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MEDICAL LABORATORY OBSERVER

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CE

Monoclonal antibody therapy

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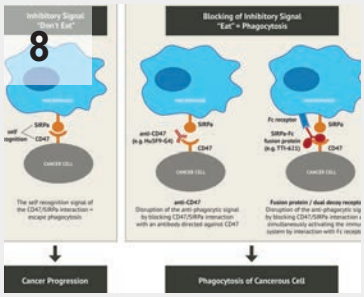

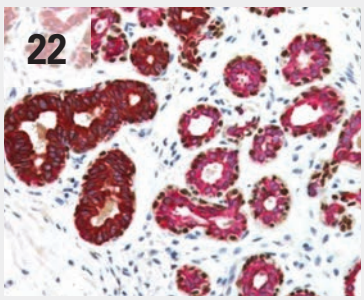

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Retaining your employees

"I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel."
– Maya Angelou

By Lisa Moynihan
Editor

Medical Laboratory Observer's (MLO's) primary audience is managers. Specifically, those who manage clinical laboratorians. A hot topic in the healthcare industry today is the rapidly aging and retiring workforce. With more than 200,000 registered laboratories in the United States[1], the need for clinical laboratory science professionals is prolific. While laboratorians will be retiring in droves within the next ten years, the incoming workforce looks bleak, with a desperate call for chemistry majors, medical technologists, and phlebotomists to fill the shoes of those who came before them.

Regardless of industry, finding a good employee can be challenging, but it's keeping them that is the hard part.

Our August 2019 issue featured an enlightening article entitled, "A self-reflection on recruitment and retention" by Carleen Van Siclen, Manager of Laboratory Staff Education and Professional Development at Mayo Clinic in Jacksonville, FL. It read, "You have heard the adage, 'People leave managers, not companies,' right? It's a common phrase often heard when corporate leadership is discussed.

According to a 2018 Gallop poll, only one in three workers in the U.S. strongly agrees that they received recognition or praise for doing good work in the past seven days. At any given company, it's not uncommon for employees to feel that their best efforts are routinely ignored. Further, employees who do not feel adequately recognized are twice as likely to say they'll quit in the next year.[2]

Van Siclen goes on to say, "As a manager, how often do you take the opportunity to thank your employees for a job well done? Do you share how proud you are of your staff to others within the organization? What is the culture at your institution?" I've shared just three of Carleen's many thought-provoking questions.

Our July 2019 issue featured a stimulating interview with ELLKAY executive Lior Hod. Hod was proud to share, "Since the time we started the business in my basement, we have always paid for lunch for our employees. We also provide cold drinks, the best coffee, bagels, fresh fruits, fresh-baked cookies, ice cream, and beer on tap. I like to create an environment that rewards the hard work of our employees. I believe that in creating an atmosphere that celebrates their dedication, it encourages them to not only have fun, but also strive for excellence."

Not all of us have a beer budget, however, we all have time to say, "Thank you." It's important to remember that as leaders, we lead by example. If you are not professional, courteous, available, and grateful, how can you expect those qualities from your employees? Afterall, managers are only as strong as their team.

What do you do as a manager to acknowledge your employees and/or your professional teams? What has a manager and/or supervisor done to make you feel valued and/or important? I want to hear from you! Please email me at lmoynihan@mlo-online.com.

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2477 Stickney Point Rd., Suite 221B Sarasota, FL 34231
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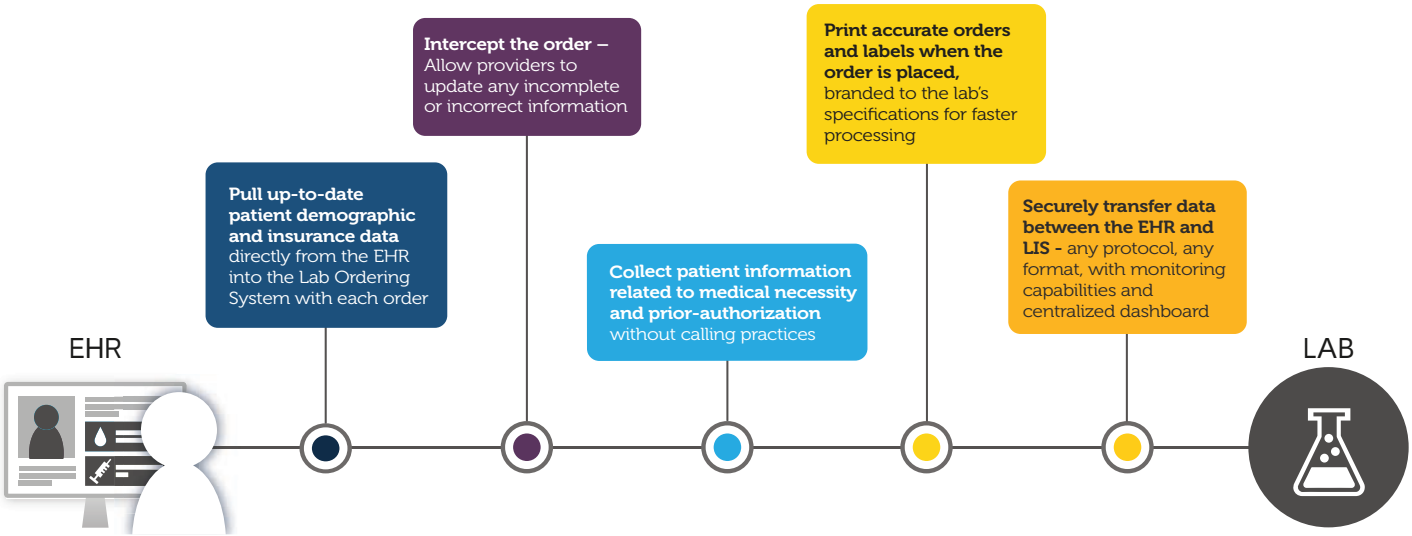

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FAST FACTS

Blood clots

A blood clot (thrombosis) is blood that has been converted from a liquid to a solid state. Blood clots are serious, but they can be prevented.

274 people

on average, die every day as a result of blood clots (ie: deep vein thrombosis or pulmonary embolism).

107 to 130

blood clot cases occurred each year, per 100,000 Caucasian individuals, from 1985–2002.

250,000

cases occurred each year between 1966–1990.

900,000

cases per year are now suggested according to recent scientific modeling and public health statistics.

100,000 to 300,000

deaths occur each year, which is greater than the total number of people who die from AIDS, breast cancer, and motor vehicle crashes combined.

600,000

non-fatal cases of deadly blood clots occur each year.

40 percent

are caused by blood clots in the lungs.

60 percent

are caused by blood clots in the legs.

547,596

hospitalizations due to blood clots occurred from 2007–2009.

Source: https://www.stopthe-clot.org/blood-clot-information/blood-clots-in-the-united-states/

TUBERCULOSIS

FDA approves new drug for treatment-resistant forms of TB that affects the lungs. The FDA approved Pretomanid in combination with bedaquiline and linezolid for the treatment of a specific type of highly treatment-resistant tuberculosis (TB) of the lungs.

"The threat of antimicrobial-resistant infections is a key challenge we face as a public health agency," said FDA Principal Deputy Commissioner Amy Abernethy, MD, PhD. "The bacterium that causes tuberculosis can develop resistance to the antibiotics used to treat it. Multidrug-resistant TB and extensively drug-resistant TB are public health threats due to limited treatment options. New treatments are important to meet patient national and global health needs. That's why, among our other efforts to address antimicrobial resistance, we're focused on facilitating the development of safe and effective new treatments to give patients more options to fight life-threatening infections. This approval also marks the second time a drug is being approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs, a pathway, advanced by Congress, to spur development of drugs targeting infections that lack effective therapies. We hope we continue to see more development of antibacterial drugs for treating serious or life-threatening infections in limited populations of patients with unmet medical needs."

Pretomanid in combination with bedaquiline and linezolid is approved for treating a limited and specific population of adult patients with extensively drug resistant, treatment-intolerant or nonresponsive multidrug resistant pulmonary TB. Multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB) are difficult to treat due to resistance to available therapies. According to the WHO, in 2016, there were an estimated 490,000 new cases of MDR TB worldwide, with a smaller portion of cases of XDR TB. The safety and effectiveness of Pretomanid, taken orally in combination with bedaquiline and linezolid, was primarily demonstrated in a study of 109 patients with extensively drug-resistant, treatment intolerant, or non-responsive multidrug-resistant pulmonary TB. Of the 107 patients who were evaluated six months after the end of therapy, 95 (89 percent) were successes, which significantly exceeded the historical success rates for treatment of XDR TB.

Pretomanid is the second drug to be approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs, or LPAD pathway, established by Congress under the 21st Century Cures Act to advance development and approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need. Approval under the LPAD pathway may be supported by a streamlined clinical development program. These programs may involve smaller, shorter, or fewer clinical trials. As required for drugs approved under the LPAD pathway, labeling for Pretomanid includes certain statements to convey that the drug has been shown to be safe and effective only for use in a limited population.

Pretomanid also received the FDA's Qualified Infectious Disease Product (QIDP) designation. The QIDP designation is given to antibacterial and antifungal drug products intended to treat serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act.

The FDA granted Pretomanid tablets Priority Review, under which the FDA's goal is to take action on an application within an expedited time frame, and Orphan Drug designation.

HPV

Large percent of cancers caused by HPV could be prevented by vaccine. During 2012—2016, an average of 43,999 HPV-associated cancers were reported each year, according to a new study published in CDC's *Morbidity and Mortality Weekly Report* (MMWR). Among the estimated 34,800 cancers probably caused by HPV, 92 percent are attributable to the HPV types that are included in the HPV vaccine and could be prevented if HPV vaccine recommendations were followed.

CDC researchers analyzed 2012-2016 data from the CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) to determine the incidence of HPV-associated cancers, and to estimate the annual number of cancers attributable to the HPV types in the currently available HPV vaccine. This report marks the first time these data are available at the state-level. Key findings include:

- During 2012-2016, an estimated average of 34,800 HPV-attributable cancers were diagnosed each year.

- The most common cancers were cervical (9,700) and oropharyngeal cancer (12,600).
- The number of cancers attributable to HPV types targeted by the vaccine ranged by state from 40 in Wyoming to 3,270 in California.
- Oropharyngeal cancer was the most common cancer attributable to vaccine types in all states except Texas where cervical cancer is most common.
- In Alaska, D.C., New Mexico, and New York, the estimates of oropharyngeal and cervical cancers attributable to the types in the currently available HPV vaccine were the same.

CDC recommends that all preteens get the HPV vaccine when they are 11 or 12 years old to protect them before they are ever exposed to the virus. However, additional data released in the MMWR show little progress toward increasing HPV vaccination rates among teens ages 13—17 years. This data, collected as part of the 2018 National Immunization Survey Teen (NIS-Teen), show a four percent increase in HPV vaccination rates among teen boys and less than a one percentage point increase among teen girls. Overall, just 51 percent of all teens had received all recommended doses of the HPV vaccine, a two percent increase from 2017.

HPV vaccination rates were higher in teens whose parents reported receiving a recommendation from their child's healthcare professional. Consistently, data shows that physicians play a key role in educating parents and are the most trusted source of information for parents of pre-teens eligible for vaccination. CDC and state health departments continue to encourage health care professionals to talk to parents and provide them with information on the benefits of vaccination to prevent cancer and save lives.

The HPV vaccine is recommended for everyone through age 26 if they did not get vaccinated when they were younger. Vaccination is not recommended for people older than 26 years. However, some adults ages 27 through 45 years who are not vaccinated for HPV may decide to be vaccinated after speaking with their doctor about their risk for new HPV infections and the possible benefits of vaccination. HPV vaccination in this age range provides less benefit, as more people have likely been exposed to HPV.

In addition to HPV vaccination, cervical cancer screening is recommended for women ages 21—65. Women ages 21—29 years can be screened with a Pap test every three years. In addition to the Pap test, a test called the HPV test looks for HPV infection. Among women ages 30 to 65 years there are three strategies: (1) Pap test alone every three years, (2) the HPV test used with the Pap test every five years, or (3) the HPV test alone every five years. The HPV test can provide additional information when Pap test results are unclear for women ages 21 and older.

Genomics

Leaders of NIH's All of Us Research Program recap progress and next steps. The All of Us Research Program at the National Institutes of Health (NIH) has made strong progress in its efforts to advance precision medicine, according to program leadership in the *New England Journal of Medicine.*

With information provided by volunteers across the U.S., All of Us is developing a robust data platform to support a wide range of health studies. The program aims to include data from 1 million or more people from diverse communities. As of July 2019, more than 230,000 people have enrolled, including 175,000 participants who have completed the core protocol. Of those, 80 percent are from groups that have been historically underrepresented in biomedical research. Participants contribute information in a variety of ways, including surveys, electronic health records (EHRs), physical measurements, blood, urine and saliva samples, and Fitbit devices. In the future, the program will add new surveys and linkages to other data sets and digital health technologies and begin genotyping and whole-genome sequencing participants' biological samples. Data will be broadly accessible to approved researchers, and participants will receive information back about themselves.

In May 2019, with enrollment ongoing, the program released initial summary data at https://www.researchallofus.org. Now, the All of Us team is planning demonstration projects to assess the usefulness and validity of the data set, in preparation for the launch of the Researcher Workbench—the secure platform where researchers will be able to conduct analyses.

The program's ongoing success will rely on several factors. The program must continue to enroll participants from across the country, including those in rural and other underserved areas. The program needs to ensure that participants, once enrolled, derive value, remain engaged, and retain trust in the program such that they continue to share data long term. Additionally, the program must continue to protect from cyberattacks, protect participant privacy, and harmonize data from different EHR systems.

The authors anticipate that the program's value will become even more rich as it matures, enabling new discoveries over time. A goal of the study is to improve population health through the identification of risk factors and biomarkers (including environmental exposures, habits, and social determinants) to allow more efficient and accurate diagnosis and screening, better understanding of diverse populations, more rational use of existing therapeutics, and the development of new treatments.

Reagents

MedTest Dx launches Certified Performance Guarantee Program. MedTest Dx, a solution provider offering integrated products and services for clinical diagnostic testing announced it will launch a new Certified Performance Guarantee Program for its Pointe Scientific branded line of clinical chemistry diagnostic reagents.

Pointe Scientific manufactures diagnostic reagents in the U.S., marketing its products globally under its own brand. The new Certified Performance Guarantee program is intended to provide an additional layer of assurance to customers that the company stands fully behind the quality and reliability of every Pointe Scientific branded clinical chemistry reagent it ships, issuing a free replacement to any customer who is not fully satisfied with the performance of their Pointe Scientific branded reagent.

"We are very proud of Pointe Scientific's well-established reputation as a quality leader in diagnostic reagents, and that its products are manufactured here in the U.S.," said Wayne Brinster, CEO of MedTest Dx. "Pointe Scientific offers an extensive line of cost-effective clinical chemistry reagents, some of which it was the first to introduce to the market. The company's long record of successful innovation and consistent high quality made the decision to implement the Certified Performance Guarantee Program an easy one. We view the Guarantee program as indicative of our ongoing commitment to serving as our customers' partner of choice for clinical diagnostic testing technologies."

