among the molecular testing disciplines. While it may not be feasible to implement cross-training outside of the molecular lab, training staff on various disciplines within the lab can greatly improve productivity, enhance career development, and optimize the contribution of skills to the success of the lab.

Challenging staff’s skills. The field of molecular pathology is evolving rapidly, and as more automated options emerge for routine IVD tests, it helps free up time to let laboratorians focus on high-value, esoteric testing that is more specialized and labor-intensive, such as lab developed tests (LDTs) or next generation sequencing (NGS). This keeps staff fresh and engaged in the process, and can provide opportunities to expand skill sets in support of the institution’s mission and improve labor ROI, job satisfaction and staff retention.

Controlling utilization. One factor that contributes to lab inefficiency and non-value-added cost is inappropriate test orders and frequency, including duplicated or repeated test orders. For example, a lab may get multiple requests for a cystic fibrosis test or a Factor V test on the same patient. But a patient’s genotype does not change over time, so the result would not be expected to change. In a large practice or integrated health

Overcome these challenges and ensure their long-term success. Ideally, they represent the foundation of a clearly defined strategic vision that can help illustrate the molecular lab’s value to the institution.

Consolidation of workflow. Market forces are creating the need for molecular labs, especially at high testing volume, to consider consolidating their high-volume routine PCR testing, such as viral loads and women’s health/STI tests, on larger, automated platforms. This shift to centralized testing and a core lab model may initially present physical and logistical challenges, but it can yield improved efficiency, lower overall cost per test, and better utilization of laboratory staff.

Our health network recently consolidated its molecular testing into a system-wide core laboratory to eliminate duplication of services that existed across our hospital system. In addition to greater efficiency and staff utilization, our goal was to improve the experience that physicians and patients have when working with the lab.

It’s important to note that this shift to centralized testing for routine PCR testing does not conflict with the emerging practice of point-of-care molecular testing (POCT) for respiratory infections. They are complementary strategies to manage different types of testing. It would be extremely challenging for a molecular lab to handle the testing volume during respiratory virus season for both inpatients and outpatients. Having near-patient molecular methods available helps labs improve healthcare outcomes and staff adequately for the increased demand for testing in respiratory virus season.

Cross-training staff. In a molecular pathology lab that incorporates testing for genetics, virology, microbiology, women’s health, and oncology markers, there is great value in having laboratorians be cross-trained among the molecular testing disciplines. While it may not be feasible to implement cross-training outside of the molecular lab, training staff on various disciplines within the lab can greatly improve productivity, enhance career development, and optimize the contribution of skills to the success of the lab.
network (IHN), a patient may be seen by several healthcare providers who may inadvertently repeat an order for a test. A reliable way to improve utilization is through a physician champion or multidisciplinary committee that seeks means to control or manage utilization.

**Additional considerations**

Molecular labs have the potential to realize two other indirect benefits by shifting their routine PCR testing to more of a core lab model.

*Improved price-performance ratio.* Labs traditionally focus on the reagent cost component of a test, but it’s important to look at the overall operational cost of testing, including hands-on time for staff, instrument time, instrument reliability, and test repeat rate. With platform consolidation and centralized testing, a lab can run multiple routine tests on a single piece of equipment, which helps limit capital expenses and uses labor effectively. Our laboratory assesses the overall price-performance ratio for tests and chooses platforms and tests to get excellent performance while controlling costs.

*Consolidated reporting.* Adopting a more centralized structure for routine molecular testing can facilitate the development of integrated, comprehensive patient test reports. In the traditional molecular model, patient test reports are often sent with only one result on the page. In contrast, chemistry and hematology labs typically present a consolidated report. By offering a consolidated report for all of areas of laboratory testing, whether it’s a multigene profile for an oncology patient or a cervical biopsy and related tests, putting the information into a single combined format increases the value of the information to the physician and to the patient.

**Demonstrating value in personalized medicine**

Molecular labs play an increasingly vital role in personalized medicine, especially in the areas of companion diagnostics and targeted therapies. Several of the benefits of adopting a core lab model for routine PCR testing—such as increased efficiency, consolidated patient reports, and more time for laboratorians to focus on specialty testing—can significantly enhance a molecular lab’s ability to demonstrate the value of test results in improving patient care. They can also make it easier for labs to collaborate effectively with other disciplines, such as pharmacy, oncology, primary care, pediatrics, and internal medicine, and thus redefine the value of the molecular laboratory in the healthcare continuum.

**REFERENCE**


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**John W. Longshore, PhD, FACMG**, serves as Director of Molecular Pathology for Carolinas Pathology Group and Carolinas HealthCare System, an integrated health network with more than 40 hospitals. He oversees molecular testing for inherited disease, virology, microbiology, hematologic malignancy, and solid tumor analysis.
Glucose or HbA1c? The answer is both

By Jack Zakowski, PhD, FACB

According to the U.S. Centers for Disease Control and Prevention (CDC), 29.1 million Americans currently have diabetes, which equates to 9.3 percent of the U.S. population. Of these, 8.1 million remain as yet undiagnosed. Another 86 million are estimated to have prediabetes, which is an increased risk of diabetes, where blood glucose or hemoglobin A1c levels are high but not high enough to be classified as diabetes.1 Though not all individuals with prediabetes will develop diabetes, the number is staggering and it does not include U.S. children, teens, and young adults (those below the age of 20), who today are increasingly diagnosed with not just type 1 (once called “juvenile”) diabetes but also type 2 (adult onset) diabetes.

Statistics show that the percentage of new-onset type 2 diabetes cases in adolescents has risen significantly. Just a decade ago, type 2 diabetes in adolescents constituted less than three percent of new adolescent cases, globally. Today, the percentage of new adolescent cases of diabetes that are classified as type 2 is 45 percent and continues to rise.2

Less than 100 years ago, type 1 diabetes meant certain and often rapid death. Children with diabetes often died within weeks; adults with type 2 diabetes were fortunate to live 10 years after diagnosis, and many died much sooner. With the introduction of insulin to treat diabetes in 1922, individuals with diabetes were able to live longer and more productive lives. However, especially when not controlled properly, complications from diabetes continue to cause blindness, kidney failure, non-traumatic lower limb amputation, shock, coma, and death. Clearly, the laboratory’s role in helping physicians and patients diagnose and manage diabetes has never been more critical.

Fasting glucose versus HbA1c testing

With type 1 diabetes mellitus, the body does not produce insulin. Complications can be sudden and dramatic. With type 2 diabetes mellitus, the body produces insulin but, over time, cells in the body no longer respond properly to it. The pancreas may continue to make insulin for some time, or may eventually stop production altogether.

The diagnosis of diabetes, as well as evaluation of the type and severity, are critical to the proper management of treatment to prevent the onset or progression of serious complications. The definitions of what constitutes diabetes are more laboratory-based than ever before; as the incidence of disease continues to grow, symptoms alone (such as excessive thirst or frequent need to urinate) are not definitive, and diagnosing and treating the disease in its earliest stages can dramatically lower a patient’s risk of developing more advanced diabetes and its attendant complications.

The two most prevalent diagnostic tests used today are the fasting plasma glucose (FPG or “glucose”) test and the hemoglobin A1c (HbA1c) test. Debates have been ongoing for some time about which test is best for an accurate diagnosis of diabetes and ongoing diabetes monitoring. The answer is: both. It is important to understand what each type of test measures and how to properly employ each test to help diabetes patient management.

FPG testing measures short-term glucose metabolism—blood sugar levels at a given point in time. Fasting for at least eight hours prior to testing is critical, as baseline glucose, not postprandial, needs to be measured. An FPG of less than 100 mg/dL is considered normal; of 100 to 125 mg/dL is considered prediabetes; 126 mg/dL and above means the patient has diabetes.3

HbA1c is a measure of longer-term glucose metabolism. Glucose in the serum reacts with an amino acid group on hemoglobin to form glycated hemoglobin. Hemoglobin A1c is defined as that product of reaction of glucose with the N-terminal amino acid of the hemoglobin beta chain. Hemoglobin A1c results are expressed as a percentage of total hemoglobin. Individuals with HbA1c levels of less than 5.7 percent are considered normal; levels of 5.7 percent to 6.4 percent are considered prediabetic; and levels ≥ 6.5 percent HbA1c are diagnostic of diabetes.3

Pros, cons, and best practices

FPG is inexpensive and globally available, and it is a standard part of a routine blood panel. Because FPG measures short-term glucose metabolism, it works well for management of acute episodes; and because it is inexpensive, it is the most appropriate first test to indicate the potential presence or future risk of diabetes. However, as noted above, the fasting component of the test is crucial—and sometimes problematic. A patient may say he or she has fasted for eight hours, but mean “except for the sugar I put into my tea and one slice of dry toast so I could take my medicines this morning.” In addition, factors such as stress, exercise, and acute illness can impact readings on any given day.

