MLO-online.com

MEDICAL LABORATORY OBSERVER

MLO®

DECEMBER 2022 • Vol 54 • No 12

The Peer-Reviewed Management Source for Lab Professionals since 1969

2022 LIS Buyer's Guide

Page 40

CE: Cytomegalovirus infection and testing

Page 8

Q&A expert
Charles Cooper, MD
Siemens Healthcare Diagnostics
Siemens Healthineers

PLUS

Drug of abuse testing and therapeutic drug monitoring

Page 16

Quality control strategies and patient outcomes

Page 32

The power to **choose**.

The **Panther**® system is the best-in-class automated platform designed for scalability. Choose from a variety of instrument add-ons and our expanding assay menu for an economical path toward consolidation and growth.

GROW ON **PANTHER SCALABLE SOLUTIONS**

ADD ON
PANTHER FUSION®

ADD ON
PANTHER® PLUS

ADD ON
PANTHER® LINK

ADD ON
PANTHER® TRAX™

HOLOGIC®

The potential to **grow**.

Consolidate your **respiratory testing** today and meet your lab's growing needs of tomorrow.

- Flu A/B/RSV
- AdV/hMPV/RV
- SARS-CoV-2/Flu A/B*
- Paraflu 1-4
- SARS-CoV-2*
- SARS-CoV-2/Flu A/B/RSV†

WOMEN'S HEALTH

- CT/NG
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- Bacterial vaginosis
- Candida vaginitis/ *Trichomonas vaginalis*
- HSV 1 & 2
- HPV
- HPV 16 18/45
- Zika Virus*

INFECTIOUS DISEASE

- HIV-1 Quant Dx
- HCV Quant Dx
- HBV Quant
- CMV Quant
- Flu A/B/RSV
- Paraflu
- AdV/hMPV/RV
- SARS-CoV-2*
- SARS-CoV-2/Flu A/B*
- SARS-CoV-2/Flu A/B/RSV† CE

- GI Bacterial†
- GI Expanded Bacterial†
- GI Viral†
- GI Parasite†
- GBS†
- EBV† CE
- BKV† CE
- C. difficile†
- M. gen macrolide resistance†
- Monkeypox†

PANTHER®

* The Aptima SARS-CoV-2, Panther Fusion SARS-CoV-2, Aptima Zika Virus and Aptima SARS-CoV-2/Flu assays have not been FDA cleared or approved. These tests have been authorized by FDA under an EUA for use by authorized laboratories; the Aptima and Panther Fusion SARS-CoV-2 assays have been authorized only for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens; the Aptima Zika Virus assay has been authorized only for the detection of nucleic acid from Zika virus, not for any other viruses or pathogens; the Aptima SARS-CoV-2/Flu assay has been authorized only for the simultaneous qualitative detection and differentiation of nucleic acid from SARS-CoV-2, influenza A virus, influenza B virus, and not for any other viruses or pathogens. The Aptima SARS-CoV-2, Panther Fusion SARS-CoV-2, and Aptima SARS-CoV-2/Flu assays are only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. The Aptima Zika assay is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

† In development and not for sale

MEDICAL LABORATORY OBSERVER
MLO®
The Peer Reviewed Management Source for Lab Professionals since 1969

Image courtesy of EUROIMMUN US

8

Photo credit: DEA

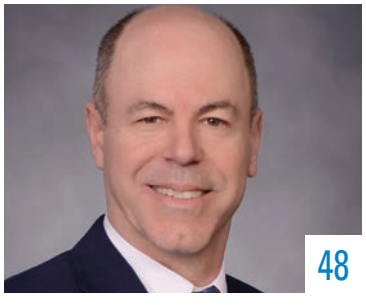
20

Photo courtesy of Advanced Instruments, LLC

36

Image by NatalyaBurova @ gettyimages.com

40



48

RALS™

PAIN RELIEF
AT THE POINT-OF-CARE

When it comes to managing point-of-care testing (POCT), if you're like most POCCs, you probably have lots of pain points, including:

Managing Operators

Can you auto-recertify?

Managing Devices

Where are they? Who is using them?

Being Inspection Ready

Inspectors are coming... are you prepared?

Measuring POCT Performance

Is my program what it should be?

RALS connectivity can help reduce your workflow pain points and provide long-lasting relief with everything from a range of operator management tools, personalized dashboards for monitoring key performance indicators, and custom saved views for quick and efficient data review.

TO SEE ALL THE WAYS RALS CAN HELP VISIT WWW.RALS.COM

Abbott

Negotiations in the lab

By Christina Wichmann
Senior Editor

Last month, *MLO* staff attended the Association for Molecular Pathology (AMP) Annual Meeting and Expo in Phoenix, AZ. The in-person conference was cancelled in 2020 and 2021 and held virtually due to COVID-19. This year, there were 1,855 attendees and 195 exhibiting companies. The conference provided numerous plenary and breakout sessions over three days, and ample opportunity to walk around the expo hall to learn about the latest technology, innovations, and patient care improvements.

One of the sessions I attended was called "Negotiating in a Hostage Session: Tips to Keep Your Lab Financially Solvent During COVID-19 and the Next Pandemic." In this session, Donna Wolk, MHA, PhD, shared her experience with developing a business plan and acquiring negotiation skills above and beyond what she had before in order to get the extra money for her lab during the initial stages of the COVID-19 pandemic. Dr. Wolk serves as the Division Director for Molecular and Microbial Diagnostics and Development in the Department of Laboratory Medicine at Geisinger, an integrated healthcare delivery network in Danville, PA.

Dr. Wolk shared with the audience that she began her self-training by reading three books:

- *Never Split the Difference: Negotiating as if Your Life Depended on it* by Chris Voss
- *Crucial Conversations: Tools for Talking When Stakes are High* by Kerry Patterson, Joseph Grenny, Ron McMillan, and Al Switzler
- *The Four Agreements* by Don Miguel Ruiz

If you are not already familiar with these books, I have summarized them below.

Never Split the Difference is a handbook of negotiation principles written by a former FBI hostage negotiator. The book is a comprehensive guide to negotiation theory and strategy and aims to provide readers the tools needed to negotiate successfully. Voss explains that people have two basic emotional needs—to feel secure and to feel in control. Successful negotiators are those who understand these two needs and use them to identify their counterparts' real desires and fears.

Crucial Conversations argues that many problems are caused by how people behave when they disagree with others about high-stake, emotional issues. Organizational performance and the quality of relationships improve significantly when people learn the skills to handle crucial conversations effectively. This book teaches individuals to be persuasive, not abrasive and the skills needed to master high-stake conversations.

The Four Agreements' premise is that there are four agreements that bring back our personal power and reverse failure and accepting "the way it is." These agreements are as follows:

1. Be impeccable with your word: Say only what you mean, speak with integrity, stop internal negative self-talk.
2. Don't take anything personally: Others see the world with different eyes; nothing they think about you is really about you—they're dealing with their own issues.
3. Don't make assumptions: These cause misunderstandings between people. Be aware, ask questions, communicate.
4. Always do your best: Let go of the past, don't judge your past behavior, keep trying if you fall short.

Perhaps one or all of these books will be helpful to you as they were for Dr. Wolk.

I welcome your comments and questions — please send them to me at cwichmann@mlo-online.com.

MEDICAL LABORATORY OBSERVER Vol.54, No.12

MLO - MEDICAL LABORATORY OBSERVER
(Print ISSN: 0580-7247/Online ISSN 2771-6759). Published monthly, with an additional issue in September, by Endeavor Business Media, LLC., 2477 Stickney Point Rd, Suite 221B, Sarasota, FL 34231 (941) 388-7050. Subscription rates: $128.00/year in the U.S.; $155.00 Canada/Mexico; Intl. subscriptions are $221.00/year. All issues of *MLO* are available on microfilm from University Microfilms International, Box 78, 300 N. Zeeb Rd., Ann Arbor, MI 48106. Current single copies (if available) $15.00 each (U.S); and $20.00 each (Intl.). Back issues (if available) $1760 each (U.S.); $22.00 each (Intl.). Payment must be made in U.S. funds on a U.S. bank/branch within the continental U.S. and accompany request. Subscription inquiries: subscriptions@endeavorb2b.com. *MLO* is indexed in the *Cumulative Index for Nursing and Allied Health Literature* and *Lexis-Nexis. MLO* Cover/CE, Clinical Issues, and Lab Management features are peer reviewed. Title® registered U.S. Patent Office. Office of publication: Periodicals Postage Paid at Nashville, TN 37209 and at additional mailing offices. **Postmaster:** Send address changes to Omeda (MLO Medical Laboratoy Observer), PO Box 3257, Northbrook, IL 60065-3257. Printed in U.S.A.

BIOMÉRIEUX

DON'T MISS THE **FULL RESPIRATORY PICTURE.**

Help her get back to the picture of health.

Multiple respiratory pathogens cause similar, overlapping symptoms. This respiratory season, get the full picture, fast, with syndromic testing. The BIOFIRE Respiratory 2.1 Panel detects 22 respiratory targets, including bacteria and viruses, with results in about 45 minutes.

US FDA cleared

Product availability varies by country. Consult your bioMérieux representative.

BIOFIRE® RESPIRATORY 2.1 PANEL

1 Test. 22 Targets. ~45 minutes.

Scan for More Information.

BFR0002-1128-01

PIONEERING DIAGNOSTICS


Photo by © Steveheap | Dreamstime.com

Fast Facts

More than 3 million youth reported using a tobacco product in 2022

A study released from the U.S. Food and Drug Administration (FDA) and the U.S. Centers for Disease Control and Prevention (CDC) found that 3.08 million (11.3%) U.S. middle and high school students reported current (past 30-day) use of any tobacco product in 2022.
The study assessed eight commercial tobacco products. Of the students that reported tobacco use:

2.51 million (16.5%)
were high school students.

530,000 (4.5%)
were middle school students.

2.55 million
reported using e-cigarettes, making it the most commonly used tobacco product among all students for the ninth consecutive year.

13.5%
of non-Hispanic American Indian or Alaska Native students reported tobacco use, the highest percentage of all race and ethnicity groups.

1 million
youth reported using any combustible tobacco product.

27.2%
of students who reported tobacco use had grades of mostly Fs.

Source: https://www.cdc.gov/media/releases/2022/p1110-youth-tobaco.html

Biomarkers that predict preeclampsia risk

In a study of pregnant women in the United States, Cedars-Sinai investigators found that a specific imbalance of two placental proteins could predict which women were at risk of developing a severe form of preeclampsia, a life-threatening blood pressure disorder.

The study is published in the journal *NEJM Evidence*.

The blinded, prospective study of women initially hospitalized for preterm hypertension involved 1,014 patients from 18 hospitals across the nation.

Investigators found that a specific protein imbalance revealed in blood tests of the hospitalized pregnant women provided a way to quantify their risk of developing severe preeclampsia. It involves levels of soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF) in the bloodstream.

NIH's Climate and Health Initiative tackles global health effects associated with a changing climate

Leaders from the National Institutes of Health discuss the agency's plan to address the risk to human health posed by a changing climate in a commentary published in *The Lancet.* As floods, hurricanes, tornados, wildfires, and heat waves become more extreme, the risk to human health grows, exacerbating existing health threats and creating new public health challenges around the world.

The authors, a coalition of leaders at NIH, outline how the NIH Climate Change and Health Initiative is uniquely poised to lead and engage with communities and agencies globally to address the health effects associated with climate change.

Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19

A new study showed that among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery in this trial that enrolled more than 1,500 participants in the United States.

A lack of treatment effect was also seen for secondary clinical outcomes including hospitalization, death, or acute care visits. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

The study was published in *JAMA*.

Cancer deaths continue downward trend; modest improvements in survival for pancreatic cancer

Overall cancer death rates continued to decline among men, women, children, and adolescents and young adults in every major racial and ethnic group in the United States from 2015 to 2019, according to the latest Annual Report to the Nation on the Status of Cancer.

From 2014 to 2018, overall cancer incidence, or new cases of cancer, remained stable for men and children but increased for women and adolescents and young adults. This year's report, published October 27, 2022, in *Cancer*, also highlights longer-term trends in pancreatic cancer, as well as racial and ethnic disparities in incidence and death rates for many individual cancer sites.

All of the findings in this report are based on data from before the COVID-19 pandemic.

The report shows that from 2015 to 2019, overall cancer death rates decreased by 2.1% per year in men and women combined. Among men, death rates decreased by 2.3% per year; among women, death rates decreased by 1.9% per year. The annual declines in death rate accelerated from 2001 to 2019 in both men and women.

The declines in death rates were steepest in lung cancer and melanoma (by 4% to 5% per year) among both men and women. Death rates increased for cancers of the pancreas, brain, and bones and joints among men, and for cancers of the pancreas and uterus among women.

The report showed that cancer incidence rates were relatively stable in men and women combined from 2014 to 2018. Among men, incidence rates remained stable during this period, but among women incidence rates rose by 0.2% per year.

Over the same time period, incidence rates increased for three of the 18 most common cancers among men: pancreas, kidney, and testis. Incidence rates in men remained stable for seven of the most common cancers and decreased for the remaining eight cancers. For women, incidence rates increased for seven of the 18 most common cancers: liver, melanoma, kidney, myeloma, pancreas, breast, and oral cavity and pharynx. Incidence rates among women remained stable for four of the most common cancers and decreased for the other seven cancers.

In men, the greatest incidence rate increase was seen in pancreatic cancer, which increased by 1.1% per year, and the steepest incidence rate decrease was seen in lung cancer, which fell by 2.6% per year. In women, melanoma had the steepest increase in incidence, rising by 1.8% per year, and thyroid cancer had the sharpest decrease, falling by 2.9% per year.

Overall cancer incidence rates during 2014 to 2018 were highest among non-Hispanic American Indian and Alaska Native (AI/AN) people, followed closely by non-Hispanic White people and non-Hispanic Black people. Overall cancer incidence rates were lowest among non-Hispanic Asian/Pacific Islander (API) and Hispanic people.

Incidence rates for all sites combined decreased among non-Hispanic Black, non-Hispanic API, and Hispanic men, but increased among non-Hispanic White, non-Hispanic API, non-Hispanic AI/AN, and Hispanic women from 2014 to 2018. Incidence rates were stable among non-Hispanic White and non-Hispanic AI/AN men and non-Hispanic Black women.

Among children younger than 15, overall cancer death rates decreased from 2015 to 2019, and incidence rates remained stable from 2014 to 2018. Overall cancer incidence rates were stable for non-Hispanic Black children over this period but increased for non-Hispanic White, non-Hispanic API, non-Hispanic AI/AN, and Hispanic children.

Among adolescents and young adults ages 15 to 39, overall cancer incidence rates increased by 0.9% per year from 2014 to 2018. The overall cancer death rate decreased by 3.0% per year from 2001 to 2005, but the decline slowed to 0.9% per year from 2005 to 2019.

The incidence of breast cancer, the most common cancer among adolescents and young adults, increased by an average of 1.0% per year from 2010 to 2018.

The researchers noted that racial and ethnic disparities exist for many individual cancer sites. For example, from 2014 to 2018, incidence rates for bladder cancer declined in non-Hispanic White, non-Hispanic Black, non-Hispanic API, and Hispanic men but increased among non-Hispanic AI/AN men. Incidence rates for uterine cancer increased among women of every racial and ethnic group from 2014 to 2018 except for non-Hispanic White women, who had stable rates.

From 2015 to 2019, prostate cancer death rates were stable among non-Hispanic White and non-Hispanic Black men but decreased among non-Hispanic API, non-Hispanic AI/AN, and Hispanic men. Colorectal cancer death rates were stable among non-Hispanic AI/AN men but decreased in men of all other racial and ethnic groups. Among women, death rates for lung, breast, and colorectal cancer decreased in nearly every racial and ethnic group. The exceptions were non-Hispanic API women, among whom breast cancer death rates remained stable, and non-Hispanic AI/AN women, among whom breast cancer death rates increased and colorectal cancer death rates remained stable.

This year's report includes a special focus on trends in pancreatic cancer incidence, death, and survival rates. Although pancreatic cancer accounts for only 3% of new cancer diagnoses, it accounts for 8% of cancer deaths and is the fourth leading cause of cancer deaths in the United States for both men and women.

Study finds personalized kidney screening for people with type 1 diabetes could reduce costs, detect disease earlier

Taking a personalized approach to kidney disease screening for people with type 1 diabetes (T1D) may reduce the time that chronic kidney disease (CKD) goes undetected, according to a new analysis performed by the Epidemiology of Diabetes Interventions and Complications study group.

The finding was published in *Diabetes Care* and provides the basis for an evidence-based kidney screening model for people with T1D.

According to the model's findings:

- People with AER of 21-30 mg per 24 hours and a HbA1c of at least 9% are at high risk for developing CKD and could be screened for urine albumin every six months.
- Those with AER ≤ 10 mg per 24 hours and a HbA1c ≤ 8% are at lower risk for developing CKD and could be screened every two years.
- All others with T1D ≥ 5 years could continue to be screened annually.

Which COVID vaccine you get can impact myocarditis risk

Incidence of myocarditis, pericarditis or myopericarditis is two- to threefold higher after a second dose of the Moderna Spikevax COVID-19 vaccine when compared to the Pfizer BioNTech COVID-19 vaccine; however, overall cases of heart inflammation with either vaccine are very rare, according to a study in the *Journal of the American College of Cardiology*.

The study showed males younger than 40 years old who received the Moderna vaccine were shown to have the highest rates of myocarditis, which according to the authors, may have implications for choosing specific vaccines for certain populations.

While there have been many studies on either vaccine, few studies have been conducted to directly compare the safety of the two mRNA vaccines. Researchers in this study sought to compare the risk of myocarditis, pericarditis and myopericarditis between the Pfizer and Moderna COVID-19 vaccines.

People in the study were 18 years old or older and had received two primary doses of either Pfizer or Moderna vaccine in British Columbia, Canada, with the second dose between Jan. 1, 2021 and Sept. 9, 2021. Individuals whose first or second shot were administered outside of British Columbia or had a history of myocarditis or pericarditis within one year prior to second dose were excluded.

In all, more than 2.2 million second Pfizer doses were given and more than 870,000 Moderna doses. Within 21 days of the second dose, there were a total of 59 myocarditis cases (21 Pfizer and 31 Moderna) and 41 pericarditis cases (21 Pfizer and 20 Moderna). Researchers also looked at rates per million doses and the rate was 35.6 cases per million for Moderna and 12.6 per million for Pfizer—an almost threefold increase after Moderna shots vs. Pfizer. Comparatively, rates of myocarditis in the general population in 2018, were 2.01 per million in people under age 40 and 2.2 per million in people over age 40.

Rates of myocarditis and pericarditis were higher with the Moderna vaccine in both males and females between ages 18 and 39, with the highest per million rates in males ages 18-29 after a second dose of Moderna.

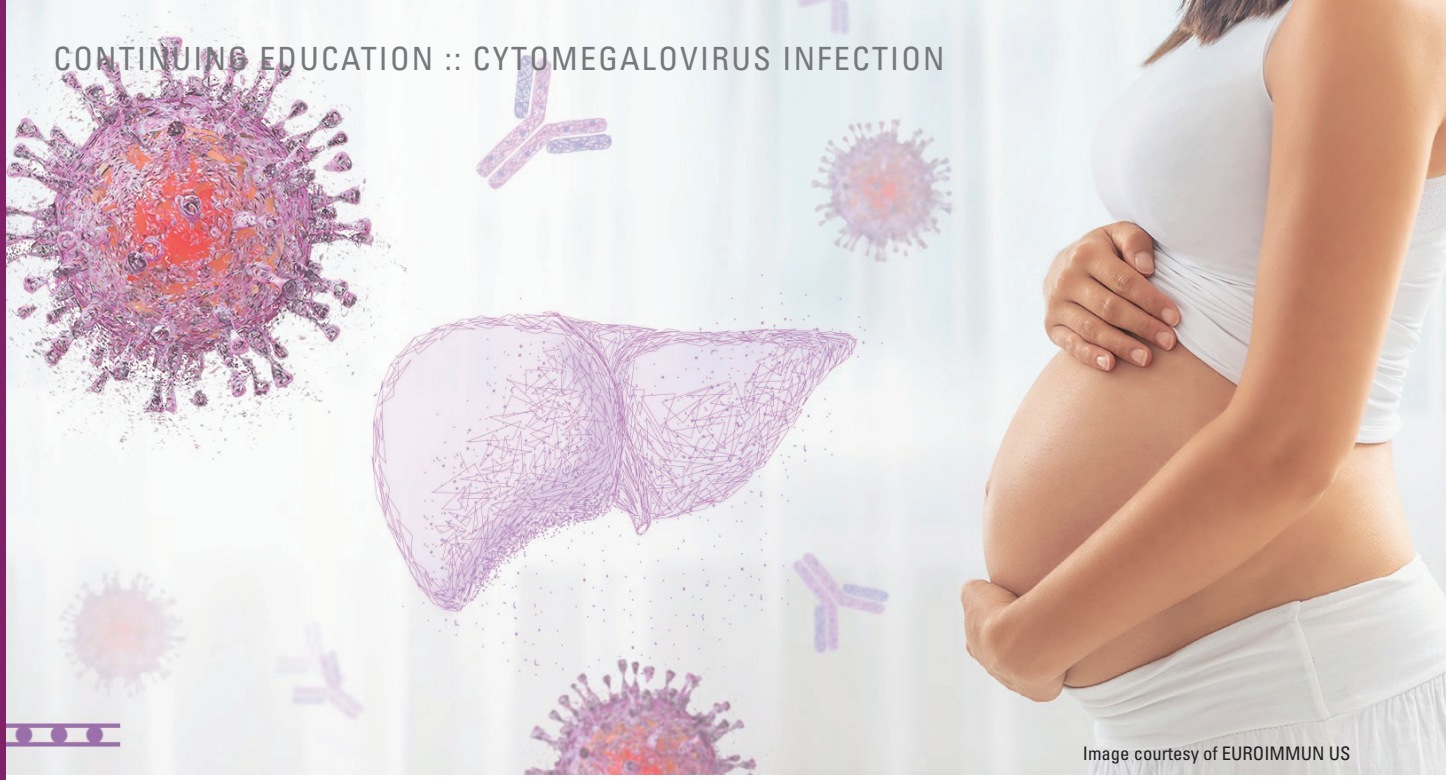


Image courtesy of EUROIMMUN US

Cytomegalovirus infection: When and why to detect antibodies

By Ilana Heckler, PhD and Maite Sabalza, PhD

Cytomegalovirus (CMV) is a beta-herpesvirus that causes viral inclusion bodies and enlarges infected cells. It is the largest herpesvirus known to infect humans, with a seroprevalence of 60–90% worldwide.[1,2] Higher prevalence occurs in lower socioeconomic groups in developing countries.[2] In the United States, nearly one-third of children have CMV by age of five, and more than half of adults have it by the age of forty.[3]

CMV is transmitted from person to person by direct contact. The virus is shed in body fluids — with main transmission via saliva and urine of young children to other children or adults. Other forms of transmission include sexual contact, blood transfusions, and organ transplants. In healthy individuals, CMV infection is often asymptomatic, but it may be fatal in immunocompromised patients.[4] Symptoms of CMV in mild cases are described as flu-like and include fever, sore throat, fatigue, and swollen glands. More serious cases, such as those occurring in people with weakened immune systems, exhibit symptoms affecting the eyes, lungs, liver, esophagus, stomach, and intestines.

