CE

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EXECUTIVE SNAPSHOT

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EXECUTIVE SNAPSHOT

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CEO, SunCoast Blood Bank
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“Cancer Moonshot” takes shape with NCI input

In his State of the Union address delivered last January, President Barack Obama asked Vice President Joe Biden to lead a major effort, a “Cancer Moonshot” to find new diagnostics, treatments, and, to the extent possible, cures for the complex of diseases that we call cancer. “I’m putting Joe in charge of Mission Control,” the president said. “For the loved ones we’ve all lost, for the families that we can still save, let’s make America the country that cures cancer once and for all.”

The Obama administration—which has been a good one for scientific research, sometimes in the face of appallingly shortsighted political opposition—will come to an end in a few months. Let’s hope that the next administration continues this valuable work.

Just after Labor Day, the Cancer Moonshot got a shot in the arm when a blue-ribbon panel of the National Cancer Institute (NCI) recommended ten scientific approaches that the project might consider. The list was presented to the vice president’s task force. Among some of its most interesting elements:

• A proposal to create a national tumor profiling network to which patients contribute their data and register for studies based on the profiles.
• A plan to set up a clinical trials network devoted to immunotherapy-based approaches.
• An increased emphasis on testing for hereditary cancers.
• A renewed focus on identifying therapeutic targets to overcome cancer drug resistance.
• The development of new technologies to treat cancer, including implantable devices that deliver targeted chemotherapy.
• Attempts to better understand the role of fusion oncoproteins in pediatric cancer.
• The creation of dynamic 3-D maps of human tumor evolution.

Along with these and other broad approaches, the NCI “road map” includes specific projects. These include “a demonstration project to test for Lynch syndrome, a heritable genetic condition that increases risk of several types of cancer; to improve early detection and prevention; the establishment of a nationwide pediatric immunotherapy clinical trials network to enhance the speed with which new immunotherapies can be tested in children; exploring patient-derived organoids; and “microdosing” devices to test drug responses in living tumors.”

Reading the list, I can’t help but be impressed by the presence of terms that would have had little practical meaning, even for the research community, only a few decades ago: tumor atlases, immunotherapy, drug resistance mechanisms, national [information sharing] ecosystem, fusion oncoproteins and inhibitors, retrospective analysis, 3-D mapping of tumor evolution, genetic lesions and cellular interactions, and tumor characterization.

Comprehensively, the orientation toward genomics and proteomics, molecular diagnostics and precision medicine, and population health management seems strikingly modern. It resonates with the way cancer is being understood now, and creates hope for significant advancements in the near future.

The “road map” also may lend impetus to efforts to win funding from the U.S. Congress to make these big ideas realities. As MLO contributor Larry Altshuler, MD, wrote in the August 2016 issue, referring to the “Moonshot” as well as the administration’s proposed Precision Medicine Initiative, “they are enormous undertakings and will require substantial resources, which may wax and wane depending on the progress observed and the priorities of political leadership” (MLO. 2016;48(8):56). Indeed, will the next Congress, particularly if it remains under Republican control, look with favor on a program championed by a President whom it sought to block at every turn while he was in office? It’s a fair question, particularly in the light of the lack of interest, bordering on downright hostility, that the Republicans have shown toward science in general in recent years. It is to be hoped that politics is put aside, and that the necessary funds are provided for such a worthy project, regardless of the results of next month’s national election. The energy provided by the NCI panel’s list must not be allowed to dissipate.
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Identify EGFR T790M mutation in patients who progress on or after EGFR TKI therapy

- Nearly 2 out of 3 cases of progression with first-generation EGFR TKIs are related to the acquired T790M mutation
- Testing at progression provides the opportunity to identify mechanisms of resistance, including the T790M mutation

TAGRISSO demonstrated efficacy and safety in two clinical trials

- TAGRISSO was researched in two separate, global, Phase II, single-arm, open-label clinical trials in patients with EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy
- A 59% objective response rate (95% CI: 54–64) observed in patients (N=411) who progressed with previous EGFR TKI therapy
- The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%)
- Interstitial lung disease (ILD) was reported in 3.3% of patients and was fatal in 0.5% of TAGRISSO patients
IDENTIFY PATIENTS APPROPRIATE FOR TAGRISSO

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IMPORTANT SAFETY INFORMATION

• There are no contraindications for TAGRISSO

• Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

• QTc interval prolongation occurred in TAGRISSO patients. Of the 411 patients in two Phase II studies, 0.2% were found to have a QTc greater than 500 msec, and 2.7% had an increase from baseline QTc greater than 60 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia

• Cardiomyopathy occurred in 1.4% and was fatal in 0.2% of 813 TAGRISSO patients. Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% of (9/375) TAGRISSO patients. Assess LVEF before initiation and then at 3 month intervals of TAGRISSO treatment. Withhold TAGRISSO if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose

• The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please see Brief Summary of full Prescribing Information on adjacent pages.

TAGRISSO™ (osimertinib) tablet, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14) in the full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSEAGE AND ADMINISTRATION

Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor specimens prior to initiation of treatment with TAGRISSO [see Indications and Usage (1) and Clinical Studies (14) in the full Prescribing Information]. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 4 tablespoons (approximately 55 mL) of non-carbonated water only. Stir until tablet is completely dispersed and swallow or administer through naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube immediately.

UNEXPECTED REACTIONS

QTc Interval Prolongation

TAGRISSO treatment is associated with QTc prolongation. QTc prolongation with signs/symptoms of QTc syndrome has been observed in a small number of patients treated with TAGRISSO.

Increased QTc interval in the presence of baseline QTc greater than 500 msec, or recovery to baseline if QTc is greater than or equal to 481 msec, then resume at 40 mg dose.

Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if QTc is greater than or equal to 481 msec, then resume at 40 mg dose.

If no improvement within 3 weeks Permanently discontinue TAGRISSO.

3 weeks

If improved to baseline LVEF, resume.

If not improved to baseline, permanently discontinue.

3 weeks

Withhold TAGRISSO for up to 3 weeks.

Symptomatic congestive heart failure

Permanently discontinue TAGRISSO.

Rescue at 80 mg or 40 mg daily.

Withhold TAGRISSO for up to 3 weeks.

If no improvement within 3 weeks Permanently discontinue TAGRISSO.

Adverse reactions and laboratory abnormalities observed in clinical trials of TAGRISSO are listed in Tables 1 and 2.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Across clinical trials, interstitial lung disease (ILD)/pneumonitis occurred in 3.3% (n=27) of TAGRISSO treated patients (n=813); 0.5% (n=4) were fatal. Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed [see Warnings and Precautions (5.1) in the full Prescribing Information].

QTc Interval Prolongation

The heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 411 patients in Study 1 and Study 2, one patient (0.2%) was found to have a QTc greater than 550 msec. In Study 1 and Study 2, 71 patients (17%) had an increase from baseline QTc greater than 60 msec [see Clinical Pharmacology (12.2) in the full Prescribing Information].

In Study 1 and 2, patients with baseline QTc of 470 msec or greater were excluded. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO if ILD is confirmed [see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information].

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, pulmonary edema, ejection fraction decreased or stress cardiomyopathy) occurred in 1.4% (n=11) of TAGRISSO treated patients (n=813); 0.2% (n=2) were fatal.

In Study 1 and Study 2, Left Ventricular Ejection Fraction (LVEF) decline >70% and a drop to <50% occurred in 2.4% (95/25) of patients who had baseline and at least one follow up LVEF assessment.
includes cases reported within the clustered terms for rash adverse events: Flash, rash generalized, rash erythematous, rash macular, rash maculopapular, rash papular, rash purpuric, erythema, folliculitis, acne, dermatitis and acneiform dermatitis.

- Includes dry skin, eczema, skin fissures, xerosis.
- Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail rigidity, onycholysis, onycholyis, onychorrhexis, paronychia.
- Includes dry eye, visual blurred, keratitis, cataract, eye irritation, blepharitis, eye pain, lacrimation increased, vitreous floaters. Other ocular toxicities occurred in <1% of patients.
- Includes deep vein thrombosis, jugular vein thrombosis, pulmonary embolism.
- No grade 4 events have been reported.

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with TAGRISSO included cerebrovascular accident (2.7%).

### Table 3 Common Laboratory Abnormalities (≥2% for all NCI CTCAE Grades) in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO N=411</th>
<th>Change from Baseline to Grade 3 or Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>3.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>1.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>44</td>
<td>2.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>3.4</td>
</tr>
</tbody>
</table>

The only grade 4 laboratory abnormality was 1 patient with grade 4 thrombocytopenia.

### Drug Interactions

Drug interaction studies with inhibitors, inducers or substrates of CYP enzymes and transporters have not been conducted with TAGRISSO.

### Effect of Other Drugs on Osimertinib

**Strong CYP3A Inhibitors**

Avoid concomitant administration of TAGRISSO with strong CYP3A inhibitors, including macrolide antibiotics (e.g., troleandomycin), antifungals (e.g., fluconazole), antivirals (e.g., raltegravir), nefazodone, as concomitant use of strong CYP3A inhibitors may increase osimertinib plasma concentrations. If no other alternative exists, monitor patients more closely for adverse reactions of TAGRISSO.[see Dosage and Administrations (2.4) and Clinical Pharmacology (12.3) in the full Prescribing Information].

**Strong CYP3A Inducers**

Avoid concomitant administration of TAGRISSO with strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John’s Wort) as strong CYP3A inducers may decrease osimertinib plasma concentrations.[see Clinical Pharmacology (12.3) in the full Prescribing Information].

### Use in Specific Populations

**Contraception**

Females.

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose.[see Use in Specific Populations (8.1) in the full Prescribing Information].

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO.[see Nonclinical Toxicology (13.1) in the full Prescribing Information].

**Infertility**

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.[see Nonclinical Toxicology (13.1) in the full Prescribing Information].

**Pediatric Use**

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

**Geriatric Use**

One hundred eighty-seven (45%) of the 411 patients in clinical trials of TAGRISSO were 65 years of age and older, and 54 patients (13%) were 75 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggest a higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modifications for adverse reactions (23% versus 17%) in patients 65 years or older as compared to those younger than 65 years.

### Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild (creatinine clearance (CLcr) 50-80 mL/min) or moderate (CLcr 30-49 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with severe renal impairment (CLcr <30 mL/min) or end-stage-renal disease.[see Clinical Pharmacology (12.3) in the full Prescribing Information].

### Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤upper limit of normal (ULN) and AST between 1 to 1.5 times ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with moderate or severe hepatic impairment.[see Clinical Pharmacology (12.3) in the full Prescribing Information].

### 17 Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Intestinal Lymph Disease/Pneumonitis

Inform patients of the risks of severe or fatal ILD, including pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms.[see Warnings and Precautions (5.1) in the full Prescribing Information].

### QTc Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc prolongation including dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications.[see Warnings and Precautions (5.2) in the full Prescribing Information].

### Cardiomyopathy

- **TAGRISSO can cause cardiomyopathy.** Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider.[see Warnings and Precautions (5.3) in the full Prescribing Information].

### Embryo-Fetal Toxicity

- **TAGRISSO can cause fetal harm if taken during pregnancy.** Advise pregnant women of the potential risk to a fetus.[see Warnings and Precautions (5.1) in the full Prescribing Information].

### Lactation

Advis women not to breastfed during treatment with TAGRISSO and for 2 weeks after the final dose.[see Use in Specific Populations (8.2) in the full Prescribing Information].

### Nonclinical Toxicology

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1947 was the year ZIKV was isolated from a sentinel rhesus monkey in the Zika Forest of Uganda.

1953 was the year human illness was first confirmed due to ZIKV infection in Nigeria.

11% of the population in French Polynesia had symptomatic ZIKV infection from October 2013 to February 2014.

80% of individuals with ZIKV infection are asymptomatic, and may transmit the virus sexually for an unknown duration of time, up to six months or longer.

1% of blood collected in 2016 from asymptomatic donors in Puerto Rico tested positive when screened for ZIKV.

58 days is the time period that whole blood had detectable viremia in patients after ZIKV symptom onset when compared to serum.

8.1 million is the number of viral copies per milliliter in serum ZIKV infection in non-pregnant individuals that may be produced, which lasts about one to two weeks, though duration of viremia may be longer.

100% of all donated whole blood and blood components should be tested for ZIKV in the U.S. The FDA advises a blood screening test authorized for use by the FDA under an IND application, or a licensed test when available. Alternatively, an FDA-approved pathogen-reduction device may be used for plasma and certain platelet products.

Zika

FDA advises ZIKV testing for all donated blood and components in United States. As a further safety measure against the emerging Zika virus outbreak, the U.S. Food and Drug Administration (FDA) has issued a revised guidance recommending universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories.

The FDA first issued guidance on Feb. 16 recommending that only areas with active Zika virus transmission screen donated whole blood and blood components for Zika virus, use pathogen-reduction devices, or halt blood collection and obtain whole blood and blood components from areas of the U.S. without active virus transmission. The revised guidance recommends that all states and U.S. territories screen individual units of donated Whole Blood and blood components with a blood screening test authorized for use by the FDA under an investigational new drug (IND) application, or a licensed test when available. Alternatively, an FDA-approved pathogen-reduction device may be used for plasma and certain platelet products.

The FDA has updated its guidance after careful consideration of all available scientific evidence and consultation with other public health agencies, and taking into consideration the potential serious health consequences of Zika virus infection to pregnant women and children born to women exposed to Zika virus during pregnancy. Testing of donated blood had already been underway in Florida and Puerto Rico, as well as in other areas, and it had shown to be beneficial in identifying donations infected with Zika virus. Expanded testing will continue to reduce the risk for transmission of Zika virus through the U.S. blood supply and will be in effect until the risk of transfusion transmission of Zika virus is reduced.

Female mosquitoes can transmit ZIKV to their eggs and offspring. New research reveals that female mosquitoes can pass the virus on to their eggs and offspring, bolstering the need for larvicide use as an integral part of the effort to stop the spread of the virus.

“Now we need to show that vertical transmission occurs in nature,” study co-author Robert Tesh says. To do that, “researchers need to collect larvae in areas where the virus is actively circulating—Latin America and the Caribbean, and now the Miami area. Finding infected larvae in an abandoned tire or water container would be evidence of vertical transmission.”

NIH collaboration helps advance potential Zika treatments. Researchers at the National Center for Advancing Translational Sciences (NCATS) recently identified compounds that potentially can block Zika virus replication and reduce its ability to kill brain cells. These compounds now can be studied by the broader research community to help combat the Zika public health crisis. NCATS is part of the National Institutes of Health (NIH).

Using NCATS’ drug repurposing screening robots, researchers identified two classes of compounds effective against Zika. One is antiviral, and the other prevents Zika-related brain cell death. The compounds include emricasan, an investigational drug currently being evaluated in a clinical trial to reduce liver injury and fibrosis, and niclosamide, a U.S. Food and Drug Administration-approved drug for use in humans to treat worm infections.