HbA1c is not impacted by fasting, stress, or exercise and it can be done with a sample taken at any time (non-fasting). It is an indicator of average glucose concentrations over the last 80 to 90 days. HbA1c values are generated using an assay standardized to an international reference material.
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The glucose vs. HbA1c controversy
Clinicians weigh arguments for both types of diabetes testing

By Maurice Owen, BSc(Hons), PhD, BD, FACB

Which test should be used for the diagnosis of diabetes: glucose or HbA1c? Over the last few years, an increasing number of countries have moved from fasting plasma glucose to HbA1c as the method of choice. The measurement of glucose, which goes back more than 100 years, far predates HbA1c, and it can be argued that it measures the analyte that is widely known as being central to diabetes. Hemoglobin does not have such a strong a pedigree as a diabetes diagnostic. The red protein that transports oxygen from the lungs to the tissues and carbon dioxide back to the lungs is an artifact, or at most an indirect measure, of average glucose. HbA1c testing has historically been recommended only to determine glucose control in those who already have been diagnosed as diabetic. Why, then, are we seeing an increasing move toward measuring HbA1c rather than fasting plasma glucose as the diagnostic test for diabetes?

Some relevant background

The red blood cell has an average circulating life of some 120 days. The cell membrane allows some reagents to cross into the cell. These so-called penetrating solutes include glucose, urea, bicarbonate, phosphate, and water. Hemoglobin, which is highly concentrated within the cell, reacts with free glucose to form glycated hemoglobin. The main glycation site is at the N-terminal valine of the beta chain. The term HbA1c refers to glycation at this specific site. Hemoglobin is also glycated at a number of ε-amino lysines such as β-66, α-16, and β-18, and also on the alpha N-terminal valine.

In 1969 Samuel Rahbar, an Iranian scientist, was the first to report the linkage between diabetes and HbA1c. He showed a band migrating ahead of HbA (toward the cathode) using agar gel electrophoresis at pH 6.2. This band had the same chromatographic mobility as the HbA1c peak on a Bio-Rex 70 column. He reported that normal, non-diabetic subjects had some bias. This means that reliance on a particular instrument method may consistently give values that are higher or lower than the actual level. Potentially a diagnosis for diabetes using HbA1c could be missed or falsely given with levels near the critical decision point.

The presence of hemoglobinopathies also may give a false result. Instruments using boronate affinity methods are largely unaffected by the common variants HbC, HbS, HbE, and HbD. Newer HPLC instruments are generally unaffected, although HbE remains a problem with some. Any condition that decreases erythrocyte age will lower the HbA1c independently of glycemia. Iron deficiency has been shown to shift HbA1c levels slightly upward. Again, this may be a problem with lower HbA1c levels where diagnostic decisions are made.

It has been proposed that some individuals have HbA1c values that are higher or lower than expected from measurements of average blood glucose or fructosamine concentrations. This has been termed the glycation gap. However, this is probably more an issue of the limitations of the fructosamine assay, including its dependence upon the albumin level, and the development of a primary reference material against which calibrators can be standardized.

Arguments in favor of HbA1c

There are real concerns about the accuracy of blood glucose measurements. The test needs to be performed promptly after collection since glucose will decrease up to 10mg/dL per hour unresolved at room temperature. Frequently there are delays in the blood sample reaching the testing laboratory, often with samples not having been kept chilled. There are also significant day-to-day variations in fasting blood glucose from the same subject, with a coefficient of variation up to 8.3 percent. In contrast, the coefficient of variation for HbA1c measurements is now consistently below 3.5 percent.

Patients may also fast for a few days prior to their appointment to give a non-representative average of fasting glucose level. Whether or not patients try to cook the results that way, it is argued that HbA1c is more convenient since it does not require a fasting sample and there is less day-to-day variation.

Selvin et al. looked at the prognostic value of HbA1c compared with fasting glucose in a population of non-diabetic adults to identify those at risk for diabetes or cardiovascular disease. They found that a fasting glucose in the pre-diabetic range of 100 mg/dL to 125 mg/dL had no predictive value for coronary heart disease, but an HbA1c between 6.0 percent and 6.4 percent showed an 88 percent risk of developing coronary heart disease. In other words, HbA1c was found to be a better predictor of cardiovascular disease than glucose.

Arguments in favor of glucose

Skepticists of HbA1c point out that all HbA1c assay methods have some bias. This means that reliance on a particular instrument or method may consistently give values that are higher or lower than the actual level. Potentially a diagnosis for diabetes using HbA1c could be missed or falsely given with levels near the critical decision point.

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problems in determining an average glucose level, rather than a glycation issue.\textsuperscript{10} 

The verdict? 
If it were an easy question, it would have an easy answer; in fact, the controversy continues. But the general trend has been a shift from glucose to HbA1c for the diagnosis of diabetes, and signs are the trend will continue.

The main problem with glucose relates to it being a fasting sample that needs to be transported on ice to the laboratory and tested promptly. In contrast, HbA1c does not require a fasting sample and is stable during transportation to the laboratory. The analyzers, thanks to the efforts of NGSP and IFCC, have very good CVs. As with any laboratory diagnostic test, the result must be interpreted in light of the subject’s clinical situation. This may mean other tests may be required to confirm the diagnosis. In many cases, glucose and HbA1c may work together for the diagnosis of diabetes.\textsuperscript{2}

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GLUCOSE vs. HbA1c
The White House Forum on Antibiotic Stewardship impacts labs across the U.S.

By Mark Miller, MD, FRCPC

It was an honor to be invited to join the first White House Forum on Antibiotic Stewardship on June 2, 2015. The Forum provided an unprecedented opportunity to collaborate with executive leaders, medical strategists, healthcare visionaries, nursing policymakers, pharmacy planners, and key physicians on ways to combat this serious issue that threatens the health of our population. This opportunity allowed me to establish new contacts, reinforce old alliances, and try to find synergies among this diverse but related group of attendees.

With more than 150 organizations represented, the Forum sent a strong message that the commitment of multiple players and stakeholders is key to achieving antibiotic stewardship. The United States government has appropriately acknowledged that no single entity can successfully tackle the problem of antimicrobial resistance and stewardship without full dedication from all of the global players. As I participated in the day’s sessions, this fact underlined the importance of collaboration and personal responsibility. Each of us has an important role to play in curbing antibiotic resistance and promoting the appropriate use of antibiotics. To succeed in reducing this public health threat, collaboration and innovation from every type of stakeholder are truly essential.

The White House Forum on Antibiotic Stewardship and the national strategy to Combat Antibiotic-Resistance Bacteria (CARB) have succeeded in further raising awareness on the topic of antibiotic resistance. These two initiatives have helped to make antibiotic resistance a national priority, and should lead to accelerated efforts to curb this substantial threat.

As a result of this national push, we hope to see an increase in new technological advancements and tests from the diagnostics industry; new antibiotic use protocols in the food animal production industry; and antibiotic stewardship program implementation across American healthcare facilities. Global real-time antibiotic surveillance networks, nucleic acid-based research, and better diagnostics that can detect important bacterial infections and multiple antibiotic resistance genes directly and quickly from a sample may be part of the long-term answer and align specifically with President Obama’s CARB plan. We will certainly see more developments of this sort as organizations move to support the Administration’s efforts.

The outcomes of the Forum are likely to impact the overall healthcare system, since the CARB plan’s ambitious five-year goals include reducing antibiotic resistance by establishing and enhancing antimicrobial stewardship programs across all healthcare settings; reducing inappropriate antibiotic use by 50 percent in outpatient settings and by 20 percent in inpatient settings; monitoring and reporting regionally important multi-drug resistant organisms in every state; and eliminating the use of medically important antibiotics in America’s meat supply.

With that in mind, six important actions have emerged as strategies to help curb antibiotic resistance:

• Obtaining surveillance data to determine and quantify the amount, type, and extent of antibiotic resistance in an area of interest such as a healthcare facility or geographic region
• Avoiding prescribing antibiotics when unnecessary
• Creating and supporting antibiotic stewardship programs in all healthcare facilities
• Performing appropriate diagnostic tests to provide information that will allow adjustment of the antibiotics to the narrowest spectrum choice which is clinically effective or to avoid antibiotics completely when testing demonstrates they are not indicated
• Avoiding the use of antibiotics in food sources, unless necessary to treat disease, in order to limit the emergence of resistance at the food source or at the time of consumer ingestion
• Creating new therapies for bacterial infections, including non-antibiotic options.

We should not underestimate the meaningful and important part that each of us plays in helping to curb antibiotic-resistant infections. They are not “just” a public health problem; they are indeed, as President Obama has said, “a threat to our national security.”