Monoclonal antibody therapy: What compatibility testing labs need to know

By Wyenona Hicks, MS, MT(ASCP) SBB, and Juan A. Merayo-Rodríguez, MD

Utilizing immunotherapy to treat hematologic malignancies and solid tumors is becoming more commonplace. This article reviews the effects of monoclonal antibody (mAb) drugs on red blood cells and pretransfusion testing, as well as available methods used to minimize adverse effects. A widely used term for cell markers in immunophenotyping is Cluster of Differentiation (also known as cluster of designation or classification determinant and often abbreviated as CD). CDs are cell surface molecules expressed on leukocytes and other cells pertinent to the immune system. The purpose of this nomenclature is to provide standardization as each antigen is assigned a unique CD number that correlates to the antibody which bind to its cognate antigen. More than 400 molecules have already been described that are being used as targets for cell immunophenotyping.[1] Particularly, a number of CD molecules expressed on tumor cells are being studied in order to develop more precise, targeted treatment for cancers. At the time of this publication, the two most frequently encountered therapeutic monoclonal antibodies seen in blood banks are anti-CD38 and anti-CD47.

In 2015, Darzalex (Daratumumab or "Dara") became the first human CD38 mAb approved by the FDA for the treatment of relapsed or refractory multiple myeloma in patients who have received at least three prior treatments.[5] Other anti-CD38 agents, such as MOR202, are in trials. In June 2019, the FDA approved a combination of Darzalex-Revlimid-dexamethasone to treat newly diagnosed multiple myeloma (MM) patients with who failed to qualify for autologous stem cell transplant.[2] Isatuximab (SAR-650984) is another CD38 IgG1 mAb in clinical trials for the treatment of patients with MM. It received orphan designation for relapsed/refractory multiple myeloma by the FDA in the second quarter of 2019.[3]

CD47 mAbs are currently undergoing clinical trials for multiple solid and hematologic malignancies, (e.g., Hu5F9-G4, CC-90002, SFR231) and in 2018 the FDA granted SFR231 orphan drug designation for MM.[4] Refer to **Figure 1** of a bone marrow aspirate with plasma cells in MM.

CD38 and CD47 overview

CD38 is a type II transmembrane glycoprotein and found in low levels on the surface of many types of cells including B and T lymphocytes, natural killer (NK) cells, plasma cells, platelets, and red blood cells (RBCs). It functions as a receptor and adhesion molecule, as well as a manufacturer and hydrolyzer of an intracellular calcium ion-activating messenger. CD38 is highly expressed on plasma cells in MM; this makes it a desirable target for MM therapy. The binding of CD38 mAb to the CD38 receptor inhibits the growth

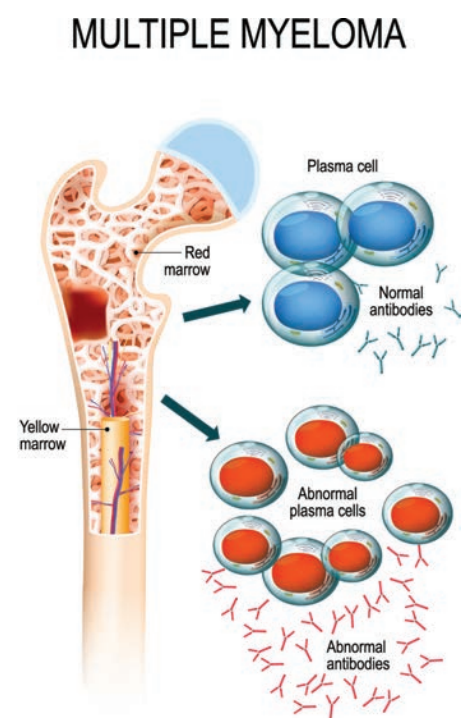

Figure 1. Representation of the overproduction of plasma cells in the bone marrow in multiple myeloma (MM) that produce high levels of monoclonal immunoglobulin (M protein).

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LEARNING OBJECTIVES

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

1. Discuss the discovery of immune therapy and the diseases that specific anti-CD markers can treat.
2. Recall the immune mechanisms involved in CD38 and CD47 therapy.
3. Describe the blood banking testing problems associated with CD38mAb therapy and techniques used to mitigate them.
4. Describe the blood banking testing problems associated with CD47mAb therapy and techniques used to mitigate them.

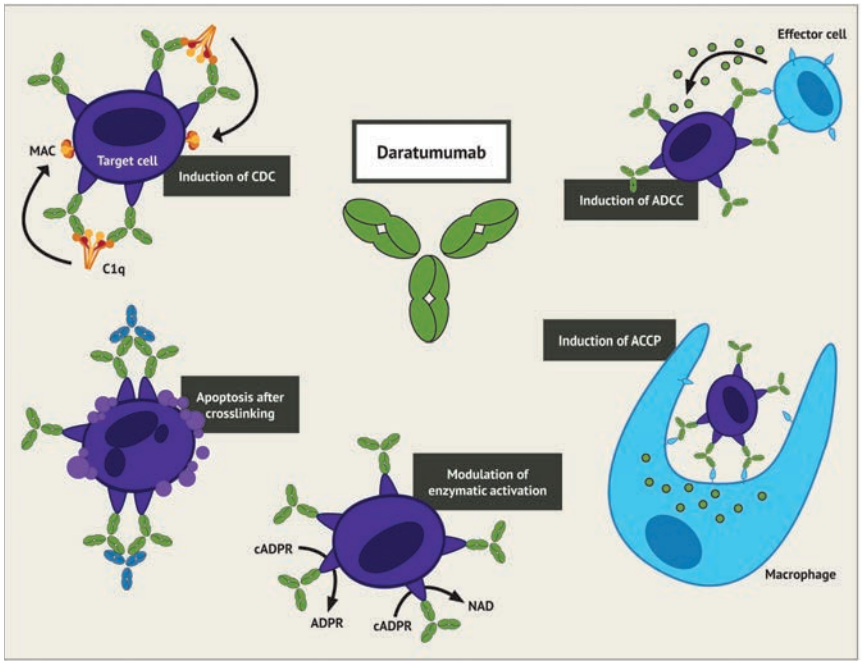

Figure 2. The various immune mechanisms of the anti-tumor activity of Daratumumab[6]

and proliferation of MM cells and induces tumor cell death or apoptosis through a variety of immunological mechanisms. This includes Fc-dependent immune-effector mechanisms, direct apoptotic activity, and immunomodulatory effects by the elimination of CD38-expressing regulatory T, regulatory B, and myeloid-derived suppressor cells.[6,7] (**Figure 2**)

Expressed on virtually all tissue and cell types including RBCs and platelets, CD47 has many functions including cell migration, cell adhesion, and T cell function. CD47 is an integrin-associated transmembrane protein (IAP) that has high affinity for thrombospondin (TSP) and signal-regulatory protein alpha (SIRPα) on the macrophage membrane that is directly involved in the prevention of phagocytosis by macrophages.[8] This "don't eat me" signal protects transfused RBCs and platelets from rapid elimination by macrophages in the spleen. CD47 is also a transmembrane protein and part of the Rh complex. The expression of CD47 is affected by Rh phenotype; rr (dce/dce) having the highest expressions, compared to D-positive, and Rh_{null} having the least. Studies demonstrate that CD47 expression decreases as RBCs age, so it additionally functions as a "eat me" signal and considered a marker of senescence.[9,10]

A cell surface protein called calreticulin (CRT) appears to be expressed on malignant cells, but not on most normal cells. As cancer cells are dying, (e.g., during chemotherapy treatment) CRT is upregulated and emits "danger" signals (part of the warning system known as damage-associated molecular patterns or DAMPs). CRT interacts with pattern recognition receptors (PRRs) expressed on myeloid and lymphoid cells, such as low-density lipoprotein receptor-related protein 1 (LRP-1), to promote phagocytosis. Also highly expressed on cancer cells and in opposition, the CD47-SIRPαpathway impedes macrophage-mediated destruction. As a therapeutic human monoclonal IgG4 antibody, anti-CD47 (e.g., Hu5F9-G4) blocks interaction of CD47-SIRPα, allowing the pro-phagocytic calreticulin/LRP-1 collaboration to facilitate the "eat me" signal. As a consequence, treating patients with anti-CD47 paves the way for clearing malignant cells. Refer to **Figure 3** for proposed mechanism of action of CD47-targeted anti-tumor therapy.[11-13]

Although new monoclonal antibodies show promise for improved outcomes, patients receiving these treatments for MM and other hematological diseases present many challenges for both technologists performing pretransfusion compatibility testing and physicians that interpret the clinical significance of the results.

Interference in blood bank testing when samples contain anti-CD38

After treatment with anti-CD38 commences, immediate spin reactions are unaffected, but residual immunotherapeutic antibody in the patient's plasma cross-reacts with RBCs. This causes unexpected, generally

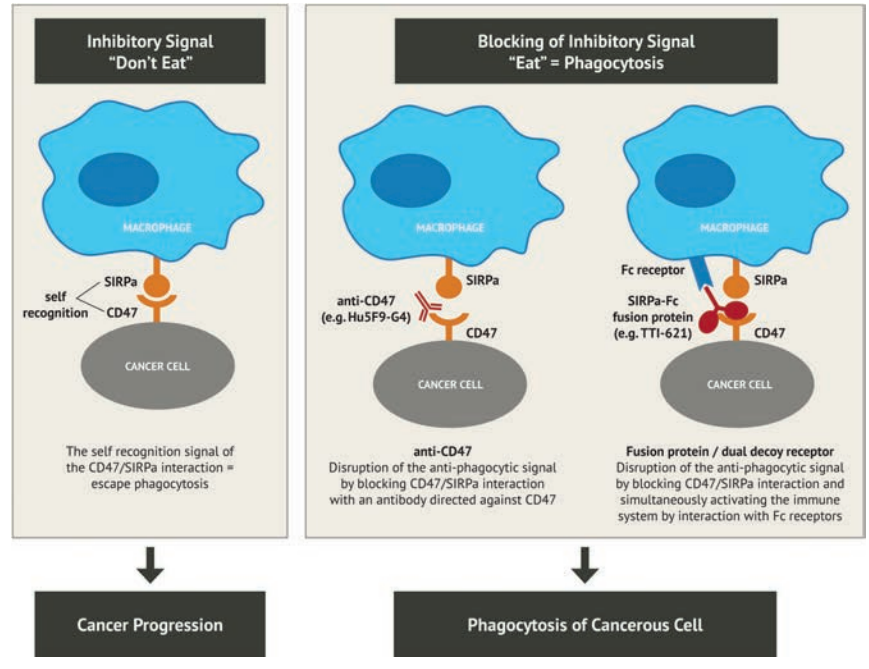

Figure 3. Proposed mechanism of action of CD47-targeted anti-tumor therapy[11]

weak, panreactive serologic reactions when utilizing the indirect antiglobulin test (IAT) (e.g., antibody screens, antibody identification panels, phenotype tests, and crossmatches). Interference is seen with all media (e.g., saline, LISS [low-ionic-strength solution], and PeG [polyethelene glycol]), by all common test methods (tube, gel, and solid phase), and can persist for six months following treatment.[14,15] The autocontrol (AC) and direct antiglobulin test (DAT) may be positive or negative (most often), and results frequently resemble an antibody to a high incidence antigen or a warm autoantibody. Adsorptions using untreated or chemically treated cells are not effective.

Mitigation of anti-CD38 interference

The goal of any blood bank technologist when faced with panreactivity due to mAb treatment is to ensure clinically significant alloantibodies are not underlying the drug antibody. The most practical and inexpensive method employed to eliminate the interference of anti-CD38 is pretreating reagent red cells with dithiothreitol (DTT). DTT is a reducing agent that disrupts disulfide bonds formed between cysteine residues. The CD38 molecule (also on RBCs) has five disulfide bonds, so when a patient's plasma is tested with reagent red cells treated with DTT, reactivity from anti-CD38 is abolished. It is important to keep in mind that Kell, Knops, Dombrock, Lutheran, Yt (formerly Cartwright), and JMH blood group system antigens, as well as the LWa antigen, are destroyed by DTT, which cannot be excluded during antibody identification.

Generally used by large reference laboratories, the patient's plasma may be tested with a panel of cord RBCs that have been extensively phenotyped.[16] Cord RBCs have very little CD38, if expressed at all. Recombinant soluble human CD38 or anti-daratumumab idiotype can be utilized to eliminate interference, but is not widely available at this time.[14]

For patients with a negative antibody screen using DTT-treated RBCs, an electronic or immediate-spin crossmatch with ABO/RhD compatible units may be performed.[15] Units negative for the K (KEL1) antigen should be issued if the patient is negative for this antigen, or the antigen typing is unknown. For patients with known alloantibodies, antigen negative RBCs must be provided. This can be accomplished by providing phenotype or genotype matched units. Indirect antiglobulin crossmatches will be incompatible and local policies regarding ordering physician signature must be followed before transfusing blood products. Refer to **Figure 4** for summary of anti-CD38 interference and mitigation strategies.[7]

Interference in blood bank testing when samples contain anti-CD47

Once treatment with anti-CD47 begins, false positive reactions can be seen in all phases of testing (immediate spin, 37°C, and IAT), with all media (e.g., saline, LISS, and PeG), and with all methods of IAT testing (i.e., tube, gel, solid phase). ABO discrepancies occur due to false positive results in the reverse typing (all types except for O), and false positive results in the forward typing due to spontaneous agglutination of patient RBCs. Because of the high level of CD47 on RBCs, these reactions may mimic those seen with IgM antibodies. Cord RBCs are also reactive in all phases. DATs may be falsely negative due to a "blocking effect" caused by high levels of antibody present, but eluates are strongly positive. False negative phenotyping test results can occur due to RBCs heavily coated by anti-CD47.

Mitigation of anti-CD47 interference

The most practical and cost-effective method currently available to eliminate the interference of anti-CD47 is to utilize an anti-IgG reagent that does not bind to IgG4, such as anti-IgG (Murine Monoclonal) Gammaclone (Hu5F9-G4 and CC-90002 are monoclonal IgG4 anti-CD47). Occasionally, even using this method, it may still demonstrate a weak reactivity because of carryover to the IAT phase of testing. Allogenic adsorption or adsorption using pooled platelets or papain treated RBCs generally require four adsorptions.[11]

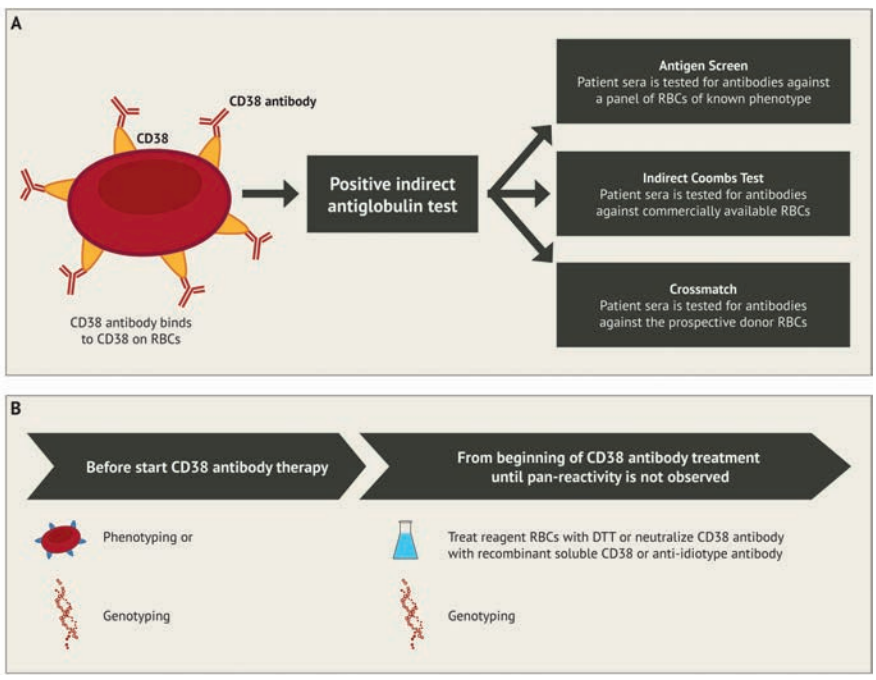

Figure 4. (A) Summary of anti-CD38 interference in blood bank testing. (B) Strategies to mitigate anti-CD38 interference in blood bank testing.[7]

What compatibility testing labs and clinicians need to know

Without a medication history when samples are submitted for work-up, regardless of the presentation, a blood bank technologist may be confounded and unknowingly waste precious time and resources chasing "ghosts." With

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this said, it is very important that clinicians and other healthcare providers understand that pretransfusion testing, including an extended phenotype should be performed before initiating treatment (either serology or predictive genotype for D, C, c, E, e, K, Jka, Jkb, Fya, Fyb, S, and s antigens). In addition, a complete, accurate history (e.g., diagnosis, medications, transfusions, transplants, and pregnancies) must be provided any time pretransfusion testing and/or antibody identification is required. This information can be instrumental in helping the blood bank technologist provide the safest donor red blood cells for transfusion. As with any other emergent acute, life-threatening circumstance, group O-negative or O-positive RBCs can be transfused with physician approval, following institutional protocols.