In addition, the researchers identified nine cyclin-dependent kinase (CDK) inhibitors. CDK usually is involved in regulation of cellular processes as well as normal brain development, but the Zika virus can negatively affect this process.

NCATS researcher Wei Zheng, PhD, and his team led the drug repurposing screen to test three strains of Zika: Asian, African, and Puerto Rican. The scientists first devel-
opped an assay using caspase 3, a protein that causes brain cell death when infected by the virus. The next step was screening 6,000 FDA-approved and investigational compounds, which resulted in the identification of more than 100 promising compounds. The team then evaluated the protective effect of these compounds in brain cells after Zika virus infection. Three lead compounds, emiracsan, niclosamide, and a CDK inhibitor known as PHA-690509, were identified as reducing neuronal cell death caused by Zika virus infection. These compounds were effective either in inhibiting the replication of Zika or in preventing the virus from killing brain cells. For example, emiracsan prevents cell death, and niclosamide and the nine CDK inhibitors stop the virus’s replication.

NCATS’ screening effort enabled the broader research team to quickly translate its earlier discoveries toward work to develop treatments for Zika virus infection. Johns Hopkins University is working on a mouse model to study the neuroprotective effects of the compounds identified from the screen and studying the mechanism of action of the lead compounds. Florida State University is testing the efficacy of these compounds in a Zika virus mouse model and is also studying the mechanism of action of the lead compounds.

**STIs**

**WHO issues new treatment guidelines for chlamydia, gonorrhea, and syphilis.** New guidelines for the treatment of common sexually transmitted infections (STIs) have been issued by the Geneva, Switzerland-based World Health Organization (WHO) in response to the growing threat of antibiotic resistance. Chlamydia, gonorrhea, and syphilis are all caused by bacteria and are generally curable with antibiotics. However, these STIs often go undiagnosed and are becoming more difficult to treat, with some antibiotics now failing as a result of misuse and overuse. It is estimated that, each year, 131 million people are infected with chlamydia, 78 million with gonorrhea, and 5.6 million with syphilis.

Resistance of these STIs to the effect of antibiotics has increased rapidly in recent years and has reduced treatment options. Of the three STIs, gonorrhea has developed the strongest resistance to antibiotics. Strains of multdrug-resistant gonorrhea that do not respond to any available antibiotics have already been detected. Antibiotic resistance in chlamydia and syphilis, though less common, also exists, making prevention and prompt treatment critical.

When left undiagnosed and untreated, these STIs can result in serious complications and long-term health problems for women, such as pelvic inflammatory disease, ectopic pregnancy, and miscarriage. Untreated gonorrhea and chlamydia can cause infertility in both men and women. Infection with chlamydia, gonorrhea, and syphilis can also increase a person’s risk of being infected with HIV two- to three-fold. An untreated STI in a pregnant woman increases the chances of stillbirth and newborn death.

**Ebola**

**Ebola virus lingers longer than expected in semen.** Initial data from a Liberian public health program show about nine percent (38) of 429 male Ebola survivors had fragments of Ebola virus in their semen. Of those, 83 percent had semen samples that tested positive for Ebola fragments a year after recovering from the disease and, in one man’s case, at least 565 days after he recovered. Men older than 40 were more likely than younger men to have a semen sample test positive.

The report provides preliminary results from Liberia’s Men’s Health Screening Program (MHSP), the first national semen testing program for Ebola virus. It is the largest analysis to date to look at Ebola virus persistence in male survivors. The tests detect Ebola virus genetic material but cannot tell if live virus is present and capable of spreading disease.

As part of the Liberia MHSP, male Ebola survivors ages 15 and older can enroll and have their semen tested monthly. Men receive counseling on safe sex practices and receive condoms at each visit. Men who have two consecutive negative semen tests “graduate” from the program.

The potential role that sexual contact could play in sparking new outbreaks of Ebola in West Africa came to light in March 2015 when a woman from Monrovia, Liberia, became ill with Ebola and died. The nation had been declared free of Ebola at the time, and the woman’s only known exposure to Ebola was through unprotected sexual intercourse with an Ebola survivor. The man’s semen was tested and found to be positive 199 days after he first became ill with Ebola. Genetic analysis showed that the infections of the man and woman closely matched each other.

Scientists have long known that Ebola virus can survive in certain sites within the body that the immune system may have trouble reaching, including the testes and eyes. This report provides new understanding of how long virus fragments can persist in the body. It also is shedding light on the individual differences in the length of time that traces of Ebola can remain in survivors’ semen.

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**Drugs of Abuse**

**FDA announces Opioids Action Plan.** After an extensive review of the latest scientific evidence, the FDA has announced it is requiring class-wide changes to drug labeling, including patient information, to help inform healthcare providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines.

Among the changes, the FDA is requiring boxed warnings—the agency’s strongest warning—and patient-focused Medication Guides for opioid analgesics, opioid-containing cough products, and benzodiazepines (nearly 400 products in total), with information about the serious risks associated with using these medications at the same time. Those risks include extreme sleepiness, respiratory depression, coma, and death.

The actions are among a number of steps the FDA is taking as part of the agency’s Opioids Action Plan, which focuses on policies aimed at reversing the prescription opioid abuse epidemic, while still providing patients in pain access to effective and appropriate pain management.

Given the importance of reaching healthcare professionals and the public with information about the risks of using these products together, the FDA also issued a Drug Safety Communication. Through the Drug Safety Communication and by requiring patient Medication Guides, the agency also provides information for anyone who is taking, or who knows someone taking, either of these types of medications and encourages them to better understand the risks of taking them together; and, when it is medically necessary, for healthcare providers, to remind them to be careful to prescribe them as directed, without increasing the dose or dosing frequency for either drug.

The FDA’s data review showed that physicians have been increasingly prescribing opioids and benzodiazepines together, and this has been associated with adverse outcomes. The agency reported from 2004 to 2011, the rate of ED visits involving non-medical use of both drug classes increased significantly, with overdose deaths (from taking prescribed or greater than prescribed doses) involving both drug classes nearly tripling during that period.

Additionally, the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41 percent between 2002 and 2014, which translates to an increase of more than 2.5 million opioid analgesic patients receiving benzodiazepines.
Perfecting the art and science of transfusion safety

Zika reminds us all how high the stakes are.

By Sam Rose, PhD, and Jeff Linnen, PhD

In recent years, blood testing has become increasingly concentrated in large laboratories located near airports to better manage blood specimen transportation and permit efficient use of multiple testing instruments and computerized systems for identification and test result management, enabling faster donation-to-result turnaround time. Commercial automated instrumentation is used to perform high-throughput testing of the plasma or serum portion of donations. Results of the testing are communicated back to the collection center, and if the testing is negative, the blood or blood fractions/components are released for transfusion. This combination of sensitive testing technology, automation to improve efficiency and reduce the likelihood of human error, and quality systems has now reduced the possibility of viral transfusion-transmitted infections (TTIs) to about one transfusion per million in the U.S.3 Collections of platelets obtained from apheresis are tested for bacterial contamination by culture, normally started within 24 hours of collection. In contrast, whole blood-derived platelets are typically tested with immunoassays.

New infectious disease threats

Like other viral outbreaks before it, the recent Zika virus outbreak has demonstrated the importance of researchers, healthcare experts, governments, and industry working together on epidemiological surveillance, biological research, development, and implementation of tests that use the most advanced screening technologies. These are all essential to tracking and controlling the spread of the disease, and they serve as models for addressing future threats.

Zika

Zika virus (ZIKV) was unknown in the Americas until May 2015.1 It was first identified in 1947 in a rhesus monkey in the Zika forest of Uganda2 and it is transmitted by Aedes mosquitoes. The virus is closely related to other viruses in the family Flaviviridae such as West Nile, dengue, and yellow fever. Sporadic cases in Africa and Asia were reported before an outbreak occurred in Micronesia in 2007. The virus spread to French Polynesia and New Caledonia in the Pacific Ocean.3 It may have entered Brazil in 2014. The first locally transmitted cases were reported in that nation’s northeastern region in 2015.4 The World Health Organization declared the outbreak a global public health emergency on February 1, 2016. ZIKV infections are often asymptomatic. In the early incubation period, blood donors may feel well enough to donate.5 In contrast to related arboviruses, ZIKV infection carries a risk of microcephaly, fetal loss, and additional adverse outcomes in babies born to mothers infected during pregnancy.6 There is also growing evidence of risk for Guillain-Barré Syndrome in infected adults,7 although that appears to occur at low incidence.

Dedicated manufacturing steps in plasma fractionation—such as solvent-detergent, caprylate or heat treatment and nanofiltration—have the capacity to destroy or eliminate pathogens with

continued on page 14

Testing today

In the U.S., donated blood is tested for infectious disease according to guidance issued by the Food and Drug Administration (FDA). The blood is tested by both immunoassays (IA) and nucleic acid tests (NAT) for the viruses HIV-1, HIV-2, HBV, and HCV. Testing for some infectious agents uses only NAT-based assays (West Nile Virus) or uses only immunoassays (HTLV-I and II, syphilis). A limited number of donations are screened for cytomegalovirus (CMV) antibodies to meet the needs of a select subset of patients for CMV-negative blood products in any particular region.

For more than 75 years, blood banks and transfusion centers have been dramatically increasing the safety of blood transfusions. Through better donor and donation screening, automation of laboratory testing, and commercial introduction of pathogen reduction technology for blood components, the risk of transfusion-transmitted viral infections in the United States has been reduced to nearly zero today.1 Transfusion medicine professionals have perfected the art of staying keenly focused on safety while simultaneously adapting to new methods, requirements, challenges, and best practices.

This review is primarily focused on recent advances relating to laboratory screening of whole blood donations for transfusion-transmissible pathogens. It is important, however, to mention the fundamental and continuing need for blood banks to apply appropriate donor questioning and testing (e.g., blood pressure, hematocrit, body temperature) prior to collection.

In addition, blood banks, hospital transfusion centers, and other healthcare professionals overseeing transfusions must adopt rigorous quality systems as part of a coordinated hemovigilance program covering the whole transfusion chain—from blood collection centers to blood banks to the transfusion itself. These quality systems and best practices are the foundations that allow the technical advances to shine. Without them, the contribution of advanced technologies will be compromised.2

Continuing Education

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:
1. Discuss the advances of blood donor viral-transmitted disease testing in the U.S.
2. Describe the Zika virus in terms of demographics, disease transmission, and current donor testing.
3. Describe hepatitis E virus in terms of demographics, disease transmission, and current donor testing.
4. Describe Babesia infection in terms of demographics, disease transmission, and current donor testing.
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Flaviviridae characteristics. But experts are still investigating whether the virus is transmissible through whole blood transfusion. This past summer, blood banks in suspected endemic areas (Puerto Rico, Hawaii, and Florida and other Southern states) began using investigational NAT tests to screen whole blood and blood products for Zika virus. Two NAT blood donor screening assays have been approved by the U.S. FDA under an Investigational New Drug (IND) application.

On August 26, 2016, the FDA revised its initial guidance, advising testing for Zika virus in all donated blood and blood components in the U.S. The revised FDA guidance does not apply to source plasma, which is used for further manufacture of plasma-derived products. Viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of Zika virus.

Experts continue to investigate many aspects of Zika infection; among other questions, they are seeking answers to the following:

• What is the course of ZIKV infection from time of exposure (mosquito bite) to viral clearance, and how does that differ in males vs. females and with regard to pregnancy, age, state of health (especially regarding the immune system), etc.?
• What factors predispose a threat to pregnancy, or the onset of Guillain-Barre Syndrome?
• What is the etiology of ZIKV regarding microcephaly and Guillain-Barre paralysis? Are there other (neurological) complications?
• How does ZIKV distribute itself in tissues, including cells/plasma of the blood? Are these fractions equally infectious regarding TTIs?

Two Zika screening assays currently available under IND

Although there is no FDA-licensed test for Zika virus, testing for Zika became available through two separate Investigational New Drug (IND) applications for blood collected in Puerto Rico and mainland United States. The tests became available on April 3, 2016 (Roche Molecular Systems, Inc.), and June 20, 2016 (Hologic, Inc./Grifols):

• Procleix Zika Virus Assay. The Procleix Zika Virus Assay was developed as part of a partnership between Hologic and Grifols. Procleix systems are currently used to screen blood donations around the world, and include tests for HIV, hepatitis, West Nile virus and other pathogens. The assay runs on the Procleix Panther system, which automates all aspects of nucleic acid testing (NAT)-based blood screening on a single, integrated platform and eliminates the need for batch processing.

• cobas Zika test. Manufactured by Roche, the cobas Zika test is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The cobas 6800/8800 Systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the cobas 6800/8800 software, which assigns test results for all tests as non-reactive, reactive, or invalid.

as of September 12, 2016

• Does immunity happen “normally” in healthy people after infection? How does that differ in those with compromised immunity, and is immunity life-long? Is immunity protective for all serotypes/genotypes of ZIKV? Are all tissues of the body truly sterile of ZIKV after a full immune response?
• And equally important, what are the next infectious disease threats for the safety of the blood supply? How do we best perform surveillance to anticipate these threats?

Hepatitis E

Hepatitis E virus (HEV) has been known as a transfusion-transmissible agent since the early 2000s, and TTI of HEV has been documented in several countries. Though usually a self-limiting illness, in susceptible populations HEV infection can cause serious disease including fulminant hepatitis and death. Transfusion recipients who have compromised immune systems (e.g., cancer patients undergoing chemotherapy) or patients with pre-existing liver damage are at risk. Pregnant women are also at elevated risk for severe disease.

Active infection for HEV, as analyzed using NAT testing for viral RNA, is found at varying frequencies in donor populations around the world. A recent study has shown that HEV RNA appears to be relatively rare in the U.S. donor population. Presently the only countries screening donors for HEV RNA are Japan (in Hokkaido), Spain, and Ireland. There have been recent discussions at transfusion safety expert meetings and in published editorials discussing comprehensive HEV RNA screening of donated blood. Consideration has also been given to maintaining HEV RNA-screened blood and blood fractions in quantities sufficient for recipients at risk, such as the immunosuppressed.

Babesia parasite

Babesiosis is caused by protozoan parasites that replicate within red blood cells (intraerythrocytic parasites). It is transmitted to humans by Ixodid ticks taking a blood meal. Humans are an incidental host; the usual hosts of the ticks are primarily rodents, and often the white-footed mouse.