Mark Miller, MD, FRCPC, serves as Chief Medical Officer for bioMérieux Corporation, manufacturer of the VITEK 2 microbial identification and susceptibility system, the Vitek MS Maldi-ToF microbial identification system, and the BioFire FilmArray panel series for rapid multiplex syndromic diagnosis. bioMérieux’s My Role Matters awareness campaign seeks to educate the public about the part we all can play in the battle against antibiotic resistance.
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What do MTs and MLTs do? Exploring the tasks of laboratorians

Two surveys reveal valuable information for clinical lab leaders

By Nicole Risk, PhD

American Medical Technologists (AMT) develops certification examinations for various occupational specialties in the medical field, spanning diverse allied health roles on a care team. An essential component to criterion-referenced certification exams is the relationship of test items to competent performance.1 The test blueprint used to construct a certification exam must be representative of the knowledge and skill required for entry level practice. Therefore, criterion-referenced certification examinations must rely on empirical job or task analysis of current practitioners to construct their blueprints. AMT regularly conducts task analysis studies every five to seven years in order to ensure its exam specifications and content align with current practice in the various fields. The objective and overall goal of the Medical Technologist (MT)/Medical Laboratory Technician (MLT) job task analysis was to identify the critical tasks involved in performing the job functions of an MT/MLT and bring the MT/MLT test specifications more closely into alignment with practice in the MT/MLT field. This article is a report of the most recent such analysis, based on two recently completed surveys.

Survey methodology

A committee of subject matter experts refined a set of 171 task statements that were derived from skills and knowledge areas linked to the MT/MLT practice role. These 171 statements were organized into eleven content areas (General Laboratory, Chemistry, Hematology, Coagulation and Hemostasis, Immunology and Serology, Immunohematology, Blood Banking, Bacteriology, Mycology, Parasitology, and Urinalysis) with multiple statements in each content area ranging in number from three to 47.

In order to validate the results, two different surveys were conducted. Each survey questionnaire, along with several demographic questions, was mailed to a random representative sample of 650 MTs and 650 MLTs employed in the United States. 1. The “Importance” survey: this survey utilized an importance scale, where practitioners in the field were asked to rate the importance of each task to their current job role. The survey respondents were asked to assign ratings based on a five-point Likert type scale ranging from 0 (Of No Importance) to 4 (Of Great Importance). 2. The “Percentage of Time” survey: this survey asked practitioners to specify the amount of time (in percent) they spend within each of the defined major practice areas that encompass clinical laboratory duties. This survey also included an “other” category to give participants an opportunity to specify another practice area in the event they felt part of their job was spent outside the categories that were defined.

Survey samples demographics and response rates

The respondent group consisted of 228 MTs and 185 MLTs for the “Importance” survey and 169 MTs and 113 MLTs for the “Percentage of Time” survey. Both the MT and MLT samples from the two surveys were diverse and had a good representation across all the demographic variables. Many variables show highly similar distributions by type of practitioner, with some notable exceptions consistent with the field’s definition of the different job roles.

Most notably, the expected sizable differences in education between MTs and MLTs was observed. MTs were much more likely to have a bachelor’s degree (59 percent versus 26 percent), to have been in the field for more than 20 years (52 percent versus 31 percent), and to represent an older age group, over 46 years of age (60 percent versus 46 percent), than their MLT counterparts.

The response rates were relatively high for both MTs and MLTs on the “Importance” survey—37 percent and 29.4 percent respectively. A typical response rate for these types of verification surveys is 10 percent to 35 percent. Although the response rates for the “Percentage of Time” survey were surprisingly lower, they were still on the higher end at 28.9 percent for MTs and 19.7 percent for MLTs.

Individual task importance ratings

In order to evaluate each task’s importance to the role of an MT/MLT practitioner and its relevance in the MT/MLT test blueprint, the ratings were condensed and converted to a linear scale. High values indicated tasks that were regarded as highly important to the job role, and low values indicated tasks that were thought to be less important to the job role. Tasks were then ranked from 1 to 171, with 1 representing the most important task. The importance rankings were also transformed to relative percentages of weight, and these task weight percentages were collapsed across the larger practice areas to construct content weights for the test blueprint.

On the whole, the results of the “Importance” ratings indicate that practitioners felt most tasks were of high importance to the job role of an MT and MLT, where ratings were consistently high across many of the task items. Only two practice areas were represented in the top 10 most important tasks for MTs, and only three practice areas for MLTs. Of those rated as the most important, the majority came from the general laboratory practice area. A wider representation of practice areas appeared among the ten tasks rated as least important. These included Chemistry, Coagulation and Hemostasis, Hematology, Immunohematology, Immunology and Serology, Mycology, and Parasitology.

As a result, these low task importance ratings transformed to weight percentages of 0 percent or less. Any tasks that yielded no weight were flagged and recommended for review by our subject matter expert committee for revision or possible removal from future test specifications. For the sake of brevity, Tables 1 and 2 (pages 32 and 34) highlight the top 10 MOST important and the top 10 LEAST important tasks for both MTs and MLTs.  

continued on page 32
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Amount of time spent in laboratory practice areas

The results of the “Percentage of Time” survey were intended to verify the content weight breakdown derived from the “Importance” survey. For the “Percentage of Time” survey, means and standard deviations for the numerical percentages in each of the practice areas were computed. The percentage breakdowns allocated to each of the practice areas were used to compare and verify the content weights that the “Importance” survey produced.

Overall, the percentage of time spent in each practice area as allocated by MT and MLT practitioners coincided with the content weight percentages calculated from their task importance ratings. Both MTs and MLTs spent the most amount of time in the Chemistry and Hematology practice areas (about 20 percent of total time in each area). The least amount of time was spent in the Mycology and Parasitology practice areas for both groups (about one percent in each for MTs and less than one percent each for MLTs). The eleven practice areas presented in the survey accounted for a considerable amount of both MT and MLT practitioner time. The two groups indicated that these practice areas represented over 97 percent of their clinical lab time.

Table 1. Top 10 most important tasks as ranked by MTs and MLTs

<table>
<thead>
<tr>
<th>Rank</th>
<th>Practice Area</th>
<th>Task</th>
<th>Practice Area</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General Laboratory</td>
<td>Perform quality control for all laboratory procedures and determine the acceptance or rejection of an analysis based on QC rules</td>
<td>General Laboratory</td>
<td>Assure continual accuracy of patient identification</td>
</tr>
<tr>
<td>2</td>
<td>General Laboratory</td>
<td>Assure continual accuracy of patient identification</td>
<td>General Laboratory</td>
<td>Perform quality control for all laboratory procedures and determine the acceptance or rejection of an analysis based on QC rules</td>
</tr>
<tr>
<td>3</td>
<td>General Laboratory</td>
<td>Employ laboratory safety</td>
<td>General Laboratory</td>
<td>Employ laboratory safety</td>
</tr>
<tr>
<td>4</td>
<td>General Laboratory</td>
<td>Perform proficiency testing</td>
<td>General Laboratory</td>
<td>Perform proficiency testing</td>
</tr>
<tr>
<td>5</td>
<td>General Laboratory</td>
<td>Employ proper infection control</td>
<td>General Laboratory</td>
<td>Determine the suitability of specimens for analysis</td>
</tr>
<tr>
<td>6</td>
<td>General Laboratory</td>
<td>Determine preanalytical, analytical, and/or postanalytical causes of erroneous results</td>
<td>General Laboratory</td>
<td>Employ proper infection control</td>
</tr>
<tr>
<td>7</td>
<td>General Laboratory</td>
<td>Determine the suitability of specimens for analysis</td>
<td>General Laboratory</td>
<td>Determine preanalytical, analytical, and/or postanalytical causes of erroneous results</td>
</tr>
<tr>
<td>8</td>
<td>General Laboratory</td>
<td>Know laws and regulations related to HIPAA</td>
<td>General Laboratory</td>
<td>Know laws and regulations related to HIPAA</td>
</tr>
<tr>
<td>9</td>
<td>General Laboratory</td>
<td>Perform microscopy</td>
<td>Hematology</td>
<td>Perform QC and investigate QC failures</td>
</tr>
<tr>
<td>10</td>
<td>Hematology</td>
<td>Perform QC and investigate QC failures</td>
<td>Urinalysis</td>
<td>Perform physical examination of urine</td>
</tr>
</tbody>
</table>

There were also some notable differences between the importance and time spent for a few of the practice areas. For example, both MT and MLT practitioners indicated that they spend over eight percent of their time in the Immunology and Serology practice areas; however, their importance ratings for those tasks suggest a content weight of less than four percent. The “Percentage of Time” survey also included an “Other” practice area category not represented in the “Importance” survey. This might have contributed to some of the discrepancy in a few of the areas. “Other” practice areas reported for MTs included phlebotomy, mycobacteriology, molecular diagnostics, cyto-genes, virology, teaching, and supervisor/management duties. MLTs indicated “other” practice areas such as phlebotomy, molecular biology and pathology, toxicology, paperwork, and management duties.

Conclusion

In job or task verification analyses, current practitioners evaluate the generation or the revision of tasks or knowledge areas by providing ratings of importance, frequency, and/or other rating dimensions for each element. The feedback AMT received from the MT/MLT community is valuable as it keeps continued on page 34
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the organization up to date on the present state of practice and any recent changes that may have occurred, and aids its efforts to update and restructure the exam content accordingly. The results of this task analysis highlighted both the differences and similarities in the MT and MLT job roles.