Similar to interfering in RBC antibody detection, plasma containing anti-CD38 or anti-CD47 may also affect detection of antibodies to HLA Class I and platelet antigens, as well as interfere with platelet crossmatch testing. CD47 is weakly expressed or absent from the rare Rh_{null} cells.[8,17] Clinically significant alloantibodies may be masked by the presence of monoclonal antibodies. More extensive testing beyond standard methods can lead to delays in providing RBCs for transfusion. Hospitals must communicate to the compatibility testing laboratory when patients are expected to begin monoclonal antibody therapies.

In conclusion

Rapid development and use of monoclonal antibodies continue to be investigated for clinical applications, such as acute lymphoblastic leukemia (ALL), lymphomas, and acute myeloid leukemia (AML), as well as in solid tumors. Unfortunately, interference of such immunotherapies on pretransfusion testing results is often missed or insufficiently investigated. The impact on blood bank testing is only recognized when patients require a blood transfusion, yet clinically significant alloantibodies fail to be eliminated using routine test methods. Blood bank technologists and other healthcare providers must stay vigilant to remain up-to-date on published literature, workshops, and other educational venues for best practices to mitigate mAb interference during such testing.

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Wyenona Hicks, MS, MT(ASCP) SBB, serves as Program Manager of Medical Technology Education, **OneBlood, Inc.**

Juan A. Merayo-Rodríguez, MD, serves as Medical Director, **LifeSouth Community Blood Centers, Inc.**

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TEST QUESTIONS

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1. **The use of monoclonal antibody (mAb) drugs causes some technical problems in**
   - a. white blood cells and pretransfusion testing.
   - b. red blood cells and pretransfusion testing.
   - c. red blood cells and clotting factors.
   - d. white blood cells and differentials.

2. **Cluster of Differentiation cells (CDs) are mostly expressed on**
   - a. leukocytes.
   - b. red blood cells.
   - c. platelets.
   - d. all of the above.

3. **The two most-frequent monoclonal antibodies that are encountered in the blood bank are**
   - a. anti-CD20 and anti-CD38.
   - b. anti-CD45 and anti-CD38.
   - c. anti-CD45 and anti-CD47.
   - d. anti-CD47 and anti-CD38.

4. **CD38 mAb drugs are currently used in the treatment of**
   - a. multiple myeloma.
   - b. solid tumors.
   - c. autoimmune disorders.
   - d. all of the above.

5. **CD47 mAbs are currently approved for the use of patients with solid tumors and hematologic malignancies.**
   - a. True
   - b. False

6. **CD38 is highly expressed on**
   - a. platelets.
   - b. plasma cells.
   - c. red blood cells.
   - d. monocytes.

7. **Which action is achieved by the binding of anti-CD38 to CD38 in patients with multiple myeloma (MM)?**
   - a. inhibits the growth and proliferation of MM
   - b. induces apoptosis
   - c. both a. and b.
   - d. none of the above

8. **CD47 is expressed on almost all cell types and tissues.**
   - a. True
   - b. False

9. **The Rh phenotype that has the highest expression of CD47 is _____ and the Rh phenotype that has the lowest expression of CD47 is _____.**
   - a. Rh_{null}; rr
   - b. rr; r″
   - c. R1r; Rh_{null}
   - d. rr; Rh_{null}

10. **Which immune action of anti-CD47 therapy is achieved in patients with malignancies?**
    - a. Induces an inhibitory signal that helps the malignance cell escape phagocytosis
    - b. Blocks an inhibitory signal that promotes phagocytosis of malignant cells
    - c. Induces apoptosis by self-recognition
    - d. all of the above

11. **Anti-CD38 treatment will exhibit panreactive serologic reactions in all IAT tests and can persist for up to**
    - a. 2 months.
    - b. 6 months.
    - c. 1 year.
    - d. 5 years.

12. **Which enzyme is used in blood banking that abolishes the panreactivity from anti-CD38?**
    - a. DTT
    - b. ficin
    - c. papain
    - d. all of the above

13. **Which clinically significant antibody is destroyed by the action of DTT?**
    - a. Fy^a
    - b. Jk^b
    - c. Kell
    - d. E

14. **Which type of red blood cells can be used to eliminate panreactivity in IAT testing because they have very little CD38 expressed on the cell surface?**
    - a. rabbit red blood cells
    - b. cord red blood cells
    - c. elderly adult red blood cells
    - d. none of the above

15. **ABO discrepancies are commonly seen in patients being treated with anti-CD38.**
    - a. True
    - b. False

16. **Anti-CD47 interferes with which of the following tests?**
    - a. DAT
    - b. ABO forward and reverse
    - c. IAT
    - d. all of the above

17. **What is the most commonly used reagent that eliminates the interference of anti-CD47 treatment?**
    - a. anti-IgG that does not bind to IgG1
    - b. anti-IgG that does not bind to IgG2
    - c. anti-IgG that does not bind to IgG3
    - d. anti-IgG that does not bind to IgG4

18. **It is important that clinicians order extended phenotyping tests on their patients before immune therapy begins so the blood bank technologists are able to find the safest donor red blood cells for transfusion.**
    - a. True
    - b. False

19. **In addition to anti-CD38 and anti-CD47 affecting detection of red cell antibodies, which other types of antibodies do these drugs affect detection of?**
    - a. HLA class I antibodies
    - b. HLA class II antibodies
    - c. platelet antibodies
    - d. all of the above

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How labs can benefit from LIS to EHR connectivity

By Shreya Patel

From regulatory changes and decreased reimbursements to time and resource constraints, it is no secret that laboratories today are facing growing challenges in an increasingly digital healthcare environment. To succeed, as we shift toward data-driven, patient-centric care, laboratories need new approaches and solutions that will improve workflows while empowering them to maintain profitability.

Physical medical charts, handwritten requisitions, paper orders, and results sent by faxing or couriers, and airmailed medical data are becoming a thing of the past. With the rapid increase in adoption of electronic health record (EHR) systems in the last couple of decades, nearly all practices are now not only entering their patients' demographics, insurance information, billing formation, and clinical data into their EHRs, but they are expecting to have the capability to order lab tests and receive lab results directly from within their system.

Interfacing between the EHR and the lab

Practices expect laboratory connectivity not just for convenience but also to satisfy requirements for meaningful use. However, not all laboratories have the bandwidth to build and maintain interfaces between their laboratory information system (LIS) and their provider clients' EHRs.

While some laboratories are investing in their own interface platforms and development resources to enable LIS integration with EHR systems, interface fees can be costly, and employing an IT department dedicated to building and maintaining multiple interfaces with multiple systems can be a big strain on a small lab.

Many labs are cutting costs and reducing internal resources by utilizing an interface management platform with easy-to-configure, built-in connectivity to top EHRs in the market. This strategy can significantly reduce deployment speeds and IT resources, cut support costs, and empower laboratories to allocate more time toward growing their business and achieving organizational efficiency.

While the necessity to interface the LIS with EHRs may seem like an added challenge, labs can also view the adoption of EHRs as an opportunity to increase profitability by leveraging the data collected within the EHR.

Laboratory errors

Laboratory errors directly lead to increased healthcare costs and decreased patient satisfaction. It's estimated that more than 25 percent of all pre-analytical errors result in unnecessary investigation or inappropriate patient care, resulting in additional financial burdens throughout the healthcare system.

Additionally, pre-analytical errors represent between 0.23 percent and 1.2 percent of total hospital operating costs. This unnecessary expenditure can be extrapolated to a typical U.S. hospital with approximately 650 beds to $1.2 million per year.

The financial impact of inaccurate data is not the only item laboratories must manage. As a result of the shift toward value-based care, laboratories play an increasingly important role in delivering patient-centric healthcare.

With an estimated 70 to 80 percent of clinical decisions being made based on laboratory results, the meaningful information labs deliver deeply impacts a patient's diagnosis and treatment. Duplicate tests, mismatched patient records, and a lack of the total patient healthcare history contribute to a damaging patient experience, and often produce profound long-term results for the patient.

Laboratories face immense pressure to send accurate results every time to circumvent negative financial impact and to improve patient safety, experience, and satisfaction.

Leveraging data from the EHR to maximize reimbursements

The good news? Over 90 percent of claim denials are preventable. Most denials can be attributed to a user error or technical error, including claims with missing information such as absent or incorrect patient demographic data and technical errors, lack of medical necessity, lack of pre-authorization, erroneous patient demographic information, incorrect provider data, and more.

Reducing denied claims is a significant way for laboratories to maximize reimbursements and increase profitability. Laboratory solution providers are innovating new technologies for laboratories to leverage to collect clean orders data from the EHR not only during the time of the order, but also after the physician hits "send" and even after the order is received by the lab.

This end-to-end connectivity to EHRs for clean orders data delivered directly to the LIS not only improves the quality of care, it helps labs decrease operational costs while improving their bottom lines.

Accessing clean demographic and insurance data from the EHR

While laboratories are integrating LIS systems with many EHRs for HL7 order transfers, labs that provide physicians an external ordering system to place test orders may encounter a higher risk of

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receiving inaccurate patient demographic and billing information on orders. When physician staff are tasked to retype patient information into a second system while filling out a requisition, this process quickly becomes tiresome, and the duplicate data entry inevitably leads to typos, missing fields, and inaccuracies.

Bridging the laboratory ordering system with the practice management or EHR system via demographic interface ensures the patient demographic and insurance information received by the lab is the same clean, up-to-date information residing in the EHR. Demographic data is pulled into the lab requisition at the time of the order, which saves the practice staff the time and effort it takes to retype patient data and increases satisfaction for the provider as a laboratory client.

Ensuring complete test order data and generating ABNs at the time the order is placed

In addition to ensuring up-to-date patient demographic data, laboratories may face the challenge of ensuring other data included in the order is accurate and complete such as provider information and diagnosis codes, eligibility for insurance, Advanced Beneficiary Notices (ABNs), and Ask at Order Entry (AOE) Questions pertaining to certain tests. This information is imperative to laboratories to ensure they are ultimately paid for their services.

Technology is available today that allows laboratories to configure rules that intercept the order, verify the inclusion and accuracy of data, and alert physicians of incomplete or incorrect information including data related to patient demographics, insurance, provider information, patient history, additional authorization and medical necessity information, specific laboratory-rules-based AOE Questions and ABN checks. This type of software supports error correction for the entire order before accessioning and can automatically generate ABN and necessary documents to be sent along with the specimen, reducing the work the laboratory has to do to retrieve complete information.

Automating the retrieval of medical necessity and prior-authorization details

Required clinical documentation is often still missing in orders the laboratory receives, without which claims are denied. While providers may have collected this information at the time of the order and entered it into the EHR, often times they do not provide documentation with an order to support a claim of medical necessity.

To be reimbursed for their services, laboratories need access not just to demographic and insurance information, but also to clinical documentation of medical necessities and insurance pre-authorizations.

Payers often request additional documentation after claim review, which requires the lab to request encounter notes and other clinical documentation from providers. Payers are increasingly requesting prior-authorization paperwork with orders, adding cost to providers as well as significant lab cost to obtain when such information is not initially provided.

CMS has listed insufficient documentation, including a missing signed progress note, signed office visit note or signed physician order, or documentation to support the medical necessity of ordered services as the top reason for improper payments for laboratory services by Medicare, and commercial insurers require similar information. It is widely reported that missing information is a top reason for avoidable or preventable denied claims across all insurers. Studies have shown that the average price to rework a single claim is twenty-five dollars. Medical Group Management Association (MGMA) reports that 50 to 65 percent of denials are never reworked, a number that quickly adds up to millions of lost dollars for a high-volume laboratory.

Conclusion

Fortunately, labos today have the option of automating the collection of data required for medical necessities directly from the EHR without having to reach out to the practice for each incomplete claim.

Establishing clinical data connectivity to physician EHRs to extract and deliver clinical data and encounter documentation for a patient empowers laboratories to access the pre-authorization details required for medical necessities taken at the time of the order but not included in the requisition. This data can be submitted with the claim, used to validate prior-authorization form fields received from providers based on demographics, test codes ordered, diagnosis codes, and histories used by the provider to bill the encounter, or held for later requests or appeals.

By leveraging connectivity to the practice's EHR, laboratories can receive 100 percent clean orders that include essential patient demographic, insurance, and clinical data. The result is a streamlined ordering process that reduces the risk of most pre-analytical laboratory errors, minimizes laboratory calls to practices and hospitals, increases first-time claims submissions, reduces operational costs for the laboratory and the practice, improves provider experience, and provides more reliable results for better patient care.

Shreya Patel serves as Vice President of Product Management and Strategy, **ELLKAY**. Patel is responsible for the ELLKAY product roadmap and introducing innovative new solutions. She holds a Bachelor of Science in Engineering from North Carolina State University.

