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President, American Proficiency Institute

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References: 1. Panther Fusion GBS assay. US package insert AW-17997-001. Hologic, Inc.; 2019. **2.** CDC. Group B Strep (GBS) Fast Facts. Centers for Disease Control and Prevention website. Last reviewed October 18, 2022. Accessed April 14, 2023. https://www.cdc.gov/groupbstrep/about/fast-facts.html

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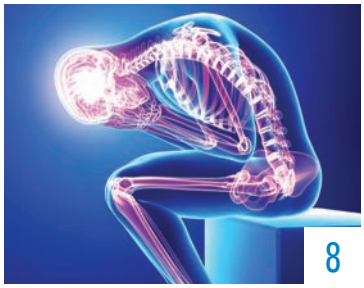
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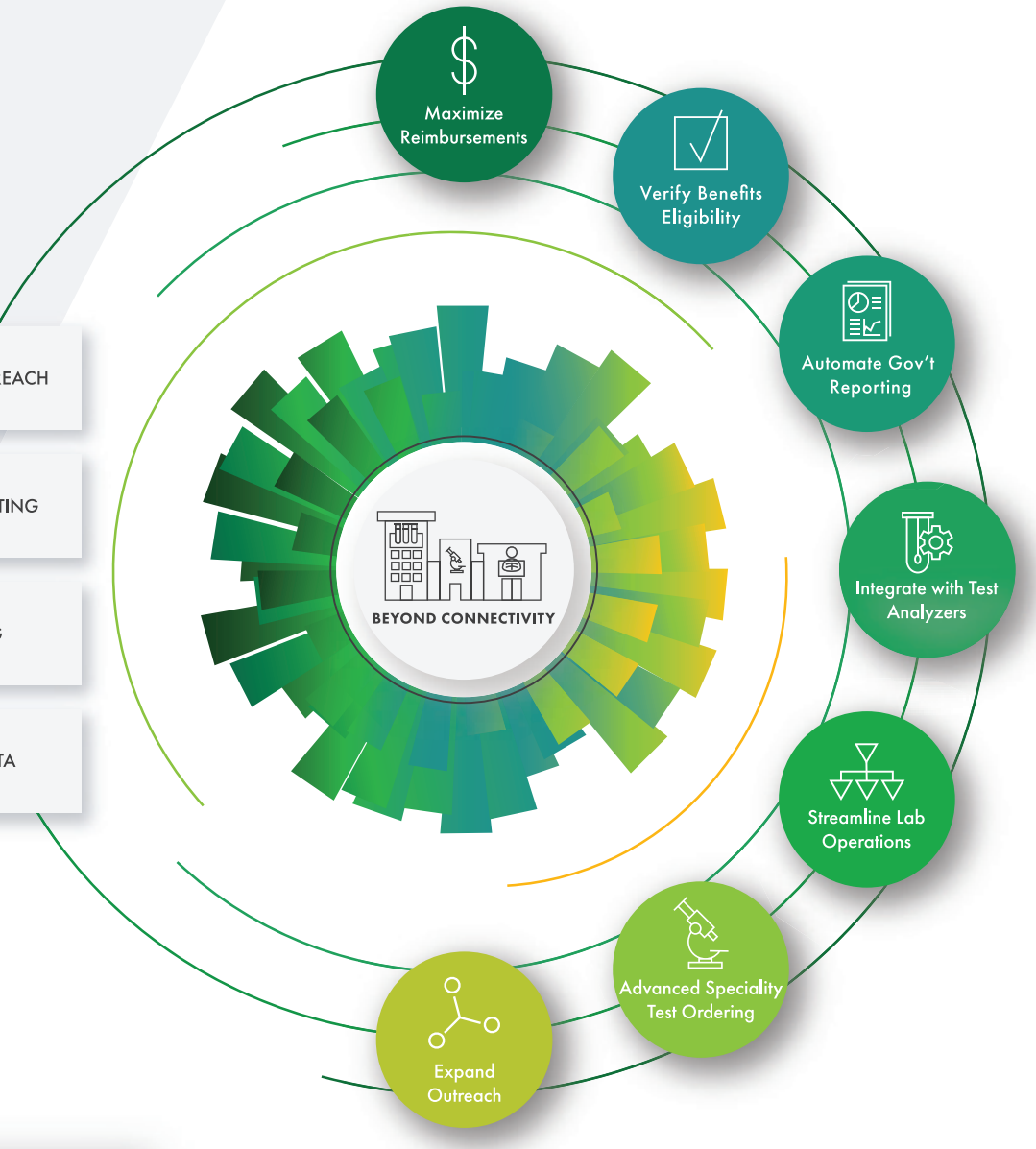

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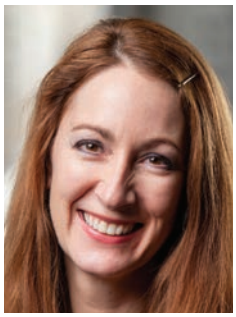
Our mental health



By Christina Wichmann
Editor in Chief

Mental health is not a common topic for a clinical laboratory magazine. However, I read two reports that I thought would also be interesting to you—particularly in regard to the topic of employee recruitment and retention. Grant Thornton, one of America's largest accounting and advisory firms, recently released its "2023 State of Work in America" survey results and Dr. Vivek Murthy, the U.S. Surgeon General, released an advisory, "Our Epidemic of Loneliness and Isolation."[1,2]

In the Grant Thornton survey, mental health emerged as a primary concern and an issue employees want their employers to address and support. When responding to what is causing burnout at work, 53% of respondents indicated mental/emotional stress as the top concern. Long hours (42%), workload (42%), and shortage of workers (41%) followed. Regarding the question, "What is keeping you at your organization," 38% said benefits and 35% said base pay. 63% of respondents stated that their benefits meet their needs; however, fewer than half (48%) see their benefits as unique or different from what another employer would provide. Kim Jacoby, a People & Organization director at Grant Thornton said, "Tailoring a total rewards package that stands out from competitors' offerings could be a differentiator in attracting and retaining talent."