In the U.S., infection by Babesia microti has been considered an emerging infectious disease, with an increasing number of cases reported annually. Most infections occur in the Northeast and upper Midwest states, which is the normal geographical range of Ixodes scapularis. The incidence of infection outside of these regions is lower but not unknown, and often caused by other species (Babesia duncani or Babesia divergens). Outside of the U.S., human infections caused by Babesia venatorum have been documented. Infections can be asymptomatic; thus donors can be unaware of an infection and pass normal screening. Babesia is the most frequent infectious cause of transfusion-transmitted mortality in the U.S. Between 1979 and 2009, more than 159 transfusion infections, resulting in multiple deaths, have been recorded. Investigational tests are currently being used in the U.S. to screen blood donors for Babesia using NAT and immunodiagnostic technology. This screening is currently targeted at those areas endemic for Ixodes ticks and cover a portion of blood donations.

Conclusion

Huge strides in interdicting infected blood donations have greatly improved the safety of the blood supply in the U.S. There is no doubt that in the next 75 years, scientific advances will reduce the residual risk even further.
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BLOOD BANKING

continued from page 14

REFERENCES


1. The continued increase in safety of blood transfusions has led to a risk reduction of viral transfusion-transmitted infections down to nearly:
   a. five percent.
   b. three percent.
   c. zero percent.
   d. none of the above

2. Maintaining quality transfusion systems and following best practices are important components that allow the technological advances in the safety of blood transfusion to thrive:
   a. True
   b. False

3. Which regulatory agency issues guidelines for disease testing on donated blood components?
   a. FDA
   b. JOAHO
   c. AABB
   d. EPA

4. All donated blood components are tested for CMV antibodies:
   a. True
   b. False

5. Testing methodologies for detecting viral-transmitted diseases in blood components include:
   a. immunoassays and precipitation methods.
   b. immunoassays and nucleic acid tests.
   c. nucleic acid tests and agglutination methods.
   d. nucleic acid tests, agglutination methods, and immunoassays.

6. To allow a fast donation-to-test result turnaround time, large component testing laboratories have become concentrated near:
   a. blood centers.
   b. hospitals.
   c. airports.
   d. train stations.

7. Collections of platelets obtained from apheresis are tested for bacterial contamination by:
   a. culture.
   b. NAT testing.
   c. immunoassays.
   d. agglutination methods.

8. The Zika virus was unknown in the Americas until:

9. What is the route of the Zika virus’s disease transmission to humans?
   a. food-borne
   b. mosquito
   c. droplet transmission
   d. none of the above

10. What are the symptoms of the Zika virus in individuals in the early incubation period?
    a. asymptomatic
    b. vomiting and diarrhea
    c. fever, cough, congestion
    d. none of the above

11. The FDA has approved two nucleic acid tests for donor screening of the Zika virus under an Investigational New Drug application.
    a. True
    b. False

12. The FDA has advised the testing of individual donations for Zika virus to occur in which areas in the U.S.?
    a. only the Southern states
    b. only the Midwestern states
    c. all 50 states
    d. wherever local outbreaks occur

13. What populations are most susceptible to the hepatitis E virus (HEV)?
    a. immunocompromised individuals
    b. patients with preexisting liver damage
    c. pregnant women
    d. all of the above

14. Currently, which countries use NAT testing for detecting HEV?
    a. Japan, Spain, and Ireland
    b. Japan, Germany, and Ireland
    c. Ireland, South Africa, and Spain
    d. Spain, Germany, and South Africa

15. Blood donor safety experts have been in discussion about keeping a reserve of screened HEV blood donor units available for recipients who are at greatest risk.
    a. True
    b. False

16. Where do most infections of Babesiosis occur in the U.S.?
    a. Northeastern states
    b. upper Midwest states
    c. both a and b
    d. none of the above

17. Babesia infection exhibits a multitude of symptoms and can therefore be identified in the donor screening process.
    a. True
    b. False

18. Babesia infection is transmitted to humans from:
    a. a tick
    b. food
    c. a mosquito
    d. none of the above

19. What type(s) of investigational tests for Babesia are currently being used to screen blood donors in the U.S.?
    a. NAT
    b. immunodiagnostic
    c. culture
    d. both a and b

20. What is the rate of asymptomatic Babesia infection among human donors?
    a. 5%
    b. 3%
    c. 2%
    d. 1%

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Can the type of blood collection tube used be a source of lab error?

O

t the clinical experts

I am a supervisor of a health and wellness center and am responsible for collating lab reports on specimens sent to a reference laboratory. On some reports, results are marked as NSA (not suitable for analysis)—for example, glucose levels on specimens collected in SST tubes. What are some reasons why this would occur?

It has been reported that up to 70 percent of laboratory medical errors occur during the pre-analytical phase of patient testing.1 The majority of errors are due to physical issues such as ordering the wrong test, improper preparation of the patient, mislabeling the blood collection tubes, or drawing blood from the wrong patient. Most laboratories have attempted to resolve these issues through specific quality management practices.

Additionally, some laboratory results can vary due to physiological factors such as exercise, diet, stress, posture, age, and gender.2 Other factors that influence results may include tobacco use, alcohol abuse, and serum/plasma samples that are turbid (hyperlipemia), icteric (elevated bilirubin), hemolyzed (poor blood collection technique), short draws, and clotted tubes.1,2

Another source of potential error that has been identified is more of a mechanical issue and is rarely considered a problem: the type of blood collection tube. Prior to 1990, glass collection tubes such as heparin, sodium citrate (blue), SST (red/gray or gold), non-additive tube (red), heparin (green), EDTA (lavender), and ACD (yellow)4 were commonly used. Glass tubes were made from soda-lime or borosilicate, making them resistant to shock impacts and enhanced minimization breakage and exposure to biohazards and enabling better resistance to shock impacts and enhanced tolerance to centrifugation speeds.5 One such tube that is used in most laboratories is the serum-separator tube (SST).

SST serum-separator tubes use a gel material with a clot activator that forms a barrier between serum and red blood cells. The clot activator consists of silica particles that coat the wall of the tube, which has to be mixed thoroughly for activation.

Recommended collection process is to invert the tube five (5) times (180° inversion and return X 5), allow to sit for thirty (30) minutes, and then centrifuge at 1,000-1,300 relative centrifugal force (RCF) in a swing bucket for ten (10) minutes.7 An SST specimen should be centrifuged within two (2) hours after collection.6

To achieve accurate test results, good blood collection technique is essential. This means performing a clean phlebotomy and drawing tubes in the proper order of anticoagulant: blood culture, sodium citrate (blue), SST (red/grey or gold), non-additive tube (red), heparin (green), EDTA (lavender), and ACD (yellow).4 Additionally, the tube must be filled to its designated volume in an upright position, inverted completely and the proper number of times, and centrifuged in a timely fashion.

In addressing the specific query regarding glucose testing, more information is needed to resolve specific events (physical, physiological, or mechanical) that may contribute to “unsuitable” specimens.6

However, it should be noted that in a recent, small study, blood was collected in three types of tubes (red-top serum separator tubes, gray-top fluoride tubes, and green-top heparin tubes) and measured for glucose.3 The investigators found that the least variation in results occurred with the red-top separator tubes. Studies by one manufacturer showed that there were no clinically significant differences when comparing collection tubes for most routine chemistry tests.7,8

Manufacturers of blood collection tubes have done their best to minimize potential interfering materials from collection tubes that may be incorporated during the blood collection. Yet laboratorians should be aware that spurious interferences may be present and that each laboratory is ultimately responsible for evaluating equipment and developing normal reference ranges.

Careful evaluation of how specimens are collected, centrifuged, stored, and transported should be considered. Further, open communication between the facility staff and the laboratory staff should be pursued to ensure best patient outcomes, minimize unnecessary costs, limit the need to redraw patients, improve laboratory productivity, and decrease testing turnaround time.

REFERENCES:

Editor’s note: Anthony Kurec, MS, H(ASCP)DLM, is Clinical Associate Professor, Emeritus, at SUNY Upstate Medical University in Syracuse, NY. He is also a member of the MLO Editorial Advisory Board.
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Sinc it was first described in 1948 by Hartert in Heidelberg, Germany,1 “thrombelastographie,” a method of measuring the viscoelastic properties of a blood clot during its formation, has evolved significantly. In the early 1990s a modified thromboelastograph system was developed in Munich, Germany. Later termed “rotational thromboelastometry” or “ROTEM,” the test was made simpler to operate and to interpret, which allowed the device to be used in a broader range of clinical settings. The testing could now be performed more easily by clinicians in an emergency or decentralized laboratory setting and remotely deliver results more rapidly and reliably to the point-of-care location. These results, in conjunction with other laboratory assays, can be helpful for guiding therapeutic intervention during acute bleeding events.

Benefits of thromboelastometry
The benefits of implementing thromboelastometry for the management of perioperative bleeding are multiple. Diagnostic performance, safety, efficacy, and cost-effectiveness have all been shown to be improved by using a goal-directed therapy that includes thromboelastometry-guided protocols as opposed to conventional laboratory testing alone. These benefits were previously described in detail in MLO7 and in several other publications.8-5

Thromboelastometry, in combination with other laboratory assays, improves diagnostic performance by delivering additional information more quickly and therefore can help guide therapeutic intervention more quickly. According to Haas et al, the turnaround time of thromboelastometry results is significantly shorter (15 to 20 minutes) than that of conventional laboratory results (45 to 60 minutes).4 Since the remote display provides visualization of real-time clot development, clinicians can then assess the different phases of clot development as they occur and treat deficiencies accordingly. Rapid assessment of clot initiation, propagation rate, and clot firmness is critical to determine appropriate treatment of severe bleeding and can be delivered to any point-of-care location regardless of where the actual testing is performed. Using well-designed algorithms that are guided by thromboelastometry has been shown to be clinically efficacious and can increase patient safety and improve outcomes.7-4 Thromboelastometric measurements have been shown to be predictive of the need for massive transfusion,8 and protocols that include thromboelastometry-guided therapy can help prevent massive transfusion. Likewise, these protocols can help improve patient outcomes by guiding hemostatic therapy and avoiding unnecessary transfusions as well as the deleterious effects of allogeneic blood transfusions.7-5 Thromboelastometric analysis and guided therapy has also been shown to be able to predict and help prevent thromboembolic events.7-9

The ability of thromboelastometry to predict bleeding and risk of thrombosis and confirm hyperfibrinolysis and the need for activating a massive transfusion protocol (MTP) allows for faster intervention. Therefore, protocols that include thromboelastometry can then aid by stopping microvascular bleeding quickly and avoiding massive transfusion and thrombosis at the same time.7-9

The financial benefit that an established bleeding management program can provide to a hospital system can be significant. Thromboelastometry has been shown to be an important tool to reduce the primary costs of blood products within hospitals.7,31-35 In addition to primary acquisition costs of the blood products, activity-based costs of blood transfusion and secondary costs of complications related to allogeneic blood transfusion have to be considered.7,34,35 Thromboelastometry has also been shown to reduce the incidence of transfusion-related adverse events and accordingly may reduce corresponding hospital costs. Reducing these secondary costs of blood may even exceed the cost-savings for blood transfusion requirements themselves and improve patients’ clinical outcomes.

It is important to note that the results from thromboelastometric analysis should not be the sole basis for a patient diagnosis and treatment. These results should be considered along with a clinical assessment of the patient’s condition and other coagulation laboratory tests.

Evidence and recommendations
A recent search revealed well over 1,000 publications on thromboelastometry and showed a broad range of clinical and research applications. The main body of evidence involves publications on research and application in the traditional clinical settings of cardiac surgery, liver transplantation, and trauma. There is, however, an increasing interest in researching and applying thromboelastometry in the areas of OB hemorrhage, neurosurgery, spine surgery, and critical care medicine, and we now better understand the coagulopathies common in these settings. As such, physicians are increasingly using thromboelastography (TEG) and ROTEM-guided protocols to help manage hemostatic derangement outside of the traditional areas.

Guided protocols that include thromboelastometry testing are moving closer to becoming the standard of care for bleeding management in the United States. The European Society of Anesthesiology has already given its grade of strong recommendation based on solid evidence that thromboelastometry should be included in perioperative bleeding management protocols since 2013.8 In 2015, the American Society of Anesthesiology published an update to practice guidelines for perioperative bleeding management8 which included recommendations for the use of bleeding algorithms, goal-directed therapy, and the use of TEG or ROTEM when available. Also, in 2015, The American College of Surgeons published specific guidelines for the use of TEG or ROTEM for massive transfusion protocol management.20

Meeting the new quality standard: IQCP
Prior to Individualized Quality Control Plan (IQCP) adoption, Equivalent Quality Control (EQC), QSA.02.04.01.2 was the available option when determining the required frequency of external controls. As of 2003, a reduced frequency of external QC was allowed if the instrument’s design included internal monitors. As an example, the integrated system function checks monitor the optical and electromechanical components of the ROTEM device and, therefore, it qualified for EQC option 2. Without such features, under CFR 42, Section 493.1269, a lab had to test two levels of external QC each day a non-waived test was run, and coagulation tests fell under even a more stringent criterion, requiring QC every eight hours of patient testing. Regardless, EQC remained controversial. Thus, laboratory professionals, along with government officials and industry, joined to determine the best patient-focused approach to QC. The outcome was IQCP. Prior to full adoption, laboratories were allowed to continue with EQC, option 2, a full two years before the mandated IQCP deadline of Jan. 1, 2016. This grace period provided professionals an
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LAB MANAGEMENT
HEMOSTASIS
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t opportunity to evaluate IQCP and the widely accepted Clinical Laboratory Standards Institute (CLSI) standard, EP 23.

IQCP: The new standard
To facilitate IQCP implementation, CLSI developed a risk-based method for determining QC procedures and frequency. CLSI EP 23, Laboratory Quality Control Based on Risk Management. IQCP is designed to assess hazards and failure modes, evaluate those risks, and identify the control mechanisms that mitigate those risks. Fortunately, the clinical laboratory was already practicing many components of IQCP but assimilating all the quality parts had not been required prior to Jan. 1, 2016.

While IQCP is mandated for a broad range of in vitro diagnostic tests and assays, each device from a particular manufacturer has unique features as part of its integrated quality system. Because of this, these authors have the expertise to describe the specific features of the ROTEM device that allow for implementation into a laboratory’s IQCP program.

The developer of the ROTEM evaluated the instrument design against the CLSI EP 23 standard. The evaluation resulted in a full risk assessment template which is provided to users developing their ROTEM-specific IQCP.

The Risk Assessment outline of the ROTEM device includes all phases of testing: pre-analytic, analytic, and post-analytic.