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IHC biomarkers for breast cancer in the era of molecular testing

By Maria Marsh, BS, MBA and Kwok-Fai Ng, BS

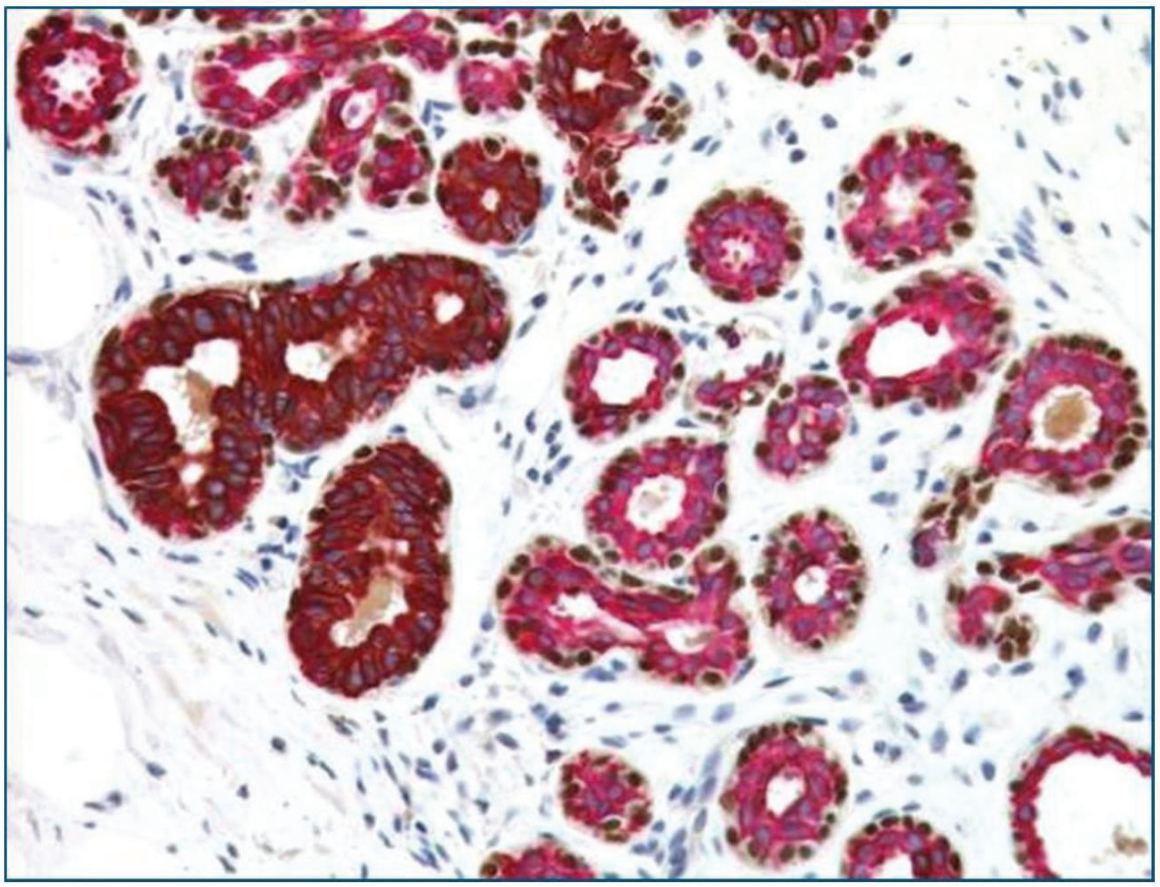

Figure 1. Multiplex IHC - Normal Breast Stained with CK5, CK14, p63, CK7, and CK18 antibodies. Breast basal cells express cytokeratins 5 and 14 (DAB; brown), myoepithelial cells express those same cytokeratins along with p63 (DAB; brown), and luminal cells express cytokeratins 7 and 18 (red).[7]

Breast cancer is the most diagnosed cancer in the United States, comprising about 15 percent of new cancer cases and contributing 6.9 percent of cancer deaths yearly. As of 2016, approximately 3.5 million women were living with breast cancer in the U.S. For these diagnosed cases, the five-year survival rate was 89.9 percent and the age-adjusted mortality has decreased at an average rate of 1.5 percent per year from 2012 to 2016.[1] This encouraging trend can be partly attributed to immunohistochemistry (IHC) tests used in the differential diagnosis of various carcinomas and benign lesions. Despite the plethora of multigene molecular tests becoming available over the last decade, IHC still remains as the workhorse for most pathologists in the diagnostic work-up of breast cancer.

Molecular subtypes of breast cancer and differential gene expression patterns

Breast cancer is a heterogeneous disease and can be segmented in three subtypes based on IHC markers:

I. Hormone-receptor positive (i.e. Estrogen receptor (ER)/Progesterone receptor (PgR) positive)
II. Human Epidermal Receptor positive (i.e. HER2/neu-positive)
III. Triple-negative (ER/PgR-negative and HER2-negative)

These subtypes have significant implications in the management and treatment of breast cancer patients, particularly in the selection of trastuzumab.[2] Recent advances in expression profiling technology have pushed this frontier further, resulting in additional molecular subtypes with distinct gene expression pattern as summarized in **Table 1.**

Why IHC?

It appears that the molecular determination of subtype may be able to provide more information than IHC in the clinical management of breast cancer patients. However, IHC is still widely used in the clinical setting. This is expected because:

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Molecular subtype	% breast cancer (approximate)	Prognosis	Gene expression patterns of select genes: ER	PgR	HER2	Ki-67
Luminal A	40%	Low-grade and slow, best prognosis	↑↑↑↑	↑↑↑↑	↓	●
Luminal B	20%	Slightly worse prognosis compared to luminal A	●	●	Varies	↑↑↑↑
HER2-enriched	20-30%	Grow faster and worse prognosis than luminal types	↓	↓	↑↑↑↑	
Basal-like	15%	The worst prognosis, a subset of Triple Negative.	↓	↓	↓	
Claudin-low	N/A		↓	↓	↓	
Normal Breast-like	N/A	Slightly worse prognosis than luminal A	↑↑↑↑	↑↑↑↑	↓	●

↑↑↑↑ Higher level of expression
↓ Lower level of expression/negative
● Normal level of expression

Table 1. Breast cancer subtypes based on molecular profiles.[14]

• IHC is a well-established methodology, widely used in pathology labs around the world as compared to molecular (MDx) testing which in many parts of the world is still in its infancy. The College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO) have jointly developed testing guidelines which are regularly updated with robust quality control (QC) measures in place to ensure an objective and accurate scoring of IHC results. An example is the latest update in HER2 testing for the requirement of concomitant IHC review for dual-probe ISH (in-situ hybridization) groups 2 to 4 to arrive at an accurate HER2 status designation.[3]

IHC Markers	Frequency of Expression (%)
CK 5/6	73
CK17	33
C14	44
EGFR	50
IMP3	79
c-kit (CD117)	31
p53	62
αβ-Crystallin	45
VEGF	78
Maspin	89.3
Integrinβ4	55.6
Caveolin 1	36
Caveolin 2	20
P-cadherin	79
p16INK4a	89

Table 2. Immunohistochemical markers in basal-like breast cancer and their frequency of expression.[15]

• While standard morphology examination of hematoxylin and eosin (H&E) slides by pathologists remains the preferred method in the diagnosis of breast cancer, IHC has become a validated and integral part of the testing algorithm. Heterogeneity of cancer makes spatial visualization by IHC important. IHC stains also enable pathologists to correlate the results with the morphological examination.
• IHC is also the best tool for clinical labs given the ease of analysis, low cost, and application to routine formalin-fixed paraffin-embedded (FFPE) samples combined with quick turnaround time. Advances in IHC automation, together with digital pathology capabilities, could empower high-throughput laboratories even further without the need to develop and standardize a totally new molecular workflow.

Utility of IHC biomarkers in diagnosing breast cancer

I. Identification of subtypes of breast cancer

It is apparent from **Table 1** that the identification of breast cancer subtype is very important in the selection of the appropriate treatment and determining the prognosis of the disease. ER, PgR, and HER2 are routinely tested for this purpose and well established in ASCO/CAP guidelines. The cell proliferation marker Ki-67 may also assist in differentiating the luminal subtypes (luminal A vs. B) and the choice of hormone therapy with or without chemotherapy.

II. C-erb-B2 overexpression (aka HER2/neu)

Perhaps the best-known case for IHC testing, C-erb-B2/HER2/neu overexpression is indicative of sensitivity to anti-HER2 therapies, such as trastuzumab and lapatinib. Currently, IHC and FISH are the two clinical methods approved to evaluate overexpression at cell surface and HER2 amplification, respectively. Overexpression is typically the consequence of gene amplification and the two tests should correlate well.

III. Myoepithelial markers to differentiate invasive carcinoma from carcinoma in situ

It can be challenging to distinguish ductal carcinoma in situ (DCIS) from invasive breast cancer by H&E stains alone. The utility of myoepithelial markers can be attributed to the fact that these markers should still be

contained within ducts in DCIS, whereas the myoepithelial cell layer and basement membrane would have been breached in invasive carcinoma, no longer intact, and not stained in IHC. Typical myoepithelial markers include smooth muscle actin (SMA), calponin, p63, and smooth muscle myosin heavy chain (SMMHC).[4] High-molecular-weight cytokeratins (CKs), such as CK14 and CK5/6, are relatively specific to myoepithelial cells; although, some of the CKs are also expressed in some invasive breast cancer such as basal-like.[5] Jain et al. (2011) reported reduced interobserver and intraobserver variability in the diagnosis of atypical ductal hyperplasia using a cocktail of CK5, CK14, p63, CK7, and CK18 and demonstrated how IHC biomarkers multiplexing may benefit management of these cases.[6] **(Figure 1)**[7] The list of myoepithelial markers keeps growing, but there could be significant variation in sensitivity and specificity. One must exercise caution when interpreting the loss of myoepithelial markers, supported by abnormal morphologies in H&E slides.[8]

IV. IHC biomarkers in Basal-like Breast Cancers (BLBCs) and Triple-negative Breast Cancers (TNBCs)

TNBCs have been considered as equivalent to BLBCs but in fact, TNBCs are a heterogeneous group of breast cancers with different prognoses. BLBC is one of these TNBCs with the worst prognosis. In response to this, a group of IHC markers has been proposed to distinguish BLBCs from TNBCs. **(Table 2)** High expression of the IHC markers CK5/6, IMP3, VEGF, Maspin, P-cadherin, and p16INK4a was reported in more than 70 percent of BLBC cases tested.[9] These markers, together with molecular markers such as BRCA1 and TP53, may help oncologists to derive a better treatment strategy for BLBC.

V. Other IHC markers for prognosis/treatment selection[10]

Apart from the routine ER, PgR, and HER2 tests, the following IHC biomarkers have been implicated as predictive and prognostic tools in the management of breast cancers:

- Elevated Ki-67 may be a predictive factor for a higher rate of complete pathological response in neoadjuvant chemotherapy.[11,12]
- BCL2 and p53 expression may help to define high-risk patients in the use of adjuvant chemotherapy in early breast carcinoma.

Conclusion

Over the last decade, MDx tests such as multigene signatures and Next Generation Sequencing (NGS) have been seen as the rising star of cancer diagnostic testing. However, pathologists are not readily embracing this new technology for breast cancer. In the 2013 St. Gallen Consensus Conference,[13] most panelists (70 percent) were against multi-gene expression profiling for breast cancer subtype definition. In fact, the majority considered ER, PgR, and Ki-67 sufficient to differentiate between luminal A and luminal B HER2 negative cases. Sixty percent of the panelists did not believe subtype determination could be accomplished by MDx alone, and 64 percent believed histological grading was not a substitute for Ki-67.

This outcome confirms our earlier discussion that IHC is still an indispensable diagnostic tool for breast cancer. That said, it is essential to standardize the IHC protocol and ensure that variables such as fixatives, antibody manufacturer, and the type of immunostaining methods are under control. The choice of a reliable and established reagent provider with good quality control cannot be emphasized enough.

Although new MDx tests for breast cancer will keep entering the market and generate much excitement in the years to come, the mature and well-established IHC methodology continues to be the tried and true workhorse for the majority of pathologists for routine breast cancer diagnosis in the foreseeable future.

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Maria Marsh, BS, MBA, serves as a Product Manager at **Biocare Medical**. She holds a BS in Biotechnology from the University of California, Davis and an MBA from Saint Mary's College of California.

Kwok-Fai Ng, BS, serves as Marketing Content Manager at **Biocare Medical**. He received his degree in biomedical science from the University of Technology, Syndey in Australia.

THE ROLE OF QUALITY LABORATORY PRACTICES IN DELIVERING EFFECTIVE PATIENT CARE

A Quality Assessment Plan is Key to Obtaining Consistently Valid Results

By Tammy Harper, Quality Improvement Specialist, COLA Inc.

Rachel, a 19-year old woman with Epilepsy successfully controlled with anticonvulsant medications, was prescribed another medication to treat a dermatologic condition, which could potentially affect her liver. When hepatic function tests were ordered to monitor this side effect, the results were elevated, so her physician reduced the additional therapy. The physician also wanted to verify that the new medication was not affecting the anticonvulsant medication levels. The results for both medications came back "not detectable", despite the patient's claims that she regularly took both medications. The laboratory noted the difference from her previous results, and repeated the testing. When they received the same result, her physician was notified, and he ordered the tests redrawn the same day. This sample showed both medication levels within normal therapeutic range. This triggered the laboratory's Quality Assessment (QA) Program to investigate why the first sample gave errant results. The laboratory's investigation revealed the original sample was mislabeled. The other patient involved was also redrawn. The laboratory implemented changes to reduce multi-tasking in the phlebotomy area. They plan to monitor specimen collection issues for the next three months to ensure their solution is effective.

Given the importance of quality laboratory practices in the delivery of safe, effective healthcare, it is critically important for laboratorians to carefully follow standards and procedures that can ensure accurate samples, as in the above example. Laboratory professionals act as key members of patient care teams, offering invaluable expertise to the diagnosis and treatment process.

A Quality Assessment (QA) plan is an essential tool which enables laboratories to provide consistently valid results. The QA process is designed to continuously monitor laboratories' performance to detect and identify potential problems. When a problem is discovered, the process helps laboratories investigate to determine the root cause, implement corrective actions and monitor to ensure the problem does not reoccur. Failure to carefully adhere to such standards can result in errors that may leave lasting impacts.

The COLA Inc. Quality Assessment Program

Following are COLA's recommended steps for developing a QA plan, which monitors all phases of laboratory testing:

1. State the purpose of the plan, and list the goals
2. Describe what will be reviewed (i.e., the path of workflow and all of the quality systems), the standards that are expected, and how data will be collect to assess the laboratory's activities
3. Describe how the plan will be implemented, and schedule reviews to be performed
4. Describe how identified problems will be responded to, methods for corrective action, and how follow-up reviews will be scheduled and performed
5. Develop forms to document observed problems, collect data, perform reviews, and all QA activities
6. Describe how findings will be shared with the laboratory director, staff, and other appropriate parties

As part of its commitment to quality patient care, COLA Inc. is offering laboratories a complimentary copy of its Quality Assessment Lab Guide. This guide will assist your laboratory in developing and implementing an effective Quality Assessment plan. You will learn how to:

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- Meet standards of performance, and enable laboratory managers to immediately address noted deficiencies
- Create a culture of quality in the laboratory

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Chemical management in today's laboratory

By Daniel J. Scungio, MT(ASCP), SLS, CQA(ASQ)

When it comes to the management of chemicals in today's laboratories, there are two main sets of regulations to consider, both of which have been set by the Occupational Safety and Health Administration (OSHA). These rules for handling chemicals are sometimes complicated, and they don't always provide clear answers for some of the issues you might run into during the course of day-to-day laboratory management. There are ways to make the interpretation of the regulations easier, however, there may be other resources to consider when making decisions about chemical handling and storage.

OSHA standards

The first standard that applies to laboratories using chemicals is the Hazard Communication (HazCom) Standard (29 CFR 1910.1200). These regulations apply to any employer that manufactures, distributes, or receives hazardous chemicals. The HazCom directives require that these chemicals are properly labeled, that Safety Data Sheets are available, and that employees are made aware of the hazards associated with the inventory of chemicals maintained and used on-site. The HazCom standard was originally promulgated in 1987, but a major revision in 2012 (to align with the Globally Harmonized System (GHS)) affected how every chemical must be classified and labeled.

The other OSHA standard that guides lab chemical management is the Chemical Hygiene standard, also known as the Lab standard (29 CFR 1910.1450). This set of chemical regulations from 1990 is specific for laboratories, and it supersedes HazCom statutes. OSHA realized labs have specific methods for chemical handling that the HazCom standard did not cover, so this newer rule contains guidance which speaks to a written chemical hygiene plan, lab chemical exposure, and training.

While these two standards provide a great deal of guidance for laboratories, they do not provide all of the information necessary for a complete chemical management program in the lab, and this particular lab safety topic tends to conjure more questions than any other for lab safety professionals. Because of that, it is important to look at other regulations as well. Laboratory accreditation agencies such as the College of American Pathologists (CAP) and others create standards around chemical management which must be considered—OSHA is not the only resource referenced in those standards.

The National Fire Protection Association (NFPA) is an international nonprofit agency of members and volunteers that creates fire safety standards. If a regulatory body refers to or incorporates wording from the NFPA, then complying with the standards becomes mandatory. One NFPA standard, Standard 45: Standard on Fire Protection for Laboratories Using Chemicals, contains guidelines that pertain to flammable chemical handling that must be followed in most laboratories. Other written guidance that can affect lab chemical management includes the International Fire code (IFC), and safety documents from Clinical and Laboratory Standards Institute (CLSI).