Grant Thornton's survey findings lead to some of the following conclusions:

- Employee well-being is a top concern.
- Analyze output and expectations to eliminate unnecessary work.
- Demonstrate interest in employees' personal lives by listening.
- Address the issues that permeate your organization—evaluate and adjust in real time.

The Surgeon General's report tracks a decline in social connections—especially among young people—and shows that half of adults are lonely, linking it to billions of dollars in healthcare costs. The findings show that loneliness has profound effects on mental health and is as dangerous as smoking 15 cigarettes a day, increasing the risks of heart disease, stroke, and dementia.

In regard to our work life, this report states that "Quality social support, social integration, and regular communication among co-workers of all levels are key in preventing chronic work stress and workplace burnout." In addition, "Workplace connectedness is also associated with enhanced individual innovation, engagement, and quality of work, all of which can influence career advancements, income, and overall economic stability." The report provides some of the following recommendations for employers:

- Make social connections a strategic priority in the workplace.
- Train and empower leaders to promote connections in the workplace.
- Leverage existing training, orientation, and wellness resources to emphasize the importance of social connection for workplace well-being, productivity, retention, and other markers of success.

Our healthcare industry is coping with burnout, stress, and employee retention challenges. I hope leaders are recognizing the importance of their staff's mental health.

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

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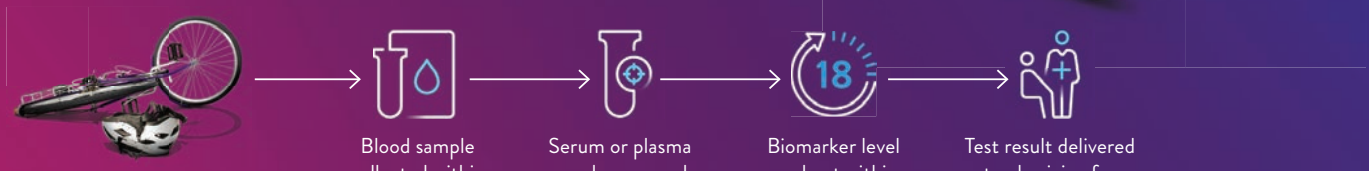

Patient presents to ER with suspected mTBI

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The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury, to assist in determining the need for a CT (computed tomography) scan of the head. A negative test result is associated with the absence of acute intracranial lesions visualized on a head CT scan.
The TBI test is intended for use in clinical laboratory settings by healthcare professionals.

IMPORTANT SAFETY INFORMATION

Instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from these instructions.
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CONTACT A REPRESENTATIVE FROM ABBOTT FOR COMMERCIAL AVAILABILITY.

1. Alinity i TBI [package insert] 802673R01. Instructions for use. Abbott Diagnostics. May 2023.
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Fast Facts

HIV declines among young people and drives overall decrease in new HIV infections

Estimated annual new HIV infections were 12% lower in 2021 compared to 2017—dropping from about 36,500 infections to about 32,100—according to new CDC data published. The decline was driven by a 34% decrease in new infections among 13- to 24-year-olds, mostly among gay and bisexual males. HIV prevention efforts must go further and progress must be faster, however, for gains to reach populations equitably and for national goals to end the HIV epidemic to be reached.

According to the CDC's latest estimates:

6,100

annual HIV infections in 2021 among 13- to 24-year-olds, a drop from 9,300 in 2017.

80%

of new infections in this age group are among young gay and bisexual males. Infections declined from 7,400 to about 4,900 during the time frame.

30%

of the 1.2 million people who could benefit from PrEP were prescribed it in 2021—a notable improvement compared to about 13% prescribed PrEP in 2017.

87%

of people with HIV were aware of their status in 2021 compared to 86% in 2017.

66%

of people with diagnosed HIV were virally suppressed due to effective treatment in 2021, an increase from 63% in 2017.

1/5

of new HIV infections in 2021 were among women, and over half of those were among Black women.

Source: https://www.cdc.gov/media/releases/2023/p0523-hiv-declines-among-young-people.html

Large study provides scientists with deeper insight into long COVID symptoms

Initial findings from a study of nearly 10,000 Americans, many of whom had COVID-19, have uncovered new details about long COVID, the post-infection set of conditions that can affect nearly every tissue and organ in the body.

Clinical symptoms can vary and include fatigue, brain fog, and dizziness, and last for months or years after a person has COVID-19. The research team, funded by the National Institutes of Health, also found that long COVID was more common and severe in study participants infected before the 2021 Omicron variant. The study, published in *JAMA*.

Researchers examined data from 9,764 adults, including 8,646 who had COVID-19 and 1,118 who did not have COVID-19. They assessed more than 30 symptoms across multiple body areas and organs and applied statistical analyses that identified 12 symptoms that most set apart those with and without long COVID: post-exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, issues with sexual desire or capacity, loss of smell or taste, thirst, chronic cough, chest pain, and abnormal movements.

They then established a scoring system based on patient-reported symptoms. By assigning points to each of the 12 symptoms, the team gave each patient a score based on symptom combinations. With these scores in hand, researchers identified a meaningful threshold for identifying participants with long COVID. They also found that certain symptoms occurred together and defined four subgroups or "clusters" with a range of impacts on health.

Based on a subset of 2,231 patients in this analysis who had a first COVID-19 infection on or after Dec. 1, 2021, when the Omicron variant was circulating, about 10% experienced long-term symptoms or long COVID after six months. The results are based on a survey of a highly diverse set of patients and are not final. Survey results will next be compared for accuracy against an array of lab tests and imaging.

In addition to establishing the scoring system, the researchers found that participants who were unvaccinated or who had COVID-19 before the Omicron strain emerged in 2021 were more likely to have long COVID and more severe cases of long COVID. Further, reinfections were also linked to higher long COVID frequency and severity, compared to people who only had COVID-19 once.

Screening all U.S. adults aged 35 and older for chronic kidney disease could be cost effective

A cost-effectiveness analysis of screening for chronic kidney disease (CKD) has found that screening all adults in the United States starting at age 35 could be cost-effective for the quality of life-years (QALY) gained, according to a release from the American College of Physicians. The analysis is published in *Annals of Internal Medicine*.