Within each phase the following aspects of risks are evaluated:
- Specimen Integrity/Acceptability
- Environmental Impact
- Reagent and QC Stability/Integrity
- Function of Test System
- Testing personnel Training and Competency

Furthermore, the QC Plan includes practices, resources, and procedures that control the quality of the test process. The reliability and accuracy of tests result in a patient-focused approach to QC. The IQCP template for the ROTEM is a synthesis of the engineering, internal, and procedural control features, submitted as recommendations to consider during the risk assessment period. The device’s design lends itself to offset risk using a simple 3 factor approach formula, Risk (SEV*COC *Q-DET), supported by Westgard JO. Six Sigma Risk Analysis. This quantitative method focuses on detect rates and estimation of the number of potentially impacted patient results, using a scale of 0-2.

The lab determines the severity of harm and the estimated occurrence rates. A high score of “2” in each category is easily offset by detectability. Since the software and hardware of the device integrate many mitigating risk features, users achieve an overall low score and can choose to continue a weekly external/liquid QC evaluation or the 30-day QC evaluation. They also can create Quality Control Plans (QCPs) in order to measure unacceptable risks. Control mechanisms are implemented to mitigate failure modes while simultaneously determining the acceptable level of risk reduction. The goal is to ensure accuracy and reliability in patient testing. Examples include:
- Controls: Type, number, and frequency
- Criteria for acceptable QC results, e.g., electronic and procedural controls as well as training and competency assessments.

Finally, once the IQCP’s initial risk assessment and QCP are complete, labs implement an ongoing monitoring protocol. Ultimately, the lab must determine if the IQCP is working to mitigate risk or not. In doing so, each lab integrates its skill sets and device knowledge. The ROTEM device offers an IQCP solution that facilitates IQCP structure while continuing to address the Quality Control Plan and ongoing Quality Assessments required by accrediting agencies.

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22. CFR, Title 42, Chapter IV, Part 493, Subchapter K, Section 493.1269 (d)(3).
The PD-L1 IHC 28-8 pharmDx interpretation training is a comprehensive online program focused on helping pathologists:

- Understand the role of immune checkpoint pathways
- Learn about technical considerations for optimal slide staining results
- Learn how to evaluate non-squamous NSCLC or melanoma specimens stained with PD-L1 IHC 28-8 pharmDx

Introducing e-Learning for PD-L1 IHC 28-8 pharmDx.

Intended Use
For in vitro diagnostic use

PD-L1 IHC 28-8 pharmDx is a qualitative immunohistochemical assay using Monoclonal Rabbit Anti-PD-L1, Clone 28-8 intended for use in the detection of PD-L1 protein in formalin-fixed paraffin-embedded (FFPE) non-squamous non small cell lung cancer (NSCLC) and melanoma tissue using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression is defined as the percentage of tumor cells exhibiting positive membrane staining at any intensity. PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO® (nivolumab). Positive PD-L1 status as determined by PD-L1 IHC 28-8 pharmDx in melanoma is correlated with the magnitude of the treatment effect on progression-free survival from OPDIVO®.

Discover e-Learning at dako.com/us/PDL1288-learning
What is a platelet? The anatomic definition of a platelet is well established: According to MedicineNet.com, it is an irregular, disc-shaped element in the blood that assists in blood clotting. During normal blood clotting, the platelets clump together (aggregate). Although platelets are often classed as blood cells, they are actually fragments of large bone marrow cells called megakaryocytes. This definition, however, does not do justice to our rapidly expanding understanding of the platelet’s roles, functions, and laboratory applications.

What the numbers say
Labs with the ability to detect platelet function defects still tend to focus on identifying the two percent of the population that have heritable platelet function defects and von Willebrand Disease. The Scientific and Standardization Committee (SCC) of the International Society on Thrombosis and Hemostasis (ISTH) has published comprehensive guidance on the diagnosis of these inherited platelet function disorders. However, most laboratories don’t have all the listed resources to follow this guideline through the second of three tiers of testing.

The Centers for Disease Control and Prevention’s (CDC) Registry for Blood Disorders data quantifies, with caveats, the reported annual rate of diagnosing patients with heritable platelet function disorders and von Willebrand Disease (vWD, types 1, 2, and 3 for purposes of this article). Those patients are likely to be referred to one of the 135 specialty centers (U.S. Hemophilia Treatment Centers Network) for care once identified. Based on self-reported data from these centers for 2012 through 2015, an average of 1,699, or about 13 patients per year per treatment center, are identified with heritable platelet function defects, and 49 percent of those patients are or become multi-year patients.

The three most common types of vWD are identified at a reported annual rate of about 5,118 cases or about 38 patients/year/center. About 52 percent of the vWD patients are or become multi-year patients.

What the lab can do
Therefore, we should largely forget what we think we know about the impact of most heritable platelet function defects on laboratory resources which are needed solely for detecting and diagnosing these dysfunctions. Instead, we should look at what the laboratory can do today, with established technologies, that will support multiple clinical specialties, improve patient care and outcomes, and provide the basis for the next generation of medical care—precision medicine. In other words, how can labs add critical value to the care process?

Platelets have critical roles in a number of basic physiologic processes. Hemostasis is one such process. Thrombosis is another. Others include inflammation, innate (natural) immunity, adaptive (acquired) immunity, tumor growth and metastasis, and the development of the lymphatic vessels. (It is likely that platelets have other roles which are not yet known.)

Platelet signaling is a multi-level, complex process involved in all their roles and functions. This signaling can result in the inhibition of highly specific or broad platelet functions, or activation of those functions. Because platelets are involved in these systemic physiologic processes, they become markers for, mediators of, and therapeutic targets in serious medical conditions and disease states.

The IVD industry may have oversold the benefits of individual platelet function tests to clinicians. Yet, Dr. Harlan Krumholz challenged multi-journal advertising for a platelet inhibition test by stating that “no study has shown that a strategy guided by platelet aggregation testing produces better outcomes for patients.” Added to that is Dr. Schaefer-Johns’ observation that “there is no perfect platelet function test….. Except for Light Transmission Aggregometry (LTA), no tests are endorsed by platelet function testing experts.”

So what do we do? Do we turn the lights out and shut down the lab, as was suggested in a ‘Vaugh’ Street Journal parody? No, but it is time to do things differently—things that matter to the clinician and the patient. Things that our laboratories can do now and do well. Things that are flexible, so that each laboratory can structure a service that suits the needs of its patient population and is within the laboratory’s functional capacity.

LTA is the gold standard for platelet function testing, including tests for the effects of drugs on platelet function. Methods for rapid, repeatable sample preparation (10-15 minutes) are available. Aggregometers are computer-driven, affordable, walk-away devices that can be comfortably operated by a hematology or other technologist. Results can be compared to local reference ranges and can be released through the pathologist or clinical pharmacist or directly to the clinician in less than 30 minutes. We must remember, though, that similar patients with the same diagnosis and treatment may very well give different results. That is the crux of why personalized medicine will be the next generation of all the inert-related medical disciplines, sciences, and technologies.

Patient non-adherence to medication plans is a major issue. As former U.S. Surgeon General C. Everett Koop was fond of saying, “Medicines do not work well in patients who do not take them.”

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Number of Patients (USA only)</th>
<th>Non Adherence Rate</th>
<th>Patients per Acute Care Hospital Monitoring Test (LTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin - Therapeutic</td>
<td>CVD, AFib, Diabetes</td>
<td>750,000 (10) 2,200,000 (14)</td>
<td>Up to 60%</td>
<td>188.6 578.3 4,269.4</td>
</tr>
<tr>
<td>Aspirin - Preventive</td>
<td>CVD, Stroke, Pre-eclampsia, Colorectal cancer</td>
<td>85,600 (10) 33,000,000 (14) 40,800 (14) 134,400 (10)</td>
<td>Up to 75%</td>
<td>21,372.9 8,267.8 10.3 33.8</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>PCI</td>
<td>2,700,000 (14)</td>
<td>About 50%</td>
<td>1,748.0</td>
</tr>
</tbody>
</table>

1 SPA: Spontaneous Platelet Aggregation: saline is used in place of an agonist. Patient baseline.
2 An SPA result greater than 7.5% indicates hyperreactive platelets.
3 Acute Care Hospital (3,977/AAH); (39% of hospitals have cath labs: 1551)
4 Each year, 15,000 people die and 100,000 people are hospitalized as the result of aspirin and other NSAIDs

By William M. Trolio, BS, MT, CLT, MBA, FBA

OCTOBER 2016
Experiences with monitoring blood glucose and international normalized ratio (INR) in clinic and home settings have taught us that when data is expected to be generated and available, patient adherence improves, as does patient care outcome.16 Elwyn17 and colleagues provide the following reasons for patient noncompliance: 1) a lack of information about the advantages and disadvantages of the treatment; 2) the benefits of treatment are not obviously apparent; and 3) the psychological adaptation required to see oneself as in need of treatment is difficult to make. I would add a fourth: financial constraints. The ranges for non-compliance run from 20 percent to 80 percent. Mortality increases with decreasing adherence.

Table 1 (pg. 24) suggests some ways that platelet-related testing can be used to personalize medicine. It brings together two high-use drugs, applicable disease states, affected population, and number of patients/hospital and lists the appropriate LTA test(s). Clearly, the entire universe of these patients is not going to be tested. The point is that the patient pool needing these basic tests is over 700 times larger than the inherited platelet dysfunction group. These patients would require periodic testing over an extended time period. This is where our focus should be. Improving the adherence rate by routine monitoring can contribute significantly to reducing the mortality rate in these patient populations. ⬤

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William M. Trollo, BS, MT, CLT, MBA, FBA, serves as Vice President and Chief Science Officer for Pennsylvania-based Bio/Data Corporation.
When most laboratorians think of next generation sequencing (NGS) techniques in a clinical setting, it’s usually in the context of examining a patient’s genome for particular diseases, susceptibility markers, profiling of cancers, or detecting exogenous sequences such as pathogens.

This month’s installment of The Primer will focus on another application which has been steadily gaining interest over the past half-decade: sequencing of the variable recombinant portions of B and T cell genomes, in a process known generally as immune repertoire analysis. Readers may also have come across one form of this under the name of “spectratyping.”

The technique stems from looking at the patient’s adaptive immune system. In a much simplified explanation, this is the system whereby developing B and T cells undergo recombination at defined genetic regions known as V – (D) – J (Variable, Diversity, and Joining) regions to develop unique antibodies and T cell receptors (TCRs) respectively. Based on their unique peptide sequences, these can create specific binding affinity for “non-self” ligands such as those present on pathogens or on transplanted organs. While such re-assortment is essentially random in nature and thus constantly samples a wide range of “sequence space” or potential binding surfaces, those individual B and T cells whose recombinant markers find a “non-self” match are positively selected for and undergo clonal expansion as the basis for cell-mediated immunity.

These V – (D) – J regions are relatively short, in the range of 500 bp each, and flanked by well conserved sequences. This combination makes the raw data collection particularly amenable to NGS techniques, which provide massive numbers of short parallel sequence reads. While this method has been applied to specific organ samples, it more generally employs readily collected peripheral whole blood from which the white cell fraction, containing the B and T cells, is separated and subject to nucleic acid extraction. This extract is then PCR-amplified by a defined primer set directed against the conserved flanking regions. The design of this primer set is non-trivial, as it should be designed for (and have been experimentally validated as) having minimal biasing; that is, it should not artificially increase the apparent frequency of some V – (D) – J recombinants at the expense of others, as that will skew the data analysis.

While absolute “impartiality” of immunorepertoire amplification primer sets is something of an impossibility, some published primer sets such as Biomed-2 have been widely validated, and use of a consistent set such as this allows for comparison of results between samples. Note that it’s also possible to perform this analysis using extracted mRNAs, as opposed to genomic DNA, as the target material; while gDNA-based methods are believed to have higher sensitivity, mRNA-based approaches can take advantage of additional techniques (beyond the scope of this article) to avoid PCR bias.

In either case, the resulting sequence data is analyzed through application of bioinformatics. The exact statistical and control approaches underlying the analysis are complex, and differ in process details between completing published and proprietary approaches (no less than 11 of which are named in reference 1 at the end of this article just in conjunction with the spectratyping approach to immune repertoire analysis). While differing in mathematical detail, all of the methods seek to provide what can be broken down to essentially two types of measurement: immune repertoire diversity, and the presence or abundance of particular clonally expanded B or T cell types. Each of these measurements or markers can provide a different sort of insight to the underlying patient health, so let’s consider them in turn.

**Diversity**

The diversity of a person’s immune repertoire is a measure of how many different B and T cell types are present at a “snapshot” in time when the sample was taken. The larger this diversity, the better the likelihood of a pathogen being effectively bound by a B or T cell, allowing for subsequent clonal expansion and a targeted immune response. Based on the numbers of possible V, D, and J sequences present in the human genome, non-proprietary mathematical models suggest that more than 1x10^11 different combinations are possible. The actual biology is a bit more restricted, however, with only certain types of V – (D) – J recombinations actually found to occur. As an example, for just T cell receptor (TCR) types, a study by Dare2 suggested that young, healthy adults have between 40,000 and 100,000 simultaneously circulating TCR types at any given time. This number is observed to decrease with age, by as much as an order of magnitude. B cell diversity may be observed to exceed that of T cells,3 possibly due to mechanisms of somatic hypermutation and affinity maturation whereby B cells can undergo additional genetic changes in response to a ligand binding stimulus.

As the reader might guess, a measure of this diversity in a patient is a measure of the robustness of his or her cell-mediated immunity systems. Considered simplistically, if the diversity of available B and T cell receptors is low, there’s less chance that an incoming previously unencountered antigen will be recognized. While finding low immune repertoire diversity doesn’t indicate what the underlying cause is, it provides a warning of apparent immune suppression which can be helpful in making a diagnosis. When the cause is known or suspected and clinical intervention is occurring, ongoing monitoring of immune repertoire diversity can help to monitor therapy. Examples where this has been clinically applied include measuring restoration of diversity following successful high-HAART in HIV patients, and assessment of organ graft tolerance versus rejection.

**Clonal expansion**

As described above, clonal expansion in a B or T cell type occurs after it has a productive binding interaction with a non-self ligand. In the context of an NGS approach,
biology. On the diversity side, a major concern arises through the potential for NGS error rates to lead to an overestimation of diversity; that is, some of the variant sequences reported and used for calculation really just arise through PCR or sequence read errors. Increases in accuracy of NGS methods, as well as methodological approaches including incorporation of spiked control sequences monitored for “misread” rates, can help to minimize this source of error. On the clonal expansion side, one example of a potentially misleading result might be in the case of benign monoclonal gammopathy—a long known and not uncommon “condition” of (as the name suggests) little clinical importance, where for unknown reasons one particular B cell clone becomes highly overrepresented. Suitable bioinformatics as well as incorporation of the entire clinical picture are tools to employ in separating these confounding effects from more useful information available through immune repertoire analysis.

