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Autism research offers new hope

When I was in grammar school, maybe third, fourth, fifth grade—50 years ago, I’m no spring chicken—there was a kid in my class who had a lot of problems. His name was L, and he just didn’t know how to fit in, didn’t know how to act. He would sometimes get into sudden, angry fights with other kids; more often, he would seem to insulate himself from class activities, downcast at his desk. He sometimes raised his hand to answer a question, but instead of answering it, he started in on long, rambling monologues, about events in the life of his family, about his hobbies (he had a rock collection, it’s funny what one remembers), about a movie he had seen two years ago, all in a raspy, whining voice. He went on for so long that the class would groan and say, “L, get to the point,” or worse. The teachers didn’t really know how to handle him, and sometimes they would roll their eyes or lash out in frustration, which only encouraged the class to mock him in the cruel way kids can pile on an outcast. I remember thinking, “He wants us to like him, but he doesn’t know how to get people to like him.” He was a frustrated, tormented, friendless figure.

Thinking back on L now, I realize that he very likely suffered from autism spectrum disorder (ASD), and unfortunately for him, there was almost no recognition of ASD then. The term autism has existed for more than 100 years, and by the 1960s researchers and specialists were beginning to define it more precisely and refine it as a diagnostic classification, but autism was certainly not part of the vocabulary of the average family doctor then, much less the average grammar school nurse or psychologist, so there was no help for L. Now there would be; he would be diagnosed, surely, with Asperger syndrome— he checked all the boxes for that ASD—and receive appropriate therapies.

What occasioned this childhood flashback for me was a fairly steady stream of news about research into more refined diagnostics for ASD—both genetic and serological—and other useful research.

• Using a novel approach that hone in on families severely affected by autism, a Johns Hopkins-led team of researchers has identified a new genetic cause of the disease. The team compared the gene sequences of autistic members of 13 such families to the gene sequences of people from a public database. They found four potential culprit genes and focused on one, CTNND2. When they studied the gene’s effects in zebrafish, mice, and cadaveric human brains, the researchers found that the protein it makes affects how many other genes are regulated.

• Scientists from Touro College of Osteopathic Medicine (New York) and Salk Institute (San Diego) found that the protein it makes affects how many other genes are regulated.

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• Scientists from Touro College of Osteopathic Medicine (New York) and Hadasah University Hospital, Jerusalem, have called for the testing of umbilical cord blood for levels of a growth protein that could help predict an infant’s propensity to later develop autism. They propose that depressed levels of a protein called insulin-like growth factor (IGF) could potentially serve as a biomarker that could anticipate autism occurrence.

• Researchers at Cincinnati Children’s Hospital Medical Center have used electronic medical records and birth information to verify and strengthen an already suspected link between autistic children and pregnant mothers with obesity and diabetes. According to study data, pregnant mothers with obesity or gestational diabetes were 1.5 times more likely to have a child with ASD. The increased risk of ASD for pregnant mothers with both obesity and gestational diabetes was two-fold.

And hot off the presses: A University of Missouri-Columbia study suggests that the common hypertension drug propranolol might improve communication and social interaction skills of children with autism. Today’s targeted research promises help on the way for today’s L’s.

Alan Lenhoff

FROM THE EDITOR

By Alan Lenhoff, Editor
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CDC goes to highest alert over Zika outbreak. The United States Centers for Disease Control and Prevention (CDC) said that the agency’s command center is going to its highest level of alert, a measure reflecting growing concern about the prospect of the Zika virus gaining a foothold in the mainland U.S.

The decision reflects the urgent demand for CDC support. Since the CDC activated the Emergency Operations Center on Jan. 22nd, agency spokesman Tom Skinner says, the clamor “for resources has increased to the extent that we need to go to this level to meet the demand.”

This represents the fourth time that the CDC’s command center has declared a Level 1 alert. The other emergencies were Hurricane Katrina, the H1N1 flu threat in 2009, and the Ebola epidemic in West Africa. During emergencies, the command center is staffed by a shifting cast of experts in fields required for the current emergency.

So far, 50 cases have been identified in the U.S., with several in Texas, Illinois, California, and Washington, D.C. In early February, Florida Gov. Rick Scott declared a state of emergency in four counties, where health officials have diagnosed nine cases of Zika virus in travelers returning from areas affected by Zika.

The CDC scientists are collaborating with local, national, and international partners to study the virus, track its spread, and assess the accuracy of Zika-related data, and exchange information about the pandemic as it evolves. Command center personnel also have the resources to ship diagnostic kits, samples and specimens, and emergency-response personnel to Zika hotspots.

CDC, WHO offer resources on Zika virus. On the heels of the World Health Organization (WHO) declaring the spread of the Zika virus an international emergency on Feb. 1, both WHO and the Centers for Disease Control and Prevention (CDC) have compiled resources and information on the virus for physicians and patients.

Zika is a disease caused by a virus that is acquired through the bite of an infected Aedes species mosquito. The most common symptoms of the disease are fever, rash, joint pain, and conjunctivitis, per the CDC. Symptoms can last anywhere from a few days to a week. A severe reaction that would require hospitalization is at this point uncommon, the CDC states on its website.

The first confirmed case of the virus was in May 2015 in Brazil, and the CDC has issued warnings to travelers to that region, as well as other countries where the virus is present. As of early February, the CDC reported that more than 30 cases had been confirmed in the United States in returning travelers.

According to the Dallas County Health and Human Services, the CDC confirmed on Feb. 2 the first case in the U.S. of the Zika virus being acquired through sexual transmission. “The patient was infected with the virus after having sexual contact with an ill individual who returned from a country where Zika virus is present,” the statement read.

Red Cross asks blood donors to wait 28 days after visiting Zika areas. The American Red Cross appealed to prospective donors who have visited Zika outbreak zones to wait at least 28 days before giving blood, but said the risk of transmitting the virus through blood donations remained “extremely” low in the continental United States.

The “self-deferral” notice for blood donors should apply to those who have visited Mexico, the Caribbean, or Central or South America. The Washington-based nonprofit disaster relief agency also asked that donors who give blood and subsequently develop symptoms consistent with Zika within 14 days of donating to notify the Red Cross so the product can be quarantined.

Cases of the Zika virus have been reported in more than 30 countries and territories. The mosquito-borne illness has been linked to “a dangerous birth defect called microcephaly, marked by abnormally small head size, and to a serious autoimmune disorder called Guillain-Barre syndrome that can cause paralysis.”

The most common symptoms of infection are flu-like, such as aches and fever. About 80 percent of people infected show no symptoms whatsoever, says Susan Stramer, a microbiologist for the Red Cross. There is no blood test for the disease.

The travel-related donor self-deferral test would be a serological blood test, in addition to the ultrasounds recommended in the CDC’s first round of guidance.

“Men who live in or travel to areas of active Zika infections and who have a pregnant sexual partner should use a condom or abstain from sex until the baby is born,” the Centers for Disease Control and Prevention (CDC) advised in guidelines aimed at preventing sexual transmission of the virus.

In late January, the CDC advised that any pregnant woman with symptoms of Zika should be tested for the virus. The agency added guidelines for pregnant women who fear they have been exposed to the virus but have no symptoms. Those tests would be serological blood tests, in addition to the ultrasounds recommended in the CDC’s first round of guidance.

“Men who live in or travel to areas of active Zika infections and who have a pregnant sexual partner should use latex condoms correctly, or refrain from sex until the pregnancy has come to term,” CDC Director Thomas Frieden MD, MPH, told CNN’s Sanjay Gupta, “or until a test is available to see if he could possibly infect her.”

While a study showed that Zika only stayed viable in blood and saliva for a week, “we don’t know how long Zika can persist in semen,” Frieden said. “We’re doing those tests now, but it could be weeks to months before we have an answer.”

Frieden added that the risk for developing Zika depends on how long a person was in the area where Zika is present, how many mosquitoes are active in that area, how many mosquito bites they had, and how well they protected themselves.

““We are not issuing guidance on kissing,” Frieden said. “We take all reports seriously, but we need more information including the methodology of any study. The bottom line is that Zika is primarily a mosquito-borne disease.”

Health officials had previously
reported isolated instances of the virus being passed via blood transfusions and sexual contact. The virus has spread to at least 29 countries. As many as three to four million people across the Americas will be infected with the virus in the next year, WHO has estimated.

Lyme disease just got nastier. Until now, scientists thought that the tick-borne illness was caused by only one species of bacteria, called Borrelia burgdorferi. But scientists from the Centers for Disease Control and Prevention (CDC) and the Mayo Clinic have discovered that a second, related species of bacteria, Borrelia mayonii, can infect people who have been bitten by the black-legged deer tick.

The new bacteria cause similar symptoms in the early stage of infection, such as fever, headache, rash, and neck pain. Arthritis can set in weeks later. But unlike B. burgdorferi, B. mayonii can infect the human nervous system and cause death.

The CDC recommends hikers reduce their risk of tick-borne infections by avoiding wooded and brushy areas with high grass, keeping the center of trails, using insect repellents with DEET or permethrin, and wearing protective clothing.

NIH researchers identify striking genomic signature shared by five types of cancer. National Institutes of Health (NIH) researchers have identified a striking signature in tumor DNA that occurs in five different types of cancer. They also found evidence that this methylation signature may be present in many more types of cancer.

The specific signature results from a chemical modification of DNA called methylation, which can control the expression of genes like a dimmer on a light switch. Higher amounts of DNA methylation (hypermethylation), like that found by the researchers in some tumor DNA, decrease a gene’s activity. Based on this advance, the researchers hope to spur development of a blood test that can be used to diagnose a variety of cancers at early stages, when treatments can be most effective. The study appeared Feb. 5, 2016, in The Journal of Molecular Diagnostics.

In this new study, researchers developed a series of steps that uncovered telltale methylation marks in colon, lung, breast, stomach, and endometrial cancers. They showed that all the tumor types and subtypes consistently produced the same methylation mark around ZNF154.

The NIH Intramural Sequencing Center sequenced the tumor DNA that had been amplified using polymerase chain reaction (PCR). Researchers then analyzed the results, finding elevated levels of methylation at ZNF154 across the different tumor types.

The researchers do not yet understand the connection between tumors and elevated DNA methylation. It may represent derailing of normal processes in the cell, or it may have something to do with the fact that tumors consume a lot of energy and circumvent the cellular processes that keep growth in check. The scientists also don’t know exactly what the gene ZNF154 does.

New marker predicts joint damage in RA. A novel biomarker found in elevated levels in the serum and synovium of patients with early rheumatoid arthritis (RA) could help predict which patients would have worse radiographic damage, Canadian researchers report.

In a univariate analysis, the baseline factors that in combination best predicted erosive progression over five years were age 65 or older, C-reactive protein (CRP) above 8 mg/L, and a level of the new biomarker 14-3-3-eta of 0.50 ng/mL or higher, according to Gilles Boire, MD, of the University of Sherbrooke in Quebec, and colleagues.

The relative risk of erosive progression with all three of those variables was 5.49 compared with the absence of all three, the researchers reported online in Arthritis Research & Therapy. “14-3-3-eta-positive status can thus assist primary care providers during referral of patients to rheumatologists, and may help rapid initiation of a targeted pharmacologic intervention,” they said.

As the treat-to-target approach to RA has become widely adopted, it has become clear that current biomarkers are inadequate to help predict which patients are at highest risk and may need intensified treatment, with one study suggesting that conventional variables such as rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), and CRP account for only 32 percent of variance in prediction of joint damage.

Researchers have therefore been searching for additional markers, and Boire’s group has identified the 14-3-3-family of intracellular proteins, and specifically the eta isoform, as potential candidates.

Cancer

NIH researchers identify striking genomic signature shared by five types of cancer. National Institutes of Health (NIH) researchers have identified a striking signature in tumor DNA that occurs in five different types of cancer. They also found evidence that this methylation signature may be present in many more types of cancer.

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Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia

By Beatriz Montull, MP, Rosario Menéndez, MD, PhD, Antoni Torres, MD, PhD, and Raúl Méndez, MP

With an incidence of three to five cases per 1,000 adults per year, community-acquired pneumonia (CAP), is a frequent cause of death worldwide. Severe sepsis, the syndrome of infection complicated by systemic inflammation and organ dysfunction, is a complication of CAP. Severe sepsis is a worldwide health problem, and a significant one in the United States, with an incidence of 343 cases per 100,000 inhabitants in the U.S. At least one-third of CAP patients present to the hospital with severe sepsis. Initial identification of the severity of sepsis is important in order to institute different management and monitoring measures. Clinicians often do not recognize the presence of severe sepsis in CAP patients, even when organ dysfunction is present. Studies aimed at identifying the CAP population at risk of developing severe sepsis in the community before arriving at the hospital are lacking.

The aim of our study was to determine the risk factors for presentation at the hospital with severe sepsis in patients with CAP.