While experts have been unable to agree whether screening for early-stage CKD improves clinical outcomes, sodium-glucose cotransporter-2 (SGLT2) inhibitors are changing the discussion. Researchers from Stanford University conducted a cost-effectiveness analysis of adults aged 35 years and older who were screened for albuminuria with and without SGLT2 inhibitors to the current standard of care for CKD. The authors assessed costs, QALYs, and incremental cost-effectiveness ratios (ICERs). The authors found that screening U.S. adults once and adding SGLT2 inhibitors between ages 35 and 75 prevented dialysis or transplant in 398,000 people, and screening every 10 years until age 75 years cost less than $100,000 per QALY gained.

FDA approves drug to treat agitation symptoms associated with dementia due to Alzheimer's disease

The U.S. Food and Drug Administration announced the supplemental approval of Rexulti (brexpiprazole) oral tablets for the treatment of agitation associated with dementia due to Alzheimer's disease. This is one of the first FDA-approved treatment options for this indication.

The effectiveness of Rexulti for the treatment of agitation associated with dementia due to Alzheimer's disease was determined through two 12-week, randomized, double-blind, placebo-controlled, fixed-dose studies. In these studies, patients were required to have a probable diagnosis of Alzheimer's dementia; have a score between 5 to 22 on the Mini-Mental State Examination, a test that detects whether a person is experiencing cognitive impairment; and exhibit the type, frequency, and severity of agitation behaviors that require medication. Trial participants ranged between 51 to 90 years of age.

In the first study patients received 1 or 2 milligrams (mg) of Rexulti; in the second study patients received 2 or 3 mg of Rexulti. The primary efficacy endpoint in these two studies was the change from baseline in the Cohen-Mansfield Agita-

tion Inventory total (CMAI) score at week 12. CMAI is a survey tool that uses input from caregivers to rate the frequency of certain agitative behaviors in dementia patients on a scale from 1 to 7. In both studies, patients who received 2 mg or 3 mg of Rexulti showed statistically significant and clinically meaningful improvements in total CMAI scores compared to patients in the placebo group at week 12.

The recommended starting dosage for the treatment of agitation associated with dementia due to Alzheimer's disease is 0.5 mg taken once daily on days 1 to 7. Patients should increase the dosage on days 8 through 14 to 1 mg once daily, and on day 15 to 2 mg once daily. The recommended target dose is 2 mg once daily. The dosage can be increased to the maximum recommended daily dosage of 3 mg once daily after at least 14 days, based on clinical response and tolerability.

The most common side effects among patients with agitation associated with dementia due to Alzheimer's disease include headache, dizziness, urinary tract infection, nasopharyngitis, and sleep disturbances (both somnolence and insomnia). Rexulti will retain the Boxed Warning for medications in this class that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

NIH-funded study highlights the financial toll of health disparities in the United States

New research shows that the economic burden of health disparities in the United States remains unacceptably high.

The study, funded by the National Institute on Minority Health and Health Disparities (NIMHD), part of the National Institutes of Health, revealed that in 2018, racial and ethnic health disparities cost the U.S. economy $451 billion, a 41% increase from the previous estimate of $320 billion in 2014. The study also finds that the total burden of education-related health disparities for persons with less than a college degree in 2018 reached $978 billion, about two times greater than the annual growth rate of the U.S. economy in 2018.

Key findings from the study included:

Economic burden by racial and ethnic minority groups

National estimates

- Most of the economic burden for racial and ethnic disparities was borne by Black/African American population (69%) due to the level of premature mortality.
- Native Hawaiian/Pacific Islander ($23,225) and American Indian/Alaska Native ($12,351) populations had the highest economic burden per person.
- Most of the economic burden was attributed to premature deaths for Native Hawaiian/Pacific Islander (NHPI) (90%), Black/African American (77%), and American Indian/Alaska Native (AI/AN) (74%) populations. For Asian (55%) and Hispanic/Latino (43%) populations, most of the burden was from excess medical care costs and lost labor market productivity, respectively.

State estimates

- Five states with the highest burden of racial and ethnic health inequities were among the most populous and diverse states: Texas ($41 billion), California ($40 billion), Illinois ($29 billion), Florida ($27 billion), and Georgia ($21 billion).
- Black/African American people had the highest economic burden of racial and ethnic health inequities in most states (33), followed by Hispanic/Latino (nine states), American Indian/Alaska Native (eight states), and Native Hawaiian/Pacific Islander (one state) individuals.
- The burden of racial and ethnic health disparities relative to each state's GDP varied from 0.14% (Vermont) to 8.89% (Mississippi). Seventeen states had a burden higher than the annual growth rate of the U.S. economy in 2018.

Economic burden by educational levels:

National estimates

- Per person, adults with a high school diploma had the highest burden ($9,982), followed closely by adults with less than a high school diploma ($9,467) and then adults with some college ($2,028).
- Although most of the burden of education-related health inequities was borne by adults with a high school diploma/GED (61%), a disproportionate share was borne by adults with less than a high school diploma/GED—they were only 9% of the population but bore 26% of the burden.
- Across all educational levels, most of the burden was attributable to premature deaths (66%), followed by lost labor market productivity (18%) and excess medical care costs (16%).

State estimates

- Per person, the economic burden of health disparities varied substantially across states by educational levels. For adults with less than a high school diploma, the burden ranged from $3,152 (California) to $21,372 (Kentucky). For adults with a high school diploma, it ranged from $6,201 (West Virginia) to $25,555 (South Carolina), and for adults with some college, it ranged from $1,072 (Illinois) to $8,374 (South Carolina).
- In 31 states, adults with less than a high school diploma/GED had the highest economic burden of education-related health inequities. In 20 states, the burden was greatest among adults with a high school diploma/GED. Adults with some college had the lowest burden of education-related health inequities in all 50 states and the District of Columbia.

The burden of education-related health inequities relative to each state's GDP varied from 1.90% (District of Columbia) to 18.29% (South Carolina). Forty-six states had a burden higher than the annual growth rate of the U.S. economy in 2018.

Policy and regulatory changes to the omnibus COVID-19 healthcare staff vaccination requirements

The Centers for Medicare & Medicaid Services (CMS) and Department of Health and Human Services (HHS) released a final rule on June 5 addressing changes to healthcare staff COVID-19 vaccination requirements.