Primary infection occurs in those who have never been infected before. As with other herpes viruses, CMV remains latent in the host after the first infection and may reactivate at a later period. Reinfection occurs when a person is infected with a different viral strain.

CMV is the leading viral cause of congenital defects. CMV can cross the placenta and infect the fetus after primary infection, reactivation, or reinfection of the mother. The transmission is most likely in women with a primary CMV infection, and the risk of transmission increases throughout the third trimester.[5,6] Infection occurs in 0.5% to 2.5% of neonates, and most babies with symptoms at birth (5%) have long-term effects including sensorineural hearing loss, microcephaly, chorioretinitis, and motor disabilities.[7] A large percentage of asymptomatic newborns (15%) subsequently suffer impairments, most often hearing loss.[7,8] Furthermore, CMV infection is the most prevalent and dangerous opportunistic infection following solid organ transplantation (SOT) or hematopoietic stem cell transplantation (SCT) and in HIV patients.[2,9] CMV infection has also been linked with atherosclerosis, glioblastoma, and other diseases.[10,11]

There is no vaccine available to prevent CMV infection but there are antiviral drugs to treat immunocompromised individuals. Antiviral medication may improve hearing and developmental outcomes in infants with congenital cytomega-

Earning CEUs

See test on page 14 or online at www.mlo-online.com under the CE Tests tab. Passing scores of 70 percent or higher are eligible for 1 contact hour of P.A.C.E. credit.

LEARNING OBJECTIVES

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

1. Discuss the viral family, prevalence, and transmission route of cytomegalovirus (CMV).
2. List the vulnerable populations and complications of CMV transmission.
3. Describe CMV testing currently used in prenatal, fetal, and newborn testing.
4. Discuss future suggestions for the screening of newborns for CMV and its utility worldwide.

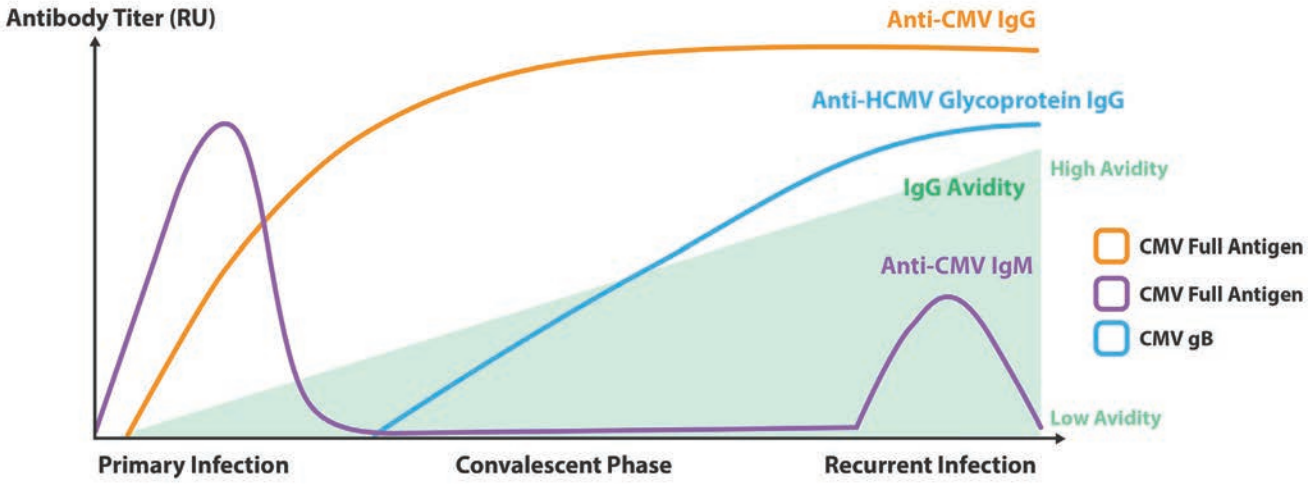


Figure 1: Antibody kinetics in CMV infection.

Serology in adults and infants older than 12 months

Initial infection leads to the production of CMV-specific immunoglobulin M (IgM) antibodies that persist in the blood for a short period of time and later to the production of IgG antibodies that can persist forever **(Figure 1)**.[13,14] The main challenge with IgM antibody detection is that some individuals can have persistent IgM levels for over a year.[15] IgM can be also detected in reactivation or reinfection. Therefore, the detection of IgM does not confirm an active primary infection. Furthermore, IgM antibodies are not highly specific and false positive results may occur.[16] A primary CMV infection can be distinguished from a past infection by measuring immunoglobulin G (IgG) seroconversion (follow-up collection samples required) and/or IgG avidity. IgG avidity tests evaluate the binding strength of IgG antibodies to the virus. Low-binding strength (low avidity) IgG antibodies are produced in response to initial CMV infection, and over the course of 2–4 months, develop into high binding strength (high avidity) **(Figure 1)**.[17] Therefore, high avidity IgG would indicate a past infection while low avidity IgG would indicate a primary infection. Due to the potential complications of CMV infection, particularly in pregnant women, is important to distinguish between primary infection, past infection, reactivation, and reinfection.

CMV testing in pregnancy

In the United States, routine screening for CMV infection during pregnancy is not recommended by the Centers for Disease infection after maternal primary infection. These estimates are based on data from the MFMU Network Randomized Trial to Prevent Congenital Cytomegalovirus.[23] This CMV calculator predicts cCMV infection in the context of primary maternal CMV infection and no ultrasonographic indications of congenital infection. Having this information may aid in patient counseling and decision making.[24] This calculator considers the results of an IgM antibody test, IgG avidity, and presence or absence of virus in maternal plasma.

Serological assays using glycoprotein B (gB) as an antigen for IgG antibody detection in pregnant women are included in some guidelines for screening pregnant women in Europe.[25-27] In general, the IgG antibody response to CMV gB is delayed by up to 100 days **(Figure 1; Table 1)**.[28] Therefore, IgG antibodies against gB indicate a past infection and a recent or primary infection can be excluded. These results are comparable to the finding of high avidity IgG antibodies. However, only 82% of CMV-infected individuals produce IgG antibodies against gB.[29] Consequently, a negative result can be a false-negative. Therefore, it is highly recommended to look at a combination of IgM, IgG seroconversion, IgG avidity, and antibodies against gB.

Fetal population testing

When an active infection is detected in a pregnant woman, the next step is to check fetal infection. There are two prenatal tests that can be used: non-invasive (ultrasound examination) and invasive (amniocentesis). CMV isolation from amniotic fluid

Detection parameter	Information gained	Primary infection detection	Discrimination between active primary vs. reactivation/reinfection
IgM	Active infection Past infection: Persistant IgM is possible.	Not possible IgM can be detected during primary, recurrent, or reinfection	Not possible IgM can be detecetd during primary, recurrent, or reinfection
IgG	Past infection: Indicates past CMV infection but does not indicate when infection occurred.	Possible IgG seroconversion	Possible Past infection by detecting IgG antibodies against late stage markers (anti-gB IgG) (only 82% of the population)
IgG avidity	Primary infection: Low avidity IgG antibodies Past infection: High avidity IgG antibodies	Possible Detected low avidity IgG antibodies	Possible High vs. low IgG avidity antibodies

Table 1: Serological testing in CMV infection.

Population	Molecular testing	Serology			
		IgM	IgG	Seroconversion	Avidity
Pregnant woman	Detection of active infection	The combination of all serology parameters will aid in determining if the infection is primary, secondary, or reinfection.			
	Not possible to differentiate primary infection from reactivation/reinfection.				
Fetus	Amniocentesis: Detection of active infection	Not relevant			
Newborn	Detection cCMV transmitted by mother within the first 2–3 weeks after birth.	Not relevant			
Transplant donor/recipient	Detection of active infection before and after transplantation	Not relevant	IgG detection important for risk assessment	Not relevant	Not relevant

Table 2: Relevant laboratory testing for different at-risk populations for CMV infection.

(amniocentesis) has been established as the gold standard due to its high sensitivity and specificity. However, amniocentesis has risks for the pregnant woman and fetus.[30] On the other hand, when fetal abnormalities are detected by ultrasound and the pregnant woman has low IgG avidity antibodies, the fetus has a higher risk of being infected. Therefore, the newborn will need to be monitored to confirm or rule out cCMV infection.[22]

Newborn testing

Molecular testing, such as quantitative polymerase chain reaction (qPCR), is the gold standard for cCMV detection in newborns within the first 2–3 weeks of life to distinguish congenital from a postnatal infection acquired during or after delivery **(Tables 1 and 2)**.[22,31] Saliva and urine are the preferred sample types for testing because they contain high viral loads of CMV. However, blood can also be used. The CDC recommends first testing saliva and then confirming positive samples with urine because CMV is also shed in breast milk. Therefore, confirmation with urine will help to rule-out false positives from breast milk.[17]

If the newborn is negative, the baby is considered uninfected, and no further tests are warranted. If a newborn is infected as indicated through a positive result from molecular testing, the newborn will be monitored for hearing loss or other sequela, thus increasing opportunities for early intervention.[32]

Serological testing for newborns within the first 2–3 weeks is not recommended because IgM antibodies are only present in 70% of infected newborns.[16] Additionally, newborn IgG antibodies mainly come from the mother and transfer through the placenta to the fetus.[33] As with molecular testing, serological tests will not distinguish prenatal from perinatal CMV infection after 2–3 weeks of life.[16]

As mentioned above, a large percentage of infected newborns are asymptomatic at birth but develop symptoms later.[7,8] Therefore, it can be helpful to screen newborns at birth. Several studies support the need of neonatal screening to identify earlier infected infants at risk to develop neurological sequelae and provide the appropriate treatment to reduce and treat CMV diseases.[34] In the United States, universal screening is not included in routine newborn screening. The CDC is investigating dried blood spot (DBS) to be used for this purpose.[17] This is important because DBS are collected from all newborns for metabolic screening and sometimes for detection of newborn disorders.[22,35] In fact, there are already commercially available assays to detect cCMV in newborns through DBS.[36] Interestingly, some states have already implemented universal screening. In February 2022, Minnesota become the first state in the nation to screen every newborn for cCMV.[37]

Transplantation population testing

Another population that is at risk of developing complications from CMV infection are recipients of organ or hematopoietic stem cell transplantation.

Direct detection of CMV by molecular testing is suggested for detecting and monitoring current infections in transplant recipients **(Table 2)**. Transplant donors must be also tested for CMV active infection prior to donation.[22,38] On the other hand, serological testing is recommended for transplant donors and recipients to reduce the risk of a primary infection and reactivation.[38,39]

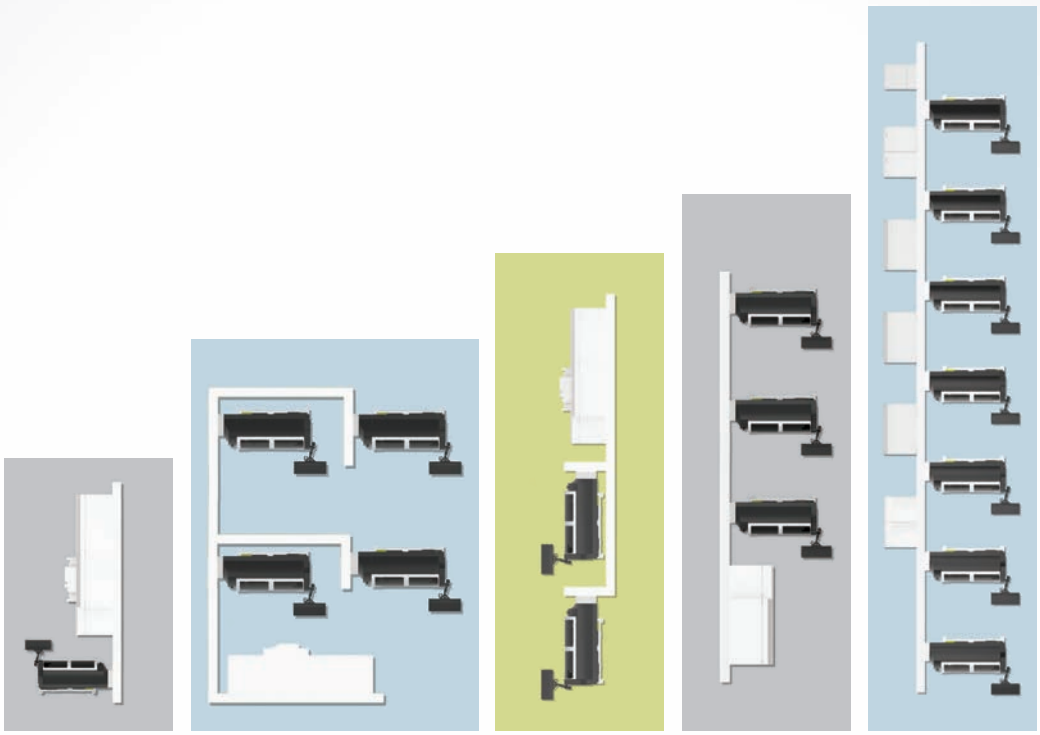
Conclusion

CMV is a common virus that can infect people of all ages. As does herpes virus, CMV remains latent in the human body. Therefore, the virus can be reactivated after primary infection and induce an active infection. Immunocompromised individuals are the main population at risk to develop complications from CMV primary infection, reactivation, and reinfection. These include pregnant women, newborns, and transplant recipients. Depending on the at-risk population, either serology or molecular testing are performed to detect an active infection or differentiate a primary infection from reactivation or reinfection.

A combination of molecular testing and serology provides the most accurate diagnosis of CMV infection. Due to the complications associated with a primary infection in pregnant women, it is important to raise awareness about CMV infection and implement initiatives to reduce the risk of transmitting the virus to the fetus. Furthermore, monitoring newborns is essential for identifying the infection quickly and administering the appropriate treatment. However, in some countries, prenatal or universal newborn screening is not recommended. One of the factors influencing that decision is the cost associated with testing. Nonetheless, it would be interesting to investigate the long-term consequences and costs of not screening these two populations.

Vaccine candidates are now being evaluated in clinical studies.[40] The approval of a vaccine to prevent CMV infection will have a significant impact on the groups at risk. In addition, there may be a shift in the role of serology in terms of monitoring the immune system's response to vaccines. While waiting for a vaccine, those at risk should adopt proper hygiene practices to avoid CMV infection. For instance, frequent handwashing and avoiding touch with another person's saliva, especially avoiding contact with the saliva and urine of small children.

HemoCELL™
SPECIALIZED
LAB AUTOMATION



Hemostasis automation that works on so many levels.

HemoCell delivers workcell efficiency, quality and standardization for Hemostasis labs. Featuring ACL TOP® 750 LAS and HemoHub™ Intelligent Data Manager, it's the only workcell to combine the leading Hemostasis testing system with specialized lab automation. And, because it can be customized to your lab's specific needs, HemoCell lets you design the automation layout that's right for you.

Make your lab a HemoCell lab.

For more information, contact your local Werfen representative.

werfen.com

werfen

REFERENCES

1. Wang Y-Q, Zhao X-Y. Human Cytomegalovirus Primary Infection and Reactivation: Insights From Virion-Carried Molecules. *Frontiers in Microbiology*. 2020;11.

2. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. *Nature Reviews Microbiology*. 2021;19(12):759-773.

3. CDC. About Cytomegalovirus (CMV). https://www.cdc.gov/cmv/overview.html. Published 2020. Accessed September 27, 2022.

4. Gupta M, Shorman M. Cytomegalovirus. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

5. Mack I, Burckhardt MA, Heininger U, Prüfer F, Schulzke S, Wellmann S. Symptomatic Congenital Cytomegalovirus Infection in Children of Seropositive Women. *Front Pediatr*. 2017;5:134.

6. CDC. Congenital CMV Infection. https://www.cdc.gov/cmv/clinical/congenital-cmv.html. Accessed September 27, 2022.

7. Belzile JP, Sabalza M, Craig M, Clark AE, Morello CS, Spector DH. Trehalose, an mTOR-Independent Inducer of Autophagy, Inhibits Human Cytomegalovirus Infection in Multiple Cell Types. *J Virol*. 2016;90(3):1259-1277.

8. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics*. 2014;134(5):972-982.

9. Jakharia N, Howard D, Riedel DJ. CMV Infection in Hematopoietic Stem Cell Transplantation: Prevention and Treatment Strategies. *Current Treatment Options in Infectious Diseases*. 2021;13(3):123-140.

10. Clark AE, Sabalza M, Gordts P, Spector DH. Human Cytomegalovirus Replication Is Inhibited by the Autophagy-Inducing Compounds Trehalose and SMER28 through Distinctively Different Mechanisms. *J Virol*. 2018;92(6).

11. Griffiths P. The direct and indirect consequences of cytomegalovirus infection and potential benefits of vaccination. *Antiviral Research*. 2020;176:104732.

12. CDC. CMV: Clinical overview. https://www.cdc.gov/cmv/clinical/overview.html. Accessed September 27, 2022.

13. Dioverti MV, Razonable RR. Cytomegalovirus. *Microbiol Spectr*. 2016;4(4).

14. Bulka CM, Bommarito PA, Aiello AE, Fry RC. Cytomegalovirus seroprevalence, recurrence, and antibody levels: Associations with cadmium and lead exposures in the general United States population. *Environ Epidemiol*. 2020;4(4):e100.

15. Prince HE, Lapé-Nixon MKP, New York 11754. Role of cytomegalovirus (CMV) IgG avidity testing in diagnosing primary CMV infection during pregnancy. Clin Vaccine Immunol. 2014;21(10):1377-1384.

16. Bonalumi S, Trapanese A, Santamaria A, D'Emidio L, Mobili L. Cytomegalovirus infection in pregnancy: review of the literature. *J Prenat Med*. 2011;5(1):1-8.

17. CDC. Laboratory Testing. https://www.cdc.gov/cmv/clinical/lab-tests.html. Published 2020. Accessed September 2022, 2022.

18. Saldan A, Forner G, Mengoli C, Gussetti N, Palù G, Abate D. Testing for Cytomegalovirus in Pregnancy. *J Clin Microbiol*. 2017;55(3):693-702.

19. Adler SP. Screening for cytomegalovirus during pregnancy. *Infect Dis Obstet Gynecol*. 2011;2011:1-9.

20. Fitzpatrick D, Holmes NE, Hui L. A systematic review of maternal TORCH serology as a screen for suspected fetal infection. *Prenat Diagn*. 2022;42(1):87-96.

21. Shimada K, Toriyabe K, Kitamura A, et al. Primary cytomegalovirus infection during pregnancy and congenital infection: a population-based, mother–child, prospective cohort study. *Journal of Perinatology*. 2021;41(10):2474-2481.

22. Razonable RR, Inoue N, Pinninti SG, et al. Clinical Diagnostic Testing for Human Cytomegalovirus Infections. *J Infect Dis*. 2020;221(Suppl 1):S74-s85.

23. Maternal-Fetal Medicine Units Network. CMV calculator: Congenital Cytomegalovirus Infection after Maternal Primary Infection. https://mfmunetwork.bsc.gwu.edu/web/mfmunetwork/cmv-calculator. Published 2022. Accessed September 27, 2022.

24. Rouse DJ, Fette LM, Hughes BL, et al. Noninvasive Prediction of Congenital Cytomegalovirus Infection After Maternal Primary Infection. *Obstetrics & Gynecology*. 2022;139(3):400-406.

25. Mikrobiologisch-infektiologischer-Qualitätsstandard, MiQ. MIQ issue: 35b infection immunological methods part 2. https://shop.elsevier.de/miq-heft-35b-infektionsimmunologische-methoden-teil-2-9783437415326.html. Published 2016. Accessed October 10, 2022.

26. Robert Koch Institute. Cytomegalovirus Infection https://www.ki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Zytomegalievirus.html. Published 2014. Accessed October 10, 2022.