Patients and data collection

A prospective, multi-center, observational cohort study was carried out in 13 hospitals belonging to the Spanish National Health System (CAP Quality Group); a complete, detailed description has been reported in a prior publication. Briefly, the inclusion criterion was a diagnosis of CAP, defined as acute symptoms or signs with a new compatible radiographic lung infiltrate. Exclusion criteria were nursing-home patients, transplant or oncologic patients, leukopenia or neutropenia (unless attributable to pneumonia), Human immunodeficiency virus-positive (HIV) patients with severe immunosuppression (CD4 <100), treatment with corticosteroids (>20 mg/day) or other immunosuppressive drugs, and patients with DNR (do not resuscitate) orders or in whom CAP was considered a terminal event. The study was approved by the ethics committee (ISS Hospital La Fe 2004/15 July, Assent 2004/0101), and the patients provided written informed consent.

We recorded data on age, gender, prior antibiotic treatment for the current episode, comorbid conditions (chronic obstructive pulmonary disease [COPD], heart, liver, neurological or renal diseases, and diabetes mellitus), clinical, analytical and radiological results, and the prognostic scales Pneumonia Severity Index (PSI) and CURB65 risk class.

Comorbidities were assessed based on clinical history along with prior discharge diagnoses and clinical records, review of medications, and results of analyses. Sepsis and severe sepsis were evaluated at CAP diagnosis on hospital admission, following previously accepted criteria. Sepsis was defined as the presence of pneumonia and systemic inflammatory response syndrome (SIRS). Severe sepsis was considered if criteria for sepsis were met and acute failure of at least one organ was present: arterial hypoxemia (PaO2/FiO2 <300), creatinine >2 mg/dL, acute confusion, or hypotension (systolic arterial tension [ST] <90 mmHg). While organ dysfunction has also been defined in terms of hepatic or hematologic failure, information on these organ systems was not available in the data set.

Microbiological analysis and diagnostic criteria

Microbiological studies comprised the following: 2,550 (62.7%) blood cultures; 3,636 (89.3%) urinary antigens for Legionella pneumophila and 3,654 (89.8%) for Streptococcus pneumonia; 1,760 (43.2%) sputum cultures, 1,902 (46.7%) paired serological studies for Chlamydia pneumoniae, Mycoplasma pneumoniae, Coxiella burnetti, and Legionella pneumophila; nasopharyngeal swabs to detect viral nucleic acids; and invasive samples obtained by bronchoscopy (285 [7%] bronchial aspirate [BAS] and 118 [2.9%] bronchoalveolar lavage [BAL]), and 276 (6.8%) pleural fluid cultures.

Microbiologic diagnostic criteria were the following: 1) positive urinary antigens for S pneumoniae and Legionella pneumophila; 2) isolation of microorganisms in BAL (≥104 UFC/mL), BAS (≥105 UFC/mL) or in pleural fluid; 3) isolation of one predominant microorganism in sputum or
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Table 1. Characteristics of CAP with severe sepsis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No, n (%)</td>
</tr>
<tr>
<td>Total No.</td>
<td>n = 2,541</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>69 (50-78)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>1473 (58.1)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1635 (64.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>574 (22.6)</td>
</tr>
<tr>
<td>Alcohol abuse*</td>
<td>273 (10.7)</td>
</tr>
<tr>
<td>Prior corticosteroid treatmentb</td>
<td>95 (3.8)</td>
</tr>
<tr>
<td>Prior antibiotic</td>
<td>651 (25.6)</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>586 (22.3)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>102 (4)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>346 (13.8)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>136 (5.4)</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>245 (9.7)</td>
</tr>
<tr>
<td>COPD</td>
<td>494 (19.8)</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td></td>
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<tr>
<td>Multilobar infiltrates</td>
<td>501 (19.7)</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>391 (15.4)</td>
</tr>
<tr>
<td>Prognostic scales</td>
<td></td>
</tr>
<tr>
<td>PSI (IV-V)</td>
<td>866 (34.1)</td>
</tr>
<tr>
<td>CURB65 (≥ 3)</td>
<td>531 (20.9)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) unless otherwise indicated.
*Data are presented as median (interquartile range).
b Previous corticosteroid treatment: less than 20 mg/day prednisone or equivalent.
*Data are presented as number (percentage) unless otherwise indicated.

Table 2. Length of stay and mortality in CAP with regard to severe sepsis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No, n (%)</td>
</tr>
<tr>
<td>Total No.</td>
<td>n = 2,541</td>
</tr>
<tr>
<td>LOS*</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td>Mortality At 30 days</td>
<td>75 (3)</td>
</tr>
<tr>
<td>At 90 days</td>
<td>102 (4.2)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) unless otherwise indicated.
*LOS: Length of stay (days). Data are presented as median (interquartile range).
b p value: the χ2 test was performed for categorical data and the Mann-Whitney U test was performed for continuous data.
c OR: Odds ratio
d CI: Confidence interval

L pneumophila in buffered charcoal yeast extract (BCYE) agar; 4) microorganisms in blood culture; 5) seroconversion or a fourfold antibody increase in titers of IgG for C pneumoniae (≥ 1:512), M pneumoniae and C burnetii, (≥ 1:160) or IgM ≥ 1:32 for C pneumoniae, and ≥ 1:80 for C burnetii; 6) positive detection of viral nucleic acids in nasopharyngeal swab.

Mixed etiology was defined as pneumonia due to more than one pathogen (virus or bacteria).11 The evaluated outcome was mortality during hospitalization and at 30-day and 90-day follow-up. Length of stay (LOS) was defined as the number of days from hospital admission to discharge.

Data analysis was performed using the SPSS statistical software package, version 15.0. Categorical variable results were expressed as count (percentage) and were compared using the χ2 test. Continuous variables were expressed as median with interquartile range (IQR) and were analyzed using non-parametric tests. PSI and CURB65 scales were categorized as low risk (PSI ≤III/ CURB65 ≤2) and high risk (PSI >III/ CURB65 ≥3). Severe sepsis was dichotomized as yes (severe-sepsis criteria at hospital admission) and no (non-severe-sepsis criteria, the reference group).

Two multivariable statistical studies were performed using stepwise logistic regression analyses. In the first model, the included independent variables were those related to characteristics of patients. In the second model, the independent variables were those related to etiology (causal microorganisms). In both models, the independent variables were those found to be significant in the univariate analyses. The Hosmer and Lemeshow goodness-of-fit test was performed to evaluate the adequacy of the models.12 The cohort comprised 4,374 patients presenting to the emergency department with CAP and admitted to the hospital. We studied 4,070 patients after excluding 237 nursing-home and 66 DNR patients: 1,529 (37.6%) had severe sepsis (Table 1).

Mortality for the whole cohort was 3.3% and the median length of stay was 7 (IQR 4–10) days. Mortality was significantly higher in severe-sepsis CAP (Table 2).

Characteristics related to severe-sepsis CAP compared to the reference group are shown in Table 1. Severe-sepsis CAP was more frequent in men, patients older than 65 years, and those with COPD and renal disease, whereas diabetes mellitus was more frequent in those without sepsis. Severe-sepsis CAP also presented with higher PSI and CURB65 scores and more multilobar infiltrates. Patients who received prior antibiotic treatment had lower rates of severe sepsis.

Etiological diagnosis in the whole cohort was reached in 1,506 (37%) patients: 859 (57%) S pneumoniae, 104 (6.9%) L pneumophila, 44 (2.9%) C pneumoniae, 50 (3.3%) C burnetii, 50 (3.3%) M pneumoniae, 45 (3%) Pseudomonas aeruginosa, 43 (2.9%) Haemophilus influenzae, 18 (1.2%) viruses, 15 (1%) E. coli and 121 (8%) mixed etiology.

Severe-sepsis CAP patients had the highest percentage of identified causal microorganisms and more bacteremic episodes. S pneumoniae was the most frequent microorganism.
found, with a higher percentage in severe sepsis. Atypical microorganisms were more frequent in patients with non-severe sepsis, whereas mixed etiology appeared more often in severe-sepsis CAP. Mixed etiology was caused mainly by *S. pneumoniae* (29.3% with virus or atypical pathogens, 13.8% with *Pseudomonas aeruginosa* and 5.1% with *S. aureus*) (Table 3).

Four independent risk factors related to patients’ characteristics were associated with severe-sepsis CAP: age >65 years, alcohol abuse, renal disease, and COPD, whereas prior antibiotic treatment and diabetes were protective factors. With regard to causal microorganisms, *S. pneumoniae*, mixed etiology, and bacteremia were found to be risk factors (Table 4).

**Discussion**

The most important findings of our study were: 1) 37.6% of hospitalized CAP patients had developed community-onset severe sepsis already at admission; 2) elderly patients, alcohol abusers, patients with renal disease, and COPD patients were more likely to develop community-onset severe sepsis, whereas prior antibiotic treatment was a protective factor; 3) *S. pneumoniae* and mixed etiology are the main causal microorganisms of severe sepsis.

Severe-sepsis CAP is not well characterized in terms of the most susceptible population even though it can appear in over one-third of the patients. We have identified the aforementioned characteristics, two of them related to comorbid conditions. However, diabetes was more frequent in those without severe sepsis, probably reflecting more lenient hospitalization criteria in diabetic patients.

At hospital admission, patients with severe-sepsis CAP had a higher PSI and CURB65 scores, although more than half of these patients had a CURB65 score ≤2, pointing out the limitations of scales for severity assessment. Patients who had initiated outpatient antibiotic treatment presented a lower frequency of severe-sepsis CAP at hospital arrival. Prior studies have reported the protective effect on mortality when antibiotic therapy was rapidly initiated between four and six hours after arrival at the hospital. Prompt antibiotic administration may rapidly reduce the bacterial load, down-regulating the inflammatory cascade and thus decreasing the risk of sepsis.

On initial severity assessment of CAP, severe-sepsis criteria should be taken into account for the decision-making process, including allocation, monitoring, and management.

The multivariable statistical analyses confirm that alcohol abuse and two comorbid conditions (COPD and renal disease) were independent host risk factors for developing severe-sepsis CAP in the community. The impact of alcohol on developing severe CAP has been linked to an abnormal immune response. Curiously, despite the increased risk for severe CAP in COPD patients, mortality is not higher, probably due to the use of previous antibiotics and corticosteroids that reduce inflammatory response. Our results suggest that patients with alcohol abuse, COPD, and renal diseases should be specifically targeted for preventive strategies.

### Table 4. Multivariable analysis results of severe sepsis related to host factors (first model) and microorganisms (second model).

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Severe Sepsis</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Total No. (%)</td>
<td>Yes, n (%)</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Known etiology n = 1,507</td>
<td>860 (33.8)</td>
<td>664 (42.2)</td>
</tr>
<tr>
<td>Gram-positive n = 866</td>
<td>466 (18.3)</td>
<td>400 (26.2)</td>
</tr>
<tr>
<td>Gram-negative n = 207</td>
<td>132 (4.8)</td>
<td>84 (5.5)</td>
</tr>
<tr>
<td>Mixed etiology</td>
<td>125 (4.9)</td>
<td>82 (5.4)</td>
</tr>
<tr>
<td>Atypical pathogens n = 144</td>
<td>102 (4.0)</td>
<td>42 (2.7)</td>
</tr>
<tr>
<td>Known etiology n = 1,507</td>
<td>800 (35.0)</td>
<td>640 (41.2)</td>
</tr>
<tr>
<td>Gram-positive n = 866</td>
<td>457 (17.8)</td>
<td>397 (25.9)</td>
</tr>
<tr>
<td>Gram-negative n = 207</td>
<td>123 (4.8)</td>
<td>83 (5.5)</td>
</tr>
<tr>
<td>Mixed etiology</td>
<td>132 (5.2)</td>
<td>85 (5.5)</td>
</tr>
<tr>
<td>Atypical pathogens n = 144</td>
<td>102 (4.0)</td>
<td>42 (2.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p value: the χ² test was performed for categorical data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05: p ≤ 0.05; 0.01: p ≤ 0.01; 0.001: p ≤ 0.001.</td>
</tr>
</tbody>
</table>

*Table 3. Etiology of CAP in relation to severe sepsis.*

<table>
<thead>
<tr>
<th>Severe Sepsis n = 1,529</th>
<th>OR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First model: Host factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data and habits</td>
<td>Age (≥65 years)</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>Alcohol abuse</td>
<td>1.31</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td>Diabetes Mellitus</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Renal disease</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>1.75</td>
</tr>
<tr>
<td>Prior antibiotic treatment</td>
<td>0.62</td>
<td>0.52-0.73</td>
</tr>
<tr>
<td>Second model: Microorganisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>1.59</td>
<td>1.31-1.95</td>
</tr>
<tr>
<td><em>L. pneumophila</em></td>
<td>1.81</td>
<td>1.14-2.86</td>
</tr>
<tr>
<td>Mixed etiology</td>
<td>1.85</td>
<td>1.10-2.49</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.37</td>
<td>1.05-1.79</td>
</tr>
</tbody>
</table>

*a OR: Odds ratio |
| 95% CI: Confidence interval |
when in contact with health systems, that is, at discharge or during scheduled outpatient visits. Moreover, if treated as outpatients for CAP, they should be closely monitored and receive instructions to rapidly recognize the signs of sepsis.