The final rule also addresses:

- Additional policy and regulatory changes to the requirements for long-term care (LTC) facilities and intermediate care facilities for individuals with intellectual disabilities (ICFs-IID) to provide COVID-19 vaccine education and offer vaccinations to residents, clients, and staff.
- Policy and regulatory changes to the long-term care facility COVID-19 testing requirements.

This final rule removes expired language addressing staff and patient COVID–19 testing requirements for LTC Facilities issued in the interim final rule.

The regulations in this final rule are effective on August 4, 2023.

Testing for inflammation

By Rajasri Chandra, MS, MBA

Inflammation is part of the body's innate defense mechanism that is triggered when tissues are injured (such as from trauma or heat) or infected by microbes or viruses. Inflammation is characterized by heat, redness, swelling, pain, and loss of function at the affected site.[1] Inflammation can be of three types:

Acute: Occurs immediately after injury and usually resolves in a few days

Chronic: May last for months or even years when acute inflammation fails to settle

Subacute: A transformational period from acute to chronic which lasts from two to six weeks[2]

The inflammatory pathway consists of a sequence of events involving inducers, sensors, mediators, and effectors. The process is initiated in the presence of inducers, which can be infectious organisms or noninfectious stimuli such as foreign bodies and signals from necrotic cells or damaged tissues. This activates the sensors, which are specialized molecules. The sensors then stimulate the inflammatory mediators including cytokines, histamine, bradykinin, prostaglandins, and leukotrienes, which are endogenous chemicals that cause blood vessels to leak fluid into the tissues, causing swelling. This event promotes the migration of neutrophils and macrophages to the area of acute inflammation.[3] The inflammatory mediators can induce pain, activate or inhibit inflammation and tissue repair, and can activate the effectors, which are the tissues and cells. Other mediators act as regulatory components to establish homeostasis after injury or prevent the inflammatory process.[4] These players can act together and give rise to multiple alternative pathways in the inflammatory process, depending on the type of stimuli.

The goal of the inflammatory process is to restore homeostasis regardless of the cause. If this inflammation does not resolve within six weeks, this will cause the acute inflammation to develop from subacute to chronic form of inflammation with the migration of T lymphocytes and plasma cells to the site of inflammation. If this persists with no recovery, then tissue damage and fibrosis will ensue. Other varieties of cells, such as macrophages and monocytes, play a role in both acute and chronic inflammation.[1]

Chronic inflammation[6] is a slow, long-term inflammation lasting several months to years. The extent and effects of chronic inflammation vary with the cause of the injury and the ability of the body to repair and overcome the damage. Chronic inflammation may happen due to:[6]

- Failure to eliminate the acute inflammation causative agent such as infectious organisms including Mycobac-

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LEARNING OBJECTIVES

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

1. Differentiate between the three different types of inflammation.
2. Describe the immune process in which inflammation plays a role in.
3. Discuss the chronic inflammatory process and its role in certain conditions.
4. List and discuss the laboratory tests that are useful in detecting and monitoring inflammation in certain diagnoses.

terium tuberculosis, protozoa, fungi, and other parasites as they are able to resist host defenses and remain in the tissue for an extended period.
- Exposure to a low level of a particular irritant or foreign material that cannot be eliminated by enzymatic breakdown or phagocytosis in the body including substances or industrial chemicals that can be inhaled over a long period, for example, silica dust.
- An autoimmune disorder in which the immune system identifies the normal component of the body as a foreign antigen, and attacks healthy tissue giving rise to diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).
- A defect in the cells responsible for mediating inflammation leading to persistent or recurrent inflammation, such as auto-inflammatory disorders (familial Mediterranean fever).
- Recurrent episodes of acute inflammation. However, in some cases, chronic inflammation is an independent response and not a sequel to acute inflammation, for example diseases such as tuberculosis and rheumatoid arthritis.
- Inflammatory and biochemical inducers causing oxidative stress and mitochondrial dysfunction such as increased production of free radical molecules, advanced glycation end products (AGEs), uric acid (urate) crystals, oxidized lipoproteins, homocysteine, and others.

More than 50% of all deaths are attributed to diseases related to systemic chronic inflammation (SCI) such as ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD), and autoimmune and neurodegenerative conditions.[7]

Shifts in the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance causing major alterations in all tissues and organs, as well as normal cellular physiology, which can increase the risk for various non-communicable diseases in both young and older individuals. SCI can also impair normal immune function, leading to increased susceptibility to infections and tumors and a poor response to vaccines. Furthermore, SCI during pregnancy and childhood can have serious developmental consequences such as elevating the risk of non-communicable diseases over an individual's life span.[8]

Tests to detect inflammation

As certain proteins are released into the bloodstream during inflammation and when their concentrations increase or decrease by at least 25%, they can be used as biomarkers to detect systemic inflammation. Although there are many inflammatory markers, also known as acute phase reactants, those most commonly measured in clinical practice are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma viscosity (PV) and procalcitonin (PCT).[9,10] These markers are not specific for a particular condition and hence cannot be used for differential diagnosis but they help to identify a generalized inflammatory state. Other tests need to be used along with these tests for differential diagnosis. Because these markers are nonspecific, the tests are not diagnostic for any particular condition, but they may help to identify a generalized inflammatory state along with other tests and aid in the differential diagnosis.