27. Zelini P, Fornara C, Furione M, et al. Determination of anti-p52 IgM and anti-gB IgG by ELISA as a novel diagnostic tool for detection of early and late phase of primary human cytomegalovirus infections during pregnancy. *J Clin Virol*. 2019;120:38-43.

28. Schoppel K, Kropff B, Schmidt C, Vornhagen R, Mach M. The Humoral Immune Response against Human Cytomegalovirus Is Characterized by a Delayed Synthesis of Glycoprotein-Specific Antibodies. *The Journal of Infectious Diseases*. 1997;175(3):533-544.

29. Rothe M, Pepperl-Klindworth S, Lang D, et al. An antigen fragment encompassing the AD2 domains of glycoprotein B from two different strains is sufficient for differentiation of primary vs. recurrent human cytomegalovirus infection by ELISA. *J Med Virol*. 2001;65(4):719-729.

30. Jummaat F, Ahmad S, Mohamed Ismail NA. 5-Year review on amniocentesis and its maternal fetal complications. *Horm Mol Biol Clin Investig*. 2019;40(2).

31. CDC. Babies Born with Congenital Cytomegalovirus (CMV). https://www.cdc.gov/cmv/congenital-infection.html. Published 2022. Accessed September 29, 2022.

32. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? *Rev Med Virol*. 2014;24(5):291-307.

33. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and Risks of IgG Transplacental Transfer. *Diagnostics* (Basel). 2020;10(8).

34. Chiereghin A, Pavia C, Turello G, et al. Universal Newborn Screening for Congenital Cytomegalovirus Infection - From Infant to Maternal Infection: A Prospective Multicenter Study. *Front Pediatr*. 2022;10:909646.

35. PerkinElmer. Newborn screening solutions from sample to result. https://rh.perkinelmer.com/newborn-products/#Kits. Accessed September 30, 2022.

36. PerkinElmer. DETECT cCMV IN A SINGLE DRIED BLOOD SPOT PUNCH. https://perkinelmer-appliedgenomics.com/home/products/neomdx-ccmv-real-time-pcr-assay/. Accessed September 30, 2022.

37. Minesotta Department of Health. Congenital cytomegalovirus approved for addition to newborn screening panel. https://www.health.state.mn.us/news/pressrel/2022/newborn020222.html. Published 2022. Accessed September 30, 2022.

38. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13512.

39. CDC. Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Published 2004. Accessed October 1, 2022.

40. Moderna. Making Strides Toward CMV Prevention. https://www.modernatx.com/en-US/media-center/all-media/blogs/making-strides-toward-cmv-prevention. Published 2021. Accessed October 10, 2022.

Ilana Heckler, PhD, is the Scientific Affairs Liaison at **EUROIMMUN US**. She holds a PhD in Chemical Biology for her studies on bacterial hemoprotein sensors of nitric oxide. As the Scientific Affairs Liaison, Dr. Heckler establishes scientific collaborations and assists in the validation of diagnostic assays for autoimmune and infectious diseases.

Maite Sabalza, PhD, is the Scientific Affairs Manager at **EUROIMMUN US**. Her academic background is in infectious diseases and diagnostics. In her role at EUROIMMUN US, she establishes relationships with key opinion leaders and supports the team with commercial activities including scientific collaborations, scientific marketing, and business development of diagnostics.

On-Demand Point of Care Educational Webinars

This guide describes over one hundred previously presented educational webinars now available for online viewing at any time. These webinars are presented by clinicians and laboratory scientists from throughout the world and describe the impact on patient outcomes of certain blood tests performed at the point of care.

Clinical areas covered include:

- Acute Kidney Injury
- Cardiovascular Disease
- Chronic Kidney Disease
- Diabetes/Glycemic Control
- COVID 19

ASCLS P.A.C.E. and American Association of Critical Care Nurses educational credits are still available for some webinars.

nova biomedical
novabiomedical.com

To receive your free on-demand webinar catalog or for more information contact Nova Biomedical at: novabiomedical.com/webinarscatalog

Cytomegalovirus infection: When and why to detect antibodies

DECEMBER 2022 *[This form may be photocopied. It is no longer valid for CEUs after JUNE 30, 2024.]*

Passing scores of 70 percent or higher are eligible for 1 contact hour of P.A.C.E. credit.

TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: ⊗

1. What kind of virus is cytomegalovirus (CMV)?
- A. Retrovirus
- B. Herpesvirus
- C. Poxvirus
- D. Adenovirus

2. What is the worldwide seroprevalence of CMV?
- A. 10-30%
- B. 30-50%
- C. 50-80%
- D. 60-90%

3. In the US, _____ of children have CMV by age _____, and more than _____ of adults have it by the age of _____.
- A. One-third; three; half; fifty
- B. Half; five; half; forty
- C. One-third; five; half; forty
- D. One-third; three; three quarters; fifty

4. CMV is transmitted through
- A. Direct contact
- B. Airborne
- C. Vectors
- D. Ingestion

5. CMV is often asymptomatic in healthy individuals but can be fatal in immunocompromised patients.
- A. True
- B. False

6. The main symptoms of CMV symptomatic infection are
- A. Fever and fatigue
- B. Sore throat
- C. Swollen glands
- D. All of the above

7. CMV infection is the leading cause of
- A. Autism
- B. Congenital defects
- C. Spontaneous abortion
- D. None of the above

8. CMV infection occurs in _____% to _____% of neonates.
- A. 0.1; 0.2
- B. 0.2; 0.5
- C. 0.5; 1.5
- D. 0.5-2.5

9. The main laboratory method(s) for diagnosing CMV are
- A. Molecular testing
- B. Serology
- C. Both a. and b.
- D. Viral culture

10. IgM testing can produce false positive results and it is difficult to determine primary infection from reinfection.
- A. True
- B. False

11. What type of testing is most beneficial to determine a past infection versus a primary infection?
- A. Molecular testing
- B. Viral culture
- C. IgM testing
- D. IgG avidity testing

12. The CDC does not recommend CMV screening testing during pregnancy.
- A. True
- B. False

13. The CMV calculator can predict congenital CMV (cCMV) infection by using test results from
- A. IgG avidity and IgM antibody tests
- B. Molecular tests and IgM tests
- C. IgG avidity test, IgM antibody tests, and viral detection in maternal plasma and IgM tests
- D. Molecular tests, viral detection in maternal plasma and IgM tests

14. While serological assays can use glycoprotein B (gB) as an antigen in IgG antibody detection in pregnant women, it is important to note that only _____% of CMV-infected individuals produce IgG antibodies against gB.
- A. 10
- B. 49
- C. 65
- D. 82

15. What test(s) can be used to detect an active CMV infection in a fetus?
- A. Amniocentesis testing
- B. Ultrasound exam
- C. Both a. and b.
- D. None of the above

16. What specimen type can be used for molecular testing for cCMV detection in newborns?
- A. Urine
- B. Blood
- C. Saliva
- D. All of the above

17. While serologic testing for newborns is inconsistent, the CDC is investigating dried blood spot testing to be used for screening purposes.
- A. True
- B. False

18. Which U.S. state became the first to screen every newborn for cCMV?
- A. New York
- B. Minnesota
- C. Florida
- D. California

Tests can be taken online or by mail. Easy registration and payment options are available through NIU by following the links found at www.mlo-online.com/ce.

PLEASE PRINT CLEARLY

NAME _____ MAILING ADDRESS _____ ☐ HOME ☐ WORK

CITY _____ STATE _____ ZIP _____ INSTITUTION/FACILITY _____

PHONE _____ E-MAIL ADDRESS _____

Send your $20 check payable to Northern Illinois University with this form to: University Outreach Services, Northern Illinois University, DeKalb, IL 60115-2860 Phone: 815-753-0031

FEE NOT REFUNDABLE OR TRANSFERABLE

P = Poor; E = Excellent

1. To what extent did the article focus on or clarify the objectives?
P ① ② ③ ④ ⑤ E

2. To what extent was the article well-organized and readable?
P ① ② ③ ④ ⑤ E

3. How will you use the CE units?
☐ state license ☐ employment ☐ recertification ☐ other

CE Licensure Information for FL and CA:

FL: Your FL license number: _____ ***(required for CE credit)***

CA: Accrediting Agency: 0001 ***(for use in submitting your CE credits to CA)***

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

We understand it is crucial to immediately diagnose and treat vulvovaginal disorders which are linked to a broad range of associated health complications, from preterm birth to an increase in Sexually Transmitted Infections.[1]

The OSOM® BVBLUE® and OSOM® Trichomonas Tests are easy-to-use, CLIA-waived and produce accurate and objective results for two of the most common causes of vulvovaginal disorders so you can get the answers fast and your patients back to doing what they love.

Like you, we understand there is a patient behind every answer—and that's what matters most.

For more information, call 800-332-1042, or visit us at osomtests.com

THE PERFECT PAIR

OSOM® TRICHOMONAS TEST

OSOM® BVBLUE® TEST

[1] Brown, H. *Improving the Diagnosis of Vulvovaginitis.* Population Health Management. Vol. 23, suppl 1, 2020

SEKISUI DIAGNOSTICS
Because every result matters™

Photo © Keng Po Leung | Dreamstime.com

Drug of abuse testing and therapeutic drug monitoring

By Rajasri Chandra

In pharmacology, a drug is a chemical substance that produces a biological effect when administered to a living organism. Drugs are classified in various ways. One widely used classification system is the Anatomical Therapeutic Chemical Classification System (ATC system).[1] In this system, drugs are classified based on the active ingredients for the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. Pharmaceutical drugs, also called medicine or therapeutic drugs, are chemical substances used to treat, cure, prevent, or diagnose a disease or to promote well-being. Depending on the level of control, these drugs are classified as prescription drugs or over-the-counter (OTC) drugs. US Pharmacopeia (USP) currently categorizes a drug or drug component under one of 49 different therapeutic classes such as analgesics, including opioids and non-opioids; anesthetics; central nervous system agents, including amphetamines; and so forth.[2] There are some drugs that mimic or alter the neurotransmitters in the central nervous system and thereby when consumed, alter perception, mood, consciousness, cognition, or behavior of the person.[3] People who consume such drugs for pleasure suffer from substance abuse. When a person is unable to stop consuming a drug(s) and the drug(s) takes control of the person, the situation is called drug addiction.

Problem of substance abuse

Substance abuse is a serious concern globally, including the United States. According to results from the 2020 National Survey on Drug Use and Health (NSDUH) conducted annually by the Substance Abuse and Mental Health Services Administration (SAMHSA), 40.3 million people aged 12 or older had a substance use disorder (SUD) in the past year, including 28.3 million with alcohol use disorder, 18.4 million with an illicit drug use disorder, and 6.5 million with both alcohol use disorder and an illicit drug use disorder **(see Figure 1)**.[4]

Deaths due to drug overdoses have been on the rise for years in the United States, but the COVID-19 pandemic worsened the situation further. Based on a provisional report from the Centers for Disease Control and Prevention (CDC), there were more than 100,000 deaths from drug overdose in 2021. The CDC data shows annual deaths were nearly 50% higher in 2021 than in 2019 **(see Figure 2)**.[5]

People in all phases of life can be addicted to a drug of abuse, which can have various consequences:

- **Teens** who use drugs may do poorly in school or drop out.[6] Using drugs at an early age, when the brain is still developing may cause lasting brain changes and put the user at increased risk of dependence in adult life.[7]

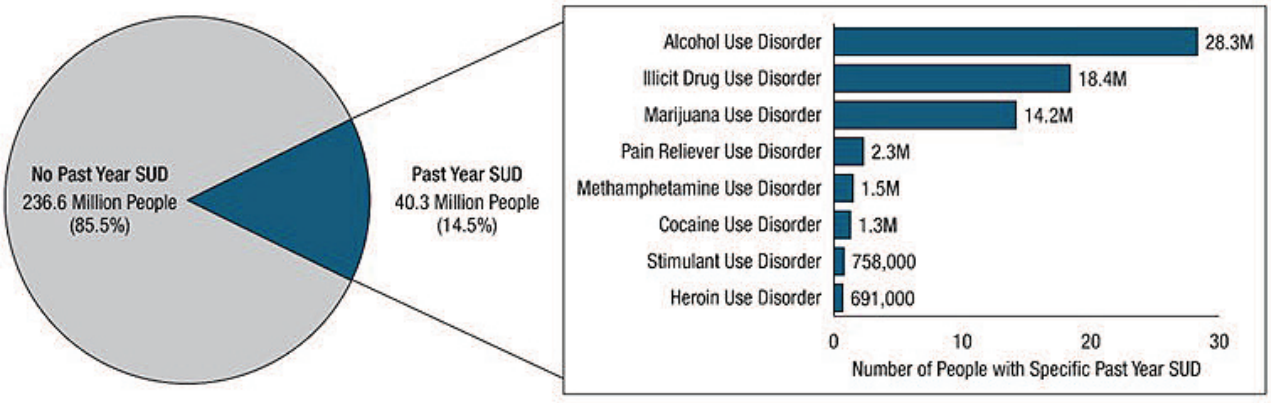


Figure 1. People aged 12 and older with a past-year substance use disorder (SUD): 2020.

- **Adults** who use drugs may have problems of clear thinking, remembering, and paying attention. Drug addiction impairs social behaviors and affects work performance and personal relationships.
- **Parents'** drug use results in chaotic, stress-filled homes and probable child abuse and neglect.[8] Such conditions harm the well-being and development of children, and they also may resort to drug abuse.[9]
- **Pregnant women** who abuse drugs during pregnancy risk premature and underweight babies. This situation also affects the child's ability to learn and behavior later in life.[10] The child may also become dependent on opioids or other drugs used by the mother during pregnancy, a condition called neonatal abstinence syndrome (NAS).

Scientific reasons behind drug addiction

Drug addiction manifests as a behavioral disorder where the patient exhibits compulsive drug-seeking behavior. It is a brain disorder, that is caused by functional changes to the brain circuits involved in reward, stress, and self-control. Brain images of people with addiction have shown changes in the areas of the brain that control judgement, decision-making, learning, memory, and behavior.[11] Those changes may last a long time after a person has stopped taking drugs.[12] Addiction is dependent on various factors, including genetic and environmental factors. **Figure 3** shows the factors that impact drug addiction.[3]

Drug testing

Situations requiring drug testing

Drug addiction is preventable and treatable. If left untreated, it can last a lifetime and may lead to death. Drug addiction can be determined by drug testing. Although, drug testing may be required for clinical or nonclinical reasons. A clinical reason would be when a doctor requests drug

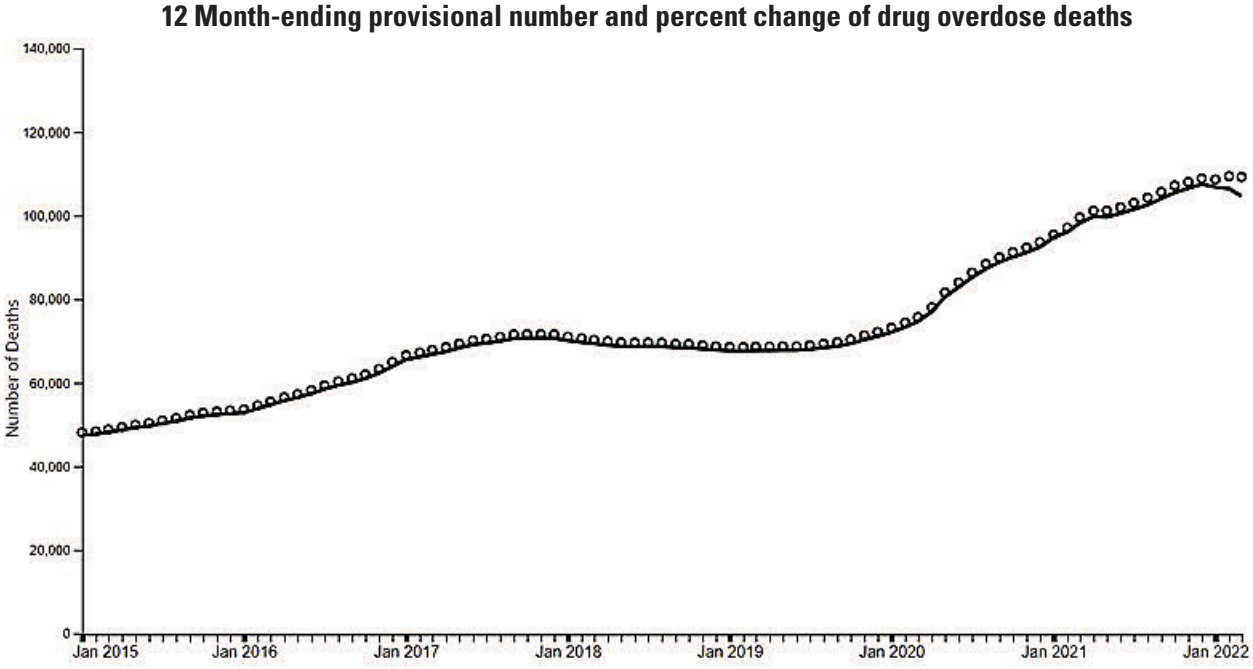


Figure 2. Based on CDC data available for analysis on August 16, 2022.

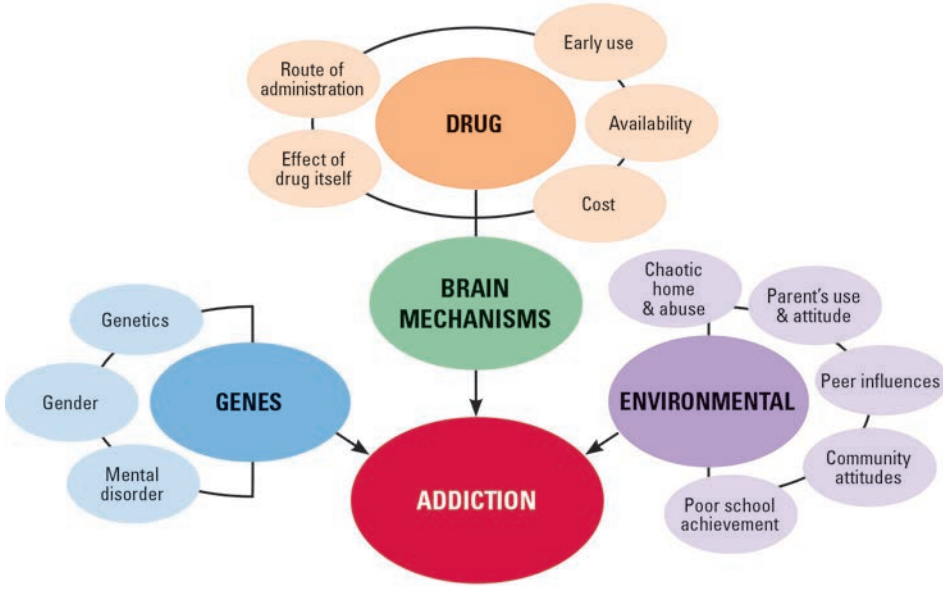


Figure 3. Factors influencing drug addiction.

testing to monitor if a patient is taking the right amount of a prescribed opioid medication. Nonclinical reasons include the following:

- Employment: Employers may request drug testing before recruitment or on-the-job.
- Sports: Athletes may be required to get tested for drugs before and/or after a competition.
- Legal or forensic purposes: Court cases may order drug testing for criminal trial or motor vehicle accident investigation.

Specimen types for drug testing

The U.S. Department of Health and Human Services (DHHS) set guidelines for drug testing. Laboratories performing drug testing include a centralized clinical chemistry laboratory, point-of-care (POC) facilities, physician's office labs, and emergency centers. Urine is the most used sample type for drug testing. The other possible matrices are hair, blood, sweat, and oral fluid (saliva). Every specimen type has its pros and cons as shown in **Table 1.**[13]

Drug of abuse testing

Drug abuse testing generally follows two steps: initial screening followed by a confirmatory test.[15] Initial drug screening is carried out most of the time using an immunoassay. In the immunoassay method, an antigen (drug) and antibody are made to bind to identify drug analytes. The antibodies are produced to be drug specific. A known amount of antibody is added to a specimen, along with a drug that has been labeled to distinguish it from the drug in a donor's urine specimen. The labeled drug and the unlabeled drug (if any) compete for the antibody to form an antigen-antibody complex. The ratio of the labeled and unlabeled drug bound to the antibody allows the measurement of the amount of drug in the donor's urine specimen. Advantages of immunoassays are their ease of use, fast turnaround times, lower costs, and results may be qualitative or semi-qualitative. Immunoassays may be of different types:

- Enzyme immunoassays (EIA)
- Cloned enzyme donor immunoassay (CEDIA)
- Fluorescence polarization immunoassay (FPIA)
- Kinetic interaction of microparticles in solution (KIMS)
- Microplate enzyme-linked immunosorbent assay (ELISA)

Specimens that are positive by immunoassay need to be confirmed using a different analytical method. A confirmatory test method needs to identify and quantify the drug or drug metabolite. The

Specimen Type	Pros	Cons
Urine	• Easy to collect • Available in sufficient quantity • Higher concentration of parent drug compared to in blood • Well-researched testing techniques • Availability of POC tests	• Easy to adulterate or substitute • Window of detection 48–72 hours on an average • May require observed collection • Some individuals experience "shy bladder" syndrome and cannot produce a specimen • Cannot measure frequency of drug use, nor can it indicate severity of addiction
Oral Fluid	• Easy to collect • Reduced risk of adulteration • Parent drug (not the metabolite) can be detected • Detects recent drug use (up to 48 hours) • Availability of POC tests	• Limited specimen volume • Salivation reduced by stimulant used • Possibility of contamination with residual drug in mouth that does not correlate with blood concentrations • Cannot detect drug use beyond 48 hours • Cannot measure frequency of drug use, nor can it indicate severity of addiction
Hair	• Long detection window (up to 90 days) • May be able to detect changes in drug use over time (from 7–10 days)	• Takes approximately 5 to 10 days from the time of drug use for detection • Costly and time consuming to prepare specimen for testing • Usually a longer turnaround time for results • Not applicable if the donor has shaved or is void of head/body hair
Blood	• Generally, detects recent use • Established laboratory test method	• Narrow detection window of 2-12 hours • Invasive specimen collection (venipuncture) that requires phlebotomist • Rarely conducted in POC setting
Sweat	• Detects recent use (fewer than 24 hours with a sweat swipe) or allows for cumulative testing with the sweat patch (worn for up to 7–14 days) • Easy, noninvasive method • Difficult to adulterate	• Few facilities & limited expertise for testing • Risk of accidental or deliberate removal of the sweat patch collection device • Unknown effects of variable sweat excretion among individuals • Only a single sweat collection patch available so multiple analyses cannot be done if needed (i.e., more than one positive initial test) • Requires two visits, one for patch placement and one for patch removal

Table 1. Drug testing specimen types and their pros and cons.