Bacteremia and etiological microorganisms are more frequently identified when CAP presents with severe sepsis, most likely due to a higher burden of pathogens in most severe episodes.2,5 S. pneumoniae was the most frequently isolated microorganism in severe CAP.1,2,22 and, specifically, some serotypes have been independently associated with septic shock.24 Mixed etiology was the second-most common etiology in severe-sepsis CAP, underscoring the impact of associated microorganisms on severity. Patients presenting with severe sepsis should benefit from optimizing microbiological tests to rule out bacte-

meria and mixed etiology, immediately before initiating a combination antibiotic therapy.

This study has some limitations. We have excluded the nurs-
ing-home population and patients with CAP considered a ter-

dinal event in order to avoid a different population with different characteristics, more frequent nosocomial infections, and/or multiring resistant microorganisms and limited therapeutic efforts; therefore, our findings are not applicable to that subset of population. Secular and microbiological diagnosis with regard to viruses was incomplete in a considerable subset of patients, the percentage of blood cultures was suboptimal (62.7%), and determination of S. pneumoniae serotypes was not performed. The indications of microbiological tests in our study relied on the attending physicians. Third, the information regarding septic shock was not recorded. Nevertheless, our strengths are the large sample size and the prospective study design.

Conclusions

Elderly patients, alcohol abuse, and some comorbidities such as COPD and renal disease are predisposing conditions for progressing to severe-sepsis CAP in the community, mainly due to S. pneumoniae and mixed etiologies. Those findings may have clinical implications for patients and physicians in primary care and emergency rooms. Preventive CAP strategies such as vaccination—influenza and S. pneumoniae—and health measures recommended in guidelines should be reinforced in the most susceptible patients. Recognition of severe-sepsis CAP signals should be encouraged for patients and for physicians in primary care and/or emergency rooms. Initial severity CAP assessment could be improved by evaluation of severe-sepsis criteria at diagnosis in order to optimize microbiological and analytical tests, to provide closer monitoring and a rapid antibiotic treatment. Efforts should be directed to encouraging actions to reduce the burden of severe-sepsis CAP episodes and facilitate its prompt recognition.

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CONTINUING EDUCATION TEST - PREDICTORS OF SEVERE SEPSIS AMONG PATIENTS HOSPITALIZED FOR COMMUNITY-ACQUIRED PNEUMONIA

MLO and Northern Illinois University (NIU), DeKalb, IL, are co-sponsors in offering continuing education units (CEUs) for this issue's article PREDICTORS OF SEVERE SEPSIS AMONG PATIENTS HOSPITALIZED FOR COMMUNITY-ACQUIRED PNEUMONIA. CEUs or contact hours are granted by the College of Health and Human Sciences at Northern Illinois University, which has been approved as a provider of continuing education programs in the clinical laboratory sciences by the ASCP P.A.C.E.® program. Approval as a provider of continuing education programs has been granted by the state of Florida (Provider No. JP0000496), Continuing education credits awarded for successful completion of this test are acceptable for the ASCP Board of Registry Continuing Competence Recognition Program. Readers who pass the test successfully (scoring 70% or higher) will receive a certificate for 1 contact hour of P.A.C.E.® credit. Participants should allow three to five weeks for receipt of certificate. The fee for this continuing education test is $20. This test was prepared by Amanda Voelker, MPH, MT(ASCP), MLS Clinical Education Coordinator, School of Allied Health and Communicative Disorders, Northern Illinois University, DeKalb, IL.

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March 2016

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CE Test Questions

1. What is the U.S. incidence rate of community-acquired pneumonia (CAP), per 100,000 inhabitants?
   a. 1,167 cases
   b. 512 cases
   c. 343 cases
   d. 150 cases

2. A syndrome defined by infection, complicated by systemic inflammation and organ dysfunction, is known as
   a. sepsis
   b. metabolic syndrome
   c. sepsis
   d. none of the above

3. Which is a concerning health complication associated with CAP?
   a. depression
   b. deafness
   c. severe sepsis
   d. diabetes

4. What were the researchers seeking to identify in the patients that presented to clinicians with CAP and severe sepsis?
   a. risk factors associated with severe sepsis
   b. causative microorganisms associated with severe sepsis
   c. both a and b
   d. neither a nor b

5. What primary diagnosis was used for inclusion criteria of the patients in the study?
   a. diabetes
   b. coronary artery disease
   c. multiple sclerosis
   d. CAP

6. Patients who were excluded from the research study included nursing-home patients, transplant/oncologic patients, immunosuppressive HIV patients, patients undergoing treatment with corticosteroids or other immunosuppressive drugs, DNR patients, and patients in which CAP was a terminal event.
   a. True
   b. False

7. According to the study, what health outcome was measured during hospitalization, and at 30-day and 90-day follow-up?
   a. hospital readmission rate
   b. mortality
   c. both a and b
   d. neither a nor b

8. Of the study population that presented to the emergency room with CAP what percentage had severe sepsis upon admission?
   a. 52.6 percent
   b. 11.8 percent
   c. 48.3 percent
   d. 37.8 percent

9. Which two factors were found to be protective with regard to the patient characteristic findings?
   a. alcohol abuse and prior antibiotic treatment
   b. elderly patients and renal disease
   c. renal disease and diabetes
   d. diabetes and prior antibiotic treatment

10. Which risk factors were more likely to be developed in community-onset severe-sepsis patients?
    a. elderly, diabetes, and COPD patients
    b. elderly, alcohol abusers, renal disease patients, and COPD patients
    c. elderly, coronary artery disease, alcohol abusers, and diabetes patients
    d. none of the above

11. Which were identified as being causal of severe sepsis?
    a. S. pneumoniae and mixed etiology
    b. H. influenzae and mixed etiology
    c. M. pneumoniae and H. influenzae
    d. S. pneumoniae and M. pneumoniae

12. When assessing a CAP patient upon admission, a main limitation found in the study was the scales that are currently in use for determining the severity.
    a. True
    b. False

13. Why was the nursing-home population excluded from the study?
    a. This population exhibits different health characteristics.
    b. This population exhibits more frequent nosocomial infections.
    c. This population exhibits more multidrug resistant microorganisms.
    d. all of the above

14. While the study had some apparent limitations, what factor(s) did the researchers believe were the strengths of the study?
    a. large sample size and prospective study design
    b. inclusion of all patient populations across healthcare settings
    c. microbiological testing that included identification of bacteria and viruses
    d. all of the above

15. The concluding recommendations on the care of CAP patients include the development of preventive CAP strategies in susceptible patients and the early recognition of severe sepsis in patients presenting with CAP
    a. True
    b. False
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CLINICAL ISSUES

HEPATITIS C

Hepatitis C: challenges and opportunities in the laboratory diagnosis of infection

By Tara Vijayan, MD, MPH, and Jeffrey D. Klausner, MD, MPH

It is estimated that more than four million people living in the United States are infected with hepatitis C virus (HCV), yet only half of them have been diagnosed with the disease. About 20 percent of HCV-infected individuals will develop life-threatening complications, including cirrhosis and liver cancer. Liver failure due to HCV infection is the leading cause of liver transplantation in the U.S., resulting in a tremendous cost and utilization burden to an already-stressed healthcare system.

Diagnosing individuals and initiating treatment well in advance of end-stage complications therefore has become a public health imperative. That is particularly true in the current era of curative 12-week oral therapy. Directly acting antiviral medications can now result in a greater than 90 percent cure rate regardless of the genotype. In 2012, the Centers for Disease Control and Prevention (CDC), and more recently the U.S. Preventive Services Task Force, recommended routine serologic testing for all people born between 1945 and 1965 in addition to those with typical risk factors (non-prescription injection drug use and recipients of blood products before 1992). Additionally, a rising incidence among men who have sex with men has necessitated routine screening of these individuals as well, particularly those who are also infected with HIV.

In this brief review, we discuss the current testing algorithms for detecting chronic hepatitis C infection, the limitations of such testing, and the implementation efforts occurring nationwide to identify HCV-infected individuals.

Current screening algorithms and limitations

The current screening algorithm for most academic, hospital, and commercial laboratories involves a third-generation enzyme-linked immunosorbant assay (ELISA) which targets antibodies to multiple viral antigens, including the core and nonstructural (NS) proteins N3, NS4, and NS5p. A positive ELISA was historically confirmed by a recombinant immunoblot assay (RIBA), which also detects antibodies against the N3, NS4, and NS5 proteins. Given the time, labor, and added costs associated with the RIBA confirmatory testing, and more importantly, the need for an HCV RNA quantitative level to diagnose active HCV infection, that two-step method was discontinued. Only the anti-HCV ELISA is used to detect anti-HCV positive individuals, despite its less than 100 percent specificity.

Screening with antibodies continues to be the preferred method of diagnosing HCV infection. Unfortunately, most microbiology laboratories do not perform reflex quantitative HCV viral loads on reactive anti-HCV results. A two-step process results in delays in the diagnosis of chronic HCV infection and missed opportunities for treatment. In one study conducted by the New York City Department of Public Health, one-third of individuals screened positive by antibody testing did not get a confirmatory HCV viral load. Such a two-step algorithm requires patients to come back for at least one, if not two visits to determine the treatment course based on the presence of HCV viremia and the associated genotype. At least one large commercial laboratory has begun reflexively testing for HCV RNA in all patients with a positive HCV antibody test. The Veterans Affairs Administration has also promoted a national policy regarding reflex testing. Incorporating reflex testing into the algorithm can enable patients to have fewer clinic visits, reduce the time to treatment, and save healthcare costs.

Other anti-HCV testing options include point-of-care (POC) diagnostics utilizing fingerstick capillary whole blood or venipuncture-collected whole blood. Those assays have been developed and validated, but remain costly.

An alternative to reflex HCV RNA testing on anti-HCV positive specimens is testing for specific hepatitis C viral proteins that are only detectable in active infection. Specifically, the HCV core antigen test has been studied as a fast and more inexpensive test to confirm active infection, particularly in low-resource settings. Though the sensitivity is not as high as HCV RNA detection, the benefit would be in reducing the number of more costly HCV RNA tests in populations where the overall prevalence of active infection is low.

Genotype and resistance testing

HCV genotyping remains a key component of the diagnostic algorithm of HCV infection. Specific direct active antivirals have different efficacy with different genotypes. That drug specificity may change as more “pan-genotypic” antivirals become available. In addition, some genotypes have lower genetic barriers to developing resistance than others, and adherence counseling becomes more crucial in patients infected with those genotypes. A number of genotyping methods are used including PCR HCV amplification followed by strip-based reverse hybridization, PCR HCV amplification followed by Sanger sequencing, and real-time PCR.

The role of viral resistance testing in patients who fail antiviral treatment is complicated. There is currently no guidance regarding when to order such tests.

Implementation of screening

Implementation of screening programs to identify HCV-infected individuals in specific cohorts has been an area of recent research. In one New York-based hospital, only 47 percent of eligible patients were routinely offered anti-HCV testing despite the 2013 New York State law mandating the offering of anti-HCV testing to individuals born between 1945 and 1965.

Researchers from the same hospital initiated a program utilizing their electronic medical record (EMR) system to create a “pop-up” window reminder to screen individuals from that birth cohort. When the “pop-up” reminder did not result in an increase in screening, the researchers initiated automatic laboratory anti-HCV testing orders for all individuals in the cohort, after confirming from the State that individual consent for routine anti-HCV screening was not needed from patients. The “pop-up” window would no longer remind providers that screening was needed, but rather that the patient had a positive HCV antibody test. Researchers were able to see a significant continued on page 18
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increase in screening rates after that intervention, from 47.2 percent to 87.9 percent.14

A similar study conducted at the Cleveland Department of Veterans Affairs Medical Center demonstrated that improving patient-centeredness of the screening process in ambulatory settings in addition to implementing reflex HCV viral loads (including using a locally developed electronic HCV management application) had resulted in a nearly 100 percent completion rate of timely HCV viral RNA testing.10

At the University of California, Los Angeles, a similar initiative has begun. A hepatitis C antibody testing reminder was added as part of the healthcare maintenance section in the EMR in August 2015. Since August, anti-HCV testing has increased from an estimated coverage in primary care of three percent to 10 percent.

Conclusion

Though screening at-risk groups for HCV infection remains a high national priority, implementation of the recommended screening algorithm has been limited. Targeted interventions, including additions to EMRs, reminders, and standing orders that include reflex HCV RNA testing on anti-HCV positive specimens, can help improve case-identification, initiate early treatment, and ultimately reduce healthcare costs.

REFERENCES

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Increasing evidence supports the need for multiplex testing of sexually transmitted infections

By Martin Crockard, PhD

An estimated one million individuals acquire a new sexually transmitted infection (STI) every day. According to the World Health Organization (WHO), each year an estimated 500 million people worldwide become ill with syphilis, gonorrhea, chlamydia, or trichomoniasis. The chronic sequelae of STIs include long-term disability and death but may also cause reduced fertility, increased infant and child mortality, and increased transmission rates of human immunodeficiency virus (HIV).