Labeling

The conversion to a new chemical labeling convention that came with the advent of the GHS in 2012 created a fairly clear path for chemical manufacturers. All primary chemical containers needed new specific label elements such as a signal word, a hazard statement, and appropriate pictograms. These updated labels were required by a specific deadline, which was difficult for some chemical manufacturers, but the direction was clear.

What was not as clear, was how laboratories were to handle secondary container labeling. Secondary or pour-off chemical containers require some sort of hazard warning as well, and many labs were using the NFPA diamond to accomplish that. Other labs were using the Hazardous Materials Identification System (HMIS) rating system. Confusion arose because the new HazCom standard created a new rating system that did not match the two that were already in use. The GHS hazard ratings scale was the opposite of what many users had experienced **(Figure 1).**

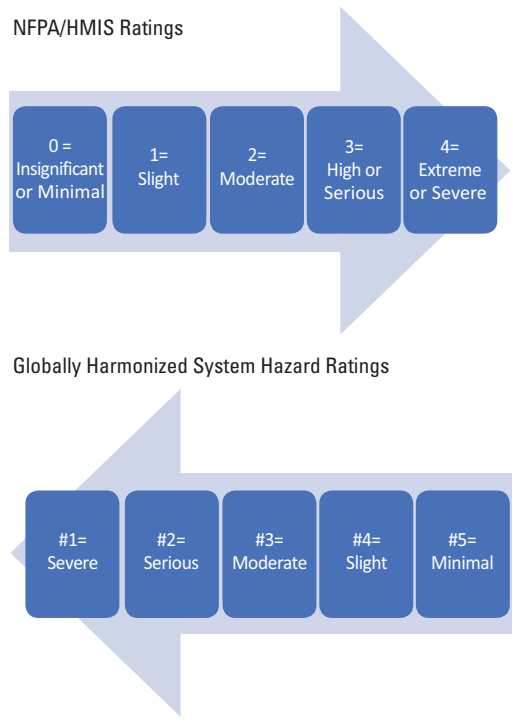

Figure 1. NFPA, HMIS, and GHS Hazard Ratings

OSHA helped to clarify the confusion by pointing out that the updated HazCom standard did not require that the new GHS rating system be displayed on chemical container labels. That meant chemical manufacturers' primary container labels would not display a numerical rating, but it also meant that laboratories could continue to use NFPA or HMIS conventions for labeling secondary chemical containers. While some laboratories have converted to GHS labeling for all containers, many still use the older conventions as well. No matter what type of hazard warning is used, OSHA does require that laboratory policies and training peak to it specifically.

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Classification of chemical mixtures

Standardized chemical hazard classification was another goal of the updated HazCom standard. The use of the newly introduced pictograms became an easy way for users to know whether or not a chemical was hazardous, and which types of hazards were present **(Figure 2).** New standardized Safety Data Sheets (SDS) were another tool laboratories had that would help provide information regarding chemical risk, and the pictograms appear on chemical labels and on the SDS. But again, these changes brought some uncertainty.

Section two of each Safety Data Sheet is where the chemical Hazard Identification and appropriate pictograms are located. However, on a SDS for a reagent that is a mixture of chemicals, there are other pictograms for each component chemical of that mixture in section three, and they may not match the pictograms seen in section two. Given that, laboratorians may become confused about which pictograms to use on a secondary container label or on a chemical inventory form.

In the case of mixtures or solutions, it is important to know that the hazards of the final solution—those identified in section two of the SDS—are those which identify which hazard and warning symbol are needed for that mixture of chemicals. Chemical mixture manufacturers have listed the data from the individual raw components on the SDS, but it may be that with dilutions or other processes used in making the final product, that those hazards listed in section three are minimized. Lab employees only need to be concerned about the hazard warnings of the final product in section two.

HCS Pictograms and Hazards

Health Hazard	Flame	Exclamation Mark
		
• Carcinogen • Mutagenicity • Reproductive Toxicity • Respiratory Sensitizer • Target Organ Toxicity • Aspiration Toxicity	• Flammables • Pyrophorics • Self-Heating • Emits Flammable Gas • Self-Reactives • Organic Peroxides	• Irritant (skin and eye) • Skin Sensitizer • Acute Toxicity • Narcotic Effects • Respiratory Tract Irritant • Hazardous to Ozone Layer (Non-Mandatory)
Gas Cylinder	**Corrosion**	**Exploding Bomb**
		
• Gases Under Pressure	• Skin Corrosion/Burns • Eye Damage • Corrosive to Metals	• Explosives • Self-Reactives • Organic Peroxides
Flame Over Circle	**Environment (Non-Mandatory)**	**Skull and Crossbones**
		
• Oxidizers	• Aquatic Toxicity	• Acute Toxicity (fatal or toxic)

Figure 2. Hazard Communication Standard Pictogram. The Hazard Communication Standard (HCS) requires pictograms on labels to alert users of the chemical hazards to which they may be exposed. Each pictogram consists of a symbol on a white background framed within a red border and represents a distinct hazard(s). The pictogram on the label is determined by the chemical hazard classification.

Chemical storage

The NFPA 45 standard limits the amount of flammable chemicals that can be stored in a lab area. The amount of allowable storage varies based on whether or not the chemicals are kept in safety cans and if there is an automated sprinkler system in place in the laboratory. Because of the limitations, the use of flammable cabinets is common in labs in order to safely store excess flammable chemicals. However, many safety professionals are not aware of the regulations that could affect the type of cabinets that should be used.

The International Fire Code (IFC) is a model code that presents minimum fire safety guidelines for buildings, facilities, storage, and processes. The adoption of the code and any associated regulations occurs at the state level. Currently, the latest version of the IFC (2018) has been adopted in 42 U.S. states.

Chapter 57 of the International Fire Code, Flammable and Combustible Liquids, contains information pertinent to laboratories that store flammable chemicals. The code states that flammable liquid storage cabinets must have doors well fitted, self-closing, and equipped with a three-point latch. This is not a widely-known standard, and many laboratories across the country use flammable cabinets that do not have self-closing doors. Possible solutions include purchasing self-closing door adapters or replacing the cabinets.

Other laboratory flammable storage regulations come from the NFPA 45 standard. The regulation requires that refrigerators or freezers in the lab that are used to store flammable material must be rated as explosion-proof. They need to be designed so that there is no risk of sparks from motors or lights. The regulation further requires that all lab cold storage units are labeled as to their capacity to store flammable materials. That means that even if your laboratory does not have explosion-proof units and you do not store flammable materials, the refrigerators and freezers still need to be labeled with signage that warns to prevent such storage.

Chemical management questions and answers

Chemical management in the laboratory is a vast safety subject matter, and the resources that regulate it are many. If you're putting together a chemical hygiene plan for the first time, there are model plans offered by OSHA and other agencies. Read the standards from your lab's accrediting bodies and make sure the lab complies with them. Continue reading articles and reach out to experts with questions if something remains unclear. Handling hazardous chemicals can be a dangerous process in the lab setting, but with a proper management plan in place and adequate staff training, safety can be attained for all who store and utilize those chemicals.

Daniel J. Scungio, MT(ASCP), SLS, CQA(ASQ), has more than 25 years of experience as a certified medical tech. He was a lab manager for 10 years before becoming the laboratory safety officer for Sentara Healthcare, a system of 12 hospitals and more than 20 labs and draw sites in VA and NC. As "Dan the Lab Safety Man" he provides consulting, education, and training in the U.S. and Canada. Visit www.danthelabsafetyman.com.

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Thoughts on clinical laboratory safety

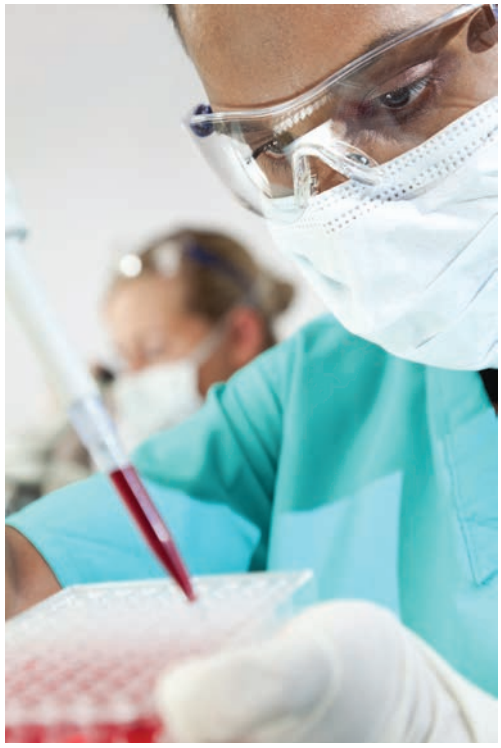
By Dr. John T. Daly

Having worked in clinical laboratories for fifty years, I have seen the good and bad but also the tremendous improvements in safety that have taken place. Many moons ago I remember visiting a facility where smoking was permitted throughout the laboratory, including microbiology! Oh, times have changed!

OHSA program

Safety in the clinical laboratory is essential to comply with the federal Occupational Safety and Health Administration (OSHA) regulations. Over and above this, we have an obligation to protect the health and well-being of our employees and our patients. Recognition of the latter leads to a true culture of safety.

The OSHA program for laboratories was inaugurated in 1991, and subsequently, the plan incorporated needle stick safety regulations. These regulations require that basic safety rules be observed by clinical laboratories, including policies to prevent exposure to biological, chemical, electrical, and fire hazards.



Biological hazards

Biological hazards immediately come to mind when thinking of clinical laboratory safety. It is essential there be protection from exposure to infectious diseases transmitted by contact with blood, blood products, and any other potential sources of infection transmission such as stool, urine, and sputum. The most commonly recognized blood-borne infectious diseases in this context are Hepatitis B and C and HIV but certainly, the hazards posed by transmission of other viruses, bacteria, Tubercle bacilli and fungal organisms are very real.

It is essential that laboratory leadership ensure safety procedures are in place and enforced to prevent transmission of infectious diseases from patient specimens. There needs to be protection of hands and skin, but also critical is protection of the eyes and mucous membranes. I personally am a big fan of plastic face shields that can provide protection of eyes and mucous membranes. I became an advocate of face shields the first time I wore one while performing an autopsy. I was appalled by the aerosol that covered the face shield when the autopsy was completed. To this day, I live in amazement I am not infected with Hepatitis C. In lesser amounts, aerosols develop when working with sputum, urine, and other body liquids.

Personal protective equipment

In microbiology, many specimens are best handled in a biological safety cabinet and wearing appropriate personal protective equipment (PPE) is vital. The front of the PPE gown should be kept closed. Ideally, the gown should close in the back. The gown should be knee-length and have long sleeves, with cuffed wrists. The fabric should be fluid resistant, and the PPE should be laundered by the employer and under no circumstances taken home by the employee. Always keep in mind that the PPE and gloves must not be worn outside the work area. There should be policies prohibiting the wearing of PPE in lunch and break areas, waiting room, lobby, or outside the confines of where the PPE has been utilized in order to prevent contamination.

In addition to wearing PPE, it is essential for phlebotomists to wash their hands before gloving for a procedure.

Following phlebotomy, the used needle must be discarded in a rigid container that is kept in a safe location beyond the reach of inquisitive children who might be intrigued to inspect the contents of the red box. Ultimately, all needles should be disposed of with the biohazardous waste in a rigid, closed safety container. When gloves are removed, hands again are washed.

Sharps

When we talk "sharps" in the laboratory, we immediately think of phlebotomy and the needles used. However, needles are not the only sharps causing injury in the laboratory. Other devices such as scalpels, broken glass from microscopic slides, and coverslips and glass capillary tubes, to name a few, can cause injury and disease transmission. These should also be discarded in the sharps container.

Equally as important is disinfection of all work areas throughout the laboratory. Disinfection is essential at intervals during the day; for example, when leaving the work area on break, after any spill and certainly at the end of the workday. There are EPA and FDA approved disinfectants that can be used.

Remember, accidents do happen! When a needle stick or other exposure to potentially infectious material occurs, you must have a written procedure in place to ensure evaluation of the source patient and ensure protection of the employee from HIV, HCV, and HBV in so far as possible. Collect blood from the injured employee and source patient and obtain baseline results for these three viral infections. If the source patient tests positive

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for any of these infectious agents or if the source patient cannot be identified, prophylaxis is given to the employee and the laboratory studies for these infectious diseases are repeated on the employee at six weeks, three months, and six months.

Safety procedures

In addition to biological hazards, you must remember chemical, fire, and electrical hazards and have written policies and procedures to guide employees. In addition, procedures and contracts must be in place for the safe disposal of biological and chemical hazards and these must conform to local and federal regulations.

It is essential that your facility have a posted floor plan. This can be vitally important in the event of an accident particularly a fire or chemical spill. Depending upon the size of the facility, you may need to post the floor plan information in several locations. The floor plan should clearly show areas of egress from the laboratory and the location of fire extinguishers, fire alarms, eyewash, safety shower, spill kits, and the Safety Data Sheet library. Location of electrical panels should also be included. It is helpful to incorporate emergency telephone numbers. It is imperative while reviewing the egress plan to assure that there be nothing blocking access to exits, fire extinguishers, fire alarms, safety showers, and eyewashes.

It is a requirement to review the safety program of the laboratory with all new employees. It is also a requirement to review the safety program on an annual basis with all employees, regardless of the length of service. There should be documentation of these reviews in the employee personnel file.

Safety audits

In addition, annual safety audits must be performed. This not only provides reassurance that all is being done in a proper manner, but also that any new potential threats are identified and appropriate safety procedures included in the safety manual. Audit templates can be found using Google, where you can locate blank audit forms developed by major institutions that, with appropriate modification, will allow you to do a thorough examination of safety in your laboratory. Some often-ignored areas that can be addressed by using a template include proper labeling and storage of chemicals, the need for a biological safety cabinet, use of fire-resistant cabinet for flammables, documentation of a complete Safety Data Sheet inventory, inappropriate storage of food or beverages in the laboratory, and expired waste disposal contracts. Be sure to involve employees in the safety audit to avoid overlooking any issues. A thorough audit involving employees sends the message loud and clear "We are concerned about your safety and the safety of our patients—please contribute to help us accomplish our goal."

John T. Daly, MD, has served as **COLA Inc.'s** Chief Medical Officer since 2011. He retired from Duke Medicine in 2009. Daly is certified by the American Board of Pathology in Anatomic, Clinical, and Forensic Pathology and is a member of the American Association for Clinical Chemistry, the College of American Pathologists and the American Society for Clinical Pathology.