Overall, for both MTs and MLTs, the results from the two surveys suggest a decrease in content coverage for the Immunohematology, Bacteriology, and Urinalysis content areas and an increase in the Hematology content area. In addition, the two surveys revealed inconsistent content weights for the Blood Banking area for both MTs and MLTs. The “Importance” survey suggested a decrease in coverage, but the “Percentage of Time” survey suggested a weight similar to the Blood Banking weight currently on the exam.

Last, the results of the two surveys also suggested a decrease in the Immunology and Serology content area for MTs and an increase in the Coagulation and Hemostasis content area for MLTs. Altogether, the largest discrepancy for both MTs and MLTs include the Blood Banking, Immunohematology, and Immunology and Serology content areas. Thus, the survey compilers made the recommendation to AMT’s subject-matter experts to pay close attention and possibly revise the tasks and content weights within these subsections.

REFERENCES

Nicole Risk, PhD, serves as a psychometrician for American Medical Technologists, a nationally and internationally recognized agency for allied health professionals. She has more than 10 years of experience in psychometrics and test development, having worked as a Research Assistant at the University of Illinois at Chicago and New York University. Dr. Risk oversees data analyses and exam development for several certification programs at AMT.

Table 2. Top 10 least important tasks as ranked by MTs and MLTs
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RNA integrity numbers: an introduction
By John Brunstein, PhD

While much of molecular diagnostics is focused on the examination of DNA, an increasingly important subset of tests instead examine RNA in samples. An obvious case is in the detection of RNA viruses. Recently, as well, there has been increased interest in detecting RNA transcripts from DNA-based pathogens (bacterial or viral), on the assumption that this can improve sensitivity (a single DNA gene may be transcribed many times, thereby creating a more abundant target and improving assay limits of detection) or to provide more meaningful information about pathogenic state. For example, observing the mere presence of human papillomavirus (HPV) DNA is not thought to be as informative as detecting active transcription of viral E6 and E7 genes to mRNA in assessing the likelihood of progression to cervical cancer. Finally, genome-wide expression profiling—the capture as it were of a snapshot of the expression levels of all active genes through their respective mRNAs present in a sample—is gaining utility in the personalized assessment of disease states such as cancer, whether performed through next generation sequencing (NGS), RNA-based exome sequencing, or array-based methods of analysis.

Confronting RNA instability

While examples such as these provide evidence for the utility of RNA-based MDx, the practical application of these approaches is less straightforward than the examination of DNA molecules. A major reason for this is that RNA is intrinsically much less chemically stable than DNA. This instability has biological utility inasmuch as the relatively short life of RNA transcripts in a cell gives the cell greater ability to respond to its environment. That is, a transcript upregulated as response to a particular stimulus does not persist forever, meaning the cell’s response and subsequent allocation of cellular resources only lasts as long as the stimulus, plus a short duration thereafter until the associated mRNA(s) decay. This dynamic nature in mRNA levels in response to cellular conditions is precisely why genome-wide expression profiling can provide critical information as to the activation status of myriad biochemical pathways in the sample examined. As the saying goes, however, “Garbage In, Garbage Out”—and if the sample being examined has had significant RNA degradation, the results of any of these tests will be erroneous. For simple RT-PCR single target assays, the main impact would be on limits of detection with subsequent false negative calls; for genome-wide expression tests, there is also significant waste of laboratory resources both in terms of reagents cost and samples processing time if it is performed on a sample doomed to yield meaningless results. It is in this genome-wide expression profiling context that we will focus the rest of our consideration.

It is, of course, possible to assess from the final experimental results whether the input sample integrity combined with downstream processing steps has led to a valid result. This is the function of various forms of experimental controls, which can take the form of exogenously added templates (which primarily validate the sample handling processes) as well as selected intrinsic RNA markers (which validate both sample integrity and process; by removal of the process component through comparison to the exogenous targets, sample integrity issues can be selectively evaluated). These critical controls ensure that the laboratorian has evidence supporting the validity of a particular test result; however, they can do nothing toward avoiding the waste of resources resulting from processing a degraded sample. What’s needed, then, is a uniform, reliable method of assessing RNA quality in a sample prior to spending time and effort on it.

Assessing RNA quality
Conveniently, there are two RNA species which are ubiquitous across eukaryotic species such as ourselves. They are physically rather large as RNAs go but clearly distinct from each other, making them resolvable by simple electrophoretic methods, and they are of very high abundance, so they make obviously distinct bands, or collections of RNA molecules of a single size, when total cellular RNA is electrophoretically size-separated. Furthermore, their integrity is a representative marker for the integrity of all other RNA molecules in the sample. I refer to the 28S and 18S ribosomal RNAs (rRNAs), which form critical building blocks of the ribosomal assemblies used for protein synthesis.

Long before RNA-based MDx methods had reached clinical laboratories, life science research labs had appreciated the potential of these two molecules to serve as a general marker for the quality of an RNA sample. Initial approaches to employing these markers were simply to run total RNA samples on a simple agarose gel, stain for nucleic acids, and assess by eye whether two distinct bands of sizes expected for the 28S and 18S rRNAs were distinctly visible in the diffuse smear arising from all the other various RNAs. While crude, this method at least allowed for the immediate detection of those samples having undergone significant degradation, as the two bands would either be very faint or not visible at all.

This approach was improved by the use of image analysis methods, with assessment of the relative band intensities of the 28S and 18S markers; a 2.0 or greater ratio of 28S to 18S was taken as evidence of acceptable sample RNA quality. While this approach was a step toward providing a numeric measure which could be compared between samples, differences in exact methodology, manual selection of band areas, and other factors contributed to make it poorly reproducible between laboratories. What was needed to make this a robust and generally applicable approach was greater standardization in the electrophoretic separation method, and heuristic analysis of what aspects of the signal, aside from just relative peak heights of the 28S and 18S, comprise the most meaningful and reproducible measures of RNA integrity.

Utilizing microfluidic capillary chips
For today’s clinical laboratorian interested in testing RNA samples, those needed improvements were realized in the guise of microfluidic capillary chips and a lengthy study of many RNA samples of various states of decay, as done by Andreas Schroeder and coworkers nearly a decade ago. Rather than separating RNA samples on individually cast gels, the approach employed uniformly mass-produced microfluidic chips with...
Similarly mass-produced buffers and uniform operating conditions imposed by the instrument used to run the chips. At its heart the technology remains electrophoretic separation, where the intrinsic charge of an RNA molecule subjects it to a motive force in the presence of a DC electric field, and the molecule size acts as a hydrodynamic impediment to this force; smaller molecules migrate faster, and larger molecules migrate slower.

The migration path is along precisely controlled microfluidic channels or capillaries, with detection of passing nucleic acids at one point along the channel by optical means. This detection is dose-responsive, allowing for a monitoring computer to output a trace of time since electric field application to the sample (a surrogate measure of molecule size) versus observed nucleic acid signal. This produces an electropherogram (Figure 1) in which the 28S and 18S molecules provide highly recognizable peaks, which can be automatically analyzed for features including relative ratios of 28S and 18S peak areas to total RNA detected of all sizes; the height of the 28S peak; the ratio of the 28S to 18S peak sizes; and a number of other metrics.

By examining a large number of such metrics for a large collection of samples of different known states of RNA decay, a set of the most informative metrics (and their relative contributions to a numerical score of RNA integrity) was developed. Together, this approach and these selected metrics can be employed to provide an RNA Integrity Number (RIN) on a eukaryotic RNA extract. Ranging in score from 10 (fully intact RNA) to 1 (completely degraded RNA), the measurement of an RIN is now accepted as an essential first step in any lengthy or costly RNA-based MDx protocol.

**Establishing RIN requirements**

To make use of these values, a laboratory (or core facility) will establish minimum RIN value requirements as starting material for different classes of experiment; that is, based on experience, the minimum level of RNA integrity that is required to get an acceptably interpretable outcome from an experiment type. You’ll note that I said “core facility,” as for experimental MDx protocols such as NGS exome analysis or whole-genome expression array screening, the infrastructural requirements are often such that a single core facility may meet these needs for multiple smaller clinical MDx laboratories in a region. If this separation occurs between you and a core lab, it’s likely you’ve never really been told the significance of, or methodology behind, this critical RIN value test as a gatekeeper for passing your samples on to the full assay. If that’s the case, hopefully the above will have demystified this somewhat and you’ll now appreciate that when the core lab comes back to you with a poor RIN value and a suggestion you not proceed with the sample, they’re doing you a favor and warning you against throwing good budget money after bad.

Two closing questions and answers on the subject of RINs: first, what should you do if you repeatedly are told your samples have poor RIN values? The most likely issues here relate to method of RNA sample preparation, and the speed with which the patient samples get into RNase-inactivating sample preparation buffers. Review of your sample collection methods with an eye to faster sample introduction to collection buffer, and/or evaluating and selecting better RNA extraction methods as a whole, would be the most likely places to start improvement.