In some diseases, serial measurements of CRP also may be of prognostic value.[11] PCT is a newer marker of inflammation that may in certain cases identify or exclude bacterial infections and guide antibacterial treatments.[12,13]

Besides CRP, ESR, and PCT, some other markers of inflammation include serum amyloid A, cytokines, alpha-1-acid glycoprotein, plasma viscosity, ceruloplasmin, hepcidin, and haptoglobin. However, high cost, limited availability, and lack of standardization may limit practical clinical use of markers other than CRP, ESR, and PCT in the evaluation of inflammation. Yet some acute phase proteins, for example, alpha-1 antitrypsin, fibrinogen and coagulation factors, and complement factors, serve a role in specific diagnoses.[9]

C-reactive protein (CRP) test: CRP is an acute-phase reactant protein synthesized by the liver; and the level rises in response to inflammation. CRP has both pro-inflammatory and anti-inflammatory properties,[14] and it plays a role in the recognition and clearance of foreign pathogens and damaged cells. It can activate the classic complement pathway and also activate phagocytic cells to expedite the removal of cellular debris and damaged or apoptotic cells and foreign pathogens. This can become pathologic, however, when it is activated by autoantibodies displaying the phosphocholine arm in autoimmune processes, such as idiopathic thrombocytopenic purpura (ITP). It can also worsen tissue damage in certain cases by activation of the complement system and thus inflammatory cytokines.[15-17]

The levels of CRP rise and fall rapidly with the onset and removal of the inflammatory stimulus.[14] Persistently elevated CRP levels can be seen in chronic inflammatory conditions such as chronic infections or inflammatory arthritides such as rheumatoid arthritis. Elevated CRP can be due to acute and chronic conditions, which can be of infectious or non-infectious etiology. However, markedly elevated levels of CRP are most often associated with an infectious cause.[18] Trauma can also cause elevations in CRP. More modest elevations tend to be associated with a broader spectrum of etiologies, ranging from sleep disturbances to periodontal disease.[14]

CRP has a narrow range of normal values, usually <3-10 mg/L in the blood, but in patients with infections or inflammatory conditions, levels can rise several hundred-fold.[19,20] CRP is also a useful measure because concentrations change rapidly within the first 6–8 hours after injury, peak after 48 hours, and return to normal levels once the issue has resolved.[20] Some studies indicate that high serial CRP measurements in hospitalized patients may be associated with poor outcomes in those who are critically ill.[11]

High-sensitivity CRP test: High-sensitivity CRP is a much more sensitive form of the standard CRP test. Small increases in the baseline levels of CRP, typically between 1 and 3 mg/L, that are only detectable with a high sensitivity CRP test are early signs of certain diseases, especially cardiovascular conditions including atherosclerosis and neurological degeneration.[21,22] Elevated high-sensitivity CRP results are frequently observed prior to cases of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death in otherwise healthy people.[23,24] They are also indicative of recurring incidents and death in patients with acute or stable coronary conditions across most other measures of coronary health (e.g., LDL cholesterol, blood pressure, etc.).[23]

Methods of CRP/hs-CRP determination: With time, the techniques used to detect CRP have evolved.[25] Earlier, CRP was detected based on antigen–antibody interaction using precipitation and agglutination reactions. Later on, CRP enzymatic assays (ELISA) came into existence, which were further modified by integration of an antigen-antibody detection system with surface plasma spectroscopy. Then followed electrochemical biosensors where nanomaterials were used to make a highly sensitive and portable detection system based on silicon nanowire, metal-oxide-semiconductor field-effect transistor/bipolar junction transistor, ZnS

nanoparticle, aptamer, field emission transmitter, vertical flow immunoassay, etc.[25]

Interpretation of CRP levels:

< 0.3 mg/dL: Normal (level seen in most healthy adults).

0.3 - 1.0 mg/dL: Normal or minor elevation (can be seen in obesity, pregnancy, depression, diabetes, common cold, gingivitis, periodontitis, sedentary lifestyle, cigarette smoking, and genetic polymorphisms).

1.0 - 10.0 mg/dL: Moderate elevation (systemic inflammation such as RA, SLE, or other autoimmune diseases, malignancies, myocardial infarction, pancreatitis, bronchitis).

>10.0 mg/dL: Marked elevation (acute bacterial infections, viral infections, systemic vasculitis, and major trauma).

>50.0 mg/dL: Severe elevation (acute bacterial infections).[14]

Interfering factors: Certain factors have been found to interfere with CRP results.[14] These include certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), statins, and magnesium supplements, which have been found to falsely decrease CRP levels. Recent injury or illness can falsely elevate CRP, especially when using this test for cardiac risk stratification. Similarly, mild elevations in CRP can be seen without any systemic or inflammatory disease in certain cases. And obesity, insomnia, depression, smoking, and diabetes can all contribute to mild elevations in CRP.

Erythrocyte sedimentation rate (ESR): The ESR measures the rate at which the red blood cells separate from the plasma and fall to the bottom of a test tube.[9] Thus, ESR is an indirect measure of plasma protein concentrations.[10] The rate is measured in millimeters per hour (mm/hr). The normal range for ESR is 0-22 mm/hr for men and 0-29 mm/hr for women.[9] This is easy to measure as there will be a number of millimeters of clear liquid at the top of the red blood after one hour. If certain proteins cover red cells, these will stick to each other and cause the red cells to fall more quickly. So, a high ESR indicates that one has some inflammation, somewhere in the body.

Levels of ESR are generally higher in females. The level also increases with age.[10] ESR is also influenced by a number of disease states. Because the ESR depends on several proteins with varying half-lives, the rate rises and falls more slowly than do CRP concentrations.[19,26] Although CRP measurements are considered a better marker for inflammation compared to ESR values, the ESR test remains useful in the diagnosis of select conditions, particularly general bone lesions and osteomyelitis.[19,27]

Plasma viscosity (PV): Plasma viscosity is measured by calculating the force needed to send plasma down a thin tube in a given time. Normal plasma viscosity is around 1.3-1.7mPas (millipascal second). The higher the result, the more viscous (or "thicker") the blood is. Increased levels of protein in the plasma (liquid) part of the blood make the blood thicker. Plasma viscosity can be used as an indirect measure of the amount of inflammation in the body. It can also detect the presence of abnormal paraproteins, which can be produced by certain types of tumors. Increased blood levels of certain proteins, such as fibrinogen (which is increased in inflammation) or immunoglobulins (which are increased in inflammation or secreted by some tumors) cause the plasma viscosity to rise.[28] However, it is more difficult to perform and hence not as widely used as ESR testing.[9]

Procalcitonin (PCT): PCT is a newer marker of inflammation that may in certain cases identify or exclude bacterial infections and guide antibacterial treatments.[12, 13] The release of PCT into the body's circulation is most often induced by bacterial infection; however, other causes, including severe viral infection, pancreatitis, tissue trauma, and certain autoimmune disorders can also increase PCT.[12, 13] PCT elevations are not usually associated with bacterial colonization, localized bacterial infection, or allergic responses.[13] Increased PCT levels have a high positive predictive value in the diagnosis of sepsis, and normal levels have a high negative predictive value.[13] PCT measurements can also be used to help personalize treatment, manage antibiotic prescriptions, and reduce antibiotic exposure, which has prompted the U.S. Food and Drug Administration (FDA) to approve the use of PCT testing to guide antibiotic use in patients with acute respiratory illnesses.[12]