For now, costs, speeds, and limited availability of NGS services to clinical standards limit the widespread adoption of this as part of the diagnostic arsenal of most molecular laboratory. As these barriers to wider adoption fall, it is to be expected that immune repertoire profiling should continue its move from the research and special application settings and start to become a more normal component of assessing health status and effectiveness of therapies influencing the immune system.

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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.
Automatic reading and segregation of cultures

The value proposition for full laboratory automation and improved time to results has arrived.

By Gabriela Franco, BS, MIM

Full laboratory automation in Microbiology is high on the wish list of many laboratories in the United States. In fact, in an article published in the Journal of Clinical Microbiology (JCM), Bourbeau and Ledeboer assert that “the changes associated with selection and implementation of microbiology automation solutions will place significant management and financial challenges upon laboratory leadership,” and that the world of clinical microbiology is “on the cusp of a dramatic change that will sweep a wave of automation into clinical microbiology laboratories.” But, as Greub and Prod’hom have expressed, “the challenge for clinical bacteriologists is to determine…the ideal automated system for their own laboratory.”

One important recent change that is hastening the adoption of full laboratory automation is the change in sample collection devices. In an important guideline prepared for the Infectious Diseases Society of America and the American Society for Microbiology, Baron et al highlight the importance of proper collection and transport of samples. They point out that “unlike other areas of the diagnostic laboratory, clinical microbiology is a science of interpretive judgment that is becoming more complex, not less. Even with the advent of laboratory automation and the integration of genomics and proteomics in microbiology, interpretation of results still depends on the quality of the specimens received for analysis.” Advances in collection devices, paired with liquid-based microbiology (LBMs), developed in recent years, have improved sample quality and have opened the door to automate front-end specimen processing, one of the most manual areas of the laboratory. In fact, Bourbeau and Ledeboer add that “the adoption of liquid microbiology specimen transport has allowed microbiology laboratories to simplify collection and identification systems, creating a workflow that can be optimized with automation.”

Different pressures, such as increasing sample volume, aging workforce, and decreasing reimbursement, are making the concept of automation a pressing need for the laboratory. “Advances in automation have reduced the time for specimen processing by using robotic systems to inoculate, label, track, and incubate plates for culture. However, culture analysis is still a time-intensive and costly procedure for the laboratory as technologists have to interpret colony counts to differentiate pathogens from normal flora for several hundred plates a day,” stated Faron et al in a scientific poster presented at the annual meeting of the European Congress of Clinical Microbiology and Infectious Diseases this year. Software that can automatically segregate patients’ sample cultures based on colony counts and/or recognition of the specific morphology or appearance of the colonies will completely revolutionize the microbiology laboratory by saving time to results and improving the speed of diagnosis of infectious disease. Image analysis capabilities and the strength of the algorithms for automatic reading and segregation of cultures, regardless of the manufacturer of plated media, will separate the mechanization of manual processes from true game-changing innovation in image analysis in the field of full laboratory automation for Microbiology, and will constitute the most important factor when choosing a system.

Automated segregation of growth and no growth

The image analysis software is the most powerful component of full laboratory automation, and it is at the heart of digital microbiology. Without strong algorithms, the return on investment and the value of full laboratory automation are limited because a lot of the tasks still have to be done manually. It is important that the algorithms use an open approach to different media manufacturers and different types of media, and that they can be applied to both whole and bi-plates. Many laboratories in North America use bi-plates for urine investigations. So, availability of reading algorithms for bi-plates is an important feature to consider when picking a full laboratory automation system.

It is well-known that, in the U.S., “urinary tract infections account for seven million visits to physicians’ offices and over one million hospital admissions per year.” So, naturally, urines are one of the highest sample volumes received in the Microbiology laboratory. In fact, “urinalysis is the third major diagnostic screening test in the clinical laboratory, only preceded by serum/plasma chemistry profiles and complete blood count analysis.” In the U.S., urines are tested on blood and MacConkey whole plates or bi-plates or blood and chromogenic bi-plates. The Clinical Microbiology Procedures Handbook, in the Protocol for workup of urine culture, calls for a 1μl loop for quantitative purposes. The urine reading algorithm must be able to use the correct sample volume to get accurate colonial separation for an accurate account. It must also work on blood/MacConkey or blood/chromogenic medium, in addition to being able to recognize the orientation of the plates no matter which side of the plate is blood and which is the other medium (Figure 1). The bi-plate urine segregation algorithm applies the appropriate rules based on a customizable expert system of rules for growth interpretation. So, two automatic results can be received instantaneously from one culture plate. For example, by applying “if and then” rules, the system could flag if the patient is a pregnant woman or is of child-bearing age, then look for small numbers of white Group B Strep colonies on the chromogenic plates or look for small numbers of hemolytic colonies on blood plates.

A recent study has been published on software that can “read digital images and provide quantitation of Colony Forming Units from blood agar plates.” The software counts Colony Forming Units (CFUs) on blood plates, and segregates no-growth cultures and can categorize growth—for example 0-10 CFUs, 10-100 CFUs, and >100 CFUs—which helps overall “to reduce the cost of urine...
cultures by sorting plates based on colony growth.” The study concluded that the quantitative software was accurate at discerning no-growth without any false results. It is important to mention that laboratorians are still required to validate the algorithms decision before the culture result is finalized in the patient record. However, the segregation helps improve efficiencies and reduce turnaround time by grouping and pre-sorting the negatives and the positives so that the staff can screen and result faster.

Analysis of different chromogenic media
According to Faron et al., “chromogenic detection module (CDM) is software that analyzes digital images for a customizable target color by converting red-green-blue (RGB) images into a 3-dimensional space composed of hue, saturation, and value (HSV), creating a ‘bubble-shaped’ tolerance level for defining ‘nonnegative’ media plates.” Another example of the value that digital microbiology and image analysis brings to the healthcare system is the application of the software to detect and differentiate methicillin-resistant *Staphylococcus aureus* (MRSA) on different types of chromogenic media. A recent multi-center, unprecedented study published by the JCM compared a “software that discriminates and segregates positive and negative chromogenic methicillin-resistant *Staphylococcus aureus* (MRSA) plates by recognition of pigmented colonies” to manual reading done by a laboratorian. The sample size was almost 60,000 specimens, and the chromogenic media used for the study was manufactured by three different companies (so the software for color recognition was not tied to a specific manufacturer’s plated media). The study concluded that “the digital software had a sensitivity of 100 percent and a specificity of 90.7 percent with the specificity ranging between 90.0 and 96.0 across all sites. The results were similar using the three different agars with a sensitivity of 100 percent and specificity ranging between 90.7 percent and 92.4 percent. These data demonstrate that automated digital analysis can be used to accurately sort positive from negative chromogenic agar cultures regardless of the pigmentation produced.” Perhaps even more impressive, the software was capable of detecting an additional 153 cases where “small colonies were not visually detected by the initial manual examination but upon review should have been called positive by the laboratory.”

An even bigger study, also published by the JCM, compared a Chromogenic Detection Module to manual reading to screen for vancomycin-resistant enterococci (VRE). This study included 153 cases where “small colonies were not visually detected by the Chromogenic Detection Module software and were missed by the laboratorian. In the study, 84 percent of all samples were negative by both systems. Currently, the laboratorian still has to confirm the negatives, but this can be batched in groups of 30 plates per screen for rapid review and reporting. The study concludes that “automatic ruling of negative plates would have several benefits such as decreasing turnaround time, especially in laboratories that are not open 24/7, support antimicrobial stewardship by allowing pharmacists and physicians and a ‘software that discriminates and segregates positive and negative chromogenic methicillin-resistant *Staphylococcus aureus* (MRSA) plates by recognition of pigmented colonies’ to manual reading done by a laboratorian. The sample size was almost 60,000 specimens, and the chromogenic media used for the study was manufactured by three different companies (so the software for color recognition was not tied to a specific manufacturer’s plated media). The study concluded that “the digital software had a sensitivity of 100 percent and a specificity of 90.7 percent with the specificity ranging between 90.0 and 96.0 across all sites. The results were similar using the three different agars with a sensitivity of 100 percent and specificity ranging between 90.7 percent and 92.4 percent. These data demonstrate that automated digital analysis can be used to accurately sort positive from negative chromogenic agar cultures regardless of the pigmentation produced.” Perhaps even more impressive, the software was capable of detecting an additional 153 cases where “small colonies were not visually detected by the initial manual examination but upon review should have been called positive by the laboratory.”

What’s next for clinical microbiology?
With the level of sophistication that lies behind current image analysis software, the next frontier for clinical microbiology is automated colony picking. The module for automated colony picking works using 3D digital coordinates previously specified by the laboratory staff to process further workup and investigations (Figure 2). The workups include McFarland suspensions for antibiotic susceptibility testing (AST) and traditional organism identification by biochemistry and purity plates, seeding MALDI-TOF target plates and applying the matrix, among others.

As microbiology laboratories around the U.S. brace for this exciting new wave of automation, it is important for lab leaders to select a system that has the software capabilities necessary to automate internal processes and the power to considerably reduce turnaround times by pre-sorting samples to facilitate a lean workflow. It is an exciting time for Microbiology: We are part of one of the largest breakthroughs in technology in this generation. 

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Gabriela Franco serves as Director of Marketing for COPAN Diagnostics. Gabriela has more than 14 years of experience in marketing and product management. She holds a BS in Business Administration and Marketing, and a Master of International Management degree.
Transfusion-related thrombocytopenia in a chronic renal failure patient

By Xiaoming Yang, PhD, MLS(ASCP), and Floyd Josephat, EdD, MT(ASCP)

Hemostasis is a process to stop bleeding that requires coordinated activities of vascular, platelet, and plasma factors. Under normal conditions, blood vessel injury will trigger endothelial cells to secrete factors that promote adhesion and activation of platelets. First, platelets bind to von Willebrand’s factor (vWF) secreted by endothelial cells through vWF receptors. Attached platelets then undergo degranulation and release factors such as serotonin, which causes vascular constriction. Activated platelets also release other mediators to attract additional platelets for aggregation at the injured sites. The platelet surface has fibrinogen receptors through which fibrinogens connect adjacent platelets. Platelets will further activate coagulation factors in the plasma and convert prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, and fibrin strands bind aggregated platelets to form blood clot. In this process, platelets play a critical role, and deficiency in platelet count or function may cause uncontrolled bleeding. Thrombocytopenia is a decrease in platelet number, and one of the most common hematological disorders associated with excessive bleeding.

There are two major causes of thrombocytopenia: decreased production and increased breakdown of platelets. Many diseases can lead to a decreased platelet production in the bone marrow. For example, the myelodysplastic syndromes, which are characterized by a defect in hematopoiesis, often cause low platelet counts as well as functionally and morphologically abnormal platelets in the peripheral blood. Liver cirrhosis can also cause thrombocytopenia because the liver is the main organ producing thrombopoietin (TPO). TPO stimulates the production and differentiation of megakaryocytes and is required for platelet production. Certain drugs such as chemotherapy drugs can cause thrombocytopenia by inhibiting the proliferation of hematopoietic progenitor cells.

Increased destruction of platelets is another major cause of thrombocytopenia in the clinical setting. Drugs such as heparin, a commonly used anticoagulant, can induce immune response. The resultant antibodies can target platelets for destruction. Under certain disease conditions, disseminated intravascular coagulation (DIC) causes blood clot formation throughout the body’s small blood vessels, which will use up platelets and clotting factors in the blood. As a result, DIC is often associated with serious internal and external bleeding.

Pathogenesis of renal failure

Renal failure is among those conditions that have been associated with thrombocytopenia. Epidemiological studies have shown that both acute and chronic renal failure are associated with anemia and thrombocytopenia. Acute renal failure is a rapid decrease in renal function, which leads to a marked increase in serum creatinine and BUN. The inability of the kidney to eliminate waste is associated with a high rate of mortality. Chronic renal failure is a progressive loss of renal function, and patients with chronic renal failure usually end up with hemodialysis. It is known that patients at various stage of chronic renal failure display many abnormalities in hemostasis. These patients have increased risks of both thrombotic events and bleeding. Chronic renal failure can also be secondary to other diseases such as type 2 diabetes. With an increasing number of type 2 diabetic patients, it is important to evaluate kidney disease-associated hemostatic disorders. In the following case study, severe thrombocytopenia refractory to transfusion in an end-stage renal failure patient is presented.

Case study presentation on end-stage renal disease

A 65-year-old African American male with end-stage renal disease was admitted to the hospital for a large abdomen mass and bleeding. Four months before, this patient had been found to have a pelvic mass, and the biopsy showed blood and necrotic debris in the mass. The diagnosis at that time was liquefying hematoma. He had returned to the hospital one month before for the accumulation of fluid in the peritoneal cavity (ascites). About 400 ml of cloudy fluid was removed and two different diphtheroids grew from the fluid, suggesting an infection. Consistent with this diagnosis, the patient had 25x10^9/ml of WBC initially but fell to the normal range quickly after the treatment.

During his admission in the hospital, the patient had several periods of thrombocytopenia, but his platelets were normalized after transfusion, and he was discharged with drains in place. The patient did not have fever, chills, or sweats. He was on Augmentin and receiving hemodialysis. Upon the
latest admission, the patient started to bleed again, and his Hgb and platelet levels were critically low (Table 1, pg. 30). Heparin-induced thrombocytopenia (HIT) was suspected and HIT screen was positive, but serotonin release assay was negative. He had been dialyzed without heparin since then. The patient had some bleeding from drain sites, but CT scan did not isolate other sources of bleeding. The amount of bleeding from the drain sites did not seem enough to explain his dropping Hgb and platelet.

The patient received two units of platelet, one unit of FFP, and one unit of RBC on the first day. The transfusions doubled his platelet count but failed to bring up his RBC (Figure 1), indicating he was still bleeding. DIC was also suspected in the patient. D-dimer value and fibrinogen level were determined on the second day. He had an elevated D-dimer (2.95 mg/ml) but normal fibrinogen (415 mg/dL). His PT and aPTT were elevated slightly, but his INR was normal (Table 1). The patient’s platelet count dropped quickly during the next couple of days.

On day 4, he received two units of platelet and two units of FFP, but that brought his platelet count up only temporarily. His platelet count kept dropping despite daily platelet and FFP transfusion (Figure 1). His CBC profile on day 10 was similar to that on day 1, with an even lower level of platelet (Table 1, pg. 30). The patient developed respiratory distress due to the volume overload, and this eventually led to respiratory arrest. The patient died on day 11.

During this 10-day period, the patient’s RBC and Hgb were low but stable, while his platelet level decreased continuously. Unlike during his previous hospital admissions, this time his thrombocytopenia was refractory to FFP and platelet transfusion transfer.