Since my article proposing more comprehensive multiplex testing for STIs was published in the December 2013 issue of this journal (http://www.mlo-online.com/combating-sexually-transmitted-infections-with-multiplex-testing.php), the evidence for the importance of such testing has become even more compelling.

A worsening problem

New data has highlighted the prevalence of Mycoplasma genitalium (MG), for example, which has caused surprise and concern among healthcare professionals. In the UK and elsewhere, infection rates have been found to be around one percent, similar to rates for Neisseria gonorrhoea (NG), which is often part of routine screening. As both infections can display common symptoms (or none) and similar long-term health effects, there is a very strong argument for routine testing for MG. This would facilitate the detection of otherwise overlooked MG infections.

In many countries, there is a minimum recommended number of STI tests to be performed, depending on symptoms. In the UK, for example, the British Association for Sexual Health and HIV (BASHH) includes Chlamydia trachomatis (CT), gonorrhea, and syphilis (Treponema pallidum) in its guidelines. Symptomatic women may also be tested for Trichomonas vaginalis (TV), which causes vaginitis and cervicitis in women and urethritis in men. However, Trichomonas infections are often asymptomatic and, because prevalence is assumed to be low, rarely tested for. In addition, wet mount microscopy, the routine diagnostic method for women, is insensitive, so TV infection remains underdiagnosed.

As with MG, new data suggests much higher incidences of TV than previously thought, and this is reflected in the new guidelines, which now recommend molecular approaches for TV detection. MG is now accepted as an STI, being implicated in urethritis and cervicitis, but the previous lack of recognition has led to inappropriate treatments and a significant rise in antimicrobial resistance.

In cases where individuals show overt physical symptoms, such as genital lesions or ulcers, herpes and syphilis testing is offered. Depending on the country, testing for tropical genital ulcerative diseases such as chancroid (Haemophilus ducreyi) is now advised according to patient history. Ureaplasma urealyticum is not routinely tested for, although there is a body of evidence implicating this bacteria in long-term health complications, similar to other bacterial STIs.

A multiplex solution

If you consider the bacterial, viral, and protozoa infections mentioned, all of which can justify routine testing, you build up a panel that could benefit from a multiplex approach. Thus a single patient sample, such as first-void urine or a genital swab, could be used to simultaneously detect infections, including those not anticipated.

Another major advantage of multiplex testing, as I noted in the 2013 article, is detection of the presence of co-infection. As many as 35 percent of individuals with STIs have been reported to have co-infections. Considering that many screening programs only look for CT and NG, there is the real possibility that this number would increase if a more comprehensive STI panel were used.

The increasing reports of antibiotic resistance among STI bacteria are also cause for concern and further highlight the need to accurately define the causal agent of infection, in order to allow tailored treatment. Widespread resistance of NG to penicillin-based and quinolone-based antibiotics has been compounded by the emerging resistance to cephalosporins, which has hindered the treatment and control of gonorrhoea. This underlines the importance of accurate diagnosis and implementation of suitable treatment in the fight against the build-up of antibiotic resistance.

BASHH guidelines also recommend that people being tested for STIs should have the most accurate diagnostic test in its class for each infection for which they are being tested and that all diagnostic samples be processed in a timely fashion in order that results can be conveyed quickly and acted on appropriately. A multiplex molecular method for all key target infections fulfills these recommendations.

Common methods for diagnosis of STIs include microscopy and wet preparation, pathogen culture, or polymerase chain reaction (PCR) to correctly identify the causative agent. For some STIs, like syphilis, detection of the host response to infection (antibodies) is the routine diagnostic method. However, microscopy is lengthy, lacks sensitivity, and is hampered by difficulties in successfully culturing fastidious species. Serological tests are prone to false positive results and often require a second, confirmatory serologic test, which targets a different antigen. Another shortcoming of serological

continued on page 24
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S
tually transmitted infections (STIs) incorporate a particular set of clin-
cal infection and disease processes typically associated with transmission through sexual activity. In 2010, the United States spent approximately $15.6 billion on identification and treatment of STIs. In addition, in 2013, according to Tucker et al. “The WHO estimated 448 million new cases of curable sexually transmitted infections...are diagnosed each year.” The testing traditionally performed by laboratory personnel is thorough, but hours or days are often required to obtain the results. This testing capability usually requires a secondary level medical facility or higher, but that level of care is difficult for many patients to obtain in outlying or rural areas and requires multiple appointments for the patient to be tested and receive results. However, several recent advancements in sexually transmitted infection (STI) detection using point-of-care testing (POCT) have enabled many medical facilities to reduce the number of physician visits, speed up turnaround times, and accurately treat patients in most parts of the country.

The classical STIs are Chlamydia trachomatis (chlamydia), Neisseria gonorrhoae (gonorrhea), Trichomonas vaginalis (trichomonas), human immunodeficiency virus (HIV), syphilis, human papil-

lomavirus (HPV), and herpes simplex virus (HSV). The most common of these (chlamydia, gonorrhea, and trichomonas) typically require a gram stain and wet mount preparation to be examined by a trained microbiology technician, a culture requiring 72 hours or more and special incubation demands. Due to the analytical time requirements, patients typically have to wait many hours and in most cases days prior to starting treatment or receiving care. Laboratory analysis for HIV, HBV, and HSV usually requires a blood sample for analysis or additional follow-up procedures, while an HPV determination often utilizes a PAP. All of these tests are performed by laboratorians; however, in recent years POCT capabilities have evolved. Many of these tests can detect or positively identify STIs, some within an hour or less. This is particularly important in ar-
eas with limited access to medical care or with patients who may not return for follow-up appointments.

The most frequently used diagnostic test for chlamydia and gonorrhea is the nucleic acid amplification test (NAAT). NAAT utilizes replication of the genetic material of a bacterium. By increasing the quantity of the bacteria within the testing matrix, it makes the target bacterium more easily detectable. However, recent advances in POCT have made quick, pre-
liminary screening for these pathogens a possibility. These kits typically incorporate internal and external controls and are able to provide results in less than 20 minutes. In some cases the sensitiv-
ity and specificity of these POC kits can be poor (some as low as 12 percent). However, this can be due to specimen contamination with menstrual blood or some noted risks of result reproducibil-
it. Some more recently approved POCT kits have demonstrated high sensitivity and reproducibility, making rapid and accurate results beneficial for both urban and rural laboratory utilization.

Trichomonas is responsible for 187 million STIs worldwide, with many pa-
tients appearing asymptomatic. While trichomonas can be manually cultured, it requires special medium, a trained eye, and several days to confirm a negative result. Trichomonas can also be seen in wet mounts and urine microscopy; however, identification can be difficult for inexperienced laboratory personnel. Rapid POCT tests for this organism have been developed over the past few years, improving sensitivity and specificity. One example of recent testing capability utilizes an immunocromatographic capillary flow method that detects Tricho-

monas vaginalis membrane proteins and

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INTENDED USE: The BioPlex® 2200 HIV Ag-Ab assay is a multiplex flow immunoassay intended for the simultaneous qualitative detection and differentiation of the individual analytes HIV-1 p24 antigen, HIV-1 (groups M and O) antibodies, and HIV-2 antibodies in human serum or plasma (fresh or frozen K2 EDTA, K3 EDTA, lithium heparin, sodium heparin; fresh citrate). This assay is intended as an aid in the diagnosis of infection with HIV-1 and/or HIV-2, including acute (primary) HIV-1 infection. The assay may also be used as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in pediatric subjects as young as two years of age, and pregnant women.

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provides results in less than 10 minutes.3 Alternately, the molecular NAAT method for trichomonas was approved by the FDA in the POC setting in October 2015. Some NAAT methods are providing results within 50 minutes and with outstanding sensitivity and specificity.

Through the prevalence of HIV has continued to decrease over the years due to prevention efforts and treatment options, the virus still affects 35 million people worldwide.7 There are several POC kits that provide rapid results that are key to reducing undiagnosed infection and targeting prevention efforts. These POC kits include hospital-based testing as well as in-home HIV identification, providing results in less than 20 minutes. Multiple POC platforms allow for early detection of the HIV virus in as few as 12 days after infection by detecting HIV antigens as well as antibodies. In addition to POC sample analysis, recent FDA-approved test kits combine testing for both HIV and syphilis testing within a single specimen.8 Syphilis, caused by the spirochete Treponema pallidum, is responsible for 37 million STIs worldwide and has devastating consequences for pregnant women and their fetuses, including low birth weight, stillbirth, premature birth, and congenital defects.7 While the standard for syphilis testing has been the rapid plasma reagin (RPR), additional serologic POC tests have been developed that have a much higher sensitivity than traditional RPR. Updated serum sample analyses demonstrate agreement with RPR results as high as 97.6 percent, although these are not POC platform items. Incorporating previously mentioned duo testing, recent POC kits produce Treponema and HIV results of fingerstick or serum blood samples within 15 minutes.

Human papillomavirus (HPV) affects 63 million worldwide and has been linked as a causative agent to cervical and anal cancer.7 While the PAP smear has long been the standard for detecting cervical cancer and HPV, a recent HPV genotyping membrane test has shown tremendous promise and is currently being developed as a POC test. When it is approved for use, clinicians can expect a >95.9 percent HPV detection sensitivity. Incorporation of POC capabilities will expand the ability of labora- tory analysis from inside the hospital to outlying clinics and medical treatment locations.

HSV affects a staggering 536 million worldwide, and in addition to causing both genital and oral herpes the virus can cause serious or fatal complications for newborns.8 While there are no FDA-cleared POC serologic assays for HSV detection, there have been several recent POC HSV molecular assays developed. These assays enable laboratory testing to rapidly produce results while maintaining sensitivity and specificity. Non-FDA cleared serologic assays are also available outside the United States, including some POC kits that have a sensitivity of >90 percent.

Testing for multiple STDs has been a trademark of in-house clinical laboratory capabilities. Introduction of many of the recent FDA-approved POC platforms has increased availability in more remote areas, bringing expanded capabilities to these more rural locations. In addition, some tests have enabled at-home laboratory procedures to become a reality. This has increased patients’ ability to accomplish screening procedures while not sacrificing sensitivity and specificity. In addition, it will enable laboratories to expand their specialization while ensuring that patients are receiving the testing needed and maintaining the accuracy expected of the laboratory capabilities.

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As Molecular Diagnostics Manager at Randox Laboratories Ltd, Martin Crockard, PhD, works with a team of more than 20 molecular biologists in his molecular group and has developed multiplex infection and mutation profiling arrays for clinical use. Martin has more than 20 years’ experience leading molecular biology projects, over 14 at Randox. He is also working with Randox Engineering to develop fully automated analyzers, to bring the molecular tests to the point of clinical need.

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diagnosis is that antibodies may persist long after successful treatment of the infection. PCR is often preferred due to its increased sensitivity and shorter turnaround times. For practical purposes, diagnosis of MG is limited to nucleic acid amplification testing (NAAT), as culture is extremely slow (up to six months), challenging, and insensitive. Improved sensitivity of molecular approaches over wet mount microscopy will also improve detection of Trichomonas vaginalis. Likewise, single or multiplexed NAAT are preferred to serology for the diagnosis of HIV infections.

The variety of PCR methods available for each STI makes the appropriate choice of diagnostic tests difficult. Most commercially available STI tests are uniplex or duplex assays. However, repeat PCR testing for multiple pathogens is time-consuming, expensive, and impractical, whereas a multiplex approach would provide a cost-effective alternative and improve patient outcomes by ensuring that more asymptomatic infections and co-infections are identified.

Conclusion

There are compelling justifications for a multiplex approach to STI detection. These include today’s greater awareness of the range of infectious agents, with higher infection rates than previously anticipated; increasing reports of antibiotic resistance; and higher co-infection rates. The increased sensitivity and specificity and reduced time to result offered by molecular technologies also are encouraging the adoption of this strategy. In combination, more rapid and accurate multiplex testing will improve detection rates, reduce risk of inadvertent spread of infection, and improve antibiotic stewardship. With increased antibiotic resistance of many of the bacterial STIs becoming a real concern, adoption of this approach is more important than ever.

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At the national level, the reduction in overall healthcare costs is a high priority. Laboratory data accounts for nearly 80 percent of disease management decisions, so ensuring the quality of laboratory data has a ripple effect in controlling hospital expenditures. One of the advantages offered by molecular testing is the addition of value to existing health data, mainly through individualized medicine. With its evidence-based practices, personalized patient care through companion diagnostics can have significant cost benefits.

The aim of multiplexed molecular testing is the detection of multiple causative agents or abnormalities from a single clinical specimen. In contrast, focused single gene testing attempts to find the specific genetic abnormality to guide personalized therapeutics. Balancing these divergent goals is crucial in developing an efficient laboratory diagnostic workflow.

Information systems contribute to patient safety by enabling easy data exchange between the laboratory and other arms of the hospital to generate the least error-prone, most efficient processes possible. The exchange of objective data can also compensate for limited patient history and physical examination details. Risk estimation tools that measure the effect on patient safety can be used for the newer molecular assays before clinical implementation.