Second, if RINs are so useful, why not employ them as a pre-screening tool for simpler RNA-based assays like simplex RT-PCRs? The answer here is one of economics and time; obtaining an RIN is as costly and time-consuming (or even more so) than just directly performing these simpler assay types. In that context, it makes the most sense to skip the RIN and employ post-assay analysis of controls to assure yourself that suitable quality input material was assayed. For the present, RIN pre-screening makes sense only when the downstream assays are costly enough in terms of reagents, time, and other resources to warrant the up-front added costs.

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**REFERENCE**


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**Figure 1.** Electropherograms. Decreasing RNA integrity numbers correspond to more degraded samples, as readily apparent in the loss of the two distinct 18S and 28S sample peaks.
The LIS, the healthcare market, and the POL

By Sandra Laughlin, MT(ASCP), and Deb Feldman, MT(ASCP)*

The Patient Protection and Affordable Care Act (PPACA) represents the greatest change to our healthcare system since the introduction of Medicare in 1965. The PPACA significantly restructures how healthcare is delivered and how providers are compensated.

The shift from volume and profitability of services (fee for service) to patient outcomes (value-based models) has had implications for all aspects of healthcare delivery, including the clinical laboratory, and certainly including the physician office lab (POL). Each stage of the testing process must be evaluated to ensure that maximum efficiencies and improved patient care are being realized. For the POL, it has made an effective laboratory information system (LIS) more important than ever. An LIS that is well-suited to the lab’s needs can no longer be seen as a luxury—if it ever really could—but now must be seen as a virtual necessity. The value of the right LIS can be seen in the pre-analytic, the analytic, and the post-analytic phases of testing.

The pre-analytic phase

With an efficient LIS, many of the pre-analytic steps are automated, which results in fewer errors. The advantages can be seen in terms of specific benefits.

Positive patient identification and accurate patient demographics: It is not uncommon for a lab order to be generated in the Electronic Medical Records (EMR). When the order is received in the LIS, a label is printed that includes at least two forms of patient ID. Patient demographic information is updated in the order messages are received from the EMR, ensuring accuracy. The ability to use a barcode printed label for samples confirms complete, accurate labeling, accurate programming on the instrument, and positive identification throughout all phases of testing. Handwritten names that are incomplete or illegible are eliminated, resulting in accurate identification. Most laboratory errors are pre-analytic labeling or collection errors. Using barcode labels will help reduce them.

Specimen requirements: The LIS allows POLs to see current procedure terminology (CPT) codes, cost, collection container, patient preparation, specimen storage, and stability with one mouse click. This saves time for phlebotomists, as they do not have to go to other sources for information.

Test utilization: Most important, the lab should assist its providers in determining which tests should be ordered in certain situations. Frequently used tests can be created in the LIS, which improves test utilization and minimizes waste. Creating “super groups” in the EMR and LIS allows each provider to order custom groups of tests, making the ordering process quicker for the provider and the phlebotomist creating the requisitions.

The analytic phase

During the analytic phase, a robust LIS assists the POL facility in providing the best patient outcomes:

Monitoring result discrepancies: The LIS includes delta checking, allowing laboratorians to alert a provider to changes in a patient’s condition.

Documenting all corrective action: The LIS documents quality control failures and corrected reports so the documentation is readily available for inspections.

Management review: The LIS can store proof of review by the managerial staff for the analytical review of the test systems for defined tests or selected personnel. In larger POLs, management review is useful when training new staff, as the new employee can complete the review but the supervisor is allowed to review what the employee did, and evaluate where the new employee might need additional training.

Quality control: The LIS assists with ensuring the QC is acceptable and can disable release of results if certain criteria are not met. The clinic where one of the present authors works no longer prints QC, as the LIS stores values, graphs, corrective action, and proof of review. Prior to the LIS implementation, staff wrote the corrective action on the printed reports, which was sometimes illegible or incomplete. Since implementation, rules have prompted the laboratorian to enter a corrective action note in the LIS, dramatically improving documentation and allowing QC to go paperless. The LIS Scheduler creates paperless schedules for the staff on external QC, maintenance, assignments, QA, and tracking. In the morning, the Task Scheduler orders AM controls with three keystrokes; printing all QC labels and ensuring everything is up and running.

Automated test reflex or testing cascade: The LIS will drive the best test utilization in this area. In the physician office setting, lab staff must work closely with providers to develop the testing rules and sequence of testing, enabling providers to order a test while the rules will automatically order the appropriate tests based on the initial results. Auto-Verification Rules allow rapid flow of results (within the pre-defined ranges) into the patient chart, eliminating the need for interface review of test results within defined ranges. They also allow users to set up ordering rules and automatic reflex testing rules based on results, eliminating the risk of forgetting to do a reflex test and generating the electronic billing change. Standing Order and Call Documentation features are also used in the LIS to keep track of orders and document attempts and outcomes of contact with a patient, enabling better patient outcomes.

The post-analytic phase

A potent LIS will also have a large impact on the lab as data access and analytics will be required as healthcare shifts to a value-based system.

Result dissemination: Labs must ensure that results are reliably sent from the point of data entry to final report destination in a timely manner. Electronic bidirectional interfaces with Electronic Health Records, Practice Management Systems, and Reference Lab systems enable accurate, up-to-date information in the LIS and all systems.

Analytics: Data management can be used to improve efficiency. Data can be analyzed to determine turnaround times, specimen rejections (QNS, hemolysis, incorrect tube, etc.), provider test utilization, and workload to ensure appropriate staffing. The LIS is more critical than ever in the physician office lab setting. Labs will need a strong LIS partner that is able to adapt as testing needs and workflows shift. The LIS must continually advance to meet the molecular testing requirements and assist the lab in delivering the data required to ensure maximum efficiency and the best possible patient care.

Sandra Laughlin, MT (ASCP), serves as a Product Manager for Compugroup Medical Inc., US, developer of CGM LABDAQ LIS and CGM LABNEXUS Outreach Solution. Deb Feldman, MT(ASCP)*, has over 35 years of experience in Lab Management and consulting. She currently serves as Laboratory Manager at the York Medical Clinic in York, Nebraska.
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Systems-guided support to enable personalized medicine

By Lâle White and Don Rule

It is a time of exciting developments in laboratory medicine. Advances in genomics and molecular diagnostics continue to improve our understanding of diseases and effective therapies, while innovations in Big Data and information technology are helping to advance genetic science and personalized medicine into clinical practice.

The federal government’s Precision Medicine Initiative will launch in 2016 to further evaluate genetic causes of disease and find new drugs that target mutations. The $215 million initiative will identify new approaches for the diagnosis and treatment of diseases, potentially saving billions of dollars and significantly improving health outcomes.

As PGx testing gains increased utility and application in the clinical environment, laboratories must be equipped to expand their laboratory information and revenue cycle management systems to store, process, and manage the volume of unique data generated by PGx tests and ensure that the systems can continually updated.

Decision support for personalized medicine

Laboratories and diagnostic service providers are well-positioned to help transform this complex data into clinical guidance using knowledge-based information technology to help clinicians order genetic tests, interpret test results, and make the most effective therapeutic decisions.

As more complicated, multi-genic predictors of therapeutic response are identified, clinicians will increasingly be required to rely on decision-support tools in order to implement new testing protocols in clinical practice, as the consistent interpretation of PGx test results will remain extremely challenging.

There is a specific need for systems that can help clinicians interpret and integrate PGx test results into practice by matching test results to a knowledge base of evidence for clinical genetics. Clinical decision-support systems designed for this purpose can provide the information and reporting capabilities necessary to guide effective clinical decision making, including understanding unique patient risk factors, which drugs are relevant, what genes affect those drugs, and which tests ensure the highest impact at the lowest cost.

As PGx testing gains increased utility and application in the clinical environment, laboratories must be equipped to expand their laboratory information and revenue cycle management systems to store, process, and manage the volume of unique data generated by PGx tests and ensure that the systems can handle the required integration, workflow management, reporting, compliance, and reimbursement issues that will emerge. Because molecular and genomics data is dynamic and ever-changing, these systems must be highly adaptable and continually updated.

Testing a patient’s genetic code may someday be routine to help guide treatment decisions from cradle to grave. By leveraging technology to help capture, interpret, and share PGx data, diagnostic service providers and labs can better support the clinical decision-making necessary to transform patient care through personalized medicine.
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Noninvasive prenatal screening: replacing confusion with clarity

By Douglas S. Rabin, MD

With so much attention focused on the growth of consumerism in healthcare, it is easy to forget that most medical services are not typical consumer products. Many of the diagnostic test services laboratories provide to physicians on behalf of patients involve complex technologies, performance characteristics, and results whose interpretation defies easy explanation to lay audiences. The result can be confusion about how to use diagnostic information for clinically appropriate actions. The exploding field of noninvasive prenatal screening (NIPS) with cell-free fetal DNA analysis is a case in point.