Medicine Type	Example
Antibiotics	Vancomycin, Gentamycin, Amakacin
Heart drug	Digoxin, Procainamide, Lidocaine
Anti-seizure drug	Phenytoin, Phenobarbital
Autoimmune disease	Cyclosporine, Tacrolimus
Bipolar disorder	Lithium, Valproic acid

Table 2. Examples of medicine types requiring therapeutic monitoring.

analytical method used for the confirmatory drug test must combine gas (GC) or liquid (LC) chromatographic separation and mass spectrometric (MS) identification. Urine specimens must undergo a specimen preparation process (i.e., extraction) prior to GC/MS analysis and may require preparation prior to LC/MS/MS analysis.

Therapeutic drug monitoring

Some therapeutic drugs also need testing in certain circumstances. Therapeutic drug monitoring is required to measure the amount of a medicine or its metabolites in the blood/plasma or serum at a specific time point to determine if a patient's drug concentrations are within the therapeutic range and are neither subtherapeutic nor potentially toxic. It is used to determine the best dosages for patients on certain hard-to-dose medicines.[16]

Some of the most common medicines that need monitoring are shown in **Table 2**.

The methods used for therapeutic drug monitoring are high performance liquid chromatography (HPLC), HPLC combined with mass spectrometry, or immunoassays such as enzyme immunoassay (EIA), fluorescence polarization immunoassay (FPIA), and microplate enzyme-linked immunosorbent assay (ELISA).

Deaths due to drug overdoses have been on the rise for years in the United States, but the COVID-19 pandemic worsened the situation further.

Conclusion

Drug abuse devastates families and is a great menace for the society. Drug addiction in individuals results in broken families, increased crime, accidents, death, overburdened jails and prisons, reduced employee productivity, increased costs on foster care, healthcare, and treatment.

As prevention is better than cure, all efforts should be made to prevent drug abuse in individuals. Strict supervision by parents of their children, family-based, school-based and community-based programs to educate on the ill effects of drug abuse and how to control mind and temptations should be followed.

Moreover, early and accurate detection of substance abuse is essential and the first step towards identification and treatment of the individuals under influence of drugs.

REFERENCES

1. Guidelines for ATC classification and DDD assignment. World Health Organization Collaborating Centre for Drug Statistics Methodology. Published 2011. Accessed October 27, 2022. https://www.whocc.no/filearchive/publications/2011guidelines.pdf.
2. USP Medicare model guidelines v. 7.0. United States Pharmacopoeia. Accessed October 27, 2022. https://www.usp.org/sites/default/files/usp/document/our-work/healthcare-quality-safety/uspmmg_v7_0_w_exampledrugs_rev170206.pdf.
3. Drugs and the Brain. National Institute on Drug Abuse. Published July 10, 2020. Accessed October 27, 2022. https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain.
4. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Substance Abuse and Mental Health Services Administration. Published 2020. Accessed October 27, 2022. Retrieved from https://www.samhsa.gov/data/.
5. Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. Published 2022. Accessed October 27, 2022. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.
6. Tice P, Lipari R, Van Horn S. Substance Use among 12th Grade Aged Youths, by Dropout Status. Rockville, MD: Center for Health Statistics and Quality, Substance Abuse and Mental Health Administration. Published August 15, 2017. Accessed October 27, 2022. https://www.samhsa.gov/data/sites/default/files/report_3196/ShortReport-3196.html.
7. Chen CY, Storr CL, Anthony JC. Early-onset drug use and risk for drug dependence problems. *Addict Behav*. 2009;34(3):319-22. doi: 10.1016/j.addbeh.2008.10.021.
8. Lander L, Howsare J, Byrne M. The impact of substance use disorders on families and children: from theory to practice. *Soc Work Public Health*. 2013;28(3-4):194-205. doi: 10.1080/19371918.2013.759005.
9. Simmons LA, Havens JR, Whiting JB, Holz JL, Bada H. Illicit drug use among women with children in the United States: 2002-2003. *Ann Epidemiol*. 2009;19(3):187-93. doi: 10.1016/j.annepidem.2008.12.007.
10. Shankaran S, Lester BM, Das A, Bauer CR, Bada HS, Lagasse L, Higgins R. Impact of maternal substance use during pregnancy on childhood outcome. *Semin Fetal Neonatal Med*. 2007;12(2):143-50. doi: 10.1016/j.siny.2007.01.002.
11. Fowler JS, Volkow ND, Kassed CA, Chang L. Imaging the addicted human brain. *Sci Pract Perspect*. 2007;3(2):4-16. doi: 10.1151/spp07324.
12. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011;20;12(11):652-69. doi: 10.1038/nrn3119.
13. Hadland SE, Levy S. Objective Testing: Urine and Other Drug Tests. *Child Adolesc Psychiatr Clin N Am*. 2016;25(3):549-65. doi: 10.1016/j.chc.2016.02.005.
14. Drug Scheduling. DEA. Published July 10, 2018. Accessed October 27, 2022. https://www.dea.gov/drug-information/drug-scheduling.
15. Medical Review Officer Guidance Manual for Federal Workplace Drug Testing Programs. Department of Health and Human Services Substance Abuse & Mental Health Services Administration (SAMHSA). Revised March 2018. Accessed October 27, 2022. https://www.samhsa.gov/sites/default/files/workplace/mro-guidance-manual-oct2017_2.pdf.
16. Mabilat C, Gros MF, Nicolau D, Mouton JW, et al. Diagnostic and medical needs for therapeutic drug monitoring of antibiotics. *Eur J Clin Microbiol Infect Dis*. 2020;39(5):791-797. doi: 10.1007/s10096-019-03769-8.

Rajasri Chandra, MS, MBA is a global marketing leader with expertise in managing upstream, downstream, strategic, tactical, traditional, and digital marketing in biotech, in vitro diagnostics, life sciences, and pharmaceutical industries. Raj is an orchestrator of go-to-market strategies driving complete product life cycle from ideation to commercialization.


Photo credit: DEA

Hidden fentanyl: A harrowing holiday reminder

By Rorie Madigan, MT(ASCP)

Whether to accept and eat candy is a widely known quandary children face. It's the predictable cautionary tale to avoid strangers. But what happens when every day, seemingly innocent candy exchanges become a real threat? At Kindergarten Meet the Teacher Night, my 5-year-old daughter accepted a piece of candy from another little girl, put it in her mouth, and then tried to hide it from me because she knew I wouldn't want her eating candy I didn't buy her. What should be a harmless childhood rite of passage at best, or an inconvenient sugar high at worst, suddenly has the potential to be deadly.

In September of 2022, the United States Drug Enforcement Administration (DEA) seized 15,000 "rainbow fentanyl" pills in New York City concealed in a LEGO box, and 40% of them contained lethal doses.[1] That same month, the Pasadena Police Department seized more than 300,000 fentanyl pills, included among them were the rainbow fentanyl pills. And in Wethersfield, CT, two men were arrested attempting to sell rainbow fentanyl pills hidden in Nerds candy boxes and Skittles candy bags. The undercover DEA agents found thousands of brightly colored fentanyl pills hidden in candy boxes inside the dealer's car.

Whether the rainbow fentanyl pills are being pushed to children or not, they are made to look like something a child may want to try. According to New York's Special Narcotics Prosecutor Bridget G. Brennan, "Using happy colors to make a deadly drug seem fun and harmless is a new low, even for the Mexican cartels. Fentanyl is already involved in more than 80% of overdose deaths in the city. If you take any drug sold on the street or through the internet, regardless of its medicinal markings or festive appearance, you risk your life."[1] The jury is still out on whether a drug dealer would give away their product for free just to target children, as this would negatively impact their profit and bottom line. Some believe the rainbow pills are a tactic by cartels to avoid detection by law enforcement.

To not get caught up in the "why" debate, lets instead focus on what we know with certainty is plaguing our communities daily — odorless, colorless, and tasteless fentanyl, concealed in fake oxycodone pills, cocaine, heroin, ecstasy, methamphetamine, and others. Drug dealers have figured out that illicitly produced fentanyl is cheap and easy to manufacture. In addition, fentanyl is highly potent and addictive, which is why we're seeing an increase in fentanyl contamination of the street drug supply. It is being added to many different drugs to turn recreational users into addicted customers. In some cases, individuals are not even aware they have taken fentanyl, and those that are, are playing a very dangerous game.[2] From April 2021 to April 2022, synthetic opioids like fentanyl, were responsible for nearly 90% of reported deaths, according to the latest Centers for Disease Control and Prevention (CDC) data.[3] Fast forward to September 2022, where now fake oxycodone pills have evolved into pills disguised as candy.

The case for fentanyl testing

Being in the drug testing field, I am acutely aware of the dangers associated with opioid use. As a result of the evolving fentanyl contamination issue, two questions come to mind:

1. If someone unknowingly takes fentanyl and they are lucky enough to wake up in an emergency department (ED) post-treatment, how does the hospital, patient, and/or the patient's family know that fentanyl was the reason for this overdose? The patient may admit to using whatever drug they thought they purchased but won't know that the added fentanyl is what sent them to the ED, unless testing is performed.

2. Thinking even more broadly, how does a community know its drug supply is contaminated with fentanyl? While "drug checking" test strips at the point-of-use exist to test the drugs themselves and potentially prevent fentanyl overdoses, many states consider them to be contraband.[4] Therefore, these test strips are illegal in many cases, even though they can save lives and community resources dedicated to overdose-related emergency incidents.

Identifying whether fentanyl is present in a community serves as a warning sign—not only at the community level, but at the individual patient level, as well. To support drug policies and rehabilitation efforts, a community must know fentanyl is present and is an ongoing, active threat.

Treatment of substance use disorders and identification of fentanyl contamination start with a laboratory test. There are several types of laboratory tests available to detect the presence of fentanyl with different sample types depending on the test. For example, several laboratory diagnostics manufacturers offer urine drug screening and serum toxicology which is performed via immunoassay methods on automated chemistry and dedicated drug testing analyzers. Rapid urine drug testing, which is considered point-of-care testing, also is available as cups, strips, and cartridges, and is manually performed and interpreted. Additionally, there is oral fluid testing to screen for the presence of fentanyl. Regardless of the screening method, it is always recommended that laboratories confirm preliminary results with a confirmatory method such as liquid chromatography followed by tandem mass spectrometry (LC-MS/MS).

Drug screening for fentanyl, and specifically norfentanyl (the major metabolite of fentanyl) serves a vital purpose as the first line of defense in combating this fentanyl contamination crisis. Since fentanyl is primarily excreted as metabolites, with only ~10% of the drug remaining unchanged in urinary excretion, it is imperative the screening assay detects norfentanyl. This helps reduce the risk of false negatives.[5] It is simply not enough to offer just any fentanyl-specific screening test. Laboratories must offer a fentanyl-specific test that demonstrates excellent sensitivity and specificity for detection of fentanyl and excellent cross-reactivity with norfentanyl.

If test strips are not available to test the drug itself and if laboratories aren't testing patient samples for fentanyl, there is no way for physicians, patients or anyone else involved to know of its presence. This lack of information could hinder a patient's treatment plan, including a patient's ability to secure space in a treatment facility, for example.

Treatment of substance use disorders and identification of fentanyl contamination start with a laboratory test.

Conclusion

Fentanyl drug screening provides that critical level of awareness needed to help facilitate proper treatment, prevent overdoses or recurrent overdoses, guide public health initiatives, and ultimately save lives—not just on Halloween, Thanksgiving, or Christmas—but on any day of the year. It is imperative that collective community resources such as hospital systems, laboratory diagnostics companies, government or local/state agencies, treatment centers, police or sheriff's departments and other organizations work together to help put an end to this "hidden" epidemic. Empowered laboratories offering fentanyl testing deliver vital test results, enabling actionable efforts that drive towards a safer and healthier population.

REFERENCES

1. Trafficker-quantities of "rainbow fentanyl" arrive in New York. DEA. Accessed October 25, 2022. https://www.dea.gov/press-releases/2022/10/04/trafficker-quantities-rainbow-fentanyl-arrive-new-york.

2. Fentanyl: What you need to know - national coalition against prescription drug abuse. National Coalition Against Prescription Drug Abuse. Published December 1, 2021. Accessed October 25, 2022. https://ncapda.org/fentanyl/?gclid=EAIaIQobChMIssyzlprW-gIVF47ICh1KBg-PEAAYAiAAEgKggvD_BwE.

3. Products - vital statistics rapid release - provisional drug overdose data. Cdc.gov. Published October 12, 2022. Accessed October 25, 2022. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

4. Facher L. Fentanyl test strips could help save lives. In many states, they're still illegal. STAT. Published September 8, 2022. Accessed October 25, 2022. https://www.statnews.com/2022/09/08/fentanyl-test-strips-could-help-save-lives-in-many-states-theyre-still-illegal/.

5. Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend.* 2020;214(108147):108147. doi:10.1016/j.drugalcdep.2020.108147.

Rorie Madigan is currently a Global Drug Testing Marketing and Product Manager for **Siemens Healthineers**. She has a B.S. in Medical Technology from the University of Delaware and began her career in the microbiology laboratory at Christiana Hospital in Newark, DE. In 2007, she joined Siemens Healthineers where she has held multiple roles in Technical Support, Education, Consulting, and Marketing.

Photo by designer491@bigstockphoto.com

Molecular diagnostics in treating lower respiratory tract infections with consideration for antimicrobial resistance

By Faranak Atrzadeh

Despite global focus on the COVID-19 pandemic, the concern around antimicrobial resistance (AMR) has continued to grow, albeit a bit further in the background. In 2019, AMR was the direct cause of at least 1.27 million deaths (See **Figure 1**). When stepping back to consider global deaths associated with AMR, that number increased to 4.95 million.[1] COVID-19 has only exacerbated existing concerns. Earlier this year, the Centers for Disease Control and Prevention (CDC) reported that drug-resistant infections in hospitalized patients rose by 15% from 2019 to 2020,[2] confirming the fears of many frontline workers and epidemiologists that COVID-19 admissions resulted in over-prescription.

In order to combat this growing threat, the global healthcare community is researching a number of both drug-based and non-drug-based solutions. Drug-based approaches pose a number of immediate and long-term challenges. The World Health Organization's (WHO) report titled"2021 Antibacterial agents in clinical and preclinical development: an overview and analysis" characterizes the current number of antibacterial drugs in preclinical and clinical development as stagnant and far from meeting global needs.[3] Further, the same WHO analysis showed that in 2021 there were only 27 new antibiotics in clinical development against priority pathogens, compared to 31 products in 2017.

Lower respiratory tract infections and AMR

Lower respiratory tract infections (LRTIs) such as pneumonia pose a particular threat to antimicrobial resistance for a number of reasons. First, these infections are highly prevalent in global populations. In 2015, it was estimated that LRTIs caused 2.74 million deaths worldwide.[4] High rates of antimicrobial resistance have been observed for the pathogens responsible for LRTIs.[5] In a 2021 study, researchers processed a total of 7,038 samples of sputum and bronchial aspirate according to the standard microbiological methods. In these samples a "very high rate of resistance" (98–100%) was observed among *Acinetobacter baumannii* isolates to Amoxicillin/Clavulanic acid, Cefotaxime, Ciprofloxacin, Ertapenem, Gentamicin, Imipenem, and Trimethoprim/Sulfamethoxazole.[5]

Where COVID-19 has already exacerbated concerns around AMR more generally,[2] the virus' targeting of the respiratory tract, particularly in its earlier mutations, only adds to the types of respiratory symptoms being treated with inappropriate antibiotics. The high rates of antimicrobial resistance are not really surprising due to how similarly many LRTIs present and the common approach of prescribing broad spectrum antibiotics.

Pneumonia, one of many LRTIs raising concerns, is among the most common reasons for inpatient antibiotic use and overuse.[6] Hospital-associated pneumonia (HAP) accounts for 22% of all

MLO LAB OF THE YEAR 2023

CALL FOR ENTRIES

MLO's Lab of the Year Award celebrates medical laboratories who demonstrate their extraordinary commitment to quality patient care. Submissions will be judged on achievements in six areas. A panel of judges selected from MLO's Editorial Advisory Board will select the winner and two runners-up. All will be featured in the April 2023 issue of MLO, in print and online, and awarded a display wall plaque, with the winner featured on the issue cover.

ALL SUBMISSIONS DUE BY JANUARY 9, 2023

Medical laboratories, utilizers of a lab's service and non-vendor affilities are welcome to submit. Submission requirements are at:
https://cdn.mlo-online.com/files/base/ebm/mlo/document/2022/09/LOY2023.6319f98769e44.pdf

MLO LAB OF THE YEAR 2023

MLO
MEDICAL LABORATORY OBSERVER

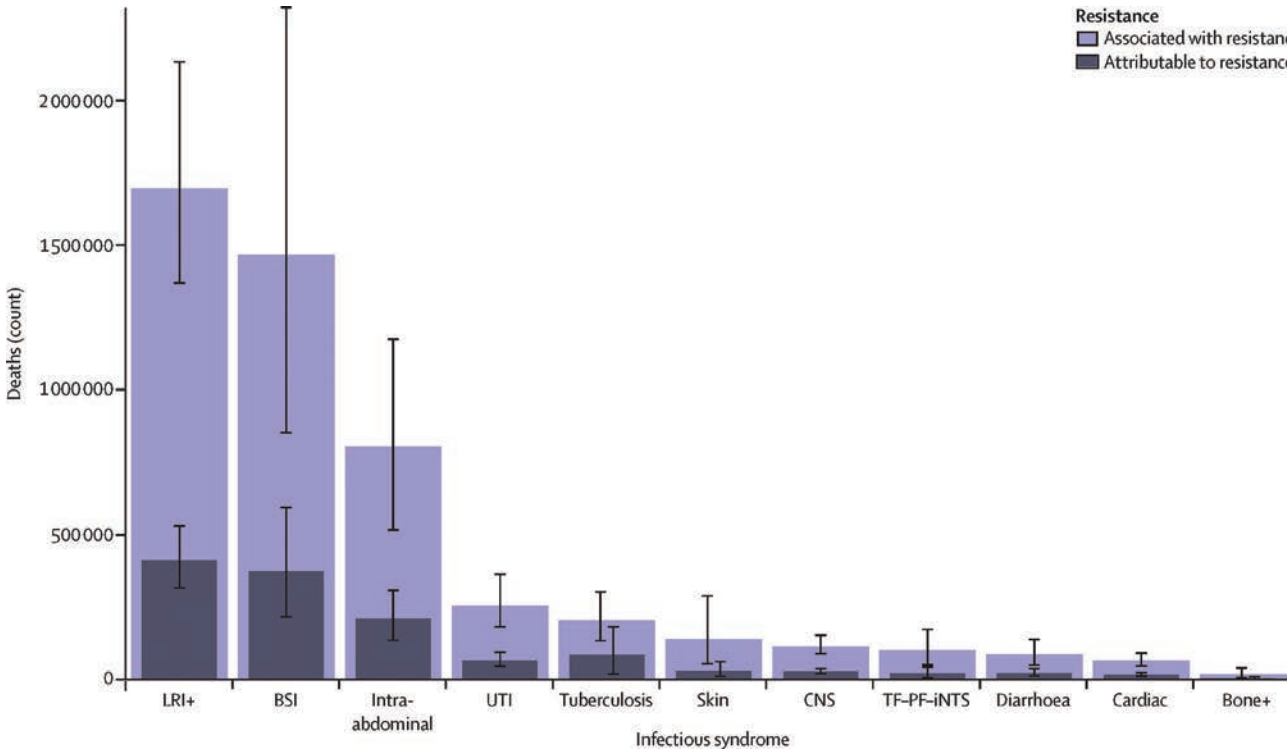


Figure 1.[1]

nosocomial infections and ventilator-associated pneumonia (VAP) mortality rates range from 20% to 60%.[7]

As such, a number of recent studies have examined best practices for antibiotic stewardship when it comes to lower respiratory tract infections and found inappropriate initial antimicrobial therapy is associated with increased mortality in patients with pneumonia.