Identifying the laboratory steps that are most error-prone using Lundberg’s Total Testing Process (TTP) model led to the development of the initial laboratory workflows. Managing process variations well could avoid temporary stopgap measures that could transform into standard laboratory practices. The purpose, testing environment, volume and costs are other important considerations in laboratory workflows. Efficient workflows eliminate unwanted steps and thus standardize protocols, as well as training.

Automation and workflow
Automation of the total testing process allows precise time-stamping and error-free, legible entries that can be easily retrieved for future reference. Zero tolerance of data entry duplications and immediate transmission of results to electronic medical records (EMRs) are other advantages of automation. Automated laboratory testing, synchronized with hospital data management systems, results in efficient disease/health management workflow. The automatic population of the data and the ability to retrospectively analyze the test ordering pattern and results are major benefits of the adoption of laboratory information systems (LIS) into the diagnostic workflow. The interoperability of the LIS and the hospital information system avoids test over-utilization and redundant or incorrect test ordering and ensures follow-up of results and better management of the reflex testing per guidelines. Web-based electronic health records and ordering options offer simple and flexible solutions for information gathering and transfer within the shortest possible time to ensure physician adherence, and better and timely patient management.

The selection of an automation system depends on the work-flow (continuous over the course of the day or batch testing), the specific patient population, and the availability of trained personnel in various shifts to operate the automated processes. To that last point, before introducing automation, a diligent assessment of the experience and the comfort level of the staff should be made. Automating only one shift, the dayshift for example, could complicate workflows and result in unwanted errors.

Workflow optimization carries benefits at the pre-analytical, analytical, and post-analytical stages. At the pre-analytical stage it can ensure error-free direct specimen testing (without pretreatments) with rapid turnaround of results. Barcoded specimen collection entry has the downstream advantages of significant savings in the processing of results, allocation of resources, and length of stay. Pre-analytical workflow can be comprised of several laboratory section-specific processes—for example, automated digital microscopy to assess the percentage of tumor nuclei, or automated microbiology tools for specimen staining and processing; plate transportation; incubation; and imaging. Open configuration of the test protocols and point-of-care (POC) analyzers with communication capabilities to multiple software platforms simplify the workflow to manageable levels. In the testing phase, products that reduce quality control steps can add value, and reference methods can allow easy intra- and inter-laboratory comparisons and auto-tiling of results. Standardization of the post-analytical phase, including reporting of the results, also enhances efficient workflow.

Molecular diagnostics and automation
Thus, persuasive arguments can be made for the automation of laboratory processes in general. How, more specifically, does...
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this apply to molecular diagnostics in clinical use? How can automation impact the MDx workflow?

During the selection phase of the molecular assays, several things need to be assessed: test volume; the need for manual specimen processing; the type of specimens to be run; the controls to be utilized; savings to be gained in both the turnaround time (TAT) and return on investment (ROI), when compared to a send-out test; and the population being targeted. In high-volume testing, a larger part of the workflow involving manual specimen processing is not desirable, even when the subsequent steps are carried out through automated analyzers. The integration of DNA/RNA sequencing, digital immunosassay, flow cytometry, genotyping, mass spectrometry, multiplexing, qPCR, and proteomic, metabolomic, and epigenetic data into the diagnostic workflow requires higher image import/export, family pedigree, and data analysis capabilities. Comparative genomic hybridization arrays capable of combining single nucleotide polymorphism (SNP) and copy number variation detection are preferred in SNP genotyping workflow due to the reduced turnaround time (TAT) and costs. This is also true in the interrogation of solid tumors with such technologies. Flow cytometry is much more quantitative than immunohistochemical methods in determining the leukocyte alkaline phosphatase score and can also rule out chronic myeloid leukemia faster than outsourced molecular testing results. In the case of acute promyelocytic leukemia diagnosis, it is crucial to identify the t(15;17) by fluorescent in situ hybridization (FISH) as quickly as possible so that the specific test volume testing, a larger part of the workflow involving manual time (TAT) and return on investment (ROI), when compared to controls to be utilized; savings to be gained in both the turnaround time (TAT) and return on investment (ROI), when compared to a send-out test; and the population being targeted. In high-volume testing, a larger part of the workflow involving manual specimen processing is not desirable, even when the subsequent steps are carried out through automated analyzers. The integration of DNA/RNA sequencing, digital immunosassay, flow cytometry, genotyping, mass spectrometry, multiplexing, qPCR, and proteomic, metabolomic, and epigenetic data into the diagnostic workflow requires higher image import/export, family pedigree, and data analysis capabilities. Comparative genomic hybridization arrays capable of combining single nucleotide polymorphism (SNP) and copy number variation detection are preferred in SNP genotyping workflow due to the reduced turnaround time (TAT) and costs. This is also true in the interrogation of solid tumors with such technologies. Flow cytometry is much more quantitative than immunohistochemical methods in determining the leukocyte alkaline phosphatase score and can also rule out chronic myeloid leukemia faster than outsourced molecular testing results. In the case of acute promyelocytic leukemia diagnosis, it is crucial to identify the t(15;17) by fluorescent in situ hybridization (FISH) as quickly as possible so that the specific therapeutic regimen can be administered to achieve best outcomes. Therefore, it is important to order the right test, in the right clinical context, either as a stat or with a regular TAT.

In the near future, the personalized selection of drugs based on biomarker patterns will become the norm rather than the exception in clinical practice. Identifying patients who would benefit from a particular disease prevention strategy will help in tailoring the clinical workflow. Extrapolation of findings from personalized medicine to larger public health initiatives could lead to increasingly cost-efficient clinical management practices. Gene expression levels used to segregate the anti-an giogenic drug responders and non-responders among ovarian cancer patients is one example of this approach. Identification of likely responders to companion diagnostic drugs for metastatic colorectal cancer with KRAS CDx test is another, and one that has been linked to substantial potential savings.1 Identifying events in the adjacent tissue of the original cancer may reveal the accurate micro-environment, to better understand the key cellular elements and pathways involved in tumor generation and progression. Similarly, re-engineering the workflow to allow the high-throughput purification of the circulating tumor cells or cell free DNA in blood to be tested by the next-generation sequencing (NGS) tools has recently become available to many labs, and thorough documentation of these efforts in the LIS is crucial.

MDx and the micro lab

Implementation of molecular methods into the microbiology workflow also requires a thorough evaluation of the benefits against the associated costs. Careful selection of the testing platforms, based on the needs of the hospital, is crucial. The conventional microbiology workflow involves sample preparation, processing, and the reading and interpretation of test results. The separation of certain activities and the unidirectional flow of staff and specimens are unique aspects of the microbiology laboratory workflow, and so is the necessity of additional workspace.

Workflow optimization can overcome the limitation of clinical specimen quantity to identify multiple infectious agents. Enclosed systems in the microbiology workflow not only can prevent contamination but also help generate rapid results. Molecular tests, in particular, were necessitated by reappearance of life-threatening infections such as Ebola virus and the unavailability of a single test to detect major infectious agents. Molecular methods, unique among testing options, allow rapid detection of organisms that are difficult to grow or to survive transport, especially if in low numbers.

Increased sensitivity, simultaneous detection of bacterial, viral, and parasitic agents and reduced TAT were the impetus for the use of multiplex molecular testing in gastrointestinal diseases. The workflow for testing for Trichomonas vaginalis, for instance, was simplified by the ability to utilize vaginal samples not restricted to collection by the clinician. The need for the most complete diagnostic solutions, sensitivity, specificity, and breadth of coverage has spurred adoption of multiplexed molecular testing in respiratory tract infections.2 Parasitic infections and allergic testing workflow are benefited by flow-through microarray technology combined with multiplexed nucleic acid/protein assays. By combining the pathogen detection and the resistance markers in a single automated procedure from native specimens, the micro lab has been able to avoid the initial culture step and put into effect a more efficient antibiotic testing workflow.

What may be next? Advanced clinical decision support systems that integrate the clinical and laboratory data for selection of the most appropriate personalized therapy are on their way. This workflow modification, with several supporting tools for the physician, has the potential to ensure continued error-free electronic laboratory orders, time and labor savings, and faster result generation. The future will see a narrowing of the traditional line of separation between laboratory sections (e.g., A1c testing on hematology analyzer from lavender top tube), and interoperability of laboratory and hospital data. Mobile apps are on the way that will be capable of executing laboratory functions that capture work orders, notes, images, and data analysis and export them to LIS. Home-based diagnostics is another emerging area in workflow optimization. In POC hemoglobin (Hb) testing, for example, translation of visual results into Hb values by the companion smart phone application will ensure self-monitoring of Hb values, similar to self-monitoring of blood pressure.

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When we consider molecular diagnostic (MDx) lab testing, it is in most cases in the context of a centralized “core lab.” There are a number of purely practical reasons for this; for example, a centralized lab can be equipped to perform a wide range of tests, meaning a single delivered sample can be readily assayed for multiple analytes as needed. It can be staffed by a group of people with focused training on the performance and interpretation of the specific test menu offered. Frequently, it can also provide opportunities for economies of scale in equipment and reagents, when compared to multiple disperse locations with mirrored test capabilities. Particularly in the molecular context, where template or amplification contamination is an ever-present risk for false positive results, infrastructural aspects designed to mitigate these risks (such as room sanitation by UV irradiation, airflow control, or workflow directionality and compartmentalization within rooms and/or process dedicated biosafety cabinets) are expensive, impractical, or both to implement in non-dedicated lab space.

Regardless of these practical considerations, a frequently expressed desire in clinical testing is to move individual tests out of the core lab and closer to the patient. The motivation for this is obvious: faster diagnosis allows for faster selection of appropriate medical intervention(s) for the patient. This is associated not just with better clinical outcomes, but also lower costs to the entire healthcare system. In idealized situations, accurate and rapid testing could be done right in the physician’s examination room with clearly interpretable results available before the physician leaves. These and similar scenarios are generally referred to as “point-of-care” or POC testing, and the expansion of molecular methods into the POC setting has both significant challenges and promises.

High, moderate, waived
Perhaps the most significant hurdle to moving MDx processes into POC settings is what’s lumped under the term “complexity.” Under U.S. CLIA regulations (and similar in other regulatory jurisdictions), tests are classified as high, moderate, or waived (i.e., low) complexity. As the names suggest, high or moderate complexity tests are ones that require significant specialized infrastructure to perform accurately, and often specialized training in their performance or result interpretation. Waived tests, on the other hand, are (and I quote from CLIA) “simple tests with a low risk for an incorrect result. They include certain tests listed in the CLIA regulations, tests cleared by the Food and Drug Administration (FDA) for home use, and tests approved for waiver by the FDA using the CLIA criteria.”

Low risk for an incorrect result is a difficult goal to achieve, as it requires both that the test process be very simple and reliable and that the interpretation be simple and obvious. Common examples of waived tests include home pregnancy tests and many of the rapid “immunospot” type tests such as those seen for the detection of common viruses. By nature, waived tests lend themselves to POC application, although the reverse is not strictly true: that is, in order to be performed as a POC test, a test does not necessarily have to be in the waived category. I quote again from CLIA: “‘Point-of-care testing’ is a phrase used to describe the location where testing is performed, such as at the bedside or near the site of patient care. While some point-of-care tests are approved for a CLIA waiver, advances in technology that enhance the rapidity of testing are allowing more complex, non-waived testing to be performed at or near the site of patient care.”

Put another way, historically, waived and POC testing were nearly synonymous, and waived class assays remain the most straightforward ones to put into POC settings. As anyone with personal front-line experience with many of the older POC test systems (particularly the immunospot-style pathogen tests) will know, the speed and convenience of these tests often came at a cost in sensitivity, specificity, or both when contrasted to higher complexity, slower tests performed by a core lab. That doesn’t mean they weren’t useful; for example, POC tests with only moderate sensitivity but high specificity can be a highly cost-effective first-line screening tool, with detected positives being accepted and allowing for immediate assignment of appropriate medical action. Less total samples (only those scoring negative in the POC test, or otherwise dictated for special considerations) get passed on to the slower, more accurate, but generally more costly centralized lab test of moderate or high complexity.

MDx and POC
Imagine, now, if we could develop POC tests based on molecular methods, with the inherently exquisite sensitivity and specificity of molecular diagnostics. The challenges in achieving this, particularly if the intent is to achieve waived status, are not trivial, as any such test system must be built in such a manner as to be highly resistant to contamination, while yielding readily interpretable results all in the hands of what would normally be referred to as “untrained users” without in-depth training on the particular assay. The potential reward, however, is significant, as such a test would be expected to enjoy the benefits common to POC tests, while providing enhanced sensitivity and/or specificity.