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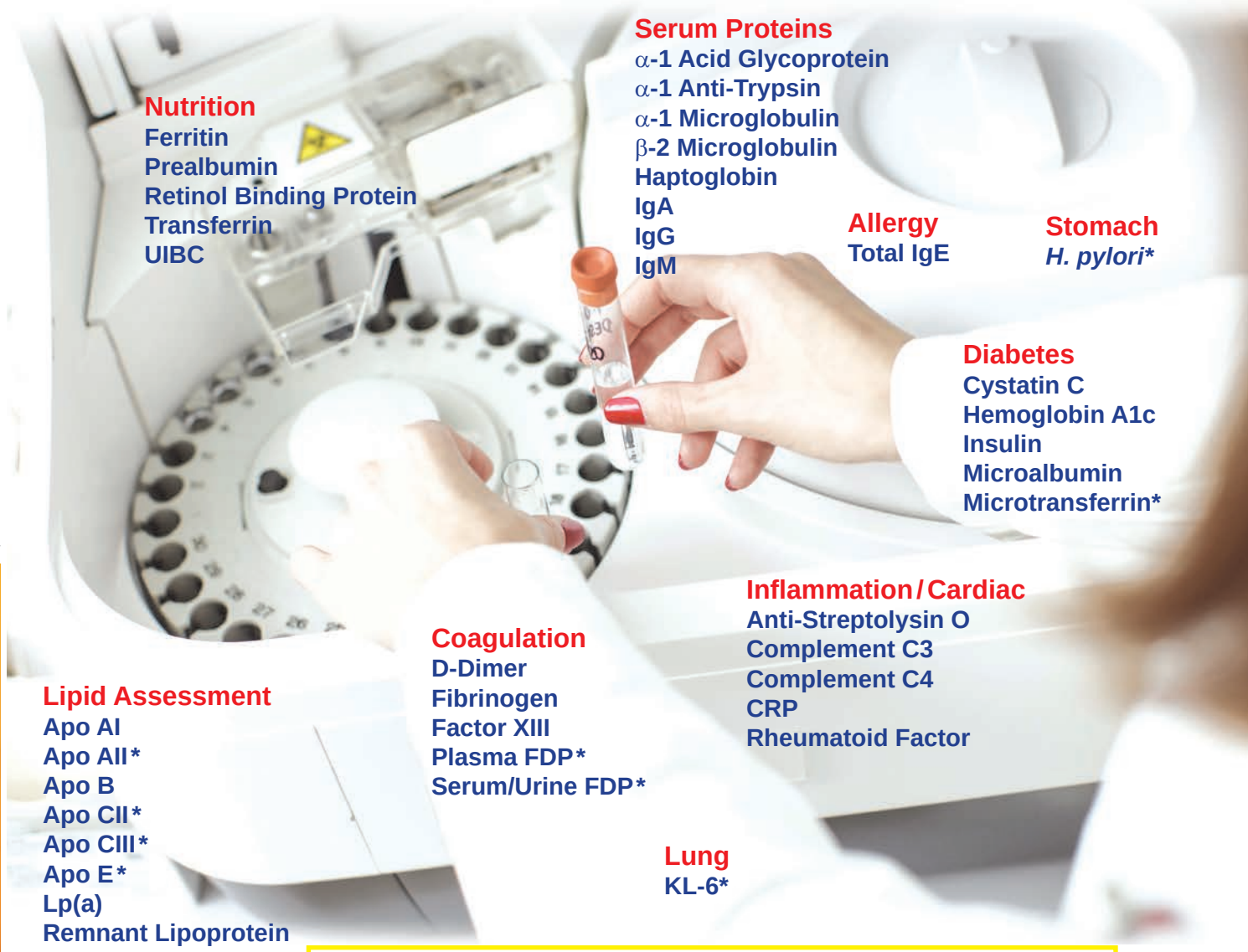

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The laboratory's role in combating the synthetic opioid and cannabinoid crisis

By Joe M. El-Khoury, PhD, DABCC, FAACC

On the evening of June 23rd, 2016, 12 patients were brought to the emergency department (ED) at Yale-New Haven Hospital from a park in downtown New Haven, CT after using a white powder advertised as cocaine and showing signs and symptoms consistent with opioid overdose.[1] Several patients required administration of multiple doses of naloxone (> 4 mg) to become alert again, and three patients died.

The white powder was identified as fentanyl, a drug 50 times more potent than heroin, and which most U.S. labs in 2016 could not detect by traditional screening assays. Over two years later on August 15th, 2018, emergency personnel responded to the same area, except this time to more than 49 overdoses from fentanyl-laced K2 (or Spice), which is made from a variety of dried plants and often sprayed with synthetic cannabinoids.[2] This was part of the latest wave of new psychoactive substances (NPS) to hit the U.S. and the culprits were synthetic cannabinoids 5F-ADB, 5F-MDMB-PICA, and AMB-FUBINACA which was also responsible for the "Zombie" outbreak in New York City in 2016.[3]

urine drug tests for relevant medications (over-the-counter, prescribed/non-prescribed) and illicit substances in pain management patients. I strongly encourage that labs involved in pain management testing review this document and follow its recommendations.

Since the mass overdose event in 2016, our hospital lab responded by implementing a new fentanyl immunoassay to provide rapid results for the ED. However, it is important for clinical labs implementing these immunoassays to fully understand what their cross-reactivities are for different fentanyl analogues, and that these cross-reactivities are communicated to their ED physicians. Warrington et al.[6] recently reviewed the performance of existing fentanyl immunoassays and they recommended that assays implemented should at least detect acetyl fentanyl, furanyl fentanyl, and carfentanil, based on recent trends in drug use and seizures.

On the other hand, immunoassays for synthetic cannabinoids are unreliable since the antibodies used do not provide sufficient cross-reactivities towards current synthetic cannabinoids.[7] Simply put, the developers of these substances are

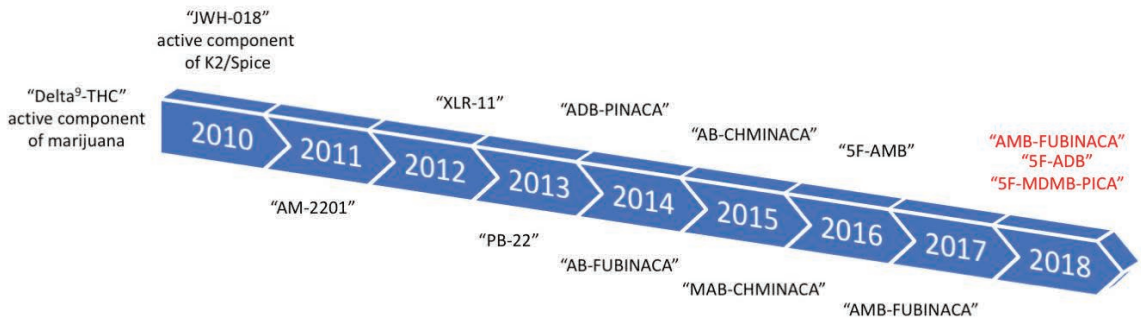

Figure 1. Evolution of synthetic cannabinoids. In black, are synthetic cannabinoids previously observed in San Francsisco, CA. In red, are the synthetic cannabinoids detected in New Haven, CT in 2018.

Synthetic opioids and cannabinoids

Synthetic cannabinoids are the fastest growing class of NPS with over 177 identified by the United Nations Office on Drugs and Crime.[4] While a few screening assays for detecting synthetic cannabinoids exist, the rapid development of NPS makes it very difficult for clinical laboratories to detect them using traditional screening and confirmatory methods. Then, what role can clinical laboratories play in the fight against synthetic opioid and cannabinoid use?

Clinical labs play a critical role in monitoring compliance with prescribed medication and abstinence from illicit compounds in pain management programs, so the first step is to ensure that they are up-to-date on best practices for monitoring drug therapy in pain management patients. Recently, the American Association for Clinical Chemistry (AACC) Academy released an executive summary and laboratory medicine practice guideline.[5] This guideline compiled evidence-based recommendations for the use of laboratory and point-of-care

introducing them at a much faster rate than IVD manufacturers and clinical labs can develop methods to detect them **(Figure 1)**. This poses a big problem for most clinical labs who without an immunoassay cannot offer rapid detection of these substances in urine. Therefore, the only reliable option for testing is confirmation testing by either liquid chromatography-mass spectrometry (LC-MS) or high resolution LC-MS (HRMS).

LC-MS vs HRMS

Mass spectrometry (MS) has been in use in clinical labs since the 1980s, but has gained widespread use in recent years as the technology became cheaper and easier to use. Due to known sensitivity and specificity issues with immunoassays, all toxicology results should be considered presumptive unless confirmed by MS, which is the "gold standard" for quantification of small molecules in biological fluids.

The predominant form of MS used in clinical toxicology labs is the triple quadrupole. This type of MS is often

employed in reference labs for confirmation testing and employs a "targeted" approach, which requires tuning the MS to detect specific substances of interest. While a "targeted" MS approach is reliable for detecting presence or absence of common drugs in urine, it is not as useful in the setting of the rapidly evolving world of NPS like synthetic cannabinoids. For that, a more versatile technology like HRMS, which can adopt an "untargeted" approach, is needed. The most common type of HRMS used in the clinical toxicology world are orbitrap and quadrupole-time of flight (QTOF).

A major advantage of using one of these platforms is that data collected in an "untargeted" mode can be retrospectively analyzed to detect additional compounds that were not identified as targets on the initial run.[7] Major drawbacks of HRMS are the expense of the platforms, the need for experienced personnel to develop methods and operate these systems, and the turnaround time is slow. As a result, HRMS has been largely restricted to specialized toxicology reference labs. Our lab ended up sending urine samples to one of these labs to determine the identities of the NPS that caused the mass overdose event in 2018.

Conclusion

Overdoses from synthetic opioids and cannabinoids are rampant in North America, with reports of similar outbreaks reported from Fresno, CA to British Columbia, Canada.[8] Sadly, the majority of clinical labs today are not equipped to deal with these outbreaks in real-time. Nevertheless, the clinical lab plays a key role in identifying the causative agents in an outbreak and disseminating this information to the public and other health providers. This information is critical for tailoring prevention and designing response strategies for future mass overdose events.

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Joe El-Khoury, PhD, DABCC, FAACC is Assistant Professor of Laboratory Medicine at Yale University and Director of the Clinical Chemistry Laboratory at Yale-New Haven Health. He is board certified by the American Board of Clinical Chemistry (ABCC) and a fellow of the AACC Academy.

Lung illness associated with using e-cigarette products

The Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), state and local health departments, and other clinical and public health partners are investigating a multistate outbreak of severe pulmonary disease associated with e-cigarette product (devices, liquids, refill pods, and/or cartridges) use. This investigation is ongoing and has not identified a cause, but all reported cases have a history of using e-cigarette products.

E-cigarettes are devices that deliver an aerosol to the user by heating a liquid that usually contains nicotine, flavorings, and other chemicals. E-cigarettes can also be used to deliver marijuana or other substances.

As of September 6, 2019, over 450 possible cases of lung illness associated with e-cigarette products have been reported to CDC from 33 states and one U.S. territory. Five deaths have been confirmed.

No evidence of infectious diseases has been identified; therefore, lung illnesses are likely associated with a chemical exposure. The investigation has not identified any specific substance or e-cigarette product that is linked to all cases. Many patients report using e-cigarette products with liquids that contain cannabinoid products, such as tetrahydrocannabinol (THC).

Severe pulmonary disease symptoms reported by some patients in this outbreak include: cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, fatigue, fever, and/or weight loss. Some patients have reported that their symptoms developed over a few days, while others have reported that their symptoms developed over several weeks.

A pulmonary infection doesn't appear to be causing the symptoms which have generally not improved with antibiotic treatment alone. Regardless of the ongoing investigation, the following should not use e-cigarette products: youth and young adults, pregnant women, and adults who do not currently use tobacco products.

As this investigation continues, CDC encourages clinicians to report possible cases of e-cigarette-associated pulmonary disease to their local or state health department for further investigation.

Automation enables the future of clinical microbiology

By Patrick R. Murray, PhD

Clinical microbiology laboratories are undergoing a rapid transformation, with many of these changes posing daunting challenges. The current vacancy rate in U.S. microbiology laboratories is over 10 percent with an additional 17.4 percent of the laboratory staff projected to retire in the next five years.[1] At a time when the complexity of diagnostic testing and associated costs are increasing, labs are experiencing reimbursement pressure from both government and commercial payers.[11] These forces are driving laboratories to consolidate and move specimens to centralized facilities with the goal to improve testing efficiencies and decrease costs and turnaround time.

Laboratory consolidation also brings challenges. Testing is potentially moved away from physicians at a time when the interpretation of sophisticated tests requires active collaboration with the microbiology staff. Also, concentration of diagnostic procedures in large centralized laboratories poses increased safety risks for the technical staff at a time when infections with antimicrobial resistant organisms and other communicable pathogens are increasing. We can accept these changes as inevitable problems, or we can view them from another perspective. We can say necessity is the mother of innovation, or to rephrase—when they give you lemons, make lemonade. Today our innovation—our lemonade—is comprehensive automation from specimen receipt to transmission of the final report.

Automation in microbiology is not simply automating the traditional practices of processing specimens and incubating cultures—that would not be transformative. Automation should be viewed as an all-encompassing approach to processing samples and communicating information that enable laboratory technologists to perform skilled tasks in ways not historically possible. This is why automation was recently described as "a paradigm shift in clinical microbiology, representing the beginning of the future."[2]

Automation in microbiology enables laboratories to do much more than eliminate the manual repetitive practices and inefficiencies of the past—the laboratory noise. Realizing the full value of automation, however, means fundamentally reexamining the entire laboratory workflow.

Specimen processing

Improved efficiency and specimen traceability are achieved with automation. Specimens are processed without delay upon receipt in the laboratory, with the automated selection of appropriate media for individual specimens, labeling the plates with barcodes, and inoculation of the media before they are transported to incubators on track systems. The accuracy of specimen inoculation is facilitated with the use of calibrated pipettes and streaking of multiple culture plates can be done simultaneously in a variety of patterns. For maximum benefits, workflow changes are required, including elimination of the practice of batching specimens, manual creation of worklists, and aligning work schedules with traditional daytime service hours. Additionally, automation challenges us to think differently about the traditional processes. We streaked plates historically in a quadrant pattern to obtain isolated colonies and perform semi-quantitation. However, this is unnecessary because automation provides more uniform, reproducible plate streaking with more isolated colonies and accurate quantitation.[3-5]

Automation also provides a level of safety never imagined. Techs do not have to handle most specimens with automated processing. Furthermore, since the steps of transferring

culture plates to incubators, examination of cultures with digital imaging, and the automation of identification and antimicrobial susceptibility testing, it is conceivable that lab technologists may never have to handle a culture plate.

Incubation and imaging of culture plates

Full laboratory automation moves plates from the processing area to incubators, eliminating delays in incubation. The plates are incubated under ideal growth conditions of stable temperature and atmosphere because the doors are not opened, and growth is monitored through images taken by sophisticated camera systems at predetermined time periods. Thus, significant growth can be detected earlier, with improved recovery of both common and slow-growing pathogens.[6-10]

Imaging algorithms are capable of creating idealized images that are more than simple photographs under different lighting conditions. These images are similar to what a photographer can create with advanced photo processing software. Software also allows these images to be examined under increased magnification so subtle differences in colony morphologies or the presence of mixed cultures can be recognized. However, interpreting these images is a new skill for technologists that must be mastered. To continue physically examining plates at a workbench that includes the "art" of the sights and smells of traditional microbiology is to deny the benefits of the "science" that comes from automation.

Automation can provide a library of images for training purposes, or the images of an individual patient's culture for

discussion with a healthcare provider. Digital imaging allows a technologist to examine culture plates in a specialized reading room, at home, or remotely hundreds or thousands of miles away from where the culture is performed, enabling technologists to consult with peers or specialists as needed. Sophisticated imaging software can also determine if growth is present on a culture plate as well as the quantity of growth, thus permitting the technologist to concentrate on processing plates with significant microbial growth.

Workup of culture plates

Again, to realize the value the imaging, digital imaging times must be selected to optimize detection of significant growth as early as possible and, more importantly, the processing of the cultures for identification (ID) and antimicrobial susceptibility testing (AST) must be initiated at the time the imaging is performed. There is little value in imaging the culture plates and then delivering the plates to an external holding area or "output stack" where the plates remain for hours before further processing.

The full benefits of automation require additional changes in traditional practices. The day starts for most traditional labs by distributing all incubated culture plates to specific desks (e.g., urine, stool, respiratory, wound, etc.). This offers the advantage of performing repetitive work in a standardized manner and facilitates teaching the processing of specific specimen types. But this also fosters inefficiencies such as uneven distribution of work across workbenches, a lack of checks and balances on the quality of work performed, and the difficulties in observing the complete diagnostic picture for an individual patient.

With automation, each culture can be incubated at a predetermined time from the initial processing, so culture plates are ready for further processing throughout the day and evening. This processing is most efficient—and informative—when an individual desk processes all specimen types, allowing a technologist to see multiple specimen types from an individual patient.