Historically, providers prescribed long durations of antibiotics for pneumonia because of concerns that short courses could lead to disease relapse or progression.[8] Recent studies, including multiple randomized controlled trials and systematic reviews, have demonstrated that shorter antibiotic therapy is safe and equally effective for most patients with pneumonia, avoiding longer antibiotic treatment that puts patients at risk for antibiotic-associated adverse events, *C. difficile* infection, and multi-drug resistant organisms (MDROs).[8] That same study found that more than two thirds (67.8%, 4,391/6,481) of patients received excess antibiotic therapy duration, largely due to excessive prescribing at discharge.[8]

A study[7] published in 2021 assessing antibiotic de-escalation in patients with nosocomial pneumonia showed that more de-escalations occurred when diagnostic tests were ordered; and importantly, in these patients de-escalation was associated with fewer antibiotic days (mean 9 vs. 11), reduced episodes of *C. diff* infection (2.2% vs. 3.8%) and shorter hospital days (mean 20 vs. 22 days), shorter ICU stays, less time on ventilator, reduced acute kidney injury (AKI) and reduced initiation of renal replacement therapy.[7] Moreover, there was no difference in in-hospital mortality, 14-day all-cause mortality, readmission for any indication, or treatment re-escalation in patients who received de-escalation versus no de-escalation

These studies demonstrate that excess antibiotic treatment is not associated with lower rates of any adverse outcomes (that is, death, readmission, emergency department visit, or *C. diff* infection). In fact, each excess day of antibiotic therapy is associated with 5% increased odds of experiencing an antibiotic-associated adverse event, and an estimated 1.03-fold increase in the odds of AMR associated with each additional day of antibiotics.

Testing methodologies

For LRTIs and other infections, microbiological cultures are widely used as the standard of care for identifying the presence of pathogens, and empirical broad-spectrum antibiotic therapy is initiated while waiting for the results. Limitations of microbiological cultures are well-acknowledged. These limitations are attributable to results taking several days, as well as factors such as dependence on microbial growth, growth being affected by sample transport time and temperature, or being inhibited by prior antibiotic treatment, contributing to sensitivity challenges. These limitations further confound the diagnostic picture in patients undergoing a long-term hospital or ICU stay for whom clinicians usually order subsequent cultures at multiple intervals throughout a patient's stay.

Alternative testing approaches can support antibiotic stewardship and limit the use of broad-spectrum antibiotics. Multiplex molecular diagnostic panels offer a rapid and complementary approach for identifying pathogens and AMR markers. Yet many question if these panels are appropriately sensitive and suitable for reliable, accurate testing.

A recent study[9] examined serial microbiological culture samples taken from hospitalized COVID pneumonia patients by comparing the results of a culture to a multiplex PCR lower respiratory panel for detection of pathogens from serial specimens collected from the same patient. Serial specimen analysis demonstrated that the multiplex Unyvero PCR panel was not only as accurate at detecting a pathogen, but in some cases, even more precise. Additional pathogens detected by the PCR panel could be confirmed in many instances by culture positivity for the same organism in another sample obtained from the same patient. This publication highlights the ability of the multiplex lower respiratory panel in detecting potential pneumonia pathogens earlier than culture or very early during an infection.

Another study[5] was conducted with patients who were admitted to the hospital with suspected pneumonia, had a clinical indication for bronchoscopy with bronchoalveolar lavage, and were at risk of Gram-negative bacterial infection. This study found that using a comprehensive multiplex molecular lower respiratory panel such as the Unyvero pneumonia test shortened inappropriate antibiotic therapy duration by 39 hours ($p<0.0001$), and reduced overall antibiotic therapy duration by 34 hours (22.5%). The multiplex panel also reduced the use of inappropriate antibiotic therapy by 45% ($p<0.0001$). In addition, patients tested with the molecular multiplex panel had a three-times higher probability of receiving appropriate antibiotic therapy.

Looking ahead

It is clear antimicrobial resistance in lower respiratory tract infections poses a significant threat to the global population. The global health community needs to continue embracing non-drug- based solutions in order to outpace growing AMR. Multiple studies have demonstrated the accuracy and impact of multiplex molecular testing. As clinicians continue to grow in confidence around the validity of multiplex PCR panels, we can develop a clearer path forward in combatting antimicrobial resistance.

REFERENCES

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022;12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0.
2. COVID-19 reverses progress in fight against antimicrobial resistance in U.S. Centers for Disease Control and Prevention. Published July 12, 2022. Accessed November 2, 2022. https://www.cdc.gov/media/releases/2022/s0712-Antimicrobial-Resistance.html.
3. 2021 antibacterial agents in clinical and preclinical development: An overview and analysis. World Health Organization. Published May 27, 2022. Accessed November 2, 2022. https://www.who.int/publications/i/item/9789240047655.
4. GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis.* 2017;17(11):1133-1161. doi: 10.1016/S1473-3099(17)30396-1.
5. Santella B, Serretiello E, De Filippis A, et al. Lower respiratory tract pathogens and their antimicrobial susceptibility pattern: A 5-year study. *Antibiotics (Basel).* 2021;13;10(7):851. doi: 10.3390/antibiotics10070851.
6. Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. *MMWR Morb Mortal Wkly Rep.* 2014;63(9):194-200.
7. Ilges D, Ritchie DJ, Krekel T, et al. Assessment of antibiotic de-escalation by spectrum score in patients with nosocomial pneumonia: A single-center, retrospective cohort study. *Open Forum Infect Dis.* 2021;8(11):ofab508. doi: 10.1093/ofid/ofab508.
8. Vaughn VM, Flanders SA, Snyder A, et al. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia: A multihospital cohort study. *Ann Intern Med.* 2019;171(3):153-163. doi:10.7326/M18-3640.
9. Tellapragada C, Ydsten KA, Ternhag A, Giske CG. Evaluation of a pneumonia multiplex PCR panel for detection of bacterial respiratory tract pathogens from serial specimens collected from hospitalized COVID-19 patients. *Eur J Clin Microbiol Infect Dis.* 2022;41(7):1093-1098. doi: 10.1007/s10096-022-04466-9.

Faranak Atrzadeh serves as Chief Marketing and Scientific Affairs Officer at **OpGen Inc.,** a precision medicine company specializing in molecular diagnostics and bioinformatics to help combat infectious disease.

Photo © Kateryna Kon | Dreamstime.com

Understanding sepsis: The importance of biomarkers in early diagnosis

By Patusa Mayfield, MBA-HCM, MT(ASCP)

It starts with a common infection leading to a chain reaction and deterioration of a person's health. The symptoms are aggressive — including an accelerated heart rate, fever, shivering, confusion or disorientation, shortness of breath, and extreme pain. It's common to hear patients say, "It feels like I am going to die." When an infection persists or gets worse, and it could lead to sepsis and septic shock.

Sepsis, a life-threatening organ dysfunction in response to infection, affects 47–50 million people worldwide each year with approximately 11 million deaths.[1] With an overall mortality rate of 15–30% leading to 30–50% of all in-hospital mortality.[2] Sepsis is the most expensive condition in modern medicine. The worldwide incidence of sepsis continues to increase, putting a high financial burden on society and the healthcare system.[2] More individuals die of sepsis than prostate cancer, breast cancer, and HIV combined.[3,4] Because anyone can get an infection, anyone can develop sepsis.

There are several factors contributing to the high toll of sepsis. When it comes to sepsis treatment, time to source control matters. For every hour treatment is delayed, there is up to a 7.9% increase in mortality and as much as a 10% increase in the odds of one-year mortality.[5,6] Early and accurate identification of sepsis is needed for successful treatment and a positive outcome.[5]

Most cases of sepsis are diagnosed in the emergency department (ED) with 87% of cases starting prior to admission.[7] When patients arrive at the ED, clinicians are tasked with quickly triaging patients based on limited diagnostic information. As the patient struggles to understand what is happening, the ED clinicians face the challenging task of assessing and determining a course of action. Sepsis identification relies on a combination of clinical suspicions based on nebulous patient symptoms with laboratory test results that can indicate multiple conditions (see **Figure 1**). Unfortunately, failure to recognize sepsis early in the disease course often leads to worse outcomes.[8]

Sepsis diagnosis requires confirmation of an underlying infection through a positive blood culture, but these tests can take two to three days for results[9] — too long for defining a sepsis care pathway. Moreover, the overlap of clinical symptoms between sepsis and other, non-infectious inflammatory conditions can confound the diagnosis.

The challenge is to diagnose sepsis as early as possible, even when a severe infection is not suspected. The answer may be leveraging an existing, routine test to include an indication of sepsis. By enhancing the most common laboratory test ordered by emergency physicians, a complete blood count (CBC) with an early sepsis indication may allow antibiotics to be administered sooner while not adding new burdens to physicians, nurses, laboratories, or the patient.

Current tests

The challenges surrounding sepsis diagnosis have led to sepsis commonly being under-or over-diagnosed.[10] Screening of suspected sepsis patients includes basic vitals—heart and respiratory rates, oxygen saturation levels, blood pressure, and temperature. Because septic patients often show signs of change in mental status[7] and speech patterns,[11] these are also evaluated. The Systemic Inflammatory Response Syndrome (SIRS) criteria were introduced in 1992 as a tool to help diagnose sepsis. Under SIRS, diagnosis of sepsis requires the presence of two or more of four basic criteria (tachycardia, tachypnea, hyperthermia, or hypothermia (>38°C or <36°C) and changes in white blood count levels).[12] In 1994, the Sequential Organ Failure Assessment (SOFA) score, based on platelet counts, creatinine levels, respiration, cognition, and liver and renal changes, was introduced as a way to describe the degree of organ failure of critically ill patients.[13]

In 2016, an international task force introduced the newest definition for sepsis: the Sepsis-3 (Sep-3) criteria. Under the Sep-3 criteria, sepsis is an infection with two or more of the previously defined SOFA points, whereas septic shock is sepsis with vasopressor-dependent hypotension and a lactate level greater than two.[14] The same task force also introduced the quick SOFA (qSOFA) criteria to identify patients at high risk for a poor outcome. qSOFA is a simple test with only three components: respiratory rate >22 breaths/min, altered mental state, and systolic blood pressure <100 mmHg.[15] Each component receives one point, and a score >2 has been found to be predictive of all-cause mortality outside of the ICU.[15]

While widely used in clinical practice for prognosis of septic patients, unfortunately, both SIRS and qSOFA have been shown to have a poor diagnostic value for sepsis.[16, 17, 18]

In addition to the patient's physical traits, physicians rely heavily on the laboratory for testing to try to pinpoint sepsis. Blood tests, including the complete blood count with differential (CBC-Diff), sputum testing, and urinalysis are commonly done in the ED to look for sepsis. Procalcitonin (PCT) is produced in response to bacterial infection, and high PCT levels can be indicative of a serious infection.[19] Similarly, levels of C-reactive protein (CRP), a substance produced in the liver, increase in response to systemic inflammation or infection.[20] While CRP has been shown to be very sensitive, it is not at all specific; increased levels can indicate, among other things, infection, cancer, or heart disease.

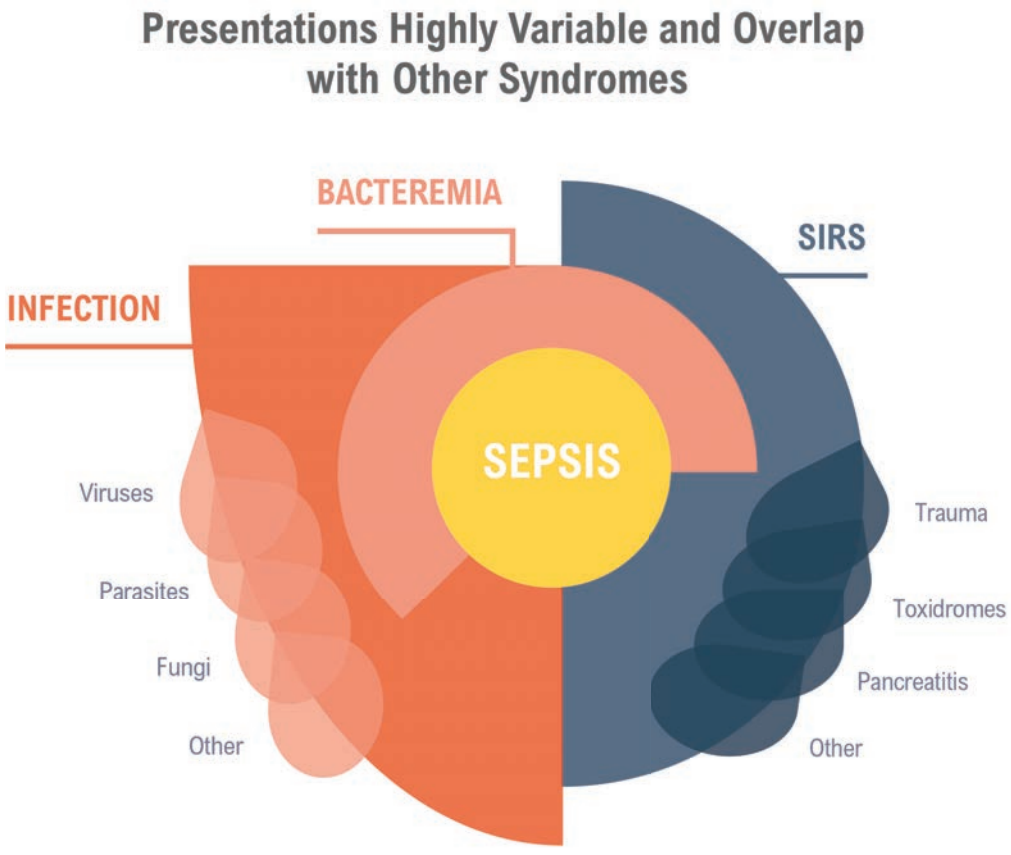


Figure 1.

The variable nature of sepsis diagnosis,[21] especially early in disease, and the poor predictive value of existing criteria[17] and aforementioned biomarkers highlight the importance of the availability of a unique, early sepsis biomarker to aid clinicians in escalating or de-escalating treatment for patients in the ED. While hundreds of studies have been published on promising sepsis biomarkers, implementing them in clinical practice in already overworked and understaffed emergency departments (EDs) and clinical laboratories has been challenging.

A valuable sepsis biomarker needs to flag when risk of sepsis is present, not when it is not. It should be easy to collect, inexpensive, and done on patients regardless of previous sepsis suspicion. Recently, there has been renewed interest in using components of the CBC-Diff to find indicators of sepsis. The CBC-Diff is the most ordered test in the ED and comprises 85% of all blood tests ordered in the ED.[22] It is easy to perform, has a rapid turnaround time, and provides a wealth of health information aiding in a differential diagnosis. Three CBC tests: red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and monocyte distribution width (MDW) have been shown to have potential as biomarkers for sepsis.

RDW is an erythrocyte index and reflects heterogeneity in the size of circulating RBCs. When used in patients with suspected sepsis, RDW has been shown to have modest value for predicting a positive blood culture, but limited value for diagnosing sepsis.[23] Likewise, NLR has prognostic value similar to that of C-reactive protein.[24] In times of physiological stress, neutrophil count increases and lymphocyte count decreases. The decrease in lymphocyte levels in early sepsis has been correlated with poorer outcomes in septic patients,[25,26] but neutrophil levels can be influenced by chronic health conditions[27] and lymphocyte levels can be decreased by certain syndromes and noninfectious health conditions[28] confounding the ratio.

The value of MDW

Monocytes are the body's first line of defense against pathogens. Part of both the innate and acquired immune responses, monocytes are activated in response to pro-inflammatory signals from infectious organisms and pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide. Monocytes express receptors for PAMPs and respond with transcriptional changes and downstream signaling that ultimately recruit leukocytes to the affected area.[29] As with the size variability of RBCs, the monocytes' response to infection causes an acute change in the size distribution.[30]The monocyte distribution width (MDW) parameter, a regulatory-cleared, in vitro diagnostic measurement, reflects a change in the volume of circulating monocytes (See **Figure 2**).

The initial feasibility study on the diagnostic value of the MDW biomarker in adult patients in the ED showed that it alone or in combination with the WBC count could be used to help establish the severity of infection and risk of sepsis in the ED.[33] When used in conjunction with other clinical parameters, the MDW biomarker has been shown to improve the early detection of sepsis during the initial ED encounter.[31] And while the exact molecular mechanism for changes in MDW is unknown, it is possible that variations in MDW biomarker correspond with the shift from a localized infection to a systemic, septic inflammatory response.[33]

One of the biggest benefits of the MDW biomarker is that it is part of the CBC-Diff. There are no additional testing requirements, thus no impact to workflow. The clinical laboratory is central to patient care, and workflow must be executed in a way

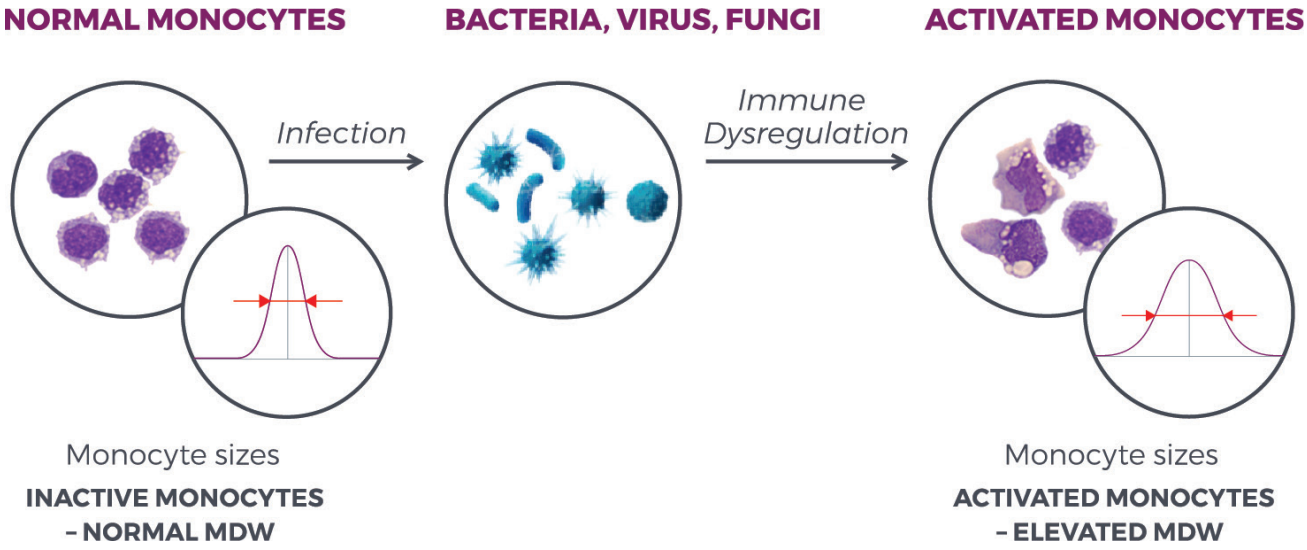


Figure 2. MDW–Monocytes Activation

that ensures the most accurate results reach the clinicians in the most efficient way possible. Results from MDW biomarker studies demonstrated that test results are comparable to those of lactate and C-reactive protein (CRP).[31,32] But as part of routine CBC testing, the MDW parameter was run in all patients whereas CRP and lactate were only run for patients with suspected sepsis. Thus, more patients received more information with lower impact to the lab.

The overwhelming dysfunctional immune response to infection leading to sepsis begins long before clinical symptoms are apparent. Having a unique biomarker that is evaluated as part of a standard test is a valuable tool to help detect patients at risk of developing sepsis.

Implementing MDW at Christus Trinity Mother Frances Health System

Earlier this year, the team at Christus Trinity Mother Frances Health System in Tyler, TX implemented the MDW parameter in seven locations — hospitals and standalone emergency departments — to aid in early sepsis detection knowing that strategically adding MDW to the EDs could be a game changer for sepsis outcomes. When patients enter the ED, they are a blank slate. Other than vital signs and the often-limited information provided by patients, very little is known. MDW allows every adult patient to be screened — not just those with specific sepsis symptoms — without interrupting the workflow in the lab or ED. The physician doesn't have to be looking for sepsis, but this allows for earlier identification. In the first week of use, the Christus team used the MDW biomarker to detect early sepsis in a patient; she was treated within two hours, and as a result, had a hospital stay of less than two days. When sepsis is diagnosed earlier, treatments can be started sooner, which leads to better patient outcomes. And achieving better patient outcomes is really what it's all about.

Closing thoughts

Monocytes react early in infection, so MDW provides an opportunity for clinicians to narrow differential diagnosis at the beginning of the patient encounter. Because the MDW parameter is measured as part of the CBC-Diff, it has value for identifying the possibility of sepsis in individuals for whom sepsis is not immediately suspected without adding to the already too-heavy workflow of the lab. The MDW parameter is not intended as a replacement for the qSOFA and SIRS criteria clinical analyses, but rather as an addition to these screening parameters to improve early sepsis detection.[33] Combined with innovative approaches to treatment, the MDW biomarker helps to identify severity of infection and sepsis, which may help to reduce the mortality rate associated with sepsis. Early sepsis detection leading to early source control can literally be the difference between life and death.

"Because the MDW is available in the CBC with differential, it's available much earlier than the other biomarkers. So MDW, in combination with other patient information, will help improve our ability to identify septic patients and improve outcomes." ~Dr. Freimer

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet*. 2020;395(10219):200-211. doi:10.1016/s0140-6736(19)32989-7.

2. Rudd KE, Kissoon N, Limmathurotsakul D, et al. The global burden of sepsis: barriers and potential solutions. *Critical Care*. 2018;22(1). doi:10.1186/s13054-018-2157-z.

3. Kumar G, Kumar N, Taneja A, et al. Nationwide Trends of Severe Sepsis in the 21st Century (2000–2007). *Chest*. 2011;140(5):1223-1231. doi:10.1378/chest.11-0352.