That reward has been incentive behind many avenues of active research and development—one of which led to the first commercial release of a molecular test (for influenza A and B, with CLIA-waived status, in January 2015. This was followed only months later by CLIA-waived status approval for a molecular assay for Group A Streptococcus. While these were all on a single platform, these approvals mark a critical milestone for all organizations looking to develop POC molecular testing. That milestone is the acceptance from a regulatory standpoint that molecular testing can be made in a format other than high-complexity and thus forcibly relegated to a centralized laboratory. Other systems will surely follow down this pathway, and the POC testing environment is likely to undergo significant changes in the near future as older, less sensitive and specific test modalities and POC systems begin to acquire the benefits of MDx.

How do the sensitivities and specificities of these first waived molecular tests compare, both with older immunospot POC tests and with core lab mainstream MDx systems? That question is difficult to answer in anything more than a very general sense, not only because of the...
wide performance range of available immunospot or similar non-molecular POC tests and the diversity of "central lab" molecular platforms and tests, but also because there are only a few of these waived molecular tests to compare against. With those caveats in mind, however, the results appear very promising. The molecular waived flu A/flu B test referred to above has stated PPA (positive percent agreement) of 96 percent on influenza A, and PPA 82.5 percent / NPA 98.4 percent for influenza B (according to the package insert). While these values clearly show room for improvement, they are appreciably better than this author’s experience with non-molecular POC tests for these same targets and only slightly below what could be expected with some current core-lab molecular methods.

Further considerations
Is this the beginning of the end for the molecular core lab? Far from it. One important reason for this is that these POC tests, and likely any that would be imagined in the near future, remain tests for at most a few specific analytes. An important strength of the core lab, and one that remains unchallenged by these advances, is the uncoupling of nucleic acid extraction from sequence-based testing; that is, once a sample is received and nucleic acids extracted, the extract can be queried by a wide range of tests either all at once, or in a descending “flow scheme” as the results of first sequential tests turn up negative. By contrast, the sample dedicated to POC type tests is lost to further testing once allocated.

Rather than seeing emerging POC molecular tests as a challenge, the agile and forward-thinking core molecular lab will actively embrace and support the use of these tests as a means to move screening for many common targets out to the physician’s offices, ERs, and hospital receiving rooms. This will have the potential to free up the more diversified capabilities and directed methodological and interpretive training of the core lab staff to focus on more challenging and less commonplace samples. If this is coupled with driving core lab capabilities further into emerging technologies such as next generation sequencing, the result will be a new lab/POC balance in molecular methods.

At least one additional factor to bear in mind in a setting where molecular techniques are brought into POC use for infectious diseases is that the front-line test users should be aware—either through product literature, training, or consultative communication with specialized core labs—that a molecular positive is not synonymous with a viable infectious organism. Without this, front-line users may not appreciate the concept of persistence of detectable organism nucleic acids past organism viability. Regardless of this and other similar challenges to be addressed through education, use of molecular techniques in POC settings can only be expected to increase and to improve patient care.

For interested readers, the CLIA quotes referenced may be found at: https://wwwn.cdc.gov/clia/Resources/TestComplexities.aspx

John Brunstein, PhD, is a member of the MLO Editorial Advisory Board. He serves as President and Chief Science Officer for British Columbia-based PathoID, Inc., which provides consulting for development and validation of molecular assays.
The case for RFID in blood banking

By Bruce Wray, MBA, and Mike Sanislo, PE

Barcode technology has been very good for the blood bank community. When it was introduced in the mid-1970s, it offered new opportunities to streamline process flows and avoid data entry errors. The latest barcode standard adopted by the international blood bank community is called “ISBT 128” and is owned by the International Council for Commonality in Blood Banking Automation (ICCBBA), a non-governmental organization recognized by the World Health Organization, and responsible for the maintenance and promulgation of the standard.

So what’s next? In 2006, the ISBT created a Task Force on Radio Frequency Identification (RFID) to study the potential of that technology in blood transfusion. The team highlighted two inherent advantages of RFID over barcodes:

• Barcodes must be seen by a human operator to be read; RFID tags, however, can be scanned without a line-of-sight. With the right combination of tags and readers, it’s possible to read an entire carton of uniquely-identified blood containers without even opening the box. That would be impossible with barcodes alone.

• Characteristics of a blood unit can change from day to day. RFID chips used to identify blood are “Read/Write,” which means data about a unit can be updated based on further processing such as irradiation or supernatant reduction. RFID chips can indicate, in real-time, the exact nature of the blood product; relabeling would still be required, of course, prior to distribution.

The first comprehensive U.S. effort to study RFID in blood banking was launched by the BloodCenter of Wisconsin in 2009 when it received a grant from the National Institutes of Health. Forming a consortium of multiple blood centers and hospitals, this group, along with the University of Wisconsin-Madison RFID lab, studied the usability, survivability, and safety of RFID in the blood supply chain. After the ISBT agreed to standardize on HF (High Frequency) RFID technology, and it was shown to the U.S. Food and Drug Administration (FDA) to have no deleterious effects on blood products, the team developed two of the first comprehensive systems for the blood supply chain. Real-world trials of RFID technology at both blood center and hospital facilities followed, and in 2013 the first FDA 510K was issued for this group’s groundbreaking blood center RFID system.

Takeaways: advantages of RFID

There were several “lessons learned” as a result of this effort:

1. Standard off-the-shelf HF RFID tags function when applied to liquid and frozen blood products.

2. These off-the-shelf tags can survive the rigors of blood component manufacturing, including centrifugation and irradiation.

3. It was possible within a blood center to significantly reduce the time to count, reconcile, and track blood products, including fully reconciling containers coming in from collection, moving from labeling to inventory, or leaving for a hospital. Locating blood products—particularly frozen plasma—was much easier and better ensured that products requiring quarantine could be quickly found and isolated. The significantly improved accuracy of reconciliation from collections greatly reduced the need for back office quality/regulatory time in investigating “lost product” situations, etc.

4. Within a hospital, the visibility of blood products within an institution was much greater, and advanced features of bedside match could improve patient safety.

5. Positive Return on Investment (ROI) based on reduction of lost products, process efficiencies, and safety/quality gains existed, if tags could be produced for less than 30 cents each, with 25 cents as a target.

6. The data gathered about the movement and use of blood products within the blood center and hospitals became a rich source of information to aid in assessing blood demand, utilization, and waste, as well as areas for improvement/efficiency in process flows. This data could be used to aid in recruitment planning, and closer to real-time. RFID would avoid the need to tap large back-end hospital systems to allow a blood center to help better manage inventory.

7. For RFID to aid in the entire supply chain, a global standard would have to be promulgated that dictates the tag type, layout, and data structures. (The first standard, entitled Guidelines for the use of RFID Technology in Transfusion Medicine, was published in the journal Vox Sanguinis, 2010; the tags involved in the Blood Center of Wisconsin study complied with that standard.)

In addition to these takeaways, consensus within the blood bank community has been reached on a couple of important points:

• RFID tags will not replace barcodes. They will, instead, be implemented as a complementary identification technology, augmenting the barcodes; the barcodes become an important new source of redundancy, further improving the reliability of the information in the supply chain. The tags will not substitute for, replace, or contradict any required barcode or key labeling information;

• ISBT 128-defined data structures, the key to the success of the entire standard, will be used within any RFID-based system. So any change to RFID is primarily a change to the medium used to communicate those data structures—from labels that are scanned with a bar code reader to smart integrated chips that communicate wirelessly in two directions using radio frequency for data transmission.

Some commercial developments have occurred in the past few years to encourage the implementation of RFID. One European company based in Spain provides a three-module (donation, production, transfusion) vein-to-vein solution; each module can be deployed independently and coupled upon request. In one region, about 200,000 RFID-labeled blood components have been processed, stored, and subsequently distributed to hospitals, while in another region, 5,000 transfusions of RFID-labeled blood have occurred with measurable improvements in safety.

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The economics of RFID in blood banking

The business case for utilizing RFID in blood banking is becoming stronger because of three factors: (1) technology costs; (2) business model; and (3) benefits of dynamic data.

Technology costs. Costs of RFID technology components—including readers, RFID labels, software, and system integration—fall as service providers identify common needs and modify product offerings accordingly. The costs of RFID inlays have fallen significantly in the past few years, as other markets have expanded their usage.

Business model. An RFID business case with implementation costs borne by the blood centers with benefits accruing to others downstream will be marginal for the blood center: the hospital benefits cannot be included in the ROI for the blood center. This situation can be addressed by raising the price of the product from the blood center to the hospital; the hospital is able to justify the increase in cost through recognition of the associated benefits. RFID solution providers in transfusion medicine can ensure that product development efforts address the needs of each participant in the value chain.

Dynamic data. Dynamic data refers to the information that can be added to the chip and stored in the user memory—information that is variable, accompanying the unique user identification data that is equivalent to the data stored today in a barcode. The information stored in the user memory can include quality indicators, time and date stamps, and even sensed information such as temperature history. One of the most exciting developments in RFID in recent years has been companion wireless sensors that provide monitored data that can be inexpensively stored on the chip. In parts of the world where the yield in the blood supply can be enhanced by improving temperature control in the supply chain, it is possible to use RFID to store the temperature history for the blood product directly in the user memory.

Other creative applications for dynamic data management will emerge as the technology is developed further and deployed in commercial transfusion medicine applications, increasing value and resulting in more compelling returns on the RFID investment.
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Emerging education program assists cytotechnologists in a changing landscape

By Lynnette Savaloja, MBA, SCT(ASCP), and Jennifer Clark, SCT(ASCP) CM MB

Cytotechnologists are medical laboratory professionals who study human cellular samples for evidence of cancer and other diseases. Perhaps the most well-known part of their professional practice work is the screening of Pap tests. As a fundamental driver of women’s gynecologic health, the Pap test has also been the “bread and butter” and a significant portion of the cytology laboratory test volume for over 60 years. Over the past decade, however, laboratories have seen a decline in Pap test volumes due to changing screening frequency recommendations, increased efficiencies in Pap test throughput as a consequence of new computer-assisted screening technologies, and primary HPV immunizations due to changing screening frequency recommendations, In addition to the decrease in Pap tests, volumes for other more complex cytology tests have increased in many laboratories. Fine-needle aspiration (FNA) and body fluid samples are more complex, requiring more time and evaluation from cytotechnologists. Ancillary tests for these samples, such as immunohistochemistry (IHC) tests, are also increasing and changing rapidly. This will require cytotechnologists to change and expand their skill sets to support these changes in workload. Cytotechnologists, with the support of professional organizations, are coming together to address these anticipated changes.

In 2014, through a memorandum of understanding and in support of the evolving cytopathology profession, a new workgroup, the “ASC/ASCP Workgroup: Focusing on Emerging Roles in Cytopathology,” was named by the leadership of both the American Society of Cytopathology (ASC) and the American Society for Clinical Pathology (ASCP). The collaboration between ASC and the ASCP is designed to help cytotechnologists identify emerging opportunities and strengthen their skill sets to ensure that they continue to be considered an essential part of clinical care teams as the profession evolves.

The ASC/ASCP workgroup is focusing on developing concrete goals toward addressing evolving practice changes while ensuring that education, practice, and trending data support the cytopathology profession’s longevity and livelihood, and supporting new roles for pathologists as cytotechnologists are increasingly expected to engage in the rapidly changing healthcare delivery system. Recognizing that change for cytotechnologists is both evident and inevitable, the workgroup is gathering and triaging information from attendees through the use of focus groups and as needs are assessed across the country. Focus groups were employed as a tool to engage the audience. Small groups of eight to 10 cytotechnologists, representing different career levels, were interviewed by ACE faculty in order to bring concerns and information back to the workgroup to provide further insights into work being done on both the profession’s current and future needs.

A popular feature of the ACE meeting was a platform for selected cytotechnologists to share their real-life stories about how they transitioned into new careers with knowledge of laboratory information systems (LIS), new technology, education, and performing as part of the clinical diagnostic team. Many of the new services and skills needed to extend a cytotechnologist’s scope of practice represent a natural extension of their current professional duties. As a result of the first ACE meeting, other work is being done toward transitioning to an entirely new profession. ASC and ASCP are collaborating on how to redefine education for cytotechnologists for the future.

The ACE meeting will travel around the country to engage professionals where they live and work, as cytotechnologists cannot always travel to national professional meetings. The program content will also be personalized according to the region, in recognition of the fact that different regions may have differing needs. A second ACE meeting will be held May 21-22, 2016, at Loyola University Medical Center in Maywood, IL, which is a suburb just west of Chicago.

Based on the results of a nationwide assessment survey to define cytotechnologists’ needs, ACE 2016 at Loyola is adding workshops in laboratory management and rapid on-site evaluation (ROSE). Respondents also expressed interest in molecular diagnostics, endoscopic ultrasound (EUS), and endobronchial ultrasound (EBUS) assessments and procedures, knowing that an understanding of those procedures improves their performance as part of the clinical care team. Additionally, telepathology was identified as a target for education, as this ever-expanding technology is reaching into more hospitals and care centers. This ACE meeting will be held in conjunction with the ASC Executive Board meeting and will engage many of these board members as faculty. The ACE meeting platform will continue to evolve as more information is gathered from attendees through the use of focus groups and as needs are assessed across the country.