NIPS screens for aneuploidies based on analysis of fetal DNA circulating in the maternal bloodstream. It was introduced to the United States from Hong Kong in 2012. NIPS uses a simple blood test to determine the need for follow-up invasive diagnostic procedures such as amniocentesis and chorionic villus sampling (CVS) in pregnant women and has rapidly gained currency with the medical community. (Amniocentesis and CVS are invasive procedures that involve direct sampling of amniotic fluid or a bit of the placenta, and they carry a small risk of miscarriage as well as discomfort.) The American College of Obstetrics and Gynecologists (ACOG) supports the use of these screening tests primarily in high-risk women, which includes those 35 years of age or older or those who have a personal or family history, among other factors, although health plans are beginning to cover NIPS for average-risk women.

However, NIPS is only a screening test, and ACOG recommends that a positive NIPS result be followed up with a diagnostic test such as amniocentesis or CVS. This is an important fact that may not be well understood by all patients—and even physicians. A recent survey of maternal fetal medicine specialists revealed that 94 percent of respondents currently offer NIPS. About 13 percent of these specialists reported that they offer noninvasive prenatal screening as a diagnostic test, indicating that “education gaps remain among MFM specialists regarding the limitations of NIPT and current professional practice guidelines.” News stories about women who have made family planning decisions based on results of NIPS, alone, also demonstrate a lack of understanding of the difference between screening tests and diagnostic tests.

Another concern regards misunderstanding about a test’s performance characteristics as a gauge of its accuracy in detecting abnormalities. While most NIPS tests available in the U.S. have sensitivity and specificity rates approaching 100 percent, other performance characteristics are important to consider. When a test is used to help detect a condition with a low prevalence—such as is the case with fetal aneuploidies—positive and negative predictive values are critical measures of a test’s reliability.

In August 2014, Genetics in Medicine published a peer-reviewed study by several of my colleagues at Quest Diagnostics that compellingly illustrates this point. The team of investigators examined the performance of a number of widely used noninvasive prenatal screening tests. They determined that the chance that a positive NIPS test result was actually a false positive could be 50 percent or higher for some aneuploidies.

The experience of NIPS highlights the need to balance the risks inherent to the use of a new technology with the significant health benefits that technology may provide. Fortunately, the medical community can align these competing dynamics to provide innovations responsibly to serve the best interests of patients.

Responsible innovation means providing medical services that are based on the best technology and robust science to produce information that is not just academically informative but clinically actionable. It also means carefully describing the advantages and limitations of a test, including the information it can and cannot provide.

The Perinatal Quality Foundation recently launched an educational and research campaign designed to address these gaps. The campaign will provide women and their healthcare providers with access to educational information about the types of prenatal screening and diagnostic tests, their strengths and limitations, test results interpretation, and actions to consider based on these results.

Another facet of this program is the development of a patient registry to track outcomes of women post-partum to help determine the true predictive values of NIPS from different providers. This effort will help to clarify the true rate of false positives and false negatives for NIPS, thereby reducing one of the limitations of these screening methods.

Clinical laboratories are responsible for more than developing and providing diagnostic innovation. In an age of advanced science and technology, we also have a responsibility to help people make use of the insights provided by our innovations so that they can take actions leading to healthier lives. When provided in a responsible manner, NIPS can advance quality screening and, ultimately, better outcomes for women.

REFERENCES

Douglas S. Rabin, MD, serves as the medical director, women’s health, for Quest Diagnostics. Quest supports the Perinatal Quality Foundation’s prenatal testing education and research campaign.
Screening with HPV-Alone invites more risk into women’s lives than you may think.

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*A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

Automated testing in hematology: the role of rules in setting a standard

By Jyh-Ching Yaur

Rules—they are the backbone of the successful operation of any system. They bring order out of (potential) chaos, and give the people who follow and depend on them the ability to predict behavior and outcomes.

Laboratories certainly require rules; lab leaders call them “review criteria” or “clinical testing guidelines.” They are the predetermined guidelines that dictate a follow-up action based on a specific test result. There are four layers of “rules” in the lab: (1) reference ranges; (2) quality control (QC); (3) delta checks; and (4) flags. An abnormal result in any of these categories can trigger a specific and predefined response. If a patient sample completes testing without violating any of the predefined rules, the test results are cleared for release to the physicians.

Rules can be enforced either manually, with lab personnel responsible for initiating the follow-up action, or through automation, by leveraging modern data management systems. Known as autoverification, this process not only improves quality but offers potential reduction in both time to results and cost. The time that was originally spent manually reviewing and validating normal results is now dedicated only to results that require attention. Because each laboratory is different, rules can be modified to meet the specific needs of the lab and the expectations of the clinicians they support. For many laboratories, data automation has become a first, important step toward gains in efficiency.

Automation can help laboratories to achieve their core goals. From pre- to post-analytics, automation can help labs increase their testing capacity, improve turnaround time, and minimize human error. They also can realize significant cost savings while keeping specialized staff focused on the most essential tasks: those that put critical information in the hands of care-givers and treatment decision-makers.

With reduced staffing becoming the norm in today’s clinical labs, the value of automation is becoming even more apparent—and that brings us more specifically to the hematology lab. Hematology benefits significantly from advances in automation, with automated labs attaining 30-minute STAT times, even with 60 percent increases in per-hour sample volume. As automation touches more and more aspects of testing in the hematology lab, however, additional checks and balances are required to ensure that results are reported with the same level of quality that clinicians have come to expect. To obtain this level of confidence, hematology labs need to look beyond their automation track, test tubes, and analyzers, and focus on their data management system and, more importantly, the rules that they employ.

Rule criteria

While automated rules can be developed to meet each lab’s individual standards, they generally fall into one of four categories:

1. Reference ranges refer to rules that compare results against an assay’s pre-established normal range being used at the time.

2. Automated review of QC can detect when an analyzer deviates from predefined control levels for a specific assay; the data management system can hold all future results from that analyzer for the particular assay for further review. The results will then remain on hold until an operator takes the proper actions to address the deviation.

3. Delta checking offers laboratories an additional layer of security, comparing a patient’s current result to a previous result to establish if the result is truly abnormal, or, in fact, trending.

4. Instrument flags. Many laboratory information systems (LIS) ignore flags. While an operator may see an asterisk next to a result, the severity of that flag may not be distinguished and may contribute to an abnormality being overlooked. Newer data management systems allow for flag rules to be applied not only to patient results, but also to system-generated flags, giving labs a higher level of validation confidence.

Rule development and customization

Modern data management systems are designed with the notion that laboratories are not one-size-fits-all. Testing discipline, patient population, analysis technology, and the demands of pathologists and clinicians the lab supports, all contribute to the creation of rules. Still, every lab, including every hematology lab, needs a starting point for its individual rule development, and advanced data management systems can help facilitate that. For example, new systems allow for integration with the International Society for Laboratory Hematology (ISLH) consensus guidelines. This option makes it easy to implement a baseline set of rules that can improve quality from day one, and can later be customized to suit the specific needs of the lab.

When labs are ready to take the next step in their rule development journey, the testing capabilities of their analyzers should factor in heavily. The technology being used in a hematology laboratory will influence how its rules are defined. Whether performing quantitative RBC morphology or accurately distinguishing a platelet from a small interfering substance (e.g., microcytic RBC or red cell fragment), the capabilities of the analyzers being used must be considered to create the most appropriate rules that will shorten time to results, reduce errors, and create confidence in the accuracy of the data.

Creating confidence

Automation is an indispensable resource for today’s hematology laboratory, creating efficiency that improves laboratory operations and delivers faster results, thus allowing caregivers to make more timely and effective treatment decisions. But as the number and types of analyzers being added to automation tracks grows, there is a real need for labs to take a proactive role in ensuring that the quality of their results remains consistent and in accordance with the standards of each stakeholder. To do this, labs need to take a hard look at their data management systems and the rules that they employ.

Recent advances in data management software have helped streamline rule development so that quality can be attained with ease. But the journey should not stop there. The rules that a hematology lab chooses to implement need to be the product of a thorough evaluation of its testing capabilities and should account for the needs of the clinicians that it supports.

Jyh-Ching Yaur serves as Vice President and Head of Engineering, Automation and Informatics, Siemens Healthcare, Laboratory Diagnostics business area.
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Critical care blood gas analyzers

Each type of analyzer possesses different operational and economic characteristics:

1. Bench-top critical care analyzers use individual biosensor technology that has been proven to be accurate and validated over many years. These analyzers typically have the broadest test menu and lowest cost of operation. Each biosensor can be individually replaced on a scheduled basis.

2. Cartridge-based POC analyzers utilize all-in-one cartridges that were developed for easier use. Non-laboratory personnel such as respiratory therapists and nurses can maintain the analyzer by periodically replacing a single cartridge containing the sensors, calibrator solutions, and, in some cases, quality control (QC) solutions, all at once. However, while replacing a combined cartridge may minimize maintenance time, it could also be more costly, as unused reagents or remaining sensor life may be discarded. Additionally, a problem isolated to any one component could only be solved by replacing all components.