Interfering factors: Although procalcitonin assays have shown promising results over the years, there are still several limitations. For example, it has been shown that PCT serum levels can also become elevated among patients during times of noninfectious conditions, such as with trauma, burns, carcinomas (medullary C-cell, small cell lung, & bronchial carcinoid), immunomodulator therapy that increase proinflammatory cytokines, cardiogenic shock, first two days of a neonate's life, during peritoneal dialysis treatment, and in cirrhotic patients (Child-Pugh Class C). PCT levels have also falsely elevated in patients suffering from various degrees of chronic kidney disease. Thus, it is vital for the clinician to rule out the above scenarios to ensure there are no confounding issues that may be obscuring the PCT measurements.[29,30]

Conclusion

The currently used tests for inflammation are majorly nonspecific and hence clinicians need additional tests for diagnosis of chronic inflammations affecting different organs — heart, lungs, pancreas, liver, intestines, etc. We hope with advancements in omics technologies, more specific biomarkers will be developed that could help clinicians to easily diagnose diseases associated with inflammation.

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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.

Testing for Inflammation

JULY 2023 *[This form may be photocopied. It is no longer valid for CEUs after January 31, 2025.]*

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: ○ X

1. **Inflammation is triggered when**
   - A. Tissues are injured
   - B. Tissues are infected by microbes
   - C. Both A and B
   - D. None of the above
2. **Which type of inflammation lasts from 2 to 6 weeks?**
   - A. Subacute
   - B. Chronic
   - C. Acute
   - D. None of the above
3. **The process of inflammation is initiated with the presence of**
   - A. Mediators
   - B. Inducers
   - C. Effectors
   - D. Sensors
4. **Cytokines, histamine, bradykinin, and prostaglandins are examples of**
   - A. Mediators
   - B. Inducers
   - C. Effectors
   - D. Sensors
5. **_____ are the tissues and cells in the inflammatory process.**
   - A. Mediators
   - B. Inducers
   - C. Effectors
   - D. Sensors
6. **Chronic inflammation is initiated when _____ and _____ move to the site of inflammation.**
   - A. Macrophages; T-cells
   - B. T-cells; neutrophils
   - C. Macrophages; neutrophils
   - D. T-lymphocytes; plasma cells
7. **The effects of _____ inflammation vary with the cause of the injury and the ability of the body to repair and overcome the damage.**
   - A. Chronic
   - B. Acute
   - C. Subacute
   - D. None of the above
8. **What percentage of deaths are being attributed to systemic chronic inflammation (SCI)?**
   - A. 10%
   - B. 20%
   - C. 50%
   - D. 80%
9. **SCI does not increase the risk of many noncommunicable diseases.**
   - A. True
   - B. False
10. **Common tests used to measure inflammation include**
    - A. CRP and PCT
    - B. ESR
    - C. PV
    - D. All of the above
11. **There are a number of other markers of inflammation, but high cost, limited availability, and lack of standardization limits their usage.**
    - A. True
    - B. False
12. **_____ is an additional acute phase protein that can serve a role in certain specific diagnoses.**
    - A. Ceruloplasmin
    - B. Hepcidin
    - C. Alpha-1 antitrypsin
    - D. Amyloid A
13. **_____ is made by the liver and can activate the classic complement pathway and phagocytic cells.**
    - A. Ceruloplasmin
    - B. Cytokine
    - C. PCT
    - D. CRP
14. **Marked elevated levels of CRP are most often associated with a(n)_____.**
    - A. Injury
    - B. Infectious agent
    - C. Autoimmune disease
    - D. Respiratory disease
15. **_____ is useful in detecting early signs of certain diseases that produce inflammation.**
    - A. Low-sensitivity CRP
    - B. High-sensitivity CRP
    - C. PCT
    - D. High-sensitivity PCT
16. **Which medication(s) can falsely increase CRP levels?**
    - A. Magnesium supplements
    - B. NSAIDs
    - C. Statins
    - D. All of the above
17. **The ESR test remains most useful for aiding in the diagnosis of**
    - A. Heart attack and stroke
    - B. Bone lesions and osteomyelitis
    - C. Autoimmune diseases
    - D. Acute injury
18. **Increased levels of _____ will be elevated by high levels of fibrinogen or immunoglobulins.**
    - A. PV
    - B. Ceruloplasmin
    - C. ESR
    - D. PCT
19. **_____ is used to identify or exclude bacterial infections and guide antibacterial treatments.**
    - A. PV
    - B. CRP
    - C. ESR
    - D. PCT
20. **Procalcitonin assays have limitations where the levels can also become elevated in certain noninfectious conditions, such as trauma, burns, and carcinomas.**
    - A. True
    - B. False

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. The certificate is automatically awarded with a passing online test score.