Analysis of case study
Thrombocytopenia is commonly seen in hemodialysis patients. Since heparin is the most commonly used anticoagulant during dialysis, heparin-induced thrombocytopenia (HIT) is a concern in dialysis patients. It has been shown that one percent to five percent of patients exposed to heparin may develop HIT.10,11 There are two types of HIT: non-pathogenic and pathogenic. Assay for HIT antibodies usually detects both types of HIT. The non-pathogenic HIT does not cause thrombocytopenia despite the presence of HIT antibodies, while pathogenic HIT may have a catastrophic consequence.

Heparin binds to PF4, and the heparin-PF4 complex is immunogenic, which induces the expression of IgG, as well as IgA and IgM antibodies against the heparin-PF4 complex. Although these antibodies could destroy platelets and lead to thrombocytopenia, HIT is rarely associated with bleeding.2 Consistent with this notion, the patient in this case had a positive HIT antibody result and low count of platelet, but his bleeding was not prominent. In fact, HIT is often associated with thromboembolic manifestations including venous thrombosis and myocardial infarction.3 This is due to the fact that heparin tends to cause platelet self-aggregation and activation. It has been shown that heparin interacts with integrins on the platelet surface, and this interaction may cause platelet self-aggregation.3 In addition, heparin can cause platelet degranulation, which activates platelets.4 That may explain HIT-associated clotting of extracorporeal circuit in dialysis patients.5 It is not clear whether this patient developed thrombosis; however, there was no report of clotting in his dialysis tubes.

In this case, HIT alone may not be sufficient to explain the critical low platelet count. It has been reported that the mean decrease of platelet count in HIT patients is about 12 percent.6 This patient had a very low level of platelet even after he had been dialyzed without heparin. Thrombocytopenia has also been linked to biocompatible membranes used in hemodialysis. In hemodialysis, the activation of complement can lead to thrombocytopenia,7 and cellulose membrane has been shown to activate complement.8 Furthermore, electron beam sterilization of polysulfone dialysis membrane has also been linked to thrombocytopenia.9 Although it is unclear what type of dialysis membrane and sterilization method was used in this patient, it is possible that dialysis equipment might have contributed to the patient’s decreased platelet count.

Besides the external factors that cause thrombocytopenia, the patient’s physical condition is probably the most important factor. Anemia and thrombocytopenia have been found in patients with acute and chronic renal failure.2,10 Red cell production is stimulated by erythropoietin (EPO), and the kidney is the source to secrete EPO. In patients with chronic renal failure, deficiency in EPO production is the main cause of the development of anemia. Anemia in this patient might be a combined consequence of EPO deficiency and bleeding. For platelet production, its stimulator, TPO, is constitutively produced by the liver but is also produced by the kidney.21 Therefore, it would be reasonable to expect TPO deficiency...
in chronic renal failure patients. However, it seems that TPO deficiency due to the kidney failure is negligible as a cause of the thrombocytopenia.21 In fact, serum TPO level is elevated in dialysis patients.22 Nevertheless, megakaryocytes are reduced in the bone marrow of renal failure patients, indicating a deficiency in platelet production, although the molecular mechanisms are not clear.

The platelet function in chronic renal failure patients is also jeopardized. Under normal conditions, ADP and serotonin are secreted to attract more platelets. In renal failure patients, their platelet granules have decreased levels of ADP and serotonin.23 Anemia could further worsen the bleeding disorder because red cells release ADP and facilitate platelets contacting with subendothelium at the damage site.23

Overall, in chronic renal failure patients both platelet count and function are decreased. What was unique in this case was that the thrombocytopenia was refractory to massive platelet transfusion. If this was due to the nonstop bleeding, then one would expect the patient’s RBC and Hgb to decrease dramatically as well. In fact, his CBC profiles showed that other cell counts were pretty stable, and no massive bleeding was noticed. These results suggested that transfused platelets were either destroyed or consumed rapidly. DIC is a common cause of the exhaustion of coagulation factors and platelets, thereby causing thrombocytopenia and bleeding. DIC was suspected in this patient.

However, the diagnosis of DIC remains difficult. An elevated level of D-dimer is one of the diagnostic elements for DIC. The patient’s D-dimer was above the normal range when he was admitted to the hospital. However, D-dimer alone may not be sufficient for DIC diagnosis. A study has shown that 70 percent to 90 percent of hospitalized patients without DIC also have D-dimer values greater than the upper limit of the reference interval.24 That study suggests a cutoff of 8.2 mg/ml to “rule in” a diagnosis of DIC.24 The patient’s D-dimer level in this case study was much lower than this cutoff value, suggesting DIC might not be a major concern for the patient. Since coagulation factors are depleted in DIC, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) are often associated with DIC. A prolonged PT or aPTT has been observed in 95 percent of patients with DIC.23,24 The patient in this case study had slightly prolonged PT (15.2 sec) and aPTT (36.2 sec) but normal INR (1.2). In addition, his fibrinogen was in normal range. Again, those results suggested that DIC might not be a major complication in this patient. In summary, thrombocytopenia in this patient was likely a combined consequence of platelet consumption and destruction, as well as bleeding.

Conclusion

Patients with chronic renal failure could develop severe thrombocytopenia and platelet dysfunction as well as bleeding. Furthermore, these conditions could be refractory to transfusion. Mechanistic research, epidemiological study, and case report on renal disease-caused hematologic disorders may help us understand the underlying mechanisms and develop treatment strategies.

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Pharmacogenomics was one of the earliest success stories of the genome era, and today serves as a foundation for the concept of precision medicine. From companion diagnostics to individual drug metabolism profiles, knowledge of a patient’s genetic variation can be critical for guiding the selection or dosing of a therapeutic. Indeed, genetic testing has allowed the pharmaceutical industry to streamline drug development while delivering therapeutics with better efficacy and reduced adverse events. This trend has also led to an increase in the types and number of genetic tests that must be tracked and made available by clinical lab professionals.

Two kinds of genetic tests have shown great utility in this area: companion diagnostics, or tests paired with a drug to ensure its use in patients who are most likely to benefit; and drug metabolism tests, which help identify patients who may not be able to tolerate a certain drug or who require different dosing for effective treatment. Together, these tests help physicians choose the best therapeutic option for a specific patient, maximizing effectiveness while minimizing the risk of severe adverse reactions.

In this article, we look at the remarkable rise of companion diagnostics and drug metabolism tests, as well as what to expect from this field in the coming years.

**Companion diagnostics**

In 1998, the U.S. Food and Drug Administration (FDA) approved Herceptin, the first therapeutic tied to a particular genetic biomarker determined by a companion diagnostic test. Since then, the march toward mainstream companion diagnostics has been slow but steady. Today, some two dozen FDA-cleared companion diagnostics are mandatory for the prescription of certain drugs, while nearly 140 drugs have labels recommending (but not requiring) pharmacogenomic testing.

According to an analysis from the Personalized Medicine Coalition, a nonprofit advocacy group, 28 percent of the new drugs approved by the FDA last year could be classified as “personalized medicine”—that is, their labels indicate that optimal patient response is linked to the use of a diagnostic test. While the earliest companion diagnostics were targeted at cancer, where the genetic profile of a tumor can point to the most-likely-to-succeed therapeutic, their use has since broadened to include drugs for infectious diseases, cystic fibrosis, and several other disease areas.

Companion diagnostics offer several advantages to pharmaceutical companies beyond safer and more effective medications for patients. Clinical trials for targeted treatments can be smaller, which makes them less expensive and faster at generating results. These tests can also be used to rescue promising investigational compounds that would otherwise be shelved for not working broadly across all patients; with the right biomarker and a companion test, these drug candidates can be safely ushered through clinical trials by delivering them only to an optimally defined patient group. In what is widely acknowledged to be the post-blockbuster-drug era, pharma and biotech companies have found a successful alternative in spending less money to develop treatments that work for high-value niche indications.

**Drug metabolism testing**

Many genetic tests analyze patients for their ability to process a particular drug or class of drugs. This testing was enabled by the discovery that the cytochrome P450 genes encode enzymes responsible for metabolizing as much as 80 percent of currently available therapeutics. These enzymes—CYP2D6, CYP2C19, CYP2C9, CYP3A4, and CYP3A5—mostly occur in the liver, where they handle the breakdown of drugs and clear them from the system. CYP2D6 alone is thought to metabolize up to 25 percent of therapeutics, including pain medications, cardiovascular drugs, and anti-psychothics.

The genes encoding these enzymes are highly variable among individuals, and extensive studies have determined that patients with specific genotypes are more likely to metabolize (and therefore respond well to) certain drugs, while patients with other genotypes may see little or no benefit because their bodies do not process the therapeutics. Based on this information, many companies have developed genetic tests to reveal a patient’s metabolism profile and guide therapy selection.

The CYP2D6 gene is particularly prone to variation, with significant fluctuations across populations and more complex variant events, such as gene deletions and duplications. Clinical researchers continue to study this gene, deploying the most sophisticated DNA sequencing and analysis technologies to characterize all possible types of variation for a better understanding of how these differences contribute to a person’s ability to tolerate and metabolize medications.

Even as our understanding of drug metabolism genotypes continues to evolve, current tests are already making a tremendous clinical difference. They are useful not only in helping physicians avoid treatments that are not likely to work for a patient, but also in selecting the appropriate dose of a treatment based on how rapidly that patient is expected to metabolize and clear the drug. This information has proven to be particularly important for optimal dosing of pain medications, for example, as well as for blood thinners like warfarin that may be harmful in higher-than-necessary doses.

**Looking ahead**

The rise of pharmacogenomic testing has been both a boon and a challenge for clinical laboratories, which often need to implement new diagnostic instruments in addition to validating and incorporating these assays into their offerings. As more types of genetic variation are understood and linked to drug response or metabolism—such as structural variants, epigenetic patterns, and distantly linked variants—these tests promise to become more complex as well. Clinical lab professionals will need to keep up with this rapidly developing field and be trained on new technologies to ensure that their teams stay at the cutting edge of molecular diagnostics.

In the future, evidence suggests that companion diagnostics will become far more common. Perhaps in the long term it will even displace one-size-fits-all drugs as the norm in prescription medication. According to a recent analysis by the Tufts Center for the Study of Drug Development, pharmaceutical companies are still ramping up their investment in diagnostic-targeted therapies. The study found that these firms anticipate allocating 33 percent more funding to personalized therapy.

*continued on page 37*
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Precision medicine and companion diagnostics join the battle against ovarian cancer

By Debora Mancini-DiNardo, PhD, and Krystal Brown, PhD

The American Cancer Society estimates that 22,280 women will be diagnosed with ovarian cancer in 2016. However, the lack of accurate screening tests for ovarian cancer means that 70 percent to 80 percent of all ovarian cancers will be diagnosed at a late stage, with a 10-year survival rate of only 35 percent. As a result, approximately 14,240 women will die of ovarian cancer in 2016, accounting for five percent of all female cancer deaths.3

The standard treatment for most women with ovarian cancer is surgery, followed by a platinum-based chemotherapy regimen. Despite initial remission, up to 80 percent of women treated with platinum-based therapies will experience disease recurrence within years, or even months.4,5 While progress has been made in ovarian cancer treatment over the last 10 years, these therapies have historically aimed to accommodate all patients. However, we now know that ovarian cancer is a heterogeneous disease with many distinct pathologies and etiologies.6,7

In the emerging era of precision medicine, clinicians hope to replace the traditional “one-size-fits-all” treatment approaches with individualized care based on underlying disease biology. With advances in genetics research and sequencing technologies, healthcare providers are now poised to utilize the information garnered from genetic testing for cancer predisposition genes both to determine hereditary cancer risks and to evaluate possible treatment options based on those results.

Defects in DNA repair pathways

Mutations are known to accumulate more rapidly in cells that are unable to repair the damage that arises in their DNA. Breaks limited to single strands of DNA are fixed by processes known as base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). Double-strand breaks are predominately repaired by two mechanisms; template-directed high fidelity homologous recombination (HR) and low fidelity non-homologous end joining (NHEJ). The loss of the error-free HR repair mechanism contributes significantly to the accumulation of mutations in ovarian cells and ultimately promotes ovarian tumor growth. Researchers estimate that 30 percent to 50 percent of ovarian cancers are associated with this HR deficiency.5 DNA-damaging agents that instigate additional DNA damage in cells that are already HR-deficient will lead to cell death through the rapid accumulation of genomic aberrations from low fidelity DNA repair. Pathogenic variants in two critical HR genes, BRCA1 and BRCA2, are among the first genetic markers of HR deficiency. As such, many studies have now documented an improved response to platinum therapy among women with ovarian cancer who carry pathogenic variants in BRCA1 and BRCA2.8,9 Although platinum therapy is currently the standard of care, these studies suggest that different therapies may need to be developed to target HR-intact ovarian tumors.

A more recent treatment strategy involves the use of a class of small molecules developed to inhibit poly ADP ribose polymerase (PARP).10,11 These PARP inhibitors disrupt the secondary pathways for DNA repair that rely upon proper PARP1 and PARP2 function (NHEJ, BER). Non-tumor cells are equipped with the full repertoire of repair mechanisms and are therefore not sensitive to PARP inhibition. This treatment strategy is therefore specifically directed toward tumor cells, resulting in a reduction in overall toxicity.

As with platinum, previous studies have shown that PARP inhibitors selectively benefit individuals with pathogenic variants in BRCA1 or BRCA2.12-17 and, as such, illustrate the benefits of personalized medicine in the selection of therapies based on individual tumor biology and patient characteristics. Cells that possess at least one normal BRCA1 and BRCA2 copy are relatively resistant to PARP inhibition. BRCA1 or BRCA2 dysfunction, defined as mutant cells lacking wild-type BRCA1 or BRCA2, sensitizes cells to PARP inhibition, leading to chromosomal instability, cell cycle arrest, and apoptosis.18,19

Although both platinum and PARP inhibitors target cells with HR deficiency,
many tumors eventually become “platinum-resistant.” Studies have shown the benefit of treatment with PARP inhibitors following platinum among women with ovarian cancer who have pathogenic variants in BRCA1 or BRCA2. Such findings are significant, as maintenance therapy in ovarian cancer is becoming more desirable due to the high rate of disease recurrence.

Companion diagnostics
Companion diagnostic tests are used to identify patients who are most likely to benefit from a particular therapy, and their growing number has the potential to transform medical practice. One such commercially available companion diagnostic test is paired with AstraZeneca’s drug Lynparza (olaparib), which is a PARP inhibitor. The assay is intended to detect germline BRCA1 and BRCA2 variants and provide a clinical interpretation of the identified variants. Single nucleotide variants and small insertions and deletions are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications are detected using multiplex quantitative PCR. Results of this test are used as an aid in the identification of ovarian cancer patients who may be considered for treatment with Lynparza.