3. Handheld, portable analyzers with single-use, disposable cartridges allow for testing at the bedside and in an ambulance. Though portable, these devices can incur higher operational costs than bench-top and POC critical care analyzers.

The next evolution of critical care blood gas analyzers—happening now—employs a POC approach using individual cartridges with all sensors miniaturized into one micro-sensor “card” and the calibrator and QC solutions contained in separate cartridges with all sensors miniaturized into one micro-sensor “card” and the calibrator and QC solutions contained in separate cartridges. Individual cartridge replacement optimizes the life of all components, greatly reducing cost and maintenance—issues that have been a challenge for cartridge-based analyzers and bench-top analyzers, respectively. Automatic, true liquid QC; continuous electronic self-monitoring; and self-verification of correct analyzer performance ensure testing quality and regulatory compliance.

2016 CMS requirements

CMS published new requirements under CLIA for laboratory QC that eliminate equivalent quality control (EQC) plans that have been used for some analyzer models. The new CLIA regulations recognize that the use of EQC plans, which provide internal electronic monitoring, as the primary means to ensure the quality of analyzer results are flawed and do not provide an effective substitute for liquid-based QC. The new CLIA requirements call for daily liquid QC, or, as an alternative, an individualized quality control plan (IQCP) based on risk management:

1. For blood gas analyzers, perform a minimum of three QC per day, or follow the manufacturer’s requirement for frequency of external quality controls, whichever is higher.

2. Develop an IQCP for a test system that is based on principles outlined in CLSI document EP23, Laboratory Quality Control Based on Risk Management; Approved Guideline. An IQCP takes into consideration the full risk profile of using an analyzer. The risk assessment identifies and evaluates potential failures and errors in the entire testing process, taking into consideration the risk of reporting a bad result. With high acuity, critically ill patients whom blood gas analyzers are expected to support, this risk profile is essential to developing a safe and effective IQCP.

CMS initiated a two-year educational/implementation period for the new quality control requirements that will end January 1, 2016. As this deadline approaches, providers that utilize critical care blood gas instrumentation will have to evaluate what “good laboratory practice” means for their critical care testing program.

Stringent QC/QA required

In developing a quality control plan, users must consider the vital role of critical care analyzers and the medical necessity for accuracy. Test results direct treatment in life-threatening situations. The risk of inaccurate POC results could be fatal, as has been the case in bedside glucose testing. The need for immediate, accurate results demands continuous, vigilant oversight of analyzer status—through QC checks. The routine use of liquid QC with known assay values is the only true way to verify the accuracy and proper functioning of critical care blood gas analyzers. Multi-level liquid QC verifies accurate performance throughout the full measurement range for all analytes.

Many of today’s critical care blood gas analyzers provide onboard QC that can be run automatically or on demand (e.g., to confirm a critical result). In addition, QC lockout features can prevent results reporting in the event of a QC failure. QC statistics verify the medical requirements for reproducibility within run and day to day. Continuous, internal self-monitoring of all analytical components provides an additional level of QA between QC runs, QC peer group programs, and inter-laboratory performance data provide yet another level of QA. Regardless of which type of blood gas analyzer is employed and which CLIA option is chosen, these features should be the foundation of any comprehensive, QC program for critical care blood gas testing.
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Hemosure’s One-Step Immunological Fecal Occult Blood Test
Hemosure’s One-Step Immunological FOB Test (iFOBT) for colorectal cancer screening employs a combination of monoclonal and polyclonal antibodies to selectively identify hemoglobin in test samples with a high degree of sensitivity, with the objective of detecting and diagnosing diseases that result in the lower GI bleeding, such as colorectal cancers and large adenomas that bleed. This allows for cancer detection at an early stage and thus reduces the mortality. Positive results for even minimally elevated levels of hemoglobin can be seen in the test as early as five minutes. Tests have a 24-month expiration from the date of manufacture when kept at room temperature. With higher sensitivity and specificity and no dietary or drug restrictions, the iFOBT lowers the rate of false positives or negatives due to greater patient compliance and results unaffected by animal blood or iron reagents. For more information, please visit: http://hemosure.com/hospital-laboratory/products/

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Randox offer a wide range of high-quality rapid tests which include Anti-Streptolysin O (ASO); C-Reactive Protein (CRP); Rheumatoid Factor, Pregnancy Test; and Syphilis (RPR and TPHA). These tests are based on agglutination, immuno-dot, immuno-chromatographic or immuno-filtration techniques. Each test is quick and easy to perform (two minutes to two hours) requiring little or no additional equipment, and is designed for use with an individual or limited number of samples, which make the tests more economical than ELISAs in low-throughput laboratories. Randox rapid tests can also be stored at room temperature for extended periods of time. These rapid tests provide same-day results, enabling timely treatment interventions. For more information, please visit: http://www.randox.com/reagents/rapid-tests-serology

Roche’s cobas Influenza A/B Test
Roche has announced that the FDA has granted CLIA waiver for the cobas Influenza A/B test for use on the cobas Liat System. This CLIA-waived, real-time PCR test can detect influenza A and B in ~20 minutes. Coupled with the CLIA waived cobas Strep A test, the cobas Influenza A/B test can now be used by healthcare providers in non-traditional testing sites, including physician offices, emergency rooms, health department clinics, pharmacy clinics, and other healthcare facilities. The CLIA-waived cobas Influenza A/B test for the cobas Liat PCR System offers an effective, new diagnostic tool to clinicians for the upcoming flu season and provides fast diagnosis and treatment for patients in primary and urgent care settings. For more information, please visit: https://usdiagnostics.roche.com/en/instrument/cobas-liat.html

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Verax Biomedical’s Platelet PGD Test
Verax Biomedical recently gained FDA clearance for expanded platelet safety measure testing indications. Verax Platelet PGD test is thus cleared for all commonly available U.S. platelet types. It is the company’s first product for the detection of bacterial contamination in platelets and has been cleared by the FDA as a Safety Measure for leukoreduced apheresis platelets within 24 hours prior to transfusion. Use of the PGD test within 24 hours of transfusion offers the opportunity to interdict and prevent the transfusion of a proportion of severely contaminated units that pose a serious risk to patient safety. The test is also FDA cleared as a QC test for leukoreduced and non-leukoreduced whole blood-derived platelets pooled within four hours of transfusion. For more information, please visit: http://www.veraxbiomedical.com/products/platelet-pgd-test.asp
Training and certification to perform urine studies

Editor’s note: Katie Scheele, PMP, MBA, BSMT(ASCP), recently retired after a distinguished career as a laboratorian. She was a Project Manager and worked at Mayo Clinic in Arizona from 1997 to 2014, managing clinical, administrative, IT, and process improvement projects.

I am very interested in being trained and certified to do studies on urine testing for illicit drug use in clinical labs. Would you please advise me on courses, classes, etc. I could take to complete this certification? Thank you!

A

The Office of Drug and Alcohol Policy and Compliance publishes regulations and provides official interpretations on drug and alcohol testing, including how to conduct tests, and the evaluation and treatment procedures necessary for returning employees to duty after testing violations. The Department of Transportation’s (DOT) rule, 49 CFR Part 40, describes the required procedures for conducting workplace drug and alcohol testing for the federally regulated transportation industry.

DOT-regulated urine specimen collections are an important part of employment and workplace screenings. Collectors perform DOT urine specimen collections for drug and alcohol testing, return-to-duty testing, and more. To be permitted to act as a collector in the DOT drug testing program, you must meet the following requirements:

- Be knowledgeable about DOT Urine Specimen Collection Procedures Guidelines and agency regulations
- Receive qualification training
- Complete five mock collections
- Receive refresher training every five years or after an error in an collection, and documentation of your training.

The following online training courses state that they meet the qualification training as outlined in Federal Regulations, 49 CFR Part 40, for DOT urine collections. Cost may vary.

- LabCE/MediaLab’s online DOT urine collection training course provides an integrated checklist feature to document completion of the required mock collections, but does not provide observers for the mock collections. This course may not be appropriate for private individuals. http://www.labcme.com/dot-urine-collection-course.aspx
- Lifeloc Technologies’ web-based collector training course provides Certified Urine Specimen Collector qualification that is updated with the latest DOT rules and regulations. http://www.lifeloc.com/collector.aspx
- OccuHealth Solutions, Inc provides live Internet Skype or Traditional Classroom Certification Training Programs in accordance with DOT 49CFR Part 40. This includes all training materials, DOT required hands-on proficiency test kits, and lab forms. They offer a flexible “live online training” schedule that allows training all days of the week, including weekends. http://www.druceollectortraining.com/
- Phamatech Laboratories & Diagnostics Urine Drug Collector Training program provides training for US DOT collections and non-DOT collections. Non-DOT collections are not as standardized/regulated, but generally follow the DOT procedures except for using different forms and single specimen containers. http://phamatech.com/lab/phamatechurinedrugcollectortraining1.html
- Quest Diagnostics provides online Substance Abuse Training with courses in Specimen Collection Training, Manager Module Training, and Substance Abuse Training. It is 100 percent compliant with training requirements mandated by federal agencies, such as the U.S. Department of Transportation. The site has videos that summarize the training modules. http://www.questdiagnostics.com/home/companies/employer/drug-screening/knowledge-center/online-training.html.