The technologists who examine images from culture plates determine which colonies represent significant growth. This skilled task may not be replaced by automation. However, the actual picking of selected colonies, preparation of a standardized inoculum, and inoculation of MALDI plates for ID testing and AST panels can be automated. The results of the ID and AST test must also be interpreted by skilled technologists, so it is important that the technologists work as a coordinated team. There is also the opportunity with today's automation and the computerized analysis of lab data, to supplement interpretation of patient data with trend analysis of infection patterns and antimicrobial resistance.

Automation may also improve laboratory operations by providing metrics to measure the efficiency of the laboratory and individual technologists. Automated systems can track the timing of all specimens as they move through the diagnostic pathway and determine when work will need to be performed and when results can be reported.

The economics of total lab automation

Finally, as we look at total lab automation, the question has frequently been asked is, "Can we afford it?" Clearly automation is a significant investment, but the more appropriate question is posed by Thomson and McElvania,[2] "Can you afford not to automate?"

In an era when laboratories have to reduce costs, improve efficiency and quality, and provide more timely, accurate results to inform patient management, automation is the only solution. Thomson and McElvania[2] demonstrated they were able to reduce staffing for both processing specimens and working up cultures, decrease time to results and costs by performing fewer subcultures and earlier reading of cultures, and increase the number of specimens processed by each technologist by using automation to eliminate inefficiencies. In their model, they were able to demonstrate a return on investment in three years rather than their projected five-year ROI through labor savings alone.

Yes, there is an initial investment in automation and the infrastructure to support automation. Yes, successful implementation of automation requires changing traditional workflow processes. Yes, strong leadership and teamwork will be needed through the transition. But the rewards are great: Improved efficiencies, more timely results for better patient management, and more cost-effective diagnostics. Automation truly is the future of clinical microbiology.

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Patrick R. Murray, PhD, serves as VP of Worldwide Scientific Affairs at **BD Life Sciences**. He received his PhD in Microbiology at UCLA, postgraduate training in Clinical Microbiology at the Mayo Clinic in Rochester, MN, and was director of clinical microbiology laboratories (Washington University of St. Louis, University of Maryland, and National Institutes of Health) for more than 35 years.

Utilizing digital imaging to determine optimal incubation times for routine urine cultures

By Cynthia C. Keyak, MT (ASCP), SSGB

Urinary tract infections (UTIs) are among the most common of all bacterial infections[1] occurring more often in women than in men, at a ratio of 8:1. Half of all women experience at least one UTI by the age of 35.[2] Approximately 20 percent of women between the ages of 18 and 24 have a UTI annually[3,4] with one in three experiencing a symptomatic UTI necessitating antibiotic treatment by age 24.[2,5,6] UTIs are also a common reason for healthcare visits in the United States. These infections result in an estimated seven million office visits, one million emergency department visits, and over 100,000 hospitalizations at an associated annual cost of $1.6 billion.[2,6,7] Therefore, it is not surprising that urine constitutes the most common type of specimen submitted to the microbiology lab for culture.

When treated promptly and properly, lower UTIs (infections of the bladder and urethra) rarely lead to complications. However, if left untreated, even an uncomplicated UTI can have serious consequences such as spread of the infection from the bladder to one or both kidneys. When bacteria infect the kidneys, they can cause damage that may permanently reduce kidney function. This can lead to kidney failure in people who already have kidney disease. Thus, the efficient detection of the causative agent of an UTI, along with the antimicrobial susceptibility testing of the pathogen, can be critical for patient care.

Digital imaging for reading of microbiology cultures can lead to expedited release of results while maximizing the efficient use of laboratory staff. The following study focused on utilizing digital imaging and artificial intelligence to determine the optimal time for urine culture incubation in order to accurately detect significant urinary pathogens.

Material and methods

The laboratory's current protocol was to process all urine specimens on an automated processing instrumentation and read urine culture images taken with the system on both blood agar and MacConkey agar plates at two time frames: 14 hours of incubation, and again at 24 hours of incubation. Previous data showed that the 14-hour image read resulted in the ability to work up approximately 20 percent of the all clinically significant culture growth.

In order to determine the optimal time for reading urine cultures, images taken from 946 patient urine cultures were compared every two hours on both media types starting at 11/12 hours of incubation up to 23/24 hours. Results for each specimen were recorded indicating the presence or absence of growth. If growth was present, the colony count and type of colonies present was recorded.

Urine specimens collected during the fall and winter months of 2017 were included in the study. All urine cultures were analyzed by observing digital images taken with the full laboratory automation every two hours.

Results

A total of 184 or 19.5 percent of the specimens were negative at each time frame images were read. Of the remaining 762 positive cultures, 109 (14.3 percent) had optimal growth at 11/12 hours of incubation, 133 (17.5 percent) after 13/14 hours, 84 (11 percent) after 15/16 hours, 412 (54.1 percent) after 17/18 hours, 10 (1.3 percent) after 19/20 hours, and 14 (1.8 percent) after 23/24 hours of incubation. (**Table 1**)

A total of 242 (31.8 percent) of all positive urine cultures could have images read optimally at 14 hours of incubation, and 96.9 percent of all positive urine cultures had optimal image reading times at or before 18 hours of incubation. Twenty-four urine cultures (2.5 percent) showed optimal growth after 18 hours of incubation, however, 100 percent (24/24) of these cultures had growth detected on the blood agar on or before this time frame. Although they had not yet reached their optimal incubation time, these cultures would not have been called negative; they would continue to be incubated until such time that appropriate work up could be performed.

Hours of incubation	11/12	13/14	15/16	17/18	19/20	21/22	23/24
Specimens with optimal reading	109 (14.3%)	133 (17.5%)	84 (11.0%)	412 (54.1%)	10 (1.3%)	0 (0.0%)	14 (1.8%)

Table 1. Specimen results

There was also a concern for possibly missing slower growing organisms after only 18 hours of incubation, such as yeast and alpha-hemolytic colonies, so these cultures were looked at individually. All cultures that contained yeast (25) or small alpha-hemolytic colonies (27) were also all detected as positive at or before 18 hours of incubation.

Discussion

Based on our patient population, changing our image reading times to 14 and 18 hours would allow for approximately 1/3 of positive urine cultures to be worked up after only 14 hours of incubation (including over half of the cultures that contained gram negative bacilli). The other approximately 2/3 of positive urine cultures could be worked up after 18 hours of incubation rather than needing to wait for a full 24 hours of incubation. In addition, the 3.1 percent of cultures that had optimal reading times after 18 hours of incubation would not have been missed as growth was detected for all of these at or before 18 hours; these cultures would continue to be incubated until they could be appropriately worked up. Likewise, the concern for possibly missing slower growing yeast and small alpha-hemolytic colonies after only 18 hours of incubation was mitigated as our data

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Developments in clinical chemistry automation

By Martin Conway, BSc

For many people, clinical laboratory testing is an unseen side of medical practice and care. However, most of the clinical conclusions doctors and clinicians make regarding a person's health are based on laboratory test results, allowing a course of action to be recommended and treatment plan implemented.

The era of automation

Clinical chemistry automation is a relatively new field in the combination of chemistry and medicine. The discipline was once documented as "pathological chemistry" or "chemical pathology" with the dedicated purpose of the analysis of bodily fluids for diagnostic and therapeutic purposes. It wasn't until the early 1900's that the American Association for Clinical Chemistry (AACC) and the International Federation for Clinical Chemistry (IFCC) introduced the term "clinical chemistry" which today has become one of the most accepted terms in in-vitro diagnostics.[1]

Clinical chemistry structures a discipline combined of chemistry, immunochemistry, biochemistry, endocrinology, toxicology, engineering, and informatics with the sole purpose of providing the support to clinicians to improve the diagnosis and treatment of patients across a wide variety of diagnostic disciplines.[1]

Over the last few decades there has been a significant decrease in the number of analytical errors in clinical laboratories much to the fact that laboratories are required to meet very high standards. The technological developments and scientific innovations in the field of clinical chemistry from the early 1950's to date have been vast, enhancing laboratory capabilities, and providing the necessary support to clinicians and laboratories to improve patient diagnosis and treatment.[2]

Today presents a new world of automation—a complex integration of robotics, liquid handling, and numerous other technologies with the fundamental purpose of saving time and improving performance through the elimination of human error and reduced risk of cross-contamination.[3]

With today's clinical advancements, current technologies include a vast variety of colorimetry/spectrophotometry, nephelometry, turbidimetry, photometry, ion specific electrodes testing (ISE), and a range of chromatographic and ligand assay methodologies such as chemiluminescence techniques.[1]

An example of today's advancements in technology and science can be identified with ELISA based techniques which are notoriously inefficient and are particularly draining on time and personnel due to the manual intervention required. The manual nature of the method also means there is greater potential for human error, ultimately resulting in lack of sensitivity and potential for cross-reactivity.[4,5]

In today's laboratory, the transitions from traditional ELISA techniques to an automated method for the detection of the same analyte will significantly improve both cost and time. However, despite the abundant advancements in automation, many clinical laboratories continue to utilize manual methods such as ELISA for some specialized chemistries.[4] The move to laboratory automation is still a premise of development, particularly in developing countries where the use of manual techniques is still in use and the availability of resources and high-quality diagnostics are reduced due to detrimental socio-economic factors.[6]

Continuous flow analysis

Based on meeting the specific needs of the clinical chemistry laboratory, significant innovations involve manufacturers focusing heavily on developments on the introduction of multichannel systems, non-selective batch analyzers, and continuous flow analysis.[7] The rise in continuous flow analysis enticed the movements in production and research on the use of discrete analysis with cuvettes and automatic mixing and pipetting of both samples and reagent, ultimately reducing the workflow of clinicians and increasing the accuracy, precision, and reliability of patient results.[8] It wasn't until the 1980's that truly sparked the move to laboratory automation where the introduction of simultaneous detection of multiple analytes at different wavelengths came into play, ultimately bestowing a new era for in vitro diagnostics.[9]

Complementing labs and automated instrumentation

In the early 1950's, to accompany laboratory automation and scientific innovation, ready-to-use reagent kits with instructions for use introduced a very significant innovation to the field of automation, eliminating the process of manually preparing reagent.[3] Scientific research and development over the past few decades have increased laboratory testing capabilities and allow for laboratories to significantly reduce time and cost consolidating routine and specialized tests onto one single platform.

An example of how this has advanced clinical chemistry testing is the two main methods for the detection of proteins in patient samples: (1) nephelometry, and (2) immunoturbidimetry. Nephelometry, although traditionally thought to be more sensitive, can be expensive due to higher consumable costs. In addition, nephelometers can be inefficient and are limited by their test menu.

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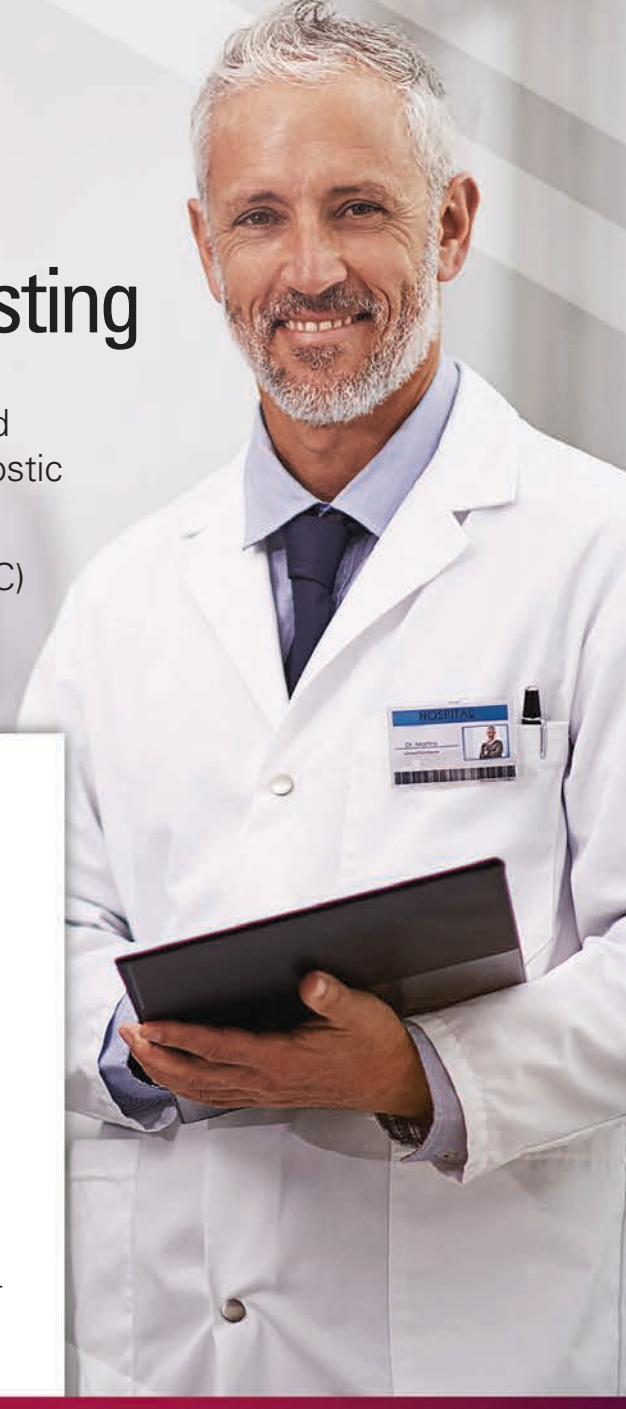

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showed that all 52 cultures with these organisms were also detected positive within an 18-hour incubation period.

The data from this study indicate that the laboratory's current 24-hour urine incubation time could be shortened to 18 hours using continuous incubation with digital reading without negatively impacting culture accuracy and reliability. In addition, we determined that the possible elimination of the first 14-hour image read would allow for streamlining the culture imaging process, reading cultures only once, and allow for more specimens to be accommodated by increasing our capacity. In our facility, instituting a single 18-hour image read would allow a more optimized work flow in the lab, effective utilization of microbiology staff, and have a positive impact to clinicians and patients delivering urine culture results hours sooner.

In summary

The final summary points from the study results are:

- Approximately 1/3 of positive urine cultures could be worked up after 14 hours of incubation (including over half of the cultures that contained gram negative bacilli).
- Approximately 97 percent of all positive urine cultures could be worked up after only 18 hours of incubation.
- Only three percent of cultures had an optimal reading time after 18 hours but they would not be missed as growth was detected at or before 18 hours of incubation.
- Instituting a single 18-hour read time for urine cultures would allow a more optimized work flow in our laboratory and have a positive impact on patients releasing urine culture results up to 6 hours earlier.

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Cynthia C. Keyak, MT (ASCP), SSGB serves as Microbiology Supervisor for Alverno Laboratories in Hammond, IN. She graduated from Purdue University with a B.S. in Biology, completed her ASCP Medical Technologist certification, and received her Six Sigma Green Belt from the University of Michigan at Ann Arbor. She is currently working towards her M.S. in Healthcare Administration.

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Immunoturbidimetry presents labs with the added advantage of consolidating a variety of chemistries on one system lowering laboratory costs as nephelometry requires the use of dedicated equipment and are much slower and require highly trained personnel.

Choosing a chemical analyzer

Choosing a chemical analyzer will depend on the types of tests the laboratory wishes to run and the throughput required. Many other factors include: sample handling, degree of automation, footprint, operational costs, turnaround time (TAT), STAT capabilities, service dependency, and whether the analyzer can handle micro volume samples.