4. National Center for Health Statistics. NCHS Data Brief, Number 62, June 2011.; 2011. Accessed September 26, 2022. http://www.cdc.gov/nchs/data/databriefs/db62.pdf

5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596. doi:10.1097/01.CCM.0000217961.75225.E9.

6. Peltan ID, Brown SM, Bledsoe JR, et al. ED door-to-antibiotic time and long-term mortality in sepsis. *Chest*. 2019;155(5):938-946. doi:10.1016/j.chest.2019.02.008.

7. Centers for Disease Control and Prevention. What is sepsis? Centers for Disease Control and Prevention. Published January 27, 2021. https://www.cdc.gov/sepsis/what-is-sepsis.html Accessed September 22, 2022.

8. Filbin MR, Lynch J, Gillingham TD, et al. Presenting symptoms independently predict mortality in septic shock: Importance of a previously unmeasured confounder. *Crit Care Med*. 2018;46(10):1592-1599. doi:10.1097/CCM.0000000000003260.

9. Dunne D, McDonald R, Ratnayake R, et al. Blood cultures in acute surgical admissions. *Annals of The Royal College of Surgeons of England*. 2015;97(1):27-31. doi:10.1308/003588414X14055925059110.

10. Confield LR, Black GP, Wilson BC, Lowe DJ, Theakstone AG, Baker MJ. Vibrational spectroscopic analysis of blood for diagnosis of infections and sepsis: a review of requirements for a rapid diagnostic test. *Analytical Methods*. 2021;13(2):157-168. doi:10.1039/d0ay01991g.

11. Wattanapaiboon K, Banditlerdruk S, Vattanavanit V. Presenting symptoms in sepsis: Is the mnemonic "SEPSIS" useful?. *Infect Drug Resist*. 2020;13:2199-2204. Published 2020 Jul 8. doi:10.2147/IDR.S263964.

12. Comstedt P, Storgaard M, Lassen AT. The Systemic inflammatory response syndrome (SIRS) in

Basic Metabolic Panel. ***STAT.***

GEM Premier ChemSTAT, a rapid Basic Metabolic Panel analyzer from Werfen. Offering a customized menu for the emergency department, lab-quality Creatinine (Crea) results and advanced connectivity, this new solution ensures simplicity at the point of care or in the lab. Features Intelligent Quality Management (iQM®) for quality-assured testing to support rapid triage and patient care—STAT.

In a single, venous or arterial lithium-heparinized whole-blood sample:						*Calculated parameters*
Na^+	K^+	Ca^{++}	Cl^-	Glu	Crea	eGFR (MDRD)
BUN	tCO_2	Hct	Lac	pH	pCO_2	eGFR (CKD-EP)

For more information, contact your local Werfen representative/distributor.

werfen.com

werfen

acutely hospitalised medical patients: a cohort study. *Scand J Trauma Resusc Emerg Med*. 2009;17(1):67. doi:10.1186/1757-7241-17-67.

13. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Critical Care*. 2019;23(1). doi:10.1186/s13054-019-2663-7.

14. Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis*. 2017;9(4):943-945. doi:10.21037/jtd.2017.03.125.

15. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis. *JAMA*. 2016;315(8):762. doi:10.1001/jama.2016.0288.

16. Askim Å, Moser F, Gustad LT, et al. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. *Scand J Trauma Resusc Emerg Med*. 2017;25(1):56. doi:10.1186/s13049-017-0399-4.

17. Tusgul S, Carron PN, Yersin B, Calandra T, Dami F. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. *Scand J Trauma Resusc Emerg Med*. 2017;25(1):108. Published 2017 Nov 3. doi:10.1186/s13049-017-0449-y.

18. Jouffroy R, Saade A, Carpentier A, et al. Triage of septic patients using qSOFA criteria at the SAMU regulation: A retrospective analysis. Prehosp Emerg Care. 2018;22(1):84-90. doi:10.1080/10903127.2017.1347733.

19. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. *Crit Care*. 2020;24(1):287. Published 2020 Jun 5. doi:10.1186/s13054-020-02993-5.

20. Póvoa P, Almeida E, Moreira P, et al. C-reactive protein as an indicator of sepsis. *Intensive Care Med*. 1998;24(10):1052-1056. doi:10.1007/s001340050715.

21. Rhee C, Kadri SS, Danner RL, et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. *Critical Care*. 2016;20(1). doi:10.1186/s13054-016-1266-9.

22. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 emergency department summary tables. National Center for Health Statistics. Available from: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf. Accessed November 12, 2022.

23. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: A narrative review. *Clin Biochem*. 2020;77:1-6. doi:10.1016/j.clinbiochem.2020.01.001.

24. Drăgoescu, A. et al. (2021). Neutrophil to lymphocyte ratio (NLR)-A useful tool for the prognosis of sepsis in the ICU. *Biomedicines*. 10(1), 75. https://doi.org/10.3390/biomedicines10010075.

25. Venet F., Davin F., Guignant C., Larue A., Cazalis M.A., Darbon R., Allombert C., Mougin B., Malcus C., Poitevin-Later F., et al. Early assessment of leukocyte alterations at diagnosis of septic shock. *Shock*. 2010;34:358–363. doi: 10.1097/SHK.0b013e3181dc0977.

26. Wesche D. et al. (2005). Leukocyte apoptosis and its significance in sepsis and shock. *J. Leukoc. Biol*. 78:325–337. doi: 10.1189/jlb.0105017.

27. Belok S.H., Bosch N.A., Klings E.S., Walkey A.J. Evaluation of leukopenia during sepsis as a marker of sepsis-defining organ dysfunction. *PLoS ONE*. 2021;16:e0252206. doi:10.1371/journal.pone.0252206.

28. Lymphopenia - Causes and Risk Factors | NHLBI, NIH. www.nhlbi.nih.gov. Accessed September 28, 2022. https://www.nhlbi.nih.gov/health/lymphopenia/causes.

29. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. *Clinical Microbiology Reviews*. 2009;22(2):240-273. doi:10.1128/cmr.00046-08.

30. Crouser ED, Parrillo JE, Seymour CW, et al. Monocyte distribution width: A novel indicator of sepsis-2 and sepsis-3 in high-risk emergency department patients. *Crit Care Med*. 2019;47(8):1018-1025. doi:10.1097/CCM.0000000000003799.

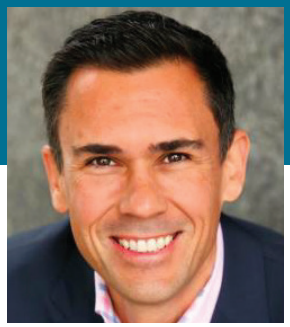
31. Crouser ED, Parrillo JE, Martin GS, et al. Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. *J Intensive Care*. 2020;8(1). doi:10.1186/s40560-020-00446-3.

32. Malinovska A, Hinson JS, Badaki-Makun O, et al. Monocyte distribution width as part of a broad pragmatic sepsis screen in the emergency department. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12679. doi:10.1002/emp2.12679.

33. Crouser ED, Parrillo JE, Seymour C, et al. Improved early detection of sepsis in the ED with a novel monocyte distribution width biomarker. *Chest*. 2017;152(3):518-526. doi:10.1016/j.chest.2017.05.039.

Patusa Mayfield is Director of Laboratory Services at **Christus Trinity Mother Frances Health System**, Tyler, Texas.

The Importance of Innovation in Molecular Diagnostics



Fernando Beils

Vice President and General Manager

qPCR Instruments

An Interview with Fernando Beils, Vice President and General Manager, qPCR Instruments, Thermo Fisher Scientific

In this interview we discussed the Applied Biosystem QuantStudio Real Time PCR Ecosystem and Thermo Fisher Scientific's commitment for innovation for molecular diagnostics.

Fernando joined Thermo Fisher Scientific in 2018 as vice president and general manager of toxicology, therapy drug monitoring, and quality controls after more than 20 years holding a number of leadership roles at Siemens Healthineers. In 2022, he began supporting qPCR instruments as part of Genetic Sciences. After obtaining his MBA in Germany, Fernando held several positions in strategy, finance, operations, and sales and marketing in medical imaging, *in vitro* diagnostic (IVD) point of care (POC), microbiology, and molecular diagnostics.

Overall, IVD tests influence about 70% of all clinical decisions and they amount to about 5% of the healthcare costs, Beils said. He further discussed the importance of molecular diagnostics and the role that Thermo Fisher had in the industry in this executive interview with the *Medical Laboratory Observer* editorial team.

Can you discuss the importance of innovation in molecular diagnostics and the role Thermo Fisher plays in the MDx industry?

Molecular diagnostic testing moved to the forefront of present-day clinical practice and through the pandemic gained attention and acknowledgment in public health.

Real-time PCR (qPCR) evolved to be the gold standard in infectious disease testing—with further evolution over next-generation sequencing (NGS) into digital PCR, which allows you a powerful combination to monitor and treat patients suffering with cancer.

We play a role being the market leader in PCR technologies, offering microarray (MA), capillary electrophoresis (CE), NGS, and POC in decentralized testing. We cover all aspects through technology, tests, key components, and ingredients to provide superb patient care for the clinical research community. We enable optimal workflow operations, with error elimination, in a fast and safe manner supporting our customers to save time and cost.

How is Thermo Fisher's commitment to innovation translating into new products this year?

After the launch of our solution for digital PCR, the Applied Biosystems™ QuantStudio™ Absolute Q™ Digital PCR System, we ensured the compliance of the Applied Biosystems™ QuantStudio™ product family: the QuantStudio™ 5 Dx Real-Time PCR System and the flagship QuantStudio™ 7 Pro Dx Real-Time PCR System with IVD regulations in both the US and EU. Furthermore, this summer we launched the new Applied Biosystems™ Diomni™ Software, an ecosystem which stands also in compliance with IVD regulations in the US and In Vitro Diagnostic Regulation (IVDR) in Europe.

Can you explain the importance of IVDR compliance and how Thermo Fisher is addressing this need?

The EU made the decision to move toward new standards of regulation for medical devices. The IVDR is built around providing patient safety with reliable results. This translates that IVD equipment providers need a safe and reliable workflow and data interpretation to ensure that the results of molecular diagnostic tests are supporting patient safety and data privacy. We therefore adapted our flagship instruments to meet this new standard and took into account that the movement of data is IVDR-safe. Diomni Software is also compliant with the IVDR standard.

Can you tell us more about the buzz around the Diomni Software ecosystem?

It is about the digital customer experience. Diomni Software is intelligent, integrated qPCR software – accessible and run by your browser. It offers multi-unit and fast qPCR workflows with innovative and AI-powered applications. It speeds up your routine and provides actionable qPCR-based results to enhance healthcare delivery and outcomes. Besides diagnostics, Diomni Software is also addressing the needs in research, academia, and pharma/biotech to improve the workflow and control your data.

For clinical applications, in a nutshell, Diomni Software is about simplifying and accelerating your workflow to clinical results—reducing time, cost, and errors, and protecting your data. Quality control is a major focus. Diomni Software future-proofs the laboratory and is also scalable while being compliant with the regulatory standards. Diomni Software empowers you to trace and track all your samples through the qPCR workflow from the patient, over liquid handling, sample prep, qPCR analysis, and automation of results, up to the integration into the laboratory information system (LIS). You can connect as many instruments as you would like with one single entry point. Through the efficiency of Diomni Software, you are also reducing the carbon footprint and making more space in your lab.

Thinking about the future—is Diomni Software targeting only qPCR workflows?

We foresee that Diomni Software will include further elements of molecular diagnostic technologies like sequencing, NGS, and microarray analysis, and could expand even further into immunochemistry and LC-MS. Diomni Software is aiming to provide all intelligence to support our partners and customers – ultimately to enable them to make this world healthier.

ThermoFisher SCIENTIFIC

www.thermofisher.com

QuantStudio 5 Dx and QuantStudio 7 Pro Dx Real Time PCR Systems and Diomni Software are for *In Vitro* Diagnostic Use.

The QuantStudio Absolute Q system is For Research Use Only. Not for use in diagnostic procedures.

The focus of quality control strategies should be on patient outcomes, not technology

By John Yundt-Pacheco and Curtis Parvin, PhD

Laboratories use quality control (QC) procedures to assure the reliability of the test results they produce and report. According to ISO 15189, the International Organization for Standardization's (ISO) document on particular requirements for quality and competence in medical laboratories, "The laboratory shall design quality control procedures that verify the attainment of the intended quality of results."[1] That is, laboratory QC procedures should assure that the test results reported by the lab are fit for use in providing good patient care. Unfortunately, there is often a temptation to focus on the instruments being used in the lab and the "big picture" view of patient outcomes can get forgotten when QC programs and strategies are designed.

Laboratory QC design

The primary tool used by laboratories to perform routine QC is the periodic testing of QC specimens, which are manufactured to provide a stable analyte concentration with a long shelf life. A laboratory establishes the target concentrations and analytic imprecision for the analytes in the control specimen assayed on their instruments. Thereafter, the laboratory periodically tests the control specimens and applies QC rules to the control specimen results to make a decision about whether the instrument is operating as intended or whether an out-of-control error condition has occurred.

Traditionally, laboratories determine how many control specimens to test and what QC rules to use based on a desire to have a low probability of making the erroneous decision that the instrument is out-of-control when it is, in fact, operating as intended (false rejection rate) and a high probability of making the correct decision that the instrument is out-of-control when indeed an out-of-control error has occurred (error detection rate).

Clearly, the in-control or out-of-control status of a laboratory's instruments influences the reliability (quality) of the patient results reported by the lab. Laboratories tend to design QC strategies with a focus limited to controlling the state of the instrument rather than controlling the risk of producing and reporting erroneous patient results that could compromise patient care.

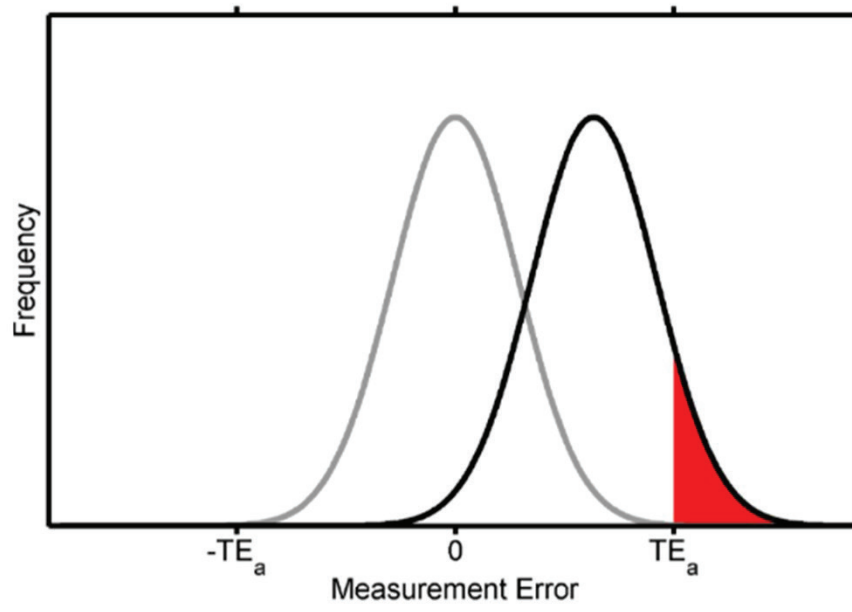


Figure 1.

A focus on the patient

One approach that more directly focuses on the quality of patient results (rather than the state of the instrument) is to design QC strategies that control the expected number of erroneous patient results reported because of an undetected out-of-control error condition in the lab.[3] What do we mean by "erroneous" patient results? The quality of a patient result depends on the difference between the patient specimen's true concentration and the value reported by the laboratory. We define an erroneous patient result as one where the difference between the patient specimen's true concentration and the value reported exceeds a specified total allowable error, TE_a. If the error in a patient's result exceeds TE_a, we assume it places the patient at increased risk of experiencing a medically inappropriate action.

How does a laboratory decide what the TE_a specification for an analyte should be? This is not a simple question to answer, but a number of different lists of TE_a specifications that include hundreds of analytes have been produced and are available from a variety of sources.

Once a TE_a for an analyte has been specified, then for any possible out-of-control state, the probability of producing patient results with errors that exceed the TE_a can be computed, as demonstrated in **Figure 1**. The gray curve represents the frequency distribution of measurement errors for an instrument operating as intended. The distribution is centered on zero and the width of the distribution reflects the inherent analytical imprecision of the instrument. The black curve represents the frequency distribution of measurement errors after a hypothetical out-of-control error condition has occurred. The out-of-control error condition causes the instrument to produce results that are too high.

The area under the out-of-control measurement error distribution that is either greater than TE_a or less than $-TE_a$ (shaded in red) reflects the probability of producing an erroneous patient result. In this case, 10% of the area under the curve is shaded red. If an out-of-control error condition of this magnitude occurred, then while the instrument was operating in this state, we'd expect 10% of the patient results produced to be erroneous.

The expected number of erroneous patient results reported while an undetected out-of-control error condition exists will not only depend on the likelihood of producing erroneous results in the presence of the error condition, but

ACCURATE AND RELIABLE LP(A) TESTING

Lipoprotein (a) or Lp(a) screening is recommended at least once in all adults to identify those at high risk of heart disease or stroke. Screening is also advised in youths with a family history of stroke, high Lp(a) or premature ASCVD. To allow accurate and reliable screening, assays suffering minimal apo(a) size related bias are recommended.

Traceable to WHO/ IFCC reference material (IFCC SRM 2B)

Dedicated 5-point calibrator accurately reflecting heterogeneity of apo(a) isoforms

Liquid ready-to-use reagents for added convenience

Available for use on most clinical chemistry analysers

Randox Cardiac Risk Assessment

Apolipoprotein A-I	Apolipoprotein E	CRP High Sensitivity
Apolipoprotein A-II	Cholesterol Total	Homocysteine
Apolipoprotein B	Cholesterol HDL	Lipoprotein (a)
Apolipoprotein C-II	Cholesterol LDL	Myoglobin
Apolipoprotein C-III	Cholesterol sdLDL	Triglycerides

Contact us today | www.randox.com | reagents@randox.com

RANDOX REAGENTS

Figure 2.

also on how many patient results are produced before the error condition is detected and corrected. This is illustrated in **Figure 2.**

In this example, each vertical line represents a patient specimen being tested on the instrument. Each diamond represents a QC event where QC specimens are tested and QC rules are applied. A green diamond implies the QC results are accepted; a red diamond means the QC results are rejected. At a point between the second and third QC event, an out-of-control error condition occurs, causing a sustained shift in the testing process (such as shown in **Figure 1**). Given the magnitude of this particular out-of-control condition and the power of the QC rules, the error condition isn't detected until the third QC event after it occurred. Each red asterisk denotes an erroneous patient result that was produced during the existence of the out-of-control error condition.

Notice some of the important relationships between QC events, the number of patients tested between QC events, and the number of erroneous patient results illustrated in **Figure 2:**

- Not all the results produced during an error condition are unreliable (the probability of producing an unreliable result during an error condition increases with the magnitude of the error).
- QC events do not always detect an error condition on the first try (the probability of a QC event detecting an error condition depends on the error detection rate of the QC rule, the number of control samples used, and the magnitude of the error).
- If the error condition in the example was smaller, we would expect proportionally fewer of the results tested during the undetected error condition to be unreliable (red asterisks in **Figure 2**), but more QC events needed to detect it. Conversely, if the error condition in the example was larger, we would expect proportionally more of the results tested during the undetected error condition to be unreliable, and fewer QC events needed to detect it. If the error condition were large enough, all of the patient test results after its occurrence would be unreliable and it would almost certainly be detected at the first QC event (third diamond in **Figure 2**).

In summary

QC that focuses on the instrument is concerned with the likelihood that a QC rule will trigger an alert after an error condition has occurred (the probability of a red diamond in **Figure 2**). Instrument-focused QC strategies are designed to control the number of QC events required to detect an error condition.

QC that focuses on the patient, on the other hand, is concerned with how many erroneous patient results are produced while an undetected error condition exists (the number of reds asterisks in **Figure 2**). Patient-focused QC strategies should be designed to control the number of erroneous patient results produced before the error condition is detected.

REFERENCES

1. International Organization for Standardization: Medical laboratories - particular requirements for quality and competence. ISO 15189:2012. International Organization for Standardization (ISO), Geneva.

2. Parvin CA. Assessing the impact of the frequency of quality control testing on the quality of reported patient results. Clin Chem. 2008;54:2049-54. doi:10.1373/clinchem.2008.113639.

John Yundt-Pacheco, MSCS, is a scientific fellow who performs research in quality control and patient risk issues in the Informatics Discovery Group at **Bio-Rad.** He has had the opportunity to work with laboratories around the world, developing practical real-time, inter-laboratory quality control and proficiency testing systems.

Curtis Parvin, PhD is retired from **Bio-Rad,** where he was Manager of Advanced Statistical Research. Prior to joining Bio-Rad, Parvin was the Director of Informatics and Statistics at the faculty of Washington University School of Medicine.

Explore the Broadest Range of Urinalysis QC Solutions.

Quantimetrix® puts you in control of quality with the most versatile and complete line of urinalysis quality controls, designed to meet your needs from the central lab to the point of care.

Optimize your QC with exceptional open and closed-vial stability across all analytes, lot-to-lot consistency and friendly, dedicated customer support.

Samples of all Quantimetrix products are available absolutely free – let us help you find your best fit today!