REFERENCES

Hardy Diagnostics PYR Test Kit

Hardy Diagnostics’ new PYR Test Kit is a colorimetric method for the presumptive identification of group A streptococci, group D enterococci, some species of coagulase-negative staphylococci, and other members of Enterobacteriaceae in an easy-to-use card format. It’s a rapid method for detecting enzymatic activity in certain groups of bacteria. The new format is a simplified mechanism for performing multiple tests simultaneously. Quick and convenient, the new card format is easier to handle than individual disks and presents a cost-effective aid in the rapid detection of potentially pathogenic bacterial infections in healthcare settings. The new format includes filter paper impregnated with l-pyroglutamic acid betanaphthylamide and is used in conjunction with the PYR Reagent, p-dimethylaminocinnamaldehyde, to yield a bright pink to cherry red color on PYR positive strains. The card can be used to perform three tests at a time and aids in the presumptive identification of pure cultures. For more information, please visit: https://catalog.hardydiagnostics.com/cp_prod/product/2176-pyr-test-kit-100-tests-with-20ml-chromogenic-developer-on-paper-disks-by-hardy-diagnostics-prefer-to-ship-ground-test-disks-strips-reagents
Beverly Hospital, a member of Lahey Health, has opportunities for Laboratory Managers in the Chemistry (Job ID#134327), Hematology (Job ID# 130541), and Microbiology (Job ID#130121) departments. Please apply at www.beverlyhospital.org or send resume to LABBOTT@nhs-healthlink.org

Job Description
Develops, plans, directs, coordinates and controls all activities of the Section to ensure the efficient operation of that section that meets and exceeds the customer’s expectation. Ensures that all activities are conducted in accordance to acceptable clinical technology, administrative policy, regulatory and accreditation requirements and medical ethics. Assumes responsibility for the creation of fiscally sound section’s salaries, supplies and capital equipment budgets and the monitoring for any and all expense variances. Investigates and recommends new/replacement instrumentation to the Administrative Director. Acts as a liaison between customers and the laboratory to promote increased customer satisfaction with laboratory services by both successfully answering inquiries/resolving problems and by presenting a positive, professional image. Provides leadership in the management of Human Resources including, but not limited to: The hiring, counseling and evaluation of employees in the section. Creating work schedules, developing applicable education and enrichment programs and conducting regular staff meetings. Demonstrates ability and initiative to problem solve with employees and other managers/supervisors. Develops and implements the Quality Improvement plan of the section and ensures the timely submission of CBI monitors and recommendations for improvement to the Administrative Director. Serves as representative to hospital committees as required or requested

Qualifications
Baccalaureate degree in a biological or physical science or Medical Technology training and have at least six years of current laboratory training or experience or have previously qualified or could have qualified as a General Supervisor under 42 CFR 493.1427 of the Federal Regulations published March 14, 1990 (55 FR 9538) on or before February 28, 1992

Certification/License: MT (ASCP), MT (HS), CLS (NCA), M (ASCP) or EQUIVALENT

Carolina Liquid Chemistries Corp.
Carolina Liquid Chemistries Corp. (CLC) recently completed its branded line of chemistry analyzers, which completes its all-new family of instruments. The FDA cleared the CLC1600 as part of the CLC6410 family for use with a variety of methods. CLC, known for providing clinical laboratories with instruments and over 80 reagents that aid in diagnosing and treating patients, now offers the CLC720i, CLC800, CLC1600, and the CLC6410. The CLC1600 meets the needs of a high-volume clinical laboratory, while offering current technology typically not available on older analyzers. The CLC1600 produces up to 900 photometric tests per hour and 1200 tests per hour when including electrolytes. Advanced features of the CLC1600 include user-friendly, intuitive Windows 7 Pro software and sample wheel with 140 positions. The CLC1600 can hold 68 two-part reagents or 132 single-part reagents. The analyzer accommodates reagents with up to four parts. This instrument can save time and decrease operational cost, while increasing productivity.

For more information, please visit: http://carolinachemistries.com/CLC/index.cfm/hurl/idsPageID=133/Type=/Carolina-Liquid-Chemistries-Home
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DeNovo Sciences is transforming the use of liquid biopsy in cancer diagnostics

If you were explaining DeNovo Sciences to someone who is not familiar with the organization, how would you characterize its areas of expertise? What major categories of solutions does DeNovo provide for its customers? For many metastatic and recurrent cancers such as lung and prostate, procuring repeat biopsy samples is extremely challenging. Liquid biopsy can be a less invasive alternative in cases where patient monitoring can help with therapy decisions. DeNovo Sciences develops automated systems for rare circulating tumor cell (CTC) enrichment and single-cell molecular analysis. The Jetta400 system performs all the sample processing needed to isolate CTCs from whole blood and performs downstream molecular analysis of the captured CTCs including immunohistochemistry (IHC), DNA FISH, or mRNA FISH. The VanGuard system analyzes the prepared images of CTCs automatically. The innovative technology is intended to provide diagnostic information to the healthcare professional to help patients’ therapy selection and outcome.

The technology is currently used by basic life science and clinical researchers by CLIA labs. In some countries, it is being validated for clinical use, and we have begun the process for U.S. FDA submission.

What role does liquid biopsy play in cancer diagnostics today? How might it be used in the future? There are two different approaches to less invasive blood-based liquid biopsies: circulating cell-free tumor DNA (ctDNA) and CTCs. While ctDNA can provide only information on DNA mutations, CTCs have the advantage of providing a complete picture of the whole cell, which includes protein, RNA and DNA analysis. Liquid biopsy uses blood or other body fluids to detect CTCs that have detached from solid tumors and entered the blood stream. Liquid biopsies may be used for cancer diagnosis, staging, prognosis, therapy selection, monitoring, and surveillance, and may, in the future, circumvent the need for invasive tumor biopsies.

What opportunities does microfluidic technology present to labs seeking to better serve their patients, or to increase their outreach? Microfluidic technology is in the forefront of oncology diagnostics. It has generated an impressive collection of medical devices, including diagnostic devices, in a few years. Many more such devices are being validated in clinical research, compared to standard-of-care procedures, and are on track to be used in the clinic for oncology diagnostics.

What are the advantages of CTCs to diagnosticians, compared to tissue biopsy? What challenges do CTCs present? Unlike tissue-based diagnostics, liquid biopsy is minimally invasive, fast, and less costly. CTC technologies can be as accurate as tissue-based diagnostics, and perhaps more useful because the testing can be performed on a more frequent basis. The challenge is enrichment of the rare CTC population and the ability to perform detailed single-cell morphological and genetic analysis of the captured cells. DeNovo’s label-free capture technology allows the researcher to customize results based on individual needs while ensuring maximum capture efficiency and high purity.

DeNovo’s products include the Jetta 100 platform for research and the Jetta 400 platform for clinical application. How does the Jetta 400 perform in the clinical lab? What do users need to know and do? Jetta400 is a fully-automated CTC preparation device that isolates and analyzes CTCs from blood samples without the need for preprocessing. It is a diagnostic device that not only allows the detection of one cancer cell in every 100 million in a single tube of blood, but also detects whether or not the CTCs present a therapeutic target. Isolation and downstream analysis are conducted on the same automated platform, ensuring a high level of reproducible and reliable results. It means that one could find and characterize cancer cells directly in the blood—essentially, comprehensive diagnostic by liquid biopsy.

What consumables are used with the Jetta 400 platform? The consumables for Jetta400 include a microfluidic chip designed and manufactured by DeNovo Sciences to isolate CTCs from a blood sample, as well as reagents required to capture and characterize CTCs using IHC, DNA FISH, and mRNA FISH. You are a widely published scientist, a patent holder, and a former executive at major companies. How does an intimate knowledge of the science and technology help you function more effectively in your business capacity? DeNovo’s CTC technology is going to transform the use of liquid biopsy in cancer diagnostics. And we have lots to do. We will focus on delivering the best quality instrument so that it will help improve clinical laboratory operations and drive improved patient outcomes. My background and experience in development of IVD diagnostics will facilitate the business’s scientific and clinical applications. Liquid biopsy is a hot area in diagnostics and will evolve in the years to come, and we realize that other diagnostic companies may pursue a similar technology and application. We will be competing for time to market, intellectual property, product claims, and in many other areas. My job is to be proactive, and to build a strategic portfolio of products and competencies for our future business.

YIXIN WANG, PhD
Chief Scientific Officer

Professional
DeNovo Sciences, CSO since July 2015; Ventana Medical Systems (a unit of Roche Diagnostics), VP, Molecular Probes Development; Executive Director, Research & Development; Pfizer, drug discovery

Education
BS, Beijing University; PhD, Cornell University; Postdoctoral fellowship, Harvard Medical School
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