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Today, the advancements in quality control software are designed to allow laboratories to meet industry and international standard requirements while ultimately ensuring accurate and reliable instrument performance.[10]

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Histone acetylation: An emerging target of epigenetic interest

By John Brunstein, PhD

Once upon a time, genetics was simple. Lamarck told us giraffe necks got longer because they were stretching to reach higher leaves and their offspring gained these traits (although he was a bit hazy on the mechanism). Darwin replaced this with a more complex theory of evolution, and Mendel and his peas (bolstered by what could be politely called selective use of his data) provided evidence for some sort of physical hereditable material coding for these traits. People such as Delbrück; Avery/McCarty/MacLeod; Hershey and Chase; and Franklin, Watson, and Crick built on this to finalize the Central Dogma of DNA as the core hereditary material by means of triplet codons of sequence, transcribed to RNA as a transient messenger, and translated to amino acid sequences on the ribosome leading to full functioning proteins.

With each new iteration, the story of how genetic information is transmitted has gotten more complex and this trend continues to hold true. While the basic concept of the Central Dogma remains unchanged, we're increasingly aware of modifications to DNA which, while not changing the underlying sequence, can influence the expression of its biological information content. Collectively known as epigenetic modifications, the one we'll look at in more detail here doesn't even modify the actual DNA bases, but the associated proteins involved in packaging of DNA. If you're going to take 205 cm of nuclear DNA (208 for women) and cram it into an average human cell nucleus with a diameter of around 6 µm, you need to do some serious compaction. A first critical step in this involves the protein family known as histones. Carrying an overall basic charge (which helps to electrostatically associate with the acidic charge of the DNA backbone phosphate groups), histones H2A, H2B, H3, and H4 in groups of two each form small "spools" around which 146 base pairs of DNA coils 1.67 turns, followed by about 80 base pairs of unspooled DNA more loosely associated with histone H1 before the structure repeats with another histone octamer and its coil. Sometimes described as "beads on a string", these structures—called nucleosomes—are the core packing motif for DNA, and by organizing them further through coiling and looping to create chromatin, individual chromosomes can be condensed down small enough to fit in the nucleus.

The closet rule: You can't have both compact storage and ready accessibility

As anyone who's ever tried to organize a closet has discovered, there's a trade-off between compactness of storage and accessibility to material stored. This holds true for DNA as well; in order for genes to be transcribed, there are various regulatory element sequences which must be accessible enough for transcriptional enhancer proteins to identify their cognate DNA binding sequences, attach, and recruit in other factors to a gene's promoter leading to productive association by an RNA polymerase. Production of transcript by the polymerase requires temporary local denaturation of the DNA strands to expose one as template (creation of the "transcription bubble"), another step which isn't going to happen while the DNA is tightly coiled around a histone spool. It seems logical therefore that any biological processes which can influence the tightness of association between the DNA and histones might influence accessibility of genes for transcription.

One such process is histone acetylation. To understand how this works, we should first consider that rather than the histone octamer being a perfect spool, the individual subunits have dangling "tails" containing lysine residues. These tails wrap into the minor groove of the associated DNA, helping to bind and bend the DNA around the nucleosome core. Normally, the side chains of these lysines carry a terminal -NH3+ group and it's these charges which contribute much of the electrostatic binding energy to the DNA backbone. In order to get the DNA free of the histone octamer and exposed enough for transcription factors to find their binding sites, this binding energy between the DNA and histones must be overcome. Put another way (and here, the ugly spectre of thermodynamics raises its head; despite best efforts to keep it at bay in this series, at times it's inescapable)—there's an equilibrium established under a given set of conditions (temperature, pH) between DNA bound to histones and DNA free of them; that equilibrium is generally in favour of the bound side.

HATs and HDACs

Enter a class of enzyme called a Histone acetyltransferase (HAT). These take the common acetyl group donor Acetyl-Coenzyme A and act to move its CH3COO- (acetyl) group over to the histone lysine tails, forming an amide bond. More importantly, this neutralizes the lysine side chain positive charge, leaving it electrostatically neutral. With that major component of binding energy removed, the equilibrium referred to above shifts to favor a larger proportion of free DNA. If you're having trouble picturing this, think about the force needed to bend the DNA around the histone octamer; remove that force (electrostatic attraction from lysine side chains) and the DNA will tend to "spring" free. Left flopping about in the open, that DNA section is much more readily available to

interact with proteins driving transcription. With this in mind, it's now easy to see how acetylation of histones is associated with locally increased rates of gene transcription. (A less obvious but viable proposed secondary mechanism for histone acetylation to influence transcriptional activity is via direct protein-protein interactions, with they acetyl groups helping recruit transcription factors.)

If this is a biological system under control, then we should expect there's also a system to reverse the acetylation. In fact, there is a class of enzymes known as Histone deacetylases (HDACs) which catalyze the hydrolysis of acetyl groups back off the histone lysines. One could now suppose that purely by altering the relative activities of HATs and HDACs in a cell, there should be a global (whole genome) influence on gene expression rates. While that's likely true, it would be a crude method of regulation at best. What's more interesting—and what gets more than a little strange—is where there are localized (and genetically transferable) variations in histone acetylation rates. In keeping with what we learned above, those areas with more histone acetylation are more transcriptionally active than those with less histone acetylation. It also turns out however that histone acetylation also acts to recruit HATs to the acetylated area, and being localized there, they have a greater chance to act on neighbouring, as-yet unacetylated histones. That is, histone acetylation begets more adjacent histone acetylation. Importantly, during chromosome replication, this means that HATs are recruited to the proximity of the nascent strand where the parental template is acetylated, leading to acetylation (and influence of transcriptional activity) on the progeny DNA. Thus, not only is the underlying DNA sequence inherited between generations, but this form of epigenetic marker can be, too. Actually, studies have shown that it can be passed down multiple generations.

Consequences of this are significant. To understand a functional human genotype, not only must you know the direct DNA sequence at both copies of a normal somatic gene locus, but the differential acetylation of these copies can influence their relative expression rates. Suddenly, those observations lumped in genetics courses as "variable penetrance" or "variable expressivity" begin to have additional plausible mechanisms. We can also begin to appreciate that undesirable changes in HAT or HDAC activity—such as in response to environmental chemicals—can act a mutagens resulting in hereditable genetic changes while leaving the base DNA sequence unchanged. Once more, our understanding of what exactly constitutes heritable genetic information has grown a little more complex than that accepted by our predecessors.

Real-life effects

That's all very interesting, but are there known clinical conditions relating to histone acetylation? In a word, yes. Although, many details are still being worked out. For example, there are actually 11 different HDAC genes conserved among mammals, in four groups based on structure and localization. In animal models, deletion of any of the Group I HDACs is embryonic lethal and deletion of a Group 2 HDAC has negative impacts on particular organ types (including heart and skeleton); Group 3 and 4 HDACs appear less critical for development in these models. Specificity of phenotypes arising from particular HDAC deletions suggests they have particular and reproducible patterns of activity, as opposed to being generic and global. On the other side of the enzymatic process, Rubinstein—Taybi Syndrome is caused by mutations in CREB binding protein (CBP), a protein with intrinsic HAT activity. Analysis of these mutations indicate they destroy the protein's HAT activity and that in turn may be the root cause of the clinical presentation. Mouse models of this, with specific deletion of CBP's HAT function, show a phenotype related to impairment of long term (but not short term) memory formation—rescuable by administration of a HDAC inhibitor, and indicating an intriguing and perhaps surprising link between chromatin packaging and long-term memory. Multiple studies have linked dysregulation of histone acetylation with Alzheimer's disease (AD) in humans, and treatment of mouse AD models with HDAC inhibitors have proven beneficial in reducing symptoms.

If these leads prove out to be clinically relevant in humans, a challenge for the molecular labs may be in how to measure or assess histone acetylation. Other epigenetic modifications such as base methylation directly modify the DNA bases and are detectable by current NGS sequencing (either through a chemical process known as bisulfite modification in sequence-by-synthesis methods, or directly by analysis of raw data in nanopore based methods). NGS methods however only examine the actual nucleic acids, discarding proteins (including histones) during sample preparation. Should histone acetylation become something needing to be measured in the lab, a different approach would be required. Targeted proteomics would seem the most promising method but would need to be applied on appropriate tissue samples—as opposed to nuclear genomic analysis which can be conducted off of any readily available tissue and yet represent whole organism.

Conclusion

The moral of this month's topic would seem to be that while our knowledge of genetics and inheritance is broad and, in many ways, actionable (or at least provides understood mechanisms for observed phenotypes), genome sequence alone isn't the whole story. There remain increasingly complex cellular mechanisms which can modulate base genetic data in heritable fashion that we are only now beginning to grasp.

John Brunstein, PhD, serves as an Editorial Advisory Board member for MLO. John is also President and CEO for British Columbia-based **PathoID, Inc.**, which provides consulting for development and validation of molecular assays.

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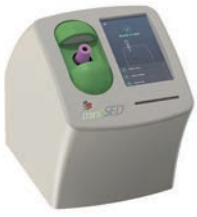

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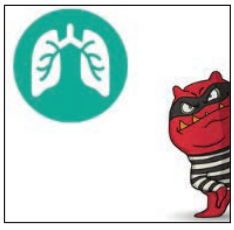

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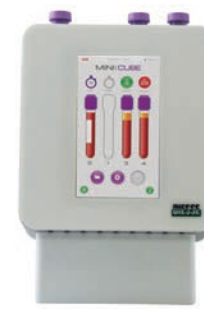

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An interview with Ramon Benet, CEO, Instrumentation Laboratory

For those readers unfamiliar with Instrumentation Laboratory (IL), what are three things you can share about the company that would enlighten a laboratory newbie? First, we are a global leader in the development, manufacture and distribution of *in vitro* diagnostic systems, including analyzers, automation, reagents, service, and information management products for clinical laboratories and hospital acute care settings.

Second, we specialize in Hemostasis and Acute Care diagnostic products, all designed to help healthcare providers improve the quality of patient care and control costs.

Third, we are very proud that every day, over 1.1 million patient samples are tested on our systems worldwide. This is a tremendous responsibility we take very seriously, as well as a measure of the positive impact we make on so many people around the globe.

As of May 2019, WHO stated, "Burnout is included in the 11th Revision of the International Classification of Diseases (ICD-1) as an occupational phenomenon." You've been with IL since 1993; 26 years! How have you avoided "occupational burnout?" I cannot say I have ever felt burnout. I love what I do, and I find it a privilege to serve my colleagues, our customers, and their patients. I do confess, I like my weekends and time off. A good work and family balance is crucial for long-term success.

In your opinion, what makes you a good leader? Well, I have been fortunate to surround myself with the best team possible—people who are much better than me at what they do. I focus on maintaining our unified vision, mission, and direction. I provide steady leadership, concentrating on what is truly crucial to fulfill our goals. I am conservative overall, but very ambitious in certain select areas.

Being a top-level executive, how often do you get to interact with working laboratorians? I love visiting hospital laboratories to see our customers in action, understand their challenges, and envision how our systems can help them fulfill their goals. In addition, we frequently invite customers to visit our IL headquarters because we find it very useful to sit down with clinical laboratory personnel of all levels to openly discuss their needs, both now and in the future, and understand how manufacturers like IL can help them.

In your 2013 interview with MLO you indicated that the primary business areas of IL within *in vitro* diagnostics were Hemostasis and Critical Care. Is that still true today? Yes, but both have become much broader. While we remain the global leader in Hemostasis analyzers and reagents, we have expanded very heavily into laboratory automation and information management systems for the Hemostasis laboratory. Additionally, we have introduced a number of innovative reagents with significant impact on the clinical management of patients with conditions, such as Heparin-Induced Thrombocytopenia (HIT) and Thrombotic Thrombocytopenic Purpura (TTP), along with many more innovations in our Hemostasis pipeline.

Our business line, formerly called Critical Care (which was essentially Blood Gas testing), has now expanded to become "Acute Care Diagnostics," through the addition and integration of our comprehensive Whole-Blood Hemostasis and Patient Blood Management portfolios. We now offer rapid, whole-blood testing for a broad range of hospital acute care settings, from the Intensive Care Unit to the Cardiovascular Operating Room, Cardiac Catherization Lab, Neurointerventional Radiology Lab, and the Emergency Department, as well as the Laboratory.

IL introduced the GEM Premier ChemSTAT *in vitro* diagnostic (IVD) analyzer with Intelligent Quality Management (iQM) at AACC Anaheim this year. How does this analyzer help identify sepsis patients faster? Rapid Lactate testing allows earlier triage and management of patients with sepsis. The new GEM Premier ChemSTAT system is designed for the emergency care environment and provides results for a complete Basic Metabolic Panel (BMP)—including Creatinine, Blood Urea Nitrogen (BUN), measured tCO2, electrolytes and Glucose, as well as Lactate, Hematocrit, pH, and pCO2. In addition to sepsis and septic shock, these are some the most widely ordered tests for diagnosing acute conditions, such as kidney injury and diabetic ketoacidosis. Recently, IL initiated commercial release of the GEM Premier ChemSTAT system in select hospitals.

What kind of advantages does this type of technology offer for these institutions? Generally, hospitals perform BMP testing in the laboratory. Now, with the GEM Premier ChemSTAT system, healthcare providers can obtain laboratory-quality results on-demand, at the point of care, in less than 70 seconds. A single sample of venous whole blood is all that's needed, with no preparation required. This enables rapid assessment of life-threatening conditions, aids in risk-stratification and prioritization of patients for expedited treatment and disposition—especially important for high-risk, acutely ill patients in the emergency department. Additionally, and very importantly, the GEM Premier ChemSTAT system integrates patented iQM, which provides unmatched quality assurance for the most accurate results with every sample and eliminating maintenance to deliver cost-efficient outcomes and improved patient care.

New FDA Regulations, Hospital Glucose Meters

FDA Product Code PZI, 2019:
"Blood Glucose Meter for Near-Patient Testing"①

FDA Product Code NBW, 2016:
"Blood Glucose Test System, Over the Counter."② "These device types are not intended for use in healthcare or assisted-use settings such as hospitals, physician offices, or long-term care facilities because they have not been evaluated for use in these professional healthcare settings."③

Use of a meter cleared by the FDA as NBW is considered "OFF LABEL" when used anywhere in a hospital. Is your hospital glucose meter cleared as FDA Product Code PZI for hospital use or NBW cleared and off label for hospital use?

Stat Strip® GLUCOSE

Cleared as FDA Product Code PZI.
Intended for use in near-patient testing.

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① U.S. Food and Drug Administration. Product classification [Product Code PZI]. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=678

② U.S. Food and Drug Administration. Product classification [Product Code NBW]. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=631

③ U.S. Food and Drug Administration. Self-monitoring blood glucose test systems for over-the-counter use. Draft guidance for industry and Food and Drug Administration staff. Silver Spring, MD: 2018.https://www.fda.gov/media/119828/download

Crack pneumonia cases faster.

Get fast, comprehensive results with the BioFire® FilmArray® Pneumonia Panel.

Respiratory infections can arise from a variety of pathogens. The BioFire Pneumonia Panel utilizes a syndromic approach—simultaneously testing for the most likely organisms to cause similar signs and symptoms. Our simple, rigorous test identifies specific pathogens—as well as levels of organism present in a given sample—all in about one hour. The BioFire Pneumonia Panel drastically improves turnaround time to organism identification, delivering fast, comprehensive results that ultimately aid in diagnosis.

Learn more at **biofiredx.com**

The BioFire Pneumonia Panel

Bacteria (semi-quantitative)
Acinetobacter calcoaceticus baumannii complex
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae group
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacteria (qualitative)
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Viruses (qualitative)
Adenovirus
Coronavirus
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza B
Parainfluenza virus
Respiratory Syncytial virus

Resistance Markers
Carbapenemase
- IMP
- KPC
- NDM
- Oxa48-like
- VIM

ESBL
- CTX-M

MRSA
- *mec*A/C and MREJ

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