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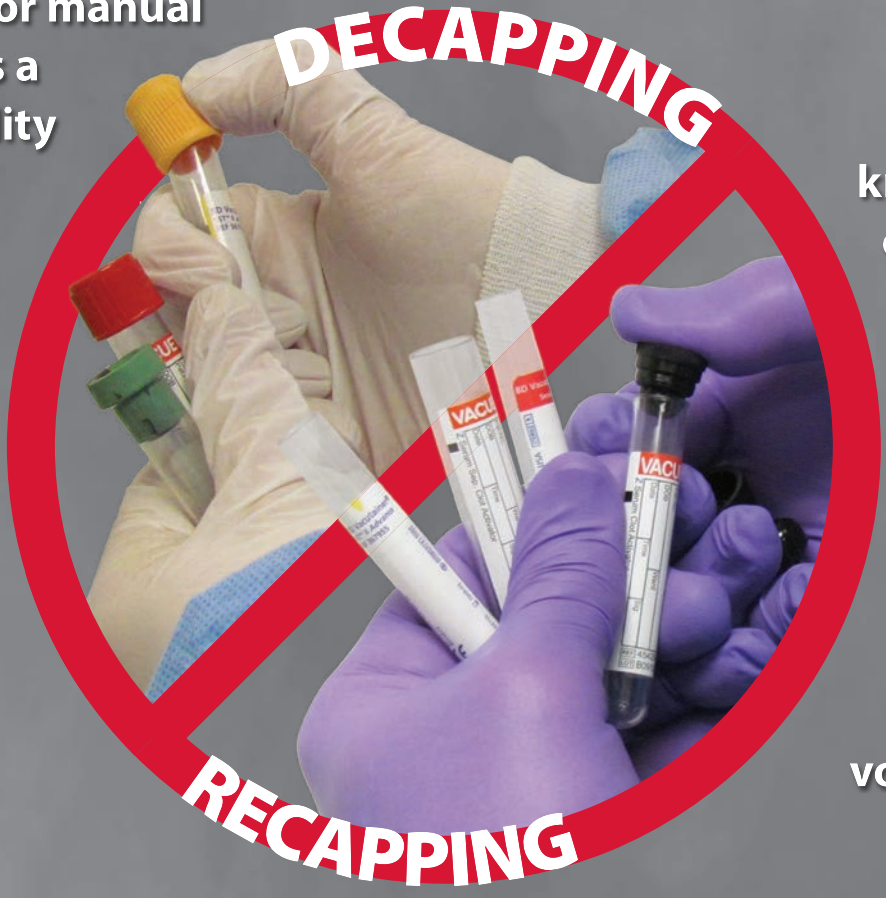

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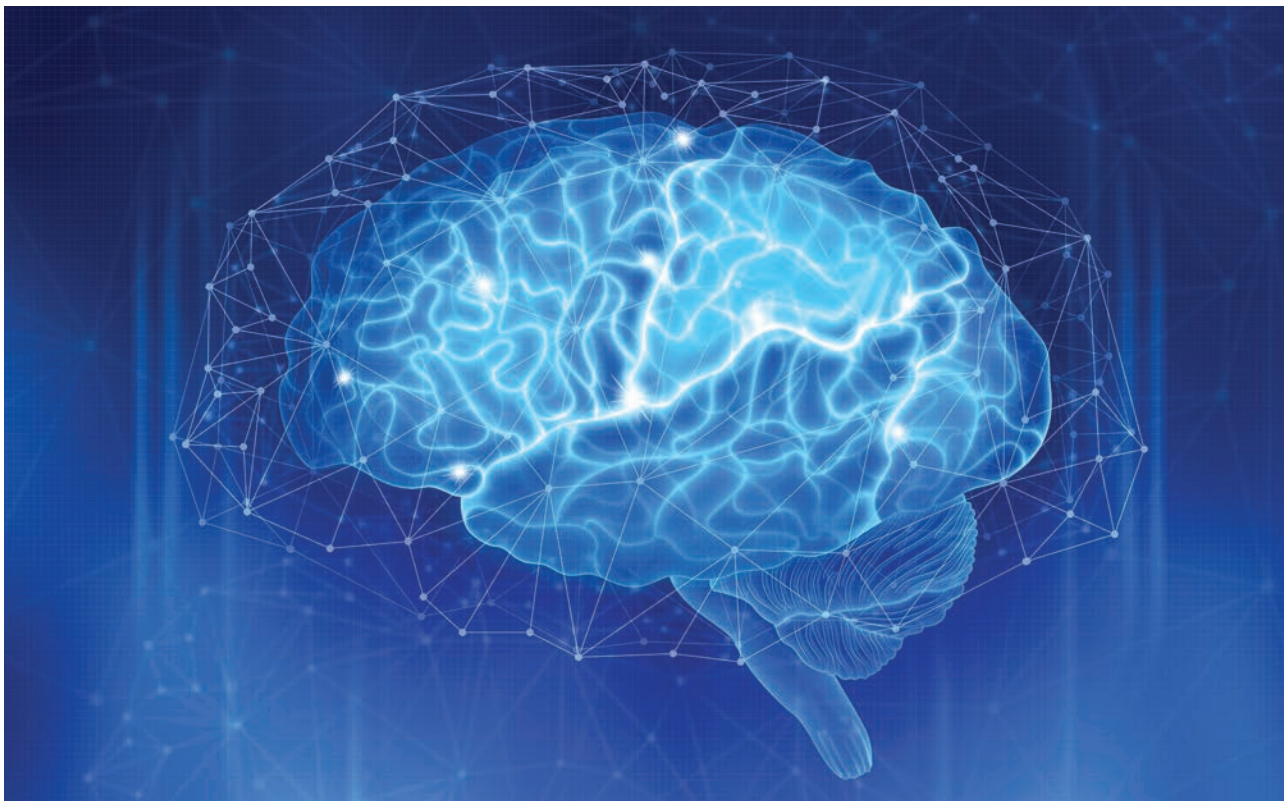

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Blood-based biomarkers challenge the standard approach for evaluation of traumatic brain injury (TBI) in acute care settings

By Madeline Leafblad, MLS(ASCP)CM; Jaime Marino, MD; Beth McQuiston, MD, RD

There are approximately 69 million traumatic brain injuries (TBI) in the world every year.[1] It is the leading cause of death and long-term disability among all trauma related injuries.[1] Accidental falls, motor vehicle accidents, being hit with or against an object, and physical violence are the most common causes of TBI.[2] Contrary to popular belief, sports-related concussions are not the most frequent cause— these account for only 3% of all TBIs.[2] The evaluation of these patients comes with many challenges for caretakers in the emergency department including the lack of simple, rapid, and objective tools to evaluate these patients. Subjective symptoms, neurologic assessment, and computerized tomography (CT) of the head are the main sources of information to determine the diagnosis and course of action.[3]