Lynnette Savaloja, MBA, SCT(ASCP), serves as Supervisor of Anatomic Pathology Operations at Regions Hospital, St. Paul, MN. She is also the primary facilitator for the ASC/ASCP Workgroup, and serves as a key planner for the Advanced Cytopathology Education (ACE) 2016 meeting.

Jennifer Clark, SCT(ASCP) CM MB, is ASCP Manager of Curriculum and Learning Strategy and cytotechnologist staff member of the ASC/ASCP Workgroup.
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March is here, the days are getting longer, the snow is gone or going fast, baseball’s spring training has come to Arizona (MLO’s home state) Florida, and here is yet another sure sign of spring: MLO is proud to present the 2016 Annual Salary Survey. Our sincere thanks to all who participated.

Like all surveys, the results of this one are both undeniably useful, and instantly obsolete. They provide a snapshot in time, but time moves on. However, MLO’s survey, which was filled out by about 400 readers in late January and compiled in early February, is about as up-to-the-minute as any you will find. And comparisons between the 2016 results and the 2015 results are especially valuable, since they are suggestive of trends—or, in many cases, of relative stasis with regard to salary and the other aspects of the profession that are covered by MLO’s questionnaire.

Summary of the basics
The average salary as reported by the 2016 survey is $71,491; that is a significant decrease from the 2015 survey figure of $80,985. Since most survey respondents did not report a reduction in salary during 2016, that statistic may seem surprising. However, the changes come from the percentage differences in respondent job functions. In 2015, 56 percent of the respondents were Lab Managers (average salary $81,992), and 17 percent Lab Directors, with an average salary of $82,288. This year’s Lab Manager respondents were just 32.4 percent, and had an average salary $77,707. Lab Directors were six percent of the respondents, with an average salary of $112,114—a considerable increase over 2015.

Perhaps the change can also be explained by the gradual entry of young laboratorians, new to the profession, who are beginning to replace retiring laboratorians. Younger cohorts (in terms of ten-year age spans) were more highly represented in this year’s survey, and that may have brought the salary numbers down. Whatever the reason(s), as you will see in what follows, reported salaries were lower by most measures in 2015 than in 2014.

The average salary for a female in the industry is $69,381 ($75,535 in last year’s survey). The average salary for a male is $81,857 ($96,539 last year). There were significant differences in this area among the regions of the United States (see regional map).

Nearly three-quarters (74.1 percent) of survey respondents are employed by hospital labs. The largest number of respondents (26.7 percent) are associated with labs that have ten or fewer employees. Younger cohorts (in terms of ten-year age spans) were more highly represented (26.7 percent) work in labs with 21 to 50 employees. The highest number of respondents (22.2 percent) are in the 46-to-55 group, compared to 32.7 percent last year. This is slight-

Another major difference is that 53.5 percent of the respondents told us they were hourly this year versus just 30 percent last year. This could be another factor in the average salary differences, as the hourly employees averaged $57,970 a year while the salaried employees average was $87,032 (46.5 percent). In 2015, only 30 percent were hourly, with average wages of $62,337, and salaried employees (69.7 percent) had salaries of $89,100.

Age distribution and comparison
The highest number of respondents were in the 56-to-65 age group—42.5 percent. This is slightly up from last year’s number, 41.7 percent. 22.2 percent were in the 46-to-55 group, compared to 32.7
percent last year. There was an uptick this year in the number of respondents in the 36-to-45 group—17.1 percent, as opposed to 14 percent last year; and 9.6 percent of the respondents were in the 26-to-35 group, nearly double last year’s five percent. The average age fell two years, from almost 55 in 2015 to almost 53 now.

Salary and education
With regard to highest academic degree, 60.2 percent of respondents held a Bachelor’s degree, the same as last year, and their average income was $69,740 ($77,977 last year). 25.1 percent held post-graduate degrees, compared to 30 percent last year, and their salary averaged $88,495 ($83,534 last year). 12.8 percent of surveyed laboratorians held an Associate’s degree, and their salary averaged $48,021. That is more in keeping with common sense than last year’s numbers, which showed Associate degree holders making more on average than Bachelor’s and Master’s degree holders.

Salary by geographic region
• As was the case last year, the Pacific Coastal region comes in as the highest-paying, with an average salary of $92,194 ($103,450 for females, $78,125 for males).
• The average salary in the Mountain states is $74,025 ($70,808 female, $65,500 male).
• In the Central region, the average salary is $69,599 ($66,944 female, $81,442 male).
• In the Northeast, the average is $72,938 ($68,511 female, $88,571 male).
• The Southeast comes in with the lowest average salary, which was also the case last year. This year’s number is $66,160 ($62,778 female, $78,000 male, but had 29 percent more respondents than last year).

Overall, salaries seem to drop as we travel across the nation from west to east, with a little salary recovery in the Northeast. What is genuinely puzzling is that women seem to get paid more than men in the Pacific (by a lot) and in the Mountain (by a little) regions, but men’s pay is higher in the other three regions. Are there economic factors east of the Rockies that cause this disparity? The editors would be pleased to hear from readers who might have theories about this surprising finding.

Increases and benefits
Nearly two-thirds (66.3 percent) of respondents reported a salary increase in 2015, while 31.3 percent said their pay remained the same, and 2.4 percent saw their salaries decrease. Looking to 2016, 18.7 percent do not expect a pay increase; 22.5 percent expect a raise of less than two percent; 44.1 percent expect an increase of two to four percent; and 3.2 percent anticipate an increase of five percent or more.

Benefits continue to be an important part of the compensation package for U.S. laboratorians. 97.6 percent have access to health insurance through their employer, and 93 percent
have a dental option. 90.4 percent have access to a 401k or pension plan. 77 percent have disability insurance available to them. Childcare is available to 5.6 percent of respondents. All of these numbers are close to last year’s, though some are slightly lower.

Length of service
It is still an aging work force, but there seems to be a statistically significant infusion of youth. Nearly half of survey participants—46.3 percent—have been employed in the lab industry for more than 30 years. Another 25.9 percent have served for 20 to 30 years. Nearly ten percent, however, have been in the industry for less than five years. That number was 1.8 percent a year ago.

Just over 36 percent have held a position with their current employer for more than twenty years; 14.2 percent have been with their current employer less than three years. The latter number is up from 10.2 percent a year ago.

Not surprisingly, survey participants who have been in the industry less than three years also report the lowest earnings at $50,893. The biggest earners from this year’s survey are those who have been in the industry for more than 30 years. That number is up from 10.2 percent a year ago.

Continuing education and certification
As in past years, medical technologist (MT) comprises the largest percentage of certifications reported by MLO respondents, at 63 percent. This certification is followed by medical laboratory technician (MLT) at 16 percent; medical laboratory scientist (MLS) at 16 percent, and clinical laboratory scientist (CLS) at 11.7 percent. The strong majority of laboratorians who participated in the survey (82.5 percent) received their certification through the American Society for Clinical Pathology (ASCP); 12.5 percent gained certification from the National Credentialing Agency for Laboratory Personnel (NCALP). Just over ten percent received state certifications.

The 2016 survey reports that more than 47.6 percent of lab professionals took ten or more Continuing Education classes annually. Only 10.7 percent did not take at least one over the course of the year. (That last number represents a mild bump over last year’s number, which was 6.7 percent.)

It’s interesting to note that those participants who did not take any CE classes over the last year made the lowest average salary, $55,075. Those who reported taking more than 20 CE classes reported an average annual salary of $75,196.

Automation, personnel shortages, test volumes, outsourcing
Automation continues to change the landscape of the laboratory and how lab professionals do their job—and the pace increased significantly last year, the survey said. 55.9 percent of respondents said their lab automated or increased automation, as opposed to 46.9 percent a year ago. The fact that labs crossed the 50 percent mark with so much room to spare may be an important signal that momentum is on automation’s side.

As in previous years, the 2015 survey asked participants what impact medical personnel shortages have on their labs. The results were very similar to the 2014 survey. 36.3 percent report a moderate impact, 30.8 percent say low, and 19.8 percent claim a large impact. Only 13.1 percent say personnel shortages had no impact on their lab.

Regarding the important question of test volume: 12.6 percent of responding labs perform more than two million tests annually, and 17.9 percent between one and two million tests. 19.5 percent perform over 1,000,000 tests, and 17.9 percent run 500,000 to 1,000,000 tests. About 24 percent of responding labs run fewer than 100,000 tests.
In 2014, only 8.2 percent of respondents said their lab outsourced more tests than it had before; that number rose to 14.7 percent in this year’s survey—possibly a sign of the shortage of laboratory personnel.

**Security and satisfaction**

The bottom line: despite challenges, the clinical laboratory professionals who responded to the 2016 MLO Salary Survey feel very or somewhat secure in their position (90.6 percent) and are very or somewhat satisfied with their job (85.8 percent). Those numbers are comparable to last year’s results.

We hope those numbers continue to be strong—or stronger—in next year’s MLO Salary Survey!

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**For the sake of comparison: the latest from the OOH**

Back in the day, when hard copy was all there was, the Department of Labor’s annual Occupational Outlook Handbook (OOH) used to anchor the office bookshelves of career counselors across the nation. Now that the OOH is available as an online resource, let’s take a look at what it has to say about some current job statistics and the future forecast for “Medical and Clinical Laboratory Technologists and Technicians” ([http://www.bls.gov/ooh/healthcare/medical-and-clinical-laboratory-technologists-and-technicians.htm](http://www.bls.gov/ooh/healthcare/medical-and-clinical-laboratory-technologists-and-technicians.htm)). The most recent available statistics are from 2014. According to the OOH:

- The median pay for technologists in 2014 was $59,430 annually; the median pay for technicians was $38,370.
- The number of available jobs in the United States was 328,200. That total was almost equally divided between technologist and technician jobs.
- For technologists, about 58 percent of the jobs were in hospitals; 17 percent were in “medical and diagnostic laboratories”; eight percent were in physician offices; and five percent were in academic settings.
- Median annual salaries were highest for hospital-affiliated technologists ($59,530) and lowest for those affiliated with academic institutions ($53,610).
- For technicians, 44 percent worked in hospitals, 19 percent in medical and diagnostic laboratories, 12 percent in physician offices, and five percent in academic settings.
- Annual wages for technologists varied significantly by state, with the Pacific Coastal states, New York, New Jersey, and some states in New England having the highest salaries. California’s annual salary averaged just over $80,000 for technologists.
- The increase in available jobs for 2014–2024 was estimated to be 14 percent for technologists and 18 percent for technicians.
- More than 52,000 jobs (technologists and technicians) were expected to be added during those ten years.

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Lab sales compensation: contexts and considerations

By Peter Francis

Upper management at commercial and hospital outreach laboratories often spends a lot of time discussing compensation for its salespeople. That’s not a surprise; their function is important, and the best can command high salaries. But lab leaders should not make the mistake of thinking that a willingness to pay more will result in greater success. Appropriate compensation is a motivator, but it does not guarantee results. The sales manager’s (or lab manager’s) oversight and the lab’s strategic objectives are also important parts of the equation.

Labs that hire full time field personnel typically offer a bifurcated payment approach: base salary plus variable compensation. Within that generalization, there can be many differences in approach—and many different results.

Here are some common questions and possible answers that seek to shed light on this important topic. Their purpose is not to recommend a particular compensation (comp) plan, but they may provide for thought for those who are creating a new payment system or want to reassess their present one.

What are some common mistakes laboratories make in compensating their sales employees?

One mistake is not being acquainted with the “Rule of 78”—the most widely used formula for devising a 12-month sales comp plan. How does this rule work? Management simply multiplies the expected monthly net revenue (or specific test volume) by 78 to arrive at a twelve-month figure. Starting with the first month of expected new business, each consecutive month adds the same pre-set dollar figure (or test number). Moving from left to right, the monthly columns grow longer by a factor of one, since the previous month figure rolls over in a consecutive fashion. The Rule of 78 provides a framework to calculate how new business relates against a pre-set expectation at any point during the year.

Another mistake is beginning the monthly sales goal immediately after hiring a field rep. With new hires (especially from outside the industry), it may be more prudent to begin the sales target several months after the rep’s start date and then insert a monthly gradient increase up to the desired level.

In conjunction with this, another mistake occurs when sales/ lab managers may set goals too aggressively within their market. If this happens, field reps may soon become dispirited, and spend more time servicing customers than finding new ones.

Some lab leaders err in a different direction by making the compensation plan too much of a cakewalk. For example, if the sales rep has a “combo” role (sales and service), and if there is a substantial variable payment for servicing and maintaining current clients, the rep can easily become complacent by focusing on “howdy-and-cupcake” visits with current clients. I know of one real-life situation that developed into a thorny issue when lab management (after several years) announced a “peddle-to-the-metal/more-new-revenue” initiative. The lab eventually released the rep involved, but not before paying an above-average base salary and commission for unproductive calls.

Should variable compensation plans pay for a specific time-period?