Notably, the companion diagnostic test for Lynparza was the first laboratory-developed in vitro companion diagnostic test approved by the FDA. Achieving FDA approval for this test was no small undertaking. The specific performance characteristics of the assay were established by 10 categories of studies and supported by over 4,000 pages of documentation. These studies were performed using whole blood samples from ovarian cancer patients, as well as samples from breast cancer patients and unaffected individuals from families that have a high risk for hereditary breast and ovarian cancer. Table 1 provides a brief description of all the studies performed.

The use of companion diagnostic tests will form the foundation for the precision medicine revolution. The increasing number of collaborations between genetic testing laboratories and biopharmaceutical companies bodes well for the development of a varied menu of treatment options for cancer patients, targeted specifically to their own underlying disease etiology. The benefits of such personalized treatment strategies are numerous and far-reaching, leading to reductions in healthcare costs and treatment time by not pursuing ineffectual therapies, and ultimately resulting in improved clinical outcomes.

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Drug metabolism testing, on the other hand, will likely become more sophisticated as scientists learn more about genetic variation within the CYP genes— but the beauty of it is that a single test result can aid in the prescription and dosing of numerous drugs. Currently, this kind of information is even available through some consumer-oriented genetic testing services, making it more likely that patients will have broad access to their own drug metabolism profiles in the near future. (It’s worth noting that this makes it even more important for clinical labs to provide high-quality genetic testing for drug metabolism to confirm or dispute the data patients may have gathered through less rigorous services before results are used to make medical decisions.)

Genetic testing has proven essential for the rise of precision medicine. With continued investment from pharmaceutical companies and diagnostic developers, as well as ongoing training among clinical lab professionals, there is good reason to believe that we are well on our way to a new era of medicine that does away with population averages and instead uses genetic and other molecular information to tailor treatment for each patient.

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CLINICAL ISSUES  LIS/LAB INFORMATICS

Considering the LIS in the molecular diagnostics context
By Megan Schmidt

Laboratories have specific needs based on their size and testing types. Physician office laboratories, for example, typically perform fairly basic testing with straightforward setups. Larger laboratories, such as reference labs or hospital labs, require multiple work stations and analyzers to be set up, necessitating interfaces that can share and receive orders in real time to multiple offices and mobile applications. Specialized labs such as toxicology, pain management, and molecular diagnostic laboratories have unique workflows and specific customizable reports that require a streamlined process.

In the lab industry, the molecular diagnostic testing market is growing at a faster pace than routine testing. In many cases, a streamlined process. Unique workflows and specific customizable reports that require special purpose applications. In some cases, laboratories may utilize customized software to manage their specific needs.

The molecular landscape
Complex molecular testing, generally conducted as laboratory developed tests (LDTs) under CLIA, requires a laboratory that is certified for non-waived testing. Conducting LDTs requires sophisticated infrastructure. The onus is on the lab to provide for quality and assay performance, and there is often complex hands-on processing involved, including sample extraction, setup, and specialized equipment. Therefore, non-waived molecular testing is often conducted in core labs and reference labs.

For physicians and clinicians not readily served by reference labs or a molecular core laboratory, molecular-based point-of-care instruments can have a positive impact on time to answer and outcomes. One commercially available alternative is a platform with an FDA CLIA Waiver for influenza and respiratory syncytial virus (RSV). It also supports detection of methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus aureus (SA) skin and soft tissue infections in less than an hour. Another system addresses acute respiratory infection, sepsis, or gastrointestinal distress, and a third has FDA-cleared tests that include influenza A and B and RSV, and work direct from a nasal swab to results in about an hour. These instruments can be operated by staff with less technical expertise than a molecular technologist. In general, they also require only a few minutes of hands-on time per specimen, without manual chemistries for extraction and processing.

The intention of referencing these instruments is not to endorse any one platform, but to illustrate that molecular diagnostics (MDx) is not always conducted in high complexity labs.

LIS functions
In both waived and non-waived testing, the laboratory information system (LIS) plays a key role. In either scenario, the order workflow can be streamlined with interfacing and rules.

Order interfaces reduce paper and manual transcription, while “Ask at Order Entry” questions can be designed to document information about an order or specimen. An LIS can also offer robust rules that can drive actions. Rules can combine or delete tests or orders, order additional tests, check for appropriateness of tests, or route orders based on patient insurance.

Waived or non-waived, support for molecular diagnostics requires integrating into an information system for quality control before posting to the patient record. This requires the input of manual results or the review and acceptance of online instrument results, depending on the application. Result entry, result review, and final acceptance can be accomplished via a workflow with an intuitive graphical user interface that can display previous patient results in tabular or graphical format.

Molecular instruments are evolving at a fast pace; some become virtually obsolete in as little as 18 months after launch. This fact, and the fact that many instrument vendors are not yet using a standardized output, make interfacing a challenge. The LIS can allow upload of data in Excel, ASCII, CSV, etc., when an ASTM or HL7 instrument interface is not available.

Molecular results can include images, such as those documenting results from a gel or other systems. During review and results reporting, images are needed to illustrate and document results. The LIS can accept and associate related attachments—such as pdf, image, graph, video—and store them in such a way that they can be retrieved by laboratorians in their workflow.

Molecular instruments vary in level of data analysis. Often, the laboratorian will need to perform calculations. Excel is a common format for the output from instruments, and, in some cases, lab personnel may utilize Excel for custom data manipulation. As a best practice, data manipulation is done at the instrument and/or in the LIS. Robust functionality for rules and calculations is a must to handle molecular data.

Laboratories conducting molecular diagnostic testing often employ a secondary review of results before releasing to the patient file. Given the technical nature of these results, users need the ability to verify that the results are correct and include the appropriate data. This involves sequential documentation in which one staff member enters or accepts results and a second staff member or supervisor completes a review before sending out the report. Since the specific review process will vary from lab to lab, users need the ability to customize the technical review process to accommodate their organization’s specific best practices.

Given the complexity from hands-on processing and interpretation, laboratories conducting LDTs require skilled staff and strong quality oversight. Laboratory information systems need to accommodate the complex multi-step workflows required for some LDTs. One must configure activities to be performed at each step and then confirm the quality and expected outcome before allowing the specimen to move on to the next step in the workflow. This can be accomplished through panels and reflex testing so that each step can have its own result, QC, and go/no go decision. QC features should also protect result quality: delta and normal range checking can highlight abnormal results, while QC failures can block resulting from filing.

Conducting complex multi-step workflows requires access to the lab’s standardized procedure documentation. Lab personnel need to access current policies and procedures, and supervisors need to ensure that the policies and procedures are up-to-date with scheduled reviews and sign offs. An embedded document management system allows users to upload documents and maintain revisions for each upload, allowing users to review or sign the versions.

There is an LIS to fit every unique laboratory and help maximize efficiency—and reimbursements. Lab leaders should look for an LIS that offers the latest technology and is streamlined and customizable for their laboratory’s specific needs.

REFERENCE
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Efficiency plus empowerment

By Carol J. Ross, MT(ASCP), CPHIMS, FACHE

Advanced middleware can keep your laboratory tuned in, on track, and in control.

In a perfect world, every laboratory information system (LIS) would give clinical laboratories exactly what they need—the ability to manage data, quickly respond to physician requests, monitor instrument QC performance to ensure quality results, and expertly adapt to ever-changing workflow needs. Unfortunately, most LISs fall short. They simply can’t deliver the flexibility and responsiveness today’s laboratories need.

It’s no surprise that many laboratories are turning to advanced middleware, a server-and-software platform that sits between the LIS and laboratory instrumentation. Middleware fills a crucial gap by providing real-time insights and functionality that put laboratories back in control. Here are four ways that middleware can empower the clinical laboratory:

1. Optimizes daily operations with exception-based results.

Middleware streamlines testing processes by automating the laboratory’s standard operating procedures (SOPs). Protocols for rerun criteria, delta checks, reflex testing, and sample flagging can be automated. With rules, laboratories can perform autoverification to automatically release results into the LIS without the need for laboratory personnel review. Laboratorians can use their specialized skills to review the outlier results requiring detailed attention. Because the laboratory staff is more focused on specific results, they have more time to evaluate challenging specimens and act upon critical results, leading to better decision-making and patient care.

2. Boosts responsiveness with a flexible rule-writing engine.

While many LIS’s offer advanced rule-writing for autoverification, few laboratories have a dedicated resource to do this programming. Instead, many labs rely on the corporate IT team or another department to build new rules, make changes, or add comments in the LIS, which means turnaround time can be slow or another department to build new rules, make changes, or add comments in the LIS, which means turnaround time can be slow and responsiveness to physician requests can suffer. Furthermore, IT analysts may not have the relevant experience to understand the nuances of clinical testing rules. The bottom line: Writing and validating rules through the LIS is often a complicated, cumbersome, and time-consuming process.

With middleware, laboratories can take control of creating their own rules directly from their own consoles, based on the urgency of the need. Laboratory personnel with appropriate security access can quickly prioritize, apply, and test new rules to accommodate dynamic workflows as their schedule demands. These changes can include rules and/or comments that apply to specific physicians and laboratory locations, rules for the review of automated CBC and differential results, and rules to enhance workflow between instruments. Having this level of rule-writing control empowers laboratory staff and drives efficiency and quality.

3. Drives consistency through network standardization.

With multiple sites, middleware can standardize rules and information across all networked locations—regardless of whether they are using the same LIS. This ability gives laboratories a cost-effective way to ensure greater consistency and control over information system-wide. The dictionary can be the same at all locations, taken from the primary site and uploaded to all other sites for enhanced standardization. Data can be easily distributed to all sites across a wide area network.

With consolidated rules, dictionaries, and databases made possible by middleware, today’s networked laboratories can gain powerful capabilities. Laboratories can:

- Perform delta checking of results from samples run in different laboratories
- Route and receive orders from one laboratory to another
- Generate reports from all laboratories into a single report
- Verify orders, review results, and review QC across laboratories regardless of where the results were generated
- Control and limit functionality and access to data
- Create review stations with the ability to review results from any laboratory
- Create a mirrored backup server that can be used if the main server goes down

Despite the network-wide visibility, middleware also allows for flexibility and control at the individual laboratory level. Each site can still write its own rules for specific physician preferences (e.g., specific add-on tests), as needed.

The Alverno Clinical Laboratory (Hammond, IN) hospital network found middleware to be the perfect solution for a potentially costly challenge. This organization needed to connect and standardize information across its 28-hospital network, but converting all the locations to the same LIS would have cost nearly $30 million and required multiple years to complete the transition. Implementing an advanced middleware solution across remote sites with different LIS’s allowed identical rules to be applied throughout the network, giving Alverno the necessary standardization at a much lower cost.

4. Ensures quality results through integrated QC management.

Advanced middleware also enables laboratories to automatically stop autoverification if commercial controls are out of limits. On one commercially available middleware, the use of exponentially weighted moving averages (EWMA) can alert users immediately about instrument trends and potential QC problems. The additional use of patient data to do continuous real-time monitoring of system performance ensures consistent, quality results between QC intervals.

Depending on how the protocol is defined, EWMA can either warn the laboratory, stop sending test requests to a specific instrument, or automatically shut-off autoverification to prevent the release of potentially erroneous results and eliminate the need for retesting, physician notification, and other corrective actions. This round-the-clock insight keeps laboratories in control of their results and provides an additional level of quality assurance.

Middleware can be the key to efficiency throughout the healthcare ecosystem. Regardless of a laboratory’s individual challenges, location and workflow needs, advanced middleware can be a crucial tool that helps the lab to fulfill its mission most effectively.
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Concerns about the proposed CMS laboratory payment reform
Will it threaten market competition and Medicare access?
By Julie Scott Allen and Mark S. Birenbaum, PhD

On April 1, 2014, President Obama signed into law the Protecting Access to Medicare Act of 2014 (PAMA). The bill, which had never undergone a congressional hearing or been subject to any study or evaluation, contained a complete overhaul of Medicare’s Part B Clinical Laboratory Fee Schedule (CLFS). PAMA required “applicable” laboratories, i.e., laboratories that receive a majority of their Medicare revenues from either the Clinical Laboratory Fee Schedule (CLFS) or the Physician Fee Schedule (PFS), to report their private insurer payment rates for every test, and the associated volumes of each test, beginning on January 1, 2016.

However, it took until October 2015 for the Centers for Medicare and Medicaid Services (CMS) to issue a proposed rule implementing this legislation, just three months before laboratories were supposed to begin reporting their private payer data. After significant pushback initiated by the National Independent Laboratory Association (NILA) and other stakeholders, and letters from members of Congress in opposition to CMS’s rushed effort to regulate, CMS did not issue a final regulation in time for the reporting process to begin on January 1, 2016. Instead, CMS issued a final rule on June 17, 2016 (almost one year late). However, CMS is still planning to rush implementation of the final rule by requiring laboratories to begin reporting private payment rates on January 1, 2017.

The intent of PAMA is to adjust Medicare payments to reflect “market” rates. However, it is the position of NILA and many others that the method for doing so outlined in CMS’s final rule does not undertake such an assessment.

The flaws in CMS’ final rule
Here’s why: The entire market includes payments received by hospital, physician office, and independent clinical laboratories. A “market rate” includes payments made to all of these entities. But CMS proposes to exclude a significant part of the market, hospitals, from reporting their private payer rates. And these hospital rates are frequently much higher than the rates paid to physician office laboratories and independent laboratories.

By excluding most hospital payment rates, CMS is arbitrarily limiting reported payment rates to the sector of the industry dominated by the two largest publicly traded laboratories. Those two laboratories frequently offer steep discounts on routine tests. CMS’s so-called market assessment will basically reassess all laboratory payment rates based on one segment of the laboratory market and will have that assessment dominated by the two large publicly-traded laboratories. This approach is a deliberate effort to dramatically reduce Medicare Part B CLFS payments.

Indeed, the Congressional Budget Office (CBO) scored PAMA laboratory payment reform at $2.5 billion in savings over 10 years. However, the budgetary impact assessment included in CMS’s final rule states that the agency anticipates $3.93 billion in savings. Clearly CMS envisions taking an ax to the Part B Clinical Laboratory Fee Schedule even before CMS conducts any assessment of laboratory payment rates. The June 17 rule provides no opportunity to understand how CMS gets to its final conclusion on revised rates. After a first run at a new, complicated program that has yet to be completely explained, CMS plans to list new rates that the laboratory community must accept. There is no transparency in this system, and community and regional laboratory businesses cannot survive extreme reductions based on skewed data reporting.

Furthermore, CMS has still not outlined in its final regulations, or otherwise, how laboratories are to report the trillions of data sets that must be provided or risk fines as high as $10,000 a day for non-compliance. The final rule states only that CMS will design and deploy a data collection system, with information forthcoming through subregulatory guidance. It is surprising that some laboratory organizations have congratulated and thanked CMS on issuing a delay in the regulation; in the absence of CMS providing more information that was not included in the final rule, applicable laboratories face nearly the same time crunch as they did when CMS tried to rush through a proposed rule last fall. Laboratories do not even have six months to begin the reporting process outlined in the June 17 final rule—and they are waiting on additional information that is nowhere in sight.