Connect with us @
quantimetrix.com

Shining renewed light on a tried-and-true test: The critical role of osmolality in improving health outcomes in patients with hyponatremia

Julie MacKenzie, MBA

Hyponatremia, defined as a serum sodium concentration of ≤135 mEq/L, is the most common electrolyte disorder encountered in clinical practice, occurring in up to 30% of hospitalized patients.[1] The prevalence of hyponatremia is conservatively estimated to range from 3.2 million to 6.1 million people in the United States on an annual basis. Most patients treated for hyponatremia are initially treated as inpatients (55%–63%), 25% are initially treated in the emergency room, and 13%–20% are exclusively treated in the office setting. See **Figure 1** for key statistics.

Hyponatremia is often observed at admission but also frequently develops during hospitalization either as a complication of an underlying illness or as the result of therapeutic interventions.[8] High incidences of hyponatremia have been reported in a variety of patient populations including those with heart failure,[9,10] renal disease,[11,12] cirrhosis,[13] cancer,[14,15,16] pneumonia,[17] and stroke.[18,19] Hyponatremia also frequently occurs after various surgical procedures including pelvic,[20] spinal,[21] and pituitary surgery.[22,23] It is particularly prevalent in the elderly, in part because of age-related decline in renal function.[24,25] Additionally, patients who receive maintenance intravenous fluids, particularly children, are in danger of developing hyponatremia.[26,27] Hyponatremia is also common with COVID-19, occurring in nearly a third of hospitalized patients.[28,29]

Photo courtesy of A[illegible]ed Instruments, LLC

Key Statistics

- Hyponatremia occurs in up to 30% of hospitalized patients[1]
- 47% increased risk of death in-hospital at 1 year associated with hyponatremia[2]
- Increase of 2 days in mean length of stay associated with hyponatremia[3]
- Increase of ~50% in the odds of having a 30-day unplanned readmission or death associated with hyponatremia[4]
- Reduction in overall mortality of 60% with hyponatremia correction[5]
- $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the U.S.[6]
- Osmolality and sodium measured in only 23% of patients with hyponatremia[7]

Figure 1.

Association of hyponatremia with poor outcomes

Numerous studies have demonstrated the association between hyponatremia and poor outcomes across diverse patient populations.[30,31,32,33] Winzeler et al. conducted a prospective observational 12-month follow-up study of 281 patients with profound hyponatremia (<125 mmol/L). During the follow-up period, 20.6% of patients died, 56.2% were rehospitalized at least once, and 42.7% had recurrent hyponatremia. However, it is not just severe hyponatremia that has been associated with adverse outcomes. Both mild (130–135 mmol/L) and moderate (125–129 mmol/L) hyponatremia have also been associated with unfavorable outcomes in the literature.[2,34] In a meta-analysis of 81 published studies encompassing 850,222 patients, Corona et al. demonstrated that moderate hyponatremia is associated with an increased risk of mortality, and that it is a negative prognostic factor across multiple com-

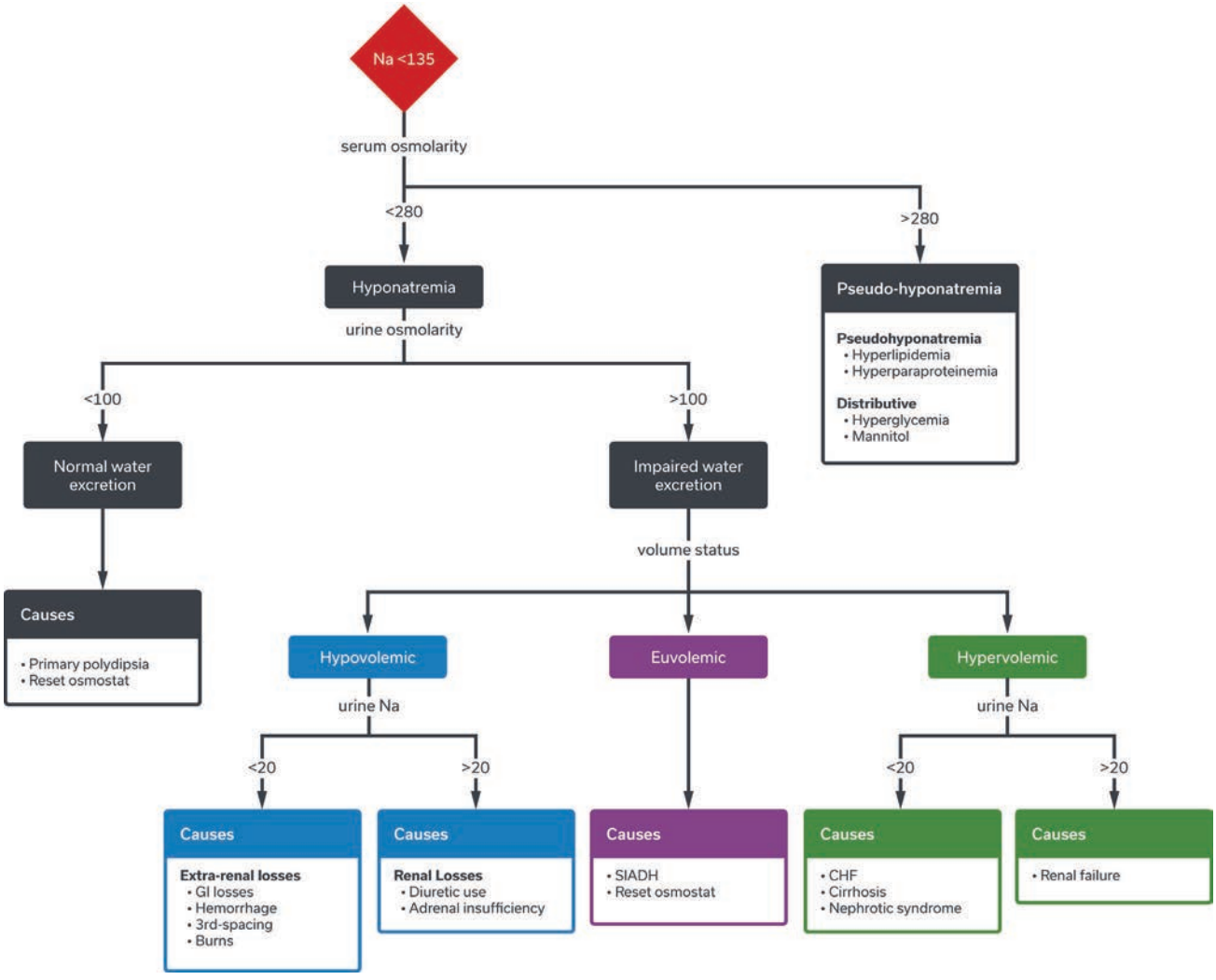


Figure 2. Clinical pathway for diagnosing hyponatremia.

monly observed clinical conditions, such as myocardial infarction, heart failure, cirrhosis, and pulmonary infections. Waikar et al. investigated in-hospital, 1-year and 5-year mortality in a prospective cohort study of 98,411 hospitalized adults and found that patients with hyponatremia had an increased risk of death in-hospital at 1 year (47%) and 5 years (25%). The increased risk of death was evident even in those with mild hyponatremia (37%) and was pronounced in patients admitted with cardiovascular disease, metastatic cancer, and those admitted for procedures related to the musculoskeletal system.[2]

Poor outcomes have also been reported in COVID patients with hyponatremia of varying severity levels.[28,35] In a retrospective, multicenter, observational cohort study, Frontera et al. identified the impact of mild, moderate, and severe admission hyponatremia on outcomes among COVID patients and reported that each level of worsening hyponatremia conferred 43% increased odds of in-hospital death. Further, the authors observed that hyponatremia was an independent predictor of in-hospital mortality and was associated with increased risk of encephalopathy and mechanical ventilation. Similarly, Carvalho et al. conducted a retrospective study of 296 adult patients with a diagnosis of COVID-19 and reported that ICU admission, mechanical ventilation, and death were significantly more frequent in hyponatremic patients compared to normonatremic patients (37% versus 14%; 17% versus 6%; 18% versus 9%).

Osmolality is well-established in the clinical pathway for hyponatremia

Correction of hyponatremia first requires proper diagnosis. The common electrolyte disorder is classified as hypoosmolar, isoosmolar, or hyperosmolar. Understanding the underlying cause of hyponatremia is important as the treatment options vary widely from fluid resuscitation for hyponatremia driven by volume depletion to volume restriction for hyponatremia driven by the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[37,38] It is important to cast a wide net in the initial workup of hyponatremia because patients may present with minimal information regarding relevant medical conditions or recent triggering events.[39] Interpreting various laboratory parameters, including serum and urine osmolality, is necessary to differentiate between the various causes of hyponatremia and ensure proper patient management.[40]

Criteria for diagnosing hyponatremia is well-established.[1,7,41,42] Measurement of serum osmolality is the first step in the laboratory diagnosis of hyponatremia, and if the test suggests a hypo-osmolar state, then urine osmolality helps determine whether the ability of the kidneys to dilute urine is intact **(Figure 2)**.[39]

SIADH is the most frequent cause of hyponatremia and the use of serum and urine osmolality to distinguish SIADH from other etiologies is critical. In 1967, Bartter and Schwartz originally defined the diagnostic criteria for SIADH, which include measuring serum osmolality, urine osmolality, and serum sodium at a minimum. Their criteria has remained

unchanged.[41] More recently, globally recognized expert panels in the United States and Europe have published evidence-based guidelines discussing the critical role that serum and urine osmolality measurements play in the classification and differential diagnosis of hyponatremia.[1,7,42]

The utility of osmolality has also been recognized in the management of COVID patients due to the prevalence of hyponatremia in this patient population.[43,44,45] O'Shea et al. published a COVID test menu for clinical laboratories that includes osmolality testing due to the potential for acute kidney injury in these patients. Similarly, Martinez et al. published guidance recommending daily monitoring of osmolality for inpatients during the acute phase of COVID-19.

Osmolality testing for proper patient management

Osmolality is a proven and medically necessary test in the management of hypontremia. Failure to measure plasma and urine osmolality in cases of hypontremia has been associated with increased mortality.[45,46] In a retrospective study of adult patients with severe hyponatremia, Whyte et al. reported that 30% of patients died when neither serum nor urine osmolality was measured compared to 9.8% when both tests were measured.[45] Similarly, Vaduganathan et al. analyzed serum osmolality measured at discharge in 3,744 patients hospitalized for heart failure and concluded that low discharge serum osmolality was independently predictive of worse discharge mortality and readmission.[46]

Knowledge and interpretation of a patient's osmolality in cases of hyponatremia enable the physician to differentiate between the various causes of the electrolyte disorder and appropriately direct treatment. This is a critical issue because treatment varies drastically based on symptoms and underlying causes. Hyponatremia is treated with fluid restriction (in the setting of euvolemia), isotonic saline (in hypovolemia), and diuresis (in hypervolemia).[47] Lack of osmolality testing makes diagnostic accuracy and subsequent treatment uncertain putting hyponatremic patients at risk.

Underutilization of osmolality impedes management of hyponatremia

Despite published guidance on its diagnosis, clear associations with poor outcomes and increased medical costs, and significant evidence that correcting hyponatremia is associated with improved outcomes and lower costs, hyponatremia is insufficiently investigated or overlooked entirely, and critical testing is not routine impacting patient treatment.[36,48,49,50]

Inadequate requisition of serum and urine osmolality is frequent in cases of hyponatremia. In a multicenter, retrospective, observational study, Tzoulis et al. found that only 23% of patients with hyponatremia had measurements of paired serum and urine osmolality and sodium.[50] The study from Tzoulis et al. is not an outlier; numerous publications in the literature have consistently reported underutilization of measured osmolality in the investigation of hyponatremia.[29,35,51,52,53]

Huda et al. evaluated the assessment and management of hyponatremia in a large teaching hospital and found that adequate investigations were rarely performed. In fact, plasma osmolality was measured in only 26% of patients with severe hyponatremia and urine osmolality was measured in only 27%. The authors observed that treatment was often illogical with significant management errors in 33% of cases. Errors included, but were not limited to, inadequate investigation which could have changed management, treatment with fluid restriction plus intravenous saline, and diuretic induced hyponatremia treated with fluid restriction. Further, mortality was significantly higher in the group with management errors (41% versus 20%). The authors suggest that more appropriate management may have reduced the overall mortality rate. Additionally, they found a trend towards more efficient normalization of serum sodium concentrations in the appropriately managed group, deemed appropriate based on standards for the major diagnostic criteria of hyponatremia.[51] Seo et al. reported similar management errors as Huda et al. The authors highlighted the importance of osmolality test results in guiding therapy.[47]

Even SIADH, the most common cause of hyponatremia, is often diagnosed without attention to the accepted diagnostic criteria.[7,29,52,53] Greenberg et al. conducted an analysis of adult patients in the Hyponatremia Registry from 225 sites in the United States and European Union and observed that only 47% of 1,524 patients with an assigned diagnosis of SIADH had all three cardinal tests (serum osmolality, urine osmolality, and serum sodium) performed and 11% had none. Serum osmolality was measured in 66% of patients and urine osmolality in 68%.[52] Burst et al. studied smaller subsets of the Hyponatremia Registry. The authors analyzed 358 cancer patients with a clinical diagnosis of SIADH and similarly found that only 46% of patients had all three tests performed, and 13% had none. They reported that test underutilization was even more pronounced in subgroups including lung cancer patients and small cell lung cancer patients with all tests performed in only 41% and 36% of patients respectively.[53]

Diagnostic rigor appears to be even worse in COVID patients. In a retrospective, multicenter, observational cohort study of hospitalized patients with laboratory-confirmed SARS-CoV-2, Frontera et al. attempted to determine the etiology of hyponatremia but were unsuccessful because serum and urine osmolality were available in less than 15% of the cohort.[29] Yen et al. reported that serum and urine osmolality measurements were available as part of admission hyponatremia workup tests in only 18% and 12% of cases respectively. Further, the authors reported that serum and urine osmolality were only ordered on the day of admission, when hyponatremia was identified, in 9% and 5.4% of cases respectively.[54] Similarly, Carvalho et al. reported that osmolality was

Stakeholder	Benefits
Patient	• Improved outcomes (i.e., better prognosis, reduced length of stay) • More effective treatment
Hospital	• Improvement in readmission rate and reduced associated penalty[59] • Increased profit from reduction in costs • Differentiation from other hospitals via better patient experience
Clinician	• Evidence-based decision-making tool to improve patient care • Improved patient outcomes
Laboratory	• Increased efficiencies • Expedited patient care

Figure 3. Osmolality testing: Key stakeholders and benefits.

rarely measured in a noninterventional retrospective cohort of patients with mild hyponatremia and COVID-19.[35]

Osmolality is a cost-effective test with a significant return on investment

Not performing osmolality testing is potentially harmful to the patient, but it is also very expensive given that some of the medications now available to treat SIADH cost $500–$1,000 per day. Just one or two misdiagnosed patients can cost the hospital system as much as the price of an osmometer, the device used to measure osmolality. This does not include the possible costs arising from litigation for malpractice due to misdiagnosis and improper treatment.[55] Further, cost per test is highly inexpensive and reimbursement for the test is well-established.[46,56,57]

The College of American Pathologists (CAP) estimated the value generation potential of proper laboratory testing of electrolyte disorders based on Prometheus data and fluid and electrolyte disorders represented 1.5 percent of all potentially avoidable costs. When scaled to the national level and expanded beyond the commercial population based on the CAP's modeling, this represents potential avoidable costs of $1.14 billion nationally.[6] Implementing osmolality testing as standard of care in patients with hyponatremia could help optimize proper patient management to avoid unfavorable outcomes and enable hospitals to recover a significant portion of the $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the United States. **Figure 3** outlines the benefits of osmolality testing to stakeholders in the circle of care.

Conclusion

In summary, hyponatremia represents a significant medical burden that is prevalent in various patient populations. Despite published guidance on its diagnosis, clear associations with poor outcomes, increased medical costs, and significant evidence that correcting hyponatremia is associated with improved outcomes, the common electrolyte disorder is often inadequately investigated or ignored. Osmolality testing is proven and medically necessary to effectively manage hyponatremia, improving outcomes and reducing excess resource utilization. However, osmolality is underutilized even though the cost per test is low, the test is classified as 'urgent,' and osmometers are well-established medical devices.[58]

When clinicians have a clear understanding of the importance of determining the etiology of hyponatremia, and the utility of measuring osmolality to do so, it follows that they would be more likely to order the test. Osmolality testing combined with education on interpreting test results are both critical in addressing suboptimal management of hyponatremia. The return on investment would be substantial due to the low cost per test and $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the United States alone. Addressing underutilization of osmolality testing in cases of hyponatremia, including education of ordering providers, is the first step in ensuring that everyone who needs an osmolality test gets one.

Please visit mlo-online.com for references.

Julie MacKenzie is Senior Manager, Clinical Product Portfolio at **Advanced Instruments, LLC.** She has been with Advanced Instruments for over 14 years. She received her Bachelor's degree in Biochemistry, Cellular, and Molecular Biology from Connecticut College and she earned her MBA from Boston College. She is passionate about improving quality of care.

Image by NatalyaBurova @ gettyimages.com

Guidance for choosing an LIS vendor

By Erin Brady

Choosing a laboratory information system (LIS) vendor is an important process that will affect a laboratory for a long time. There are several factors and issues that laboratories must consider when making the decision. *Medical Laboratory Observer* asked a number of LIS experts for their insights on choosing a vendor.

Bringing awareness to issues

Clinical laboratories and pathology groups continue to take the pain associated with rigid, legacy LIS systems that lack the functionality and flexibility to tackle today's challenges, and they don't have to, according to Suren Avunjian, CEO, LigoLab Information Systems. "Multiple disparate systems and their inherent data silos can be replaced with modern laboratory management solutions that help organizations operate more effectively by automating core processes and providing real-time visibility into both operational and financial performance."

Suren Avunjian
CEO, LigoLab
Information Systems

"Medical laboratories often question whether to choose an LIS that is designed to meet the lab's specific test processing requirements utilizing *configuration or customization*," said Jaswant S. Tony, CEO and Founder, GoMeyra. "As a condition of signing new business, labs may be asked to change their workflow sequence, add new test panels, or revise reporting formats. If they can't comply with these requests quickly, they could lose the opportunity to a competitor."

Jaswant S. Tony
CEO and Founder,
GoMeyra

Tony continued, "Configuration uses predefined, prevalidated process flows and graphical interfaces to create a sequence of steps for handling test samples according to the laboratory's needs. The core system software code is *not* rewritten to implement these steps. Customization involves rewriting the underlying programming language to meet the lab's workflow requirements, which can impact the system validation and regulatory compliance already in place. Many larger LIS vendors advocate only configuration — the approach embodied in their LIS. If the software provider does offer customization, the lab may wait months until the work is completed, again losing prospective customers in the process. GoMeyra resolves this issue with a dual approach: pre-configuration to handle the majority of a lab's requirements, then customization only where necessary. This enables much faster installation and startup while meeting 100% of the client's parameters."

Kim Futrell, Senior Strategic Marketing Manager, Orchard Software emphasized that a challenge for post-COVID laboratories is integration."Many labs are trying to repurpose molecular analyzers for other testing and these molecular devices require integration for data flow. As the industry moves toward personalized medicine, integrated molecular instruments will be more in demand. Labs typically have clinical and pathology within an integrated system; however, other areas like HLA testing and cytogenetics may not be integrated, resulting in time-consuming manual entry."

Kim Futrell
Senior Strategic Marketing Manager
Orchard Software

Futrell also brought to light the issue of security threats."The healthcare industry as a whole is a target for cyberattacks and the lab handles an enormous amount of protected health information (PHI) that must be kept secure and HIPAA-compliant. To keep sensitive data secure, the LIS has to be continuously up to date on the latest threats."

Tips for choosing a vendor

Choosing the right LIS vendor is essential. Tony, Futrell, and Avunjian all emphasized that many laboratories stick with their LIS provider for a long time, so choosing one you can trust is even more important.

Tony said,"Your LIS software provider should serve as a knowledgeable, trusted IT partner throughout the system specification, purchase, and installation process. Selecting a supportive, customer-focused LIS supplier ensures that any issues arising during system installation and startup will be quickly resolved. You can also count on them for ongoing service and support."

Tony advises labs to select a vendor who:

- Observes your daily operations, listens carefully to your needs and concerns, and proposes a system tailored to your lab's unique requirements and available budget
- Offers both configuration and customization of LIS functions, real-time repairs, upgrades and patches
- Makes customer service available 24 hours a day to handle performance issues or answer questions
- Responds to change requests as your operations evolve.

Futrell advises doing considerable research and introspection before deciding whom to partner with. She also advises before reaching out, laboratories consider the following:

- Determine your budget.
- Think about what you want the LIS to do. Make a list of the functionality and features you require. Are there any"deal-breaker"or must-have requirements?
- Consider using the request for proposal (RFP) process to vet candidates.
- Research LIS vendors. Do any of the vendor candidates resonate with you and your lab's mission?
- Ask your peers within the industry about their LIS pros and cons.

Avunjian said,"Don't look for a vendor but a partner, as laboratories cannot afford to switch systems often."

He posed some questions laboratories should ask when searching for an LIS vendor:

- Does the LIS vendor also offer a billing solution and supporting modules? If yes, does the billing solution share the same database and software infrastructure?
- Can the LIS be deployed on the cloud and on-premises, with what's best for the lab ultimately being the determining factor for server location?
- Can the LIS manage all departments and operations with no data silos?
- Does the LIS support specimen tracking with the automatic generation of a unique barcode identifier for every specimen and document?
- Does the LIS support rules and automation that streamline workflows and reduces manual touchpoints?
- Does the LIS support fully customizable lab reports based on customer preferences and multiple report delivery options?
- Does the LIS have an interface engine, or is middleware needed for interfacing?
- Does the LIS have a comprehensive and searchable audit trail that logs and archives every activity in every department?
- Does the LIS provide insight and visibility in the forms of statistical dashboards and dynamic reports?
- Does the LIS support laboratory outreach with both client and patient portals?
- Does the LIS support all established regulatory protocols and offer compliance verification at every stage?