In most situations, labs pay a variable rate for a certain time following new account activation—frequently twelve months. I have witnessed some plans that continue payments for two years, but the commission percentage reduces in Year Two. Paying for specific time periods can depend on the lab’s specialty and philosophy. For example, I know one dermatopathology lab that offers a very competitive base salary. For every account the rep activates, the owner pays $2 a biopsy for the life of the client. While $2 may seem modest, the persistent dollar stream—with no calendar endpoint—accrues rather nicely as more clients continue to activate.

What is an example of payout percentage of new business?

Some labs set a graduated scale based on the monthly volume of new business. As an example, the percentage may be five percent for the bottom tier. The next sales level may be eight percent, and the top echelon of new business for the month may be ten percent. The net revenue associated at these levels varies among organizations. However, to give one example, the bottom tier could be $5,000 to $5,999; the middle tier could be $6,000 to $9,999; and the upper level could be $10,000 or greater. In other cases, a lab may institute a simple two-tier structure: a certain percentage for business that falls below the expected new business goal for the month and a higher percentage if the goal is met or exceeded.

Due to the extra expense and, possibly, the strategic direction, some labs do not pay commission on health fairs and/or nursing homes. Other labs may compensate at a reduced percentage rate.

Is it fair to pay reps a commission if they’re not meeting their quotas?

I think it is fair. This business of laboratory sales is very challenging, and there are certain times when a field representative will not meet his/her quota in any particular month (or at any point collectively during the year). However, it is psychologically important to reward for any activated business, in spite of the fact that it does not meet a certain monthly or yearly watermark.

Should commissions be capped?

No. Capped commissions can breed sales mediocrity—if only from a conceptual standpoint. Even if a representative knows he/she will probably not achieve the capped segment, capping produces a psychological “sales pall.”

Should labs base their incentive pay on activities in addition to new sales?

I’m not in favor of providing additional pay based on the number of visits that a sales or service person may have in a certain timeframe. Upper management typically feels they compensate daily activities through base salary. What needs to occur—and this comes through management oversight—equates to an acceptable balance between efficiency (i.e., activities) and effectiveness (i.e., new business).

For field reps who are strictly assigned to servicing customers, there should be financial rewards for upselling activities.

What about variable comp and upselling activities?

For most labs, upsells are an inherent part of the job and should always be encouraged because they translate to more revenue per client. Some labs separate new accounts from upsells (and pay a greater amount for new accounts); others calculate commissions based on collective sales numbers versus the previous year (i.e.,
no distinction between new and upsell). There are two types of upsells that can be recognized through a commission plan: 1) by a specific test; or 2) by overall volume.

Labs that compute upsell business should average the previous three months’ net revenue (or specific test) when initially reported by the field person and documented as an upsell. This establishes the foundation. Beginning with the first month of the upsell, they subtract the current figure from the calculated base figure, arriving at the true upsell number for each month.

**Should attrition goals be set and a corresponding bonus be paid?**

Yes. Losing business is a real-world occurrence, and reps typically put in time and effort to avoid any losses. The definition of a “lost client” remains a lab administration decision. My definition would be when a client’s current month’s net revenue realizes a 50 percent or greater decline compared to the previous three-month’s average. (Client vacation schedules or other variables must be taken into consideration.) One methodology is to divide the year into quarterly payouts and set specific lost-account financial ranges. As an example: pay a bonus of $800 for the quarter if there was no lost business or up to an average monthly revenue of $2,999; pay $400 from $3,000 to $5,999 average lost revenue; and offer no pay-out if $6,000 or above. The average lost revenue from each account should be applied to the attrition calculation once (i.e., not totaled for the entire quarter).

**In client billing situations, should commissions be paid in relation to bad debt?**

When receivables reach 120 days old and beyond, any commissions that have been generated from that account should be deducted from future sales commissions. While companies naturally want to avoid Accounts Receivable even at 90 days, labs may, nevertheless, pay commission on these tardy-paying accounts. Going much deeper than that uncoils into a win-lose situation in which the marketer wins and the lab suffers.

**Besides the attrition bonus, are there any other sales bonuses laboratories should consider?**

Some labs recognize a salesperson’s business and selling acumen when they sell more than $1 million during a calendar year. They may pay a one-time bonus for achieving such a lofty figure, perhaps on the order of $40,000 to $50,000. Some labs combine a one-time payout with an exotic trip destination.

Another bonus consideration involves a quarterly and/or yearly reward. In addition to paying according to the traditional monthly plan, some laboratories compensate using a flat percentage bonus on all new business that exceeds the goal for any given quarter (or for the entire year).

**Any final comments?**

Commission and bonus plans are intended to help in growing a lab’s business, maintaining its client base, and providing—in some measure—motivation for a salesperson. Additionally, company culture, management practices, and strategic goals will also contribute to how field reps perform. As such, a compensation plan is part of—or a substitute for—ongoing performance-enhancing principles.

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**Peter Francis** is president of Clinical Laboratory Sales Training, LLC, a training and development company dedicated to helping laboratories increase their revenues and reputation through prepared, professional, and productive representatives. He has written extensively on the subject of laboratory sales.

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**What are lab orders costing you?**

By Aaron Harper, MD, and David Novis, MD, FACP

Almost two percent1 of the two billion2 test requisitions that laboratories receive annually lack the basic information that clinical laboratory professionals require to perform laboratory tests (Figure 1). This lack of attention to detail delays therapy and costs the medical community millions of dollars each year. A Q-PROBES study (Q-PROBES are short-term studies that provide a one-time comprehensive assessment of key processes to aid in quality improvement efforts in a laboratory) performed by the College of American Pathologists (CAP) showed that two out of every three of these requisitions fail to specify what tests physicians wanted the laboratory to perform, or even the patient diagnoses that necessitated the testing in the first place. Further, one in every six outpatients arrives at laboratory collection stations without any orders at all.

**Patient consequences**

The CAP study found that laboratory workers sometimes delayed patient testing for upwards of an hour while they tracked down the information that they required to proceed. In one out of every thousand tests, their efforts were unsuccessful and laboratory personnel had to abandon testing. Worse, some hospitals reported that when they were unable to locate the ordering physicians, their staff completed vacant requisitions by “guessing” at what tests they thought the doctor might want them to perform.

**Doing the math**

According to the National Inventory of Clinical Laboratory Testing Services (NICLTS), some seven to eight billion laboratory tests are performed yearly.2 A survey performed by George Washington University School of Public Health determined that, on average, a laboratory requisition contains orders for four tests.3 That means that laboratories process about two billion requisitions each year. Spending as little time as 10 minutes to clarify the 1.8 percent of orders that the Q-PROBES study showed needed clarification would require laboratories to consume more than five million hours of clerical full time equivalents (FTEs). According to payscale.com, with clerical labor values at $13/hour, this results in a waste of approximately $65 million annually.

If you think your hospital has a problem with faulty ordering, it probably does. The Q-PROBES study found that many participants had twice as many defective orders as they expected to have.

**What can you do?**

The good news is that the Q-PROBES authors offered ways to reduce the number of defective orders and the time that laboratory personnel spend to correct them. Here’s what laboratory professionals can do:

1. Implement policies that require caregivers ordering laboratory tests to verify that requisitions are complete.
2. Implement policies that prevent laboratory and hospital personnel from collecting specimens until requisitions contain all essential information.
3. Standardize ordering practices throughout the healthcare community.
4. Add electronic ordering with the laboratory menu to your laboratory’s capabilities.

References available online.

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Lipemia and the CBC, immunohematology results

**Q** What CBC parameters are affected when the specimen is lipemic?

**A** Lipemia in a blood specimen used for clinical evaluation can cause significant interference with obtaining accurate test values. Lipemia creates turbidity of a sample and is a result of the accumulation of lipid particles. High-density lipoproteins (HDL) range in size from 6–12.5 nm, low-density lipoproteins (LDL) range from 20–26 nm, very low-density particles range from 27–200 nm, and chylomicrons from 70–1,000 nm.\(^1\)

The turbidity seen in lipemia is mainly due to the presence of chylomicrons. These large particles create light scatter, resulting in elevated absorbance levels due to the presence of chylomicrons.\(^2\) Large particles can create volume displacement—a period of time, allowing for the natural gravitational separation of cells and plasma, of which the latter is visibly turbid. While it is impractical to visually observe each specimen submitted for the presence of lipemia, one may become aware if certain parameters do not “appear” to be correct, i.e., hematocrit is not roughly three times that of the hemoglobin and/or the mean corpuscular hemoglobin concentration (MCHC) is greater than 36. Those instruments that produce scattergrams may also be a source for review in identifying potential errors within the CBC.\(^3\)

Each laboratory must establish an appropriate policy and procedure to address such situations and provide corrective measures.\(^4\) This should include clear instructions to patients regarding the laboratory’s fasting protocol (fasting eight to 12 hours before the draw) when appropriate. However, when acute lipemic specimens are received, each laboratory must decide what standard practice(s) needs to be in place depending on the methodology used.\(^5\)

—Anthony Kurec, MS, H(ASCP)DLM

**REFERENCES**

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Mid-Valley Hospital located in Omak, WA has an opening in its Lab for a full time MT or MLT.

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Leading the way toward genomic analysis as a key component in clinical practice and prescription

If you were explaining Translational Software to someone who is not familiar with the organization, how would you characterize its primary areas of expertise? What solutions does the company provide for its customers? We are at the nexus of science and technology. Our Chief Science Officer spent ten years at the University of Washington developing databases for drug-drug and drug-gene interactions, and I spent 14 years at Microsoft learning how to make technology accessible. Our goal is to use technology to make the wealth of scientific knowledge that is becoming available simple to use for ordinary clinicians. Today our primary area of focus is in pharmacogenomics, but we have development in progress for other areas such as cystic fibrosis and tumor profiling.

Simply as a definition, what is pharmacogenetics? What will be its role in healthcare going forward? Pharmacogenetics is the study of how genetic variations among individuals affect the efficacy or toxicity of medications. From a practical standpoint, enabling clinicians to understand the role of pharmacogenetics allows them to prescribe drugs more safely and effectively. We are working toward the day when understanding the implications of a patient’s genome is the standard of care for prescribers.

How can genomics data be utilized by clinicians at the point of care? How have advances in recent years made the widespread use of such data more feasible? Today we interject ourselves into the laboratory process to provide a higher level of analysis for the test result. So rather than getting a report with A’s, G’s, C’s, and T’s or a person’s metabolic status, we report clearly what the guidelines are for prescribing specific drugs appropriately for that person’s genotype. Over the past several years, an enormous amount of investment has gone into improving the level of automation in clinical processes. So medical record systems will provide the foundation over time that will enable us to bind this more tightly into the clinical workflow.

Translational Software has developed a proprietary cloud-based platform/PGx portal that integrates genomics-based clinical decision support with laboratory and clinical information systems. Can you tell more about this and its applications? You can think of this as a technical platform and then a set of applications. The technology platform allows us to integrate with any laboratory information management system (LIMS); process inputs from all major genetic testing platforms; analyze the data to understand the patient’s clinically relevant genetic types (genotypes, haplotypes, etc.); and report on the data in a way that is customized to the recipient based upon the clinical context (e.g., cardiologist, psychiatrist, pain clinic, etc.).

The first application that we put in place was pharmacogenetics because we have world-class expertise in-house for providing insight to clinicians. With this in place, we are gradually expanding our knowledgebase and tweaking the technology to address screening for heritable disease, analyzing tumors for relevant targeted therapies, and other areas. So far, the results have been encouraging: expanding the core platform into these areas is significantly easier than building separate purpose-built systems.

How do recent developments advance personalized medicine more generally? What are the leading drivers of personalized medicine today? Innovations in testing technology and techniques are certainly advancing personalized medicine at an accelerating rate. The sheer accessibility of data makes it faster and cheaper to discover or verify new relationships between molecular profiles and clinical outcomes. By far the greatest driver for adopting personalized medicine is cost. If you can avoid re-doing a stent, or causing a major adverse reaction, or reduce an elderly patient’s mental fog to make him or her more manageable, it makes a huge difference in cost—and, of course, in the quality of life for the patient.

Will increasing public awareness of this kind of medicine play a role in its growth in the near future? Does the informed medical consumer have a part to play? It certainly does not hurt when precision medicine is mentioned during the President’s State of the Union address, as it was last year! And now that many treatment centers are actively advertising personalized medicine as a differentiator, it is creating a virtuous cycle of awareness. But realistically, doctors are trained to be conservative, and precision medicine was not a part of the core curriculum of most clinicians practicing today. So informed consumers will pay a role in asking the right questions.

What obstacles to the routine clinical use of genomics and molecular diagnostics still remain? Are reimbursement issues part of the equation? The biggest obstacle in actual practice is integrating with clinical systems so that doctors can order the right test and interpret results from the systems that they are already using. This is a huge area of investment for us. Reimbursement issues are the “Catch 22” that is holding back the industry right now. On the one hand, some payers are holding labs to stringent evidentiary standards, but labs do not have the profitability or the patent-ability that drug companies have, so there is nobody to pay for the clinical trials. This situation is slowly working itself out, but the time that it is taking means a lot of lost opportunities for cost savings and enhancing patient care.
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