Making the case
In contrast to some lab organizations, NILA has been outspoken in its opposition to the PAMA law and the corresponding

Julie Scott Allen serves as Washington representative for the National Independent Laboratory Association (NILA).

Mark S. Birenbaum, PhD, serves as NILA Administrator.
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Combating inaccuracy and inefficiency in the lab
Tips for using logistics to avoid quality control issues.

By Kevin Boykin, MT, MBA

Diagnostic errors account for the most profound patient harm and largest fraction of malpractice claims, according to a 25-year review of malpractice payouts by Johns Hopkins Medicine. This places labs at the forefront of patient safety issues, even above prescription drug overdoses and surgical mistakes.

Recent news surrounding clinical lab testing and inaccurate results has called attention to broader issues within the industry. As budgets get tighter and labs look for ways to cut costs, they must consider the danger this can pose to service to the patient and, ultimately, patient care.

Avoiding serious testing issues isn’t just an in-lab issue. It starts with effective pre-analytical processes—including specimen collection, transport, and receipt into labs.

Collecting the specimen
Sample collection kicks off a long chain of events. Once the sample is collected, to ensure its integrity, the specimen must be properly packed, labeled, and accounted for before it leaves the medical facility and starts its journey to the lab.

The right packing and transport supplies protect samples during their transport and help ensure the integrity of the sample. The integrity of the sample can be impacted by such things as light, vibration, spillage, temperature, and, obviously, breakage. As such, packaging should be properly tested and validated.

Proper labeling of samples and packaging is critical to ensure proper identification of the patient and safety of the handler. Patient samples should include two patient identifiers. A well-designed patient label can help ensure proper identification and handling, which will help reduce the amount of specimen recollection. Labeling of transport containers is also critical to the safe handling of samples for couriers and carriers. Ultimately, the labeling of transport materials is the shipper’s responsibility, but providing the proper packaging and labels can set them up for success.

Tracking the specimen
A lot can go wrong between the time a sample leaves its original location and when it arrives at the clinical lab. Improper handling, lost or mixed up samples, and delayed delivery times plague clinical lab directors, but as new technology becomes validated.

Specimen integrity matters
Specimen integrity insight saves labs from wasted resources on unviable tests, both money and time. If laboratorians find out that a sample can’t provide accurate results before going through the testing process, they can alert clients sooner to get a replacement sample, and help reduce delayed test results.

Each specimen is attached to a patient, and inefficiencies and inaccuracies in the lab negatively impact real people. They also hurt client relationships and, ultimately, labs’ bottom lines. By using advances in collection and logistics management technology to their advantage, labs can ensure financial success while optimizing the client and patient experience.

REFERENCE


Kevin Boykin, MT, MBA, serves as CEO of Path-Tec, a provider of specimen management solutions. He holds degrees from Columbus State University and Auburn University.
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Rapid molecular platform

Alere i is a rapid molecular platform for the qualitative detection of infectious diseases; it is currently available and CLIA-waived for Strep A and Influenza A & B. The Alere i system is ideal for streamlining respiratory testing in the laboratory. Features include molecular results in minutes; intuitive, user-friendly design; a sample amplification process; small footprint; and connectivity to the Alere RALS system. On August 19, 2016, Alere announced that the Alere i RSV (respiratory syncytial virus) test received 510(k) marketing clearance from the FDA for the detection of RSV infection in children and adults. It is not currently available in any markets, but is expected to make its debut this fall. Alere, www.rsleads.com/610ml-150

Droplet generator and reader

Medical practitioners in Europe can use Bio-Rad’s CE-IVD marked QX200 Droplet Digital PCR (ddPCR) System, IVD for highly accurate diagnostic detection and quantification of nucleic acids, aiding clinical decision-making in the treatment of diseases ranging from cancer to transplant rejection and viral infection. The system includes a QX200 Droplet Generator, QX200 Droplet Reader, and QuantaSoft software. The droplet generator and reader are CE-IVD marked for use in the European Union for in vitro diagnostics and are available for use in the clinical laboratory. Bio-Rad, www.rsleads.com/610ml-151

Self-contained collection and test device

Chembio Diagnostic Systems, Inc., is now marketing and selling its SURE CHECK HIV 1/2 Assay, which was previously marketed in the U.S. by Alere, Inc., as Clearview COMPLETE HIV 1/2 Assay, Part #92111. This change is in name only; the product has not undergone any changes in format or formulation and does not require re-validation. This product continues to be manufactured exclusively at Chembio’s FDA-registered, cGMP compliant and ISO 13485 certified facility in Medford, NY. SURE CHECK is an easy-to-use, self-contained collection and test device; is FDA-approved/CLIA waived (for fingerstick and whole blood); and requires only 2.5 μL of fingerstick or venous whole blood, serum, or plasma. Chembio, www.rsleads.com/610ml-152

Hemostasis testing system

ACL AcuStar Hemostasis Testing System is a fully automated, high sensitivity chemiluminescent system designed for Hemostasis specialty and routine testing. HemosIL assays improve accuracy, range, sensitivity and specificity with the simplicity of ready-to-use reagent cartridges. High-performance chemiluminescent HemosIL assays include: D-Dimer, HI-LogGP-6H+, aCL IgG, aCL IgM, aB2GPI IgG, aB2GPI IgM, VWF:RCo*, VWF:Ag*, and VWF:CB*. It features self-contained, ready-to-use reagent cartridges, stable up to six weeks on-board; is available 24 hours/day, 7 days/week; features assay calibration on lot change only and random access: no batching required. *Not available in all countries. Not currently 510(k) cleared. Instrumentation Laboratory, www.rsleads.com/610ml-153

Clinical chemistry ensemble

MedTest, exclusive U.S. distributor of the Mindray 480 Chemistry Analyzer, manufactures and distributes reagents, calibrators, and quality control products for the general chemistry and drugs of abuse testing markets. MedTest provides customized installation, on-site operator training, technical phone support, and on-site support if needed. The 480 Analyzer produces 400 photometric results per hour and 240 ISE tests per hour with an overall throughput of 560 tests per hour. Advanced features of the BS-480 analyzer include Auto-Start-Up, QC, ReRun, Pre-dilution, Post-dilution, ISE Calibration, Probe Cleaning, Reagent Blank Checks, and Probe Collision Recovery; which provides the laboratory with smooth operational and enhanced workflow efficiencies. MedTest, www.rsleads.com/610ml-154

Mycoplasma direct test

The newly FDA-cleared illumigene Mycoplasma Direct test provides highly sensitive and specific results from day one of symptoms using throat swabs and a simple procedure that takes less than two minutes of hands-on time. The illumigene molecular platform requires no capital equipment expense or service contracts. The platform’s test menu also includes molecular assays for C. difficile, Group A Streptococcus, Group B Streptococcus, HSV 1&2, and pertussis in the United States, as well as chlamydia, gonorrhea, and malaria outside of the U.S. Meridian BioScience, www.rsleads.com/610ml-155

Glucose hospital meter system

StatStrip Glucose Xpress2, StatStrip Glucose, and StatStrip Glucose Xpress are three hospital glucose meters that have been cleared by the FDA and proven to be safe and effective for use throughout all hospital and professional healthcare settings, including with critically ill patients. Use of other strip-based glucose meters with critically ill patients is considered “off-label” by the FDA and Centers for Medicare and Medicaid Services. StatStrip Glucose Xpress2 utilizes the same glucose measurement technology as StatStrip Glucose and StatStrip Glucose Xpress. StatStrip Glucose technology has been studied extensively, has been proven to be free of clinically significant interferences, and demonstrates excellent agreement with central laboratory reference methods. Nova BioMedical, www.rsleads.com/610ml-156

Chemistry assay for procalcitonin

Roche has received 510(k) clearance for its Elecsys BRAHMS PCT (procalcitonin) assay as a dedicated testing solution for people with severe sepsis or septic shock. With this clearance, Roche provides a fully integrated solution for sepsis risk assessment and management. PCT is a sepsis-specific biomarker associated with bacterial infection, and PCT levels in blood can aid clinicians in assessing the risk of sepsis as well as managing the disease when present. The Elecsys BRAHMS PCT assay can aid in assessing the risk of critically ill patients to progress from severe sepsis to septic shock and help determine the 28-day mortality risk in sepsis patients. Roche, www.rsleads.com/610ml-157
Flu and RSV test

Roche has announced that the FDA has granted 510(k) clearance and CLIA waiver for the cobas Influenza A & B and RSV test for use on the cobas Liat System. Roche is extending the value of highly accurate CLIA-waived molecular testing beyond flu A/B and strep A to include respiratory syncytial virus (RSV), a cause of more than 80 percent of acute lower respiratory tract infections in infants under one year of age. The cobas Influenza A & B and RSV test is the third assay on the cobas Liat System to receive CLIA waiver, following the cobas Strep A and cobas Influenza A & B tests, which received CLIA waiver in May and September 2015, respectively. The cobas Liat Analyzer and all three assays are FDA cleared and CLIA waived. Roche, www.rsleads.com/610ml-158

Fully automated coagulation analyzer

The Sysmex CS-2500 System from Siemens Healthineers, a fully automated coagulation analyzer, offers mid-volume and multisite hemostasis labs smartly designed technologies—including PSI technology—to improve sample management, increase efficiency, and streamline lab workflow. The system offers a wide spectrum of testing methodologies and sophisticated software to simplify lab operations, and provides an uninterrupted workflow delivered in a compact, affordable footprint. Additionally, it offers lab-to-lab consistency for multisite patient monitoring, with sample result traceability for in-depth audit capabilities and sophisticated cap-piercing technology. Compact yet powerful, the Sysmex CS-2500 is designed to reduce costs, optimize workflow, and maximize operating efficiency. Siemens, www.rsleads.com/610ml-159

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Meeting the challenges that face transfusion services today to serve Southwest Florida clinicians and patients

For readers who are not familiar with SunCoast Blood Bank (SCBB), can you please provide some information about its nearly seven-decade history? SCBB was born from Sarasota Memorial Hospital in Sarasota, FL, on Valentine’s Day, 1949. It now provides products and services for 12 hospitals or healthcare facilities in Southwest Florida.

We are much more than a traditional blood bank that collects blood from donors and distributes it to hospitals. We perform mononuclear cell therapy for patients with late-stage cancers and provide plasma and red cell exchanges that occur at the bedside within the hospitals.

We also perform DNA genotyping of the red cells to solve complex patient antibodies, and find rare units to help those complex cases in our community and around the county. SCBB also uses its expertise to provide daily phlebotomy services to one of our partner hospitals.

SunCoast Blood Bank is also evolving to assist in bio-development by providing specialty products and services in order to assist vital research.

Impressive. In that context, how would you describe SCBB’s mission and purpose? We are dedicated to providing our community with the highest quality of life-saving blood products and transfusion-related testing services possible. Our purpose is also to act as the role of a first responder organization that is quickly activated to respond to any trauma that arrives at any area hospital. Local lives depend on our role within the hospitals to provide around-the-clock patient transfusion services.

How do you serve customers in the Southwest Florida region? Do you serve institutions of different types and sizes? We serve all sizes of healthcare facilities, from large trauma centers to small surgery and rehabilitation centers. We actively communicate with our partner facilities to ensure proper service and inventory levels. We routinely keep them up to date on the latest regulatory guidance to help them navigate these varying blood service protocols.

In a time of change in the blood industry, what continuing function do you see for for-profit independent community blood banks like SCBB? Blood banks around the U.S. are challenged with more environmental forces (low reimbursements, more operational costs, cumbersome regulations, higher health insurance costs, etc.) than at arguably any time in our long histories. SCBB is not immune to these external and internal forces. Therefore, blood banks must begin diversifying to find new and sustainable revenue sources to help keep the doors open and the lights on. This includes actively fundraising in order to keep up with newest technologies and capital needs. Many blood centers are also looking for any way to further streamline their organizations in order to weather this difficult time. The low-hanging fruit has long ago been plucked, but there is still some higher-hanging fruit to be had in order to reduce operational costs.

How have patients benefited from SCBB’s pathogen-reduction platelet system? Blood is classified as a drug, and though our “drug” has much safer side effects than many drugs that you see advertised on TV, the Intercept Pathogen Reduction system makes blood platelets even safer. Pathogen-reduced platelets benefit patients by inactivating a large host of bacteria and viruses, including closing the window on HIV and hepatitis virus. Pathogen-reduced platelets also benefit our sickest patients by eliminating the rare but deadly graft-vs-host disease.

In the context of Zika, does your outreach program include blood for Puerto Rico? Puerto Rico has basically a three-pronged approach to managing its blood supply. Blood banks in Puerto Rico are now testing donated units for the Zika virus, which allows them to collect, process, and distribute units that are negative for Zika virus. They also import units from mainland blood centers to have blood on their shelves from non-endemic Zika areas. Last, they are using pathogen-reduction technologies for their single donor platelet products.

How was the Zika virus affected blood screening for SCBB? Our blood center had to amend its screening process very quickly in light of the non-travel-related Zika cases in South Florida. In fact, we had to quickly amend procedures to defer donors who traveled to those South Florida areas, and we also added other questions to our screening process. Zika can be spread by sexual contact. On August 8th, SCBB began testing 100 percent of our donors for the Zika virus, and we will continue to do so through the remainder of mosquito season. When the season is over, we will re-evaluate. We are also increasing our use of pathogen reduction for our single donor platelets in lieu of additional bacterial and Zika virus testing.

By Alan Lenhoff, Editor

Scott Bush
CEO
SunCoast Blood Bank

Professional
I have been in non-profit blood banking for over 25 years. Most recently, I have been associated with SunCoast Blood Bank for the past 11 years. For the last six, I have been acting CEO of the organization. Before that, I worked approximately 15 years for the American Red Cross Biomedical in the Ohio-Michigan Division. My responsibilities included managing the blood product manufacturing laboratories as well as the Platelet Apheresis Programs.

Education
I received a BS in Biology from Ohio Dominican University and a Masters degree in Nonprofit Management from the University of Central Florida. I was also a proud hospital corpsman in the U.S. Naval Reserve.

Personal
In my free time, I am active in animal welfare causes. I sit on the board of Animal Rescue Co-alition, a Sarasota, FL, nonprofit that works to fix the overcrowding issue at animal shelters by proactively providing spay/neuter surgeries to dogs and cats. We also have a feral cat program as well as an emergency medical fund to help treat animals with various traumas. I have a special place in my heart for injured, abused, or neglected animals; in fact, I have 16 animals that I take care of at my house. My menagerie consists of horses, dogs, cats, and doves.
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