2023 predictions

In our annual LIS Buyers' Guide Survey, *MLO* asked respondents what they saw on the horizon for LIS products in 2023. Additionally, *MLO* asked Tony, Avunjian, and Futrell what upcoming trends/needs they predict in LIS for 2023.

GoMeyra sees automation and integration accelerating in 2023."Both automation and integration in LIS software architecture are becoming increasingly important for future-proofing labs,"Tony said.

Avunjian also pointed to automation trending in 2023."With a well-documented shortage of qualified technologists and technicians to staff labs, and the cost to employ them constantly going up, more and more labs will turn to automation as a replacement for manual processes in 2023. By investing in automation, they will help relieve the staffing burden and gain more cost certainty. The LIS is the heart of lab operations, and with an all-in-one platform, redundancy is removed, workflows are streamlined, and full visibility into the operations of the laboratory is gained," he said.

Additionally, LigoLab predicted technology advances in 2023. "By embracing direct-to-consumer patient portals coupled with telemedicine capabilities, labs will no longer be faceless. Instead, they'll be able to directly connect with patients and satisfy their growing demand for easy and convenient access to a marketplace that offers enhanced specialized laboratory services. In addition to having easy and convenient on-demand testing, patients will also need assistance to better understand their lab reports and test results. In 2023 they'll be able to get this in the form of remote sessions with a medical professional connected to the patient portal," Avunjian said.

Futrell noted that, "Going forward, continued consolidation is expected as healthcare organizations and laboratories combine services to achieve the economy of scale needed in the current healthcare landscape. LIS vendors will need to be prepared to help their lab customers grow their services and integrate across locations and organizations."

She concluded, "The LIS is essential in today's laboratory and a strong LIS can make the jobs of laboratory professionals much easier, which improves employee satisfaction and retention. Having a vendor that you can trust and rely on is essential and can help ease the workload burden on lab and IT staff."

Company Name	Orchard Software Corporation	NovoPath	CompuGroup Medical	LigoLab Information System	Clinical Software Solutions
Name of system (product)	Orchard Enterprise Lab	NovoPath 360	CGM LABDAQ Laboratory Information System	LigoLab Operating Platform	CLIN1
Website URL	www.orchardsoft.com	www.novopath.com	www.cgm.com/us	LigoLab.com	www.clin1mobile.net
2015-edition certification from the Office of the National Coordinator for Health Information Technology (ONC)	No	N/A	No	N/A	No
Cloud-based version	Yes	Yes	No	Yes	Yes
Preconfigured interfaces with common lab analyzers	Yes	Yes	Yes	Yes	Yes
Preconfigured interfaces with common inpatient electronic medical record systems	Yes	Yes	No	Yes	Yes
Preconfigured interfaces with common outpatient electronic medical record systems	Yes	Yes	No	Yes	Yes
Preconfigured interfaces with common pathology imaging systems	Yes	Yes	No	Yes	Yes
Module for revenue cycle management	No	No	Yes	Yes	Yes
Automated process for tracking medical necessity verification	Yes	Yes	Yes	Yes	Yes
Lab performance management analytics	Yes	Yes	Yes	Yes	Yes
Barcode specimen tracking	Yes	Yes	Yes	Yes	Yes
Inventory control and supply chain management	No	Yes	Yes	Yes	Yes
POCT module	Yes	No	Yes	Yes	Yes
Genetic testing module	Yes	Yes	No	Yes	Yes
Anatomical pathology module	Yes	Yes	Yes	Yes	Yes
Full bidirectional integration capabilities for data exchange with digital solutions	Yes	Yes	Yes	Yes	Yes
Interoperable through API's	Yes	Yes	Yes	Yes	Yes
SaaS model pricing	Yes	Yes	No	Yes	Yes
What is the most important trend you see on the horizon for LIS products in 2023?	Advancements in molecular LIS technologies.	Consolidation - period. One platform that does every specialty from AP to Molecular to create one comprehensive report without the need for report addendum.	Increased molecular testing.	Patient engagement as a new revenue opportunity for labs. Driving market differentiation for partner labs by improving productivity, and reducing medical errors and manual processes. Utilizing automation and the latest AI technology to streamline workflows and help combat the lack of qualified laboratory technologists.	Re-shoring of development of Healthcare IT products.

Choose a lab system
built by the lab, for the lab.

Choose a strategic partner that
excels in laboratory innovation.

Choose Orchard.

ORCHARD Software

(800) 856-1948
www.orchardsoft.com
Like and follow us on social media!

Company Name	XIFIN	GoMeyra	ELLKAY LLC	SCC Soft Computer
Name of system (product)	XIFIN LIS	GoMeyra LIMS	CareEvolve	SoftLab LIS/LIMS
Website URL	www.XIFIN.com	www.gomeyra.com/	https://ellkay.com/index.php/laboratory-connectivity-solutions/careevolve	www.softcomputer.com
2015-edition certification from the Office of the National Coordinator for Health Information Technology (ONC)	No	N/A	Yes	Yes
Cloud-based version	Yes	Yes	Yes	Yes
Preconfigured interfaces with common lab analyzers	No	Yes	No	Yes
Preconfigured interfaces with common inpatient electronic medical record systems	No	Yes	Yes	Yes
Preconfigured interfaces with common outpatient electronic medical record systems	No	Yes	Yes	Yes
Preconfigured interfaces with common pathology imaging systems	Yes	Yes	No	Yes
Module for revenue cycle management	Yes	Yes	No	Yes
Automated process for tracking medical necessity verification	Yes	Yes	Yes	Yes
Lab performance management analytics	Yes	No	Yes	Yes
Barcode specimen tracking	Yes	Yes	No	Yes
Inventory control and supply chain management	Yes	Yes	No	Yes
POCT module	No	Yes	Yes	Yes
Genetic testing module	Yes	Yes	Yes	Yes
Anatomical pathology module	Yes	No	Yes	Yes
Full bidirectional integration capabilities for data exchange with digital solutions	Yes	Yes	Yes	Yes
Interoperable through API's	Yes	Yes	Yes	Yes
SaaS model pricing	Yes	Yes	Yes	Yes
What is the most important trend you see on the horizon for LIS products in 2023?	Digital Pathology: With the advancement of artificial intelligence in pathology including FDA approvals for diagnosis assistance, we see a renewed interest in digital pathology. It will be critical that lab information system providers have integrated workflow solutions for digital pathology so that slide preparation, scanning, results (image and analytics) integrations, and reporting are all seamless and automated. Digital pathology will have far-ranging impact, including greater efficiencies and faster reads, cost reduction, more precise diagnoses and support of support precision medicine. LIS systems will need to support coordinated care consultations among pathologists, radiologists and oncologists.	We see three important trends for 2023: More automation, greater integration, and going paperless wherever possible.	Automation – automating as many steps as possible to reduce the need for human intervention.	Continued automation.

Sheridan VA Health Care System wants to hire YOU!

The VA Healthcare System has openings for a Medical Technologist in Wyoming. Join our cutting-edge medical center. We offer very competitive salary, student loan repayment up to $200K.

We currently have an opportunity for a certified (ASCP-BOC, ASCP-BOR or AMT) Medical Technologist with excellent diagnostic and communication skills to join a hospital-based practice.

Our Joint Commission Accredited Clinical Laboratory Lab encompasses all Pathology Disciplines including Microbiology, Biochemistry, Special Chemistry, Hematology.

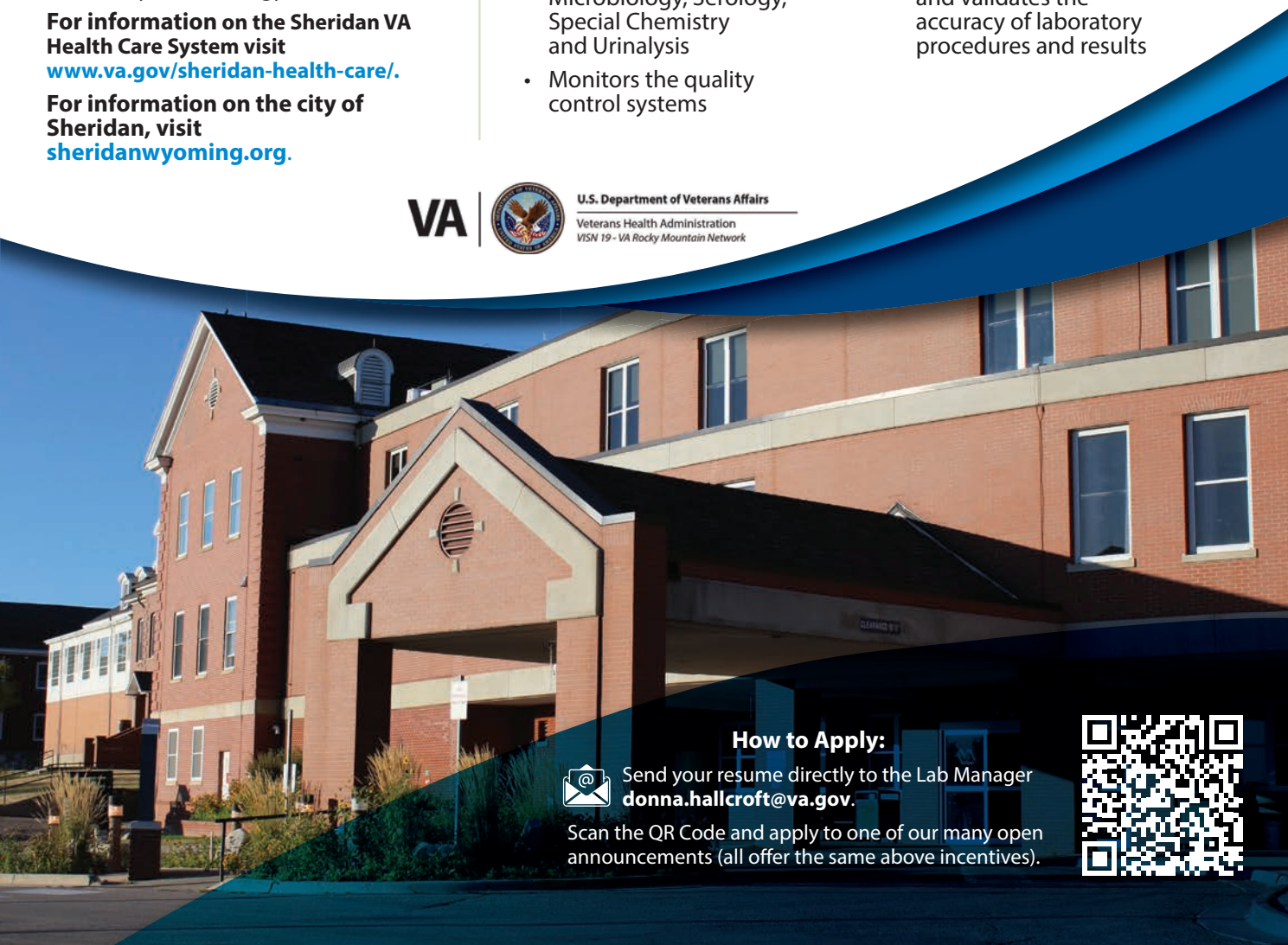
For information on the Sheridan VA Health Care System visit www.va.gov/sheridan-health-care/.

For information on the city of Sheridan, visit sheridanwyoming.org.

Medical Technologist Job Description:
Medical Technologist works throughout the lab as a generalist and works weekends, and holidays by themselves. **Duties include, but are not limited to:**

- Performs testing procedures on a variety of biological specimens and/or environmental samples using manual and automated techniques
- Requires competency in the areas of Hematology, Chemistry, Coagulation, Microbiology, Serology, Special Chemistry and Urinalysis
- Monitors the quality control systems
- Ensures timely and thorough evaluation of data, ensures discrepancies are identified and attended by troubleshooting instrument performance and/or QC material performance
- Performs, evaluates, interprets, correlates, and validates the accuracy of laboratory procedures and results

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
VISN 19 - VA Rocky Mountain Network



How to Apply:

Send your resume directly to the Lab Manager **donna.hallcroft@va.gov**.

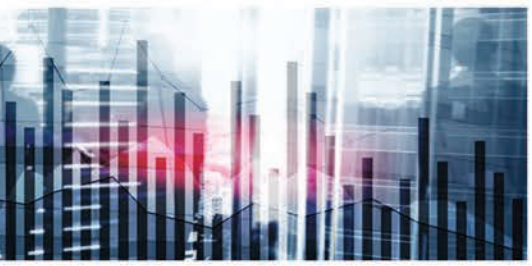
Scan the QR Code and apply to one of our many open announcements (all offer the same above incentives).

INDEX OF ADVERTISERS

MEDICAL LABORATORY OBSERVER

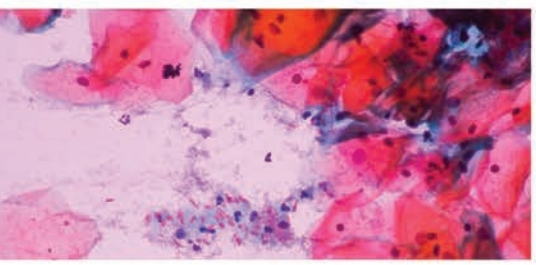
Medical Lab Professionals Forum

Join us for the Medical Laboratory Observer's online lab management series.
Each partial-day event features discussions on current topics by industry experts including videos, resaerch, whitepapers, guides, and live sessions that keep you up-to-date with the latest information on solutions critical to the medical lab. View year-long, on-demand.



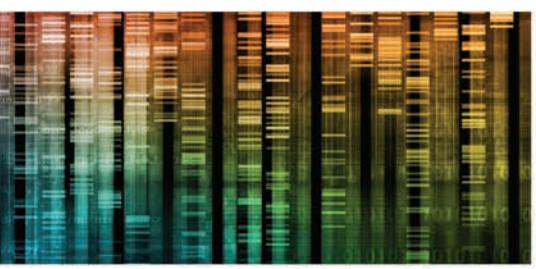
"Technology & Trends in the Clinical Lab"

Our editors present findings from our special report on Informatics in the Laboratory, with its focus on using valuable clinical analytics to inform the decision-making process in the lab. The presentation includes additional information on valuable solutions for healthcare laboratories.



"Lab Accreditation & MDx Workflow"

MLO presents an overview on maintaining practices that follow accreditation standards. What are the top laboratory deficiencies? How can workflow solutions help you address molecular diagnostic challenges? Do you have sufficient training in place to ensure your staff is confident and competent in their job?



"Molecular Diagnostics for the Future Clinical Lab"

Using data gathered from our exclusive State of the Industry report on Molecular Diagnostics published in the November issue of MLO, we will explore the increasing roles of MDx and its solutions use in the clinical laboratory.

https://endeavor.swoogo.com/mlo_forum/about

Readers' questions answered

Charles K. Cooper, MD
Chief Medical Officer
Siemens Healthcare Diagnostics,
Siemens Healthineers

Q&A

An issue that comes up for me again and again are questions from primary care physicians about interpreting positive drug screens and reflex confirmatory testing. Is there a table or quick reference that would explain what metabolites are commonly seen in patients taking different (and sometimes multiple) pain formulations? Often a doctor is prescribing one drug, but suspects the patient is taking that and others. What substances can cause false positives in drug testing? Sometimes a physician contacts me when they tell the patient that their testing suggests additional drugs and the patient disagrees, perhaps suggesting that supplements or other medications might be responsible.

Any assistance would be appreciated.

Determining when to test for drugs of abuse (DOA), which test to use, and how to interpret test results is unavoidably complex and belies the simplicity of the reported results. Clinicians should be encouraged to become familiar with important aspects of testing for DOA as there are some basic concepts that can be helpful. First, become familiar with appropriate indications for testing to maximize the clinical value of such testing and to reduce the chances of unintended consequence. Common testing scenarios include drug treatment programs, pain management programs, and psychiatric treatment. These scenarios involve patients with a higher pre-test probability, which reduces the relative likelihood of a false positive result when compared to testing done on individuals with low pre-test probability.

Second, in order to correctly interpret the results of DOA testing, it is important to understand the limitations of DOA testing, which is most often conducted via highly sensitive laboratory immunoassays. For example, these tests do not definitively prove that active intoxication is present, since sensitive immunoassays may detect the presence of levels below that which are associated with intoxication. Also, there are a number of potential causes for false positives that clinicians should become familiar with. When necessary, confirmation testing with chromatography or gas chromatography/mass spectrometry should be ordered to provide certainty, however, clinicians should be aware that such confirmation requires additional time as these methods are not as fast as automated immunoassays. Also, point-of-care tests may not be as accurate as laboratory-based immunoassay testing as numerous publications have demonstrated performance estimates that underperform labeled claims. Finally, false negative results are possible due to patient subversion techniques such as through the use of masking agents, attempts to dilute the urine via either ingestion or addition of water, addition of adulterants, and switching urine specimens.

Clinicians should be encouraged to advance their knowledge of this topic to aid in test ordering and results interpretation. There are good resources available to clinicians to advance their understanding such as a recent review article that appeared recently in the Am Fam Physician medical journal (https://www.aafp.org/pubs/afp/issues/2019/0101/p33.html) as well as a number of resources at the webpage of the National Institute on Drug Abuse (https://nida.nih.gov/nidamed-medical-health-professionals/health-professions-education/cmece-activities).

As a fully vaccinated, retired medical laboratory technologist, I have family and friends who question the need to be vaccinated against COVID-19. What are the best ways for persons like me to help counter their fears and advocate for the value of being vaccinated?

Many thanks for revival of a Q&A column in MLO!

It's not altogether surprising that people may have grown weary about COVID-19 given the extremely stressful experience that societies around the world have experienced in the past few years. However, we have to be careful not to allow pandemic fatigue to inaccurately color the importance of vaccination. The data is conclusive that COVID-19 vaccination reduces likelihood of severe disease and bad outcomes particularly for those at increased risk. When one considers the fact that the currently circulating Omicron subvariants of SARS-CoV-2 are among the most contagious and transmissible viruses that humans encounter today, it is reasonable to view infection and/or exposure as a question of when not if. With this in mind, people need to decide how they will obtain their immunity, either via immunization or infection. Immunization, with several hundreds of millions of doses administered to date, has a well described safety profile with more predictable outcomes than what may be experienced with actual infection. People who are reluctant to obtain vaccination should be encouraged to become educated about the safety profile of vaccines as well as the risk factors associated with severe disease to help them make a more informed decision and to more effectively manage personal risk. The CDC has good resources to help people understand their risk, which can be found at this website: https://www.cdc.gov/coronavirus/2019-ncov/your-health/understanding-risk.html.

I saw in your bio that you co-led the efforts to create the Quantitative Safety Division in the Center for Drug Evaluation and Research (CDER). Could you please explain what "quantitative safety" is?

Quantitative safety is a descriptor for a drug safety division that was created in CDER at FDA for the purpose of performing advanced quantitative evaluation of drug safety signals utilizing techniques such as meta-analysis and Bayesian analysis. FDA receives large amounts of high-quality phase 3 clinical trials and is in a unique position to utilize this data for the purposes of answering important safety questions.

SAFE SOLUTIONS

Even with minimal tube volumes, the potential for injury from manual decapping or manual recapping is a real possibility

You have known about our Pluggo™ decappers Now available; KapSafe™ Recappers in several models to fit any volume needs

Make your goal ZERO repetitive stress injuries

From the leader in bench-top solutions for automated decapping and recapping

Visit our website for additional information **www.lgpconsulting.com**

Laboratory Growth & Productivity

1.877.251.9246

Accommodates all major tube sizes and a variety of analyzer racks

Serving laboratories since 2002 | Contact us for literature and sales information

Quidel has developed an innovative line of respiratory products for decades.

So whatever respiratory season may bring, we're ready.

1979 Quidel founded

1996 First company to receive CLIA waiver for Strep A with QuickVue In-Line Strep A Test

1999 Receives FDA clearance for world's first rapid diagnostic flu test QuickVue Influenza Test (A/B)

2011 Quidel launches Sofia automated analyzer FIA

2015 Introduction of Solana assays

2018 Receives FDA clearance for QuickVue Influenza A+B which meets FDA's Class II RIDT requirements

2020 Receives FDA EUA for Sofia 2 SARS Antigen FIA, Sofia 2 Flu+SARS FIA (ABC), QuickVue SARS Antigen Test, and Solana SARS-CoV-2

QUIDEL®

QuickVue®
Influenza A+B, RSV, SARS* Antigen Assays

Solana®
Influenza A+B, RSV + hMPV, SARS-CoV-2*, Bordetella Complete Assays

Sofia®/Sofia 2
Influenza A+B, RSV, SARS* Antigen, Flu + SARS* Antigen Assays

To get the right RIDT for your patient, contact a Quidel Inside Sales at **858.431.5814** or visit **quidel.com**

*THESE TESTS ARE AVAILABLE FOR SALE IN THE USA UNDER EMERGENCY USE AUTHORIZATION. These SARS tests have not been FDA cleared or approved, but have been authorized by the FDA under an Emergency Use Authorization (EUA) for use by authorized laboratories for the detection of proteins (QuickVue and Sofia) or nucleic acids (Solana) from SARS-CoV-2, not for any other viruses or pathogens. These tests are only authorized for the duration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless terminated or revoked sooner.

AD10183600EN00 (06/22)