The neurologic assessment may become difficult due to confounding factors, such as baseline conditions, as well as concomitant drugs and alcohol use.[4,5] Most of the symptoms (headache, dizziness, confusion) are not sensitive or specific for TBI.[4,5] The Glasgow Coma Score (GCS) is commonly used for evaluation and classification of severity of TBI.[6] Depending on the GCS score, TBIs are classified in mild, moderate, and severe, GCS 13–15, 9–12, and 3–8, respectively.[7] The head CT is usually performed without contrast.[6] The standard clinical interview and CT do not have a high sensitivity for mild traumatic brain injury (mTBI)[8] — commonly referred to as concussion. Moreover, the diagnosis of mTBI might be missed in over 50% of cases.[9] Importantly, overutilization of CT scans has *not* provided better patient outcomes. Most mTBI patients presenting to the emergency department will receive a CT scan, however, less than 10% of these scans will demonstrate any findings related to trauma.[7] This overutilization of CTs provides unnecessary radiation exposure to patients, prolongs patient stays, and decreases scanner availability.[7,10] Furthermore, wide gaps and variability in both patient education and follow-up upon discharge exist. Disease state information provided at discharge has been estimated between 19% to 72% with only 22% to 58% of patients receiving any type of follow-up care.[11]

Clinical decision rules (CDR) such as the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC) National Emergency X-Radiography Utilization Study II have been created to mitigate some of these challenges. However, the implementation of these rules and guidelines has not been standardized and globally accepted. Interestingly, surveys have shown, for various reasons, that clinicians do not always feel comfortable using clinical decision rules.[13,14]

A promising approach to significantly improve TBI evaluation and treatment in ED settings lies within utilization of blood-based biomarkers—specifically those originating from the brain. Brain biomarkers detected in biofluid are representative of the complex array of pathophysiological processes that

occur following brain injury. A complete, broad comprehension of these processes is imperative for further development of therapies. Fortunately, the scientific advancements presented within the last decade have dramatically increased this level of understanding.[15]

Currently, the pathophysiological processes in TBI depicted by brain biomarkers include injury to the dendrites, neuronal cell body, myelin, synapses, and astroglia[16-19] due to direct injury, vascular stretch and/or neuroinflammation.[20,21] The biomarkers reach the peripheral blood via various mechanisms including disruption of the blood–brain barrier and via the glymphatic system.[22]

Many brain biomarkers have been investigated as an objective tool to aid the assessment of patients with suspected traumatic brain injury.[15] Characteristics of the ideal blood-based biomarker candidate(s) include measurability in the peripheral blood and ability to capture TBI severity. In addition, these brain proteins should be highly brain specific and correlate with TBI prognosis.[15] A wide variety of brain markers of neuronal and astrocytic/glial origin have been assessed as potential candidates. In the last decade, the S100β protein was included in some evaluation protocols for mTBI patients in Nordic and other European countries.[23] However, due to the low specificity of this protein as a brain biomarker, its implementation has been limited as this protein is also present in adipocytes, musculoskeletal cells, and melanocytes.[15]

As research has progressed, two promising acute biomarkers, Glial Fibrillar Acid Protein (GFAP) and C-terminal Ubiquitin L1 Hydrolase (UCH-L1), have been identified and U.S. Food and Drug Administration (FDA) cleared in the evaluation of mTBI patients. GFAP is a glial protein, part of the cytoskeleton of astrocytes and is present in the gray and white matter of the brain.[24] It supports the cell and blood brain barrier.[24] UCH-L1 is a specific protein in the cytoplasm of neurons, constituting up to 2% of total brain proteins.[24] A portion of this protein is also found in axons, which highlights its importance in signal transport and neuronal metabolism in the brain.[24]

UCH-L1 and GFAP levels are measurable in peripheral blood within the first hour after trauma.[12] UCH-L1 levels elevate immediately following injury, whereas GFAP levels tend to peak several hours later.[12] Both values decrease over time, however, GFAP values can remain elevated beyond seventy-two hours.[13] The difference in origin and the kinetics of these two proteins underscore the importance of measuring both in mTBI patients after acute injury. Of note, Papa et al. showed that GFAP and UCH-L1 elevations may detect intracranial lesions.[12] This study also highlighted how UCH-L1 performed best in the first hours after the trauma.[12] Both plasma and GFAP and UCH-L1 have demonstrated the ability to predict incomplete recovery after injury.[24]

Furthermore, plasma GFAP concentrations showed discrimination between CT negative and MRI (magnetic resonance imaging) positive vs. MRI negative scans when the samples were collected within 24 hours after injury.[26] A "Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK- TBI)" publication demonstrated that GFAP outperformed S100β in its ability to predict intracranial lesions in a CT scan across all severities of TBI.[27] Notably, 73% and 56% of mTBI, GCS 15, with a negative CT still had incomplete recovery at 2 weeks and 6 months after the injury, respectively.[28] A CT Scan model studied by Zimmer, et al, showed a reduction in the amount of CT scans compared to S100β.[29]

These biomarkers have been cleared for clinical use in the United States by the FDA as well as in other regulatory agencies around the world as an aid in ruling out intracranial lesions in mTBI, GCS 13–15, in patients 18 or older who are evaluated within 12 hours from injury by Banyan, 2018,[30] Abbott Point of Care, 2021,[31] and Abbott Core Diagnostics, 2023.[32] Currently, several European countries are reviewing incorporating these blood tests into their local guidelines. In 2022, the French Society for Emergency Medicine (SFMU) updated the "Management of Adult Patients with Mild Traumatic Brain Injury" to include the role of biomarkers in the assessment and management of ED patients with mild TBI.[33] To reduce the number of CT scans, these professional practice recommendations advise running a blood test combining UCH-L1 and GFAP within 12 hours following mTBI for adult patients with intermediate risk.[33] Furthermore, the National Academies of Science, Engineering, and Medicine has favorably reviewed these blood tests and published its Proceedings of a Workshop this year.[34] According to this report, GFAP and UCH-L1 "… are useful in the ED setting in predicting normal CT scans and, if widely implemented, may be able to reduce use of cranial CT."[34]

Implementation of these biomarkers into clinical practice will not only provide objective information to physicians when it matters most but also lays the groundwork for potential use of blood-based biomarkers in diagnosis of TBI,[35] monitoring of patient recovery, and development of treatments for these patients.[34] Clinical utilization of these brain biomarkers has the potential to transform what is currently the standard approach for TBI in acute care settings and helps both clinicians and patients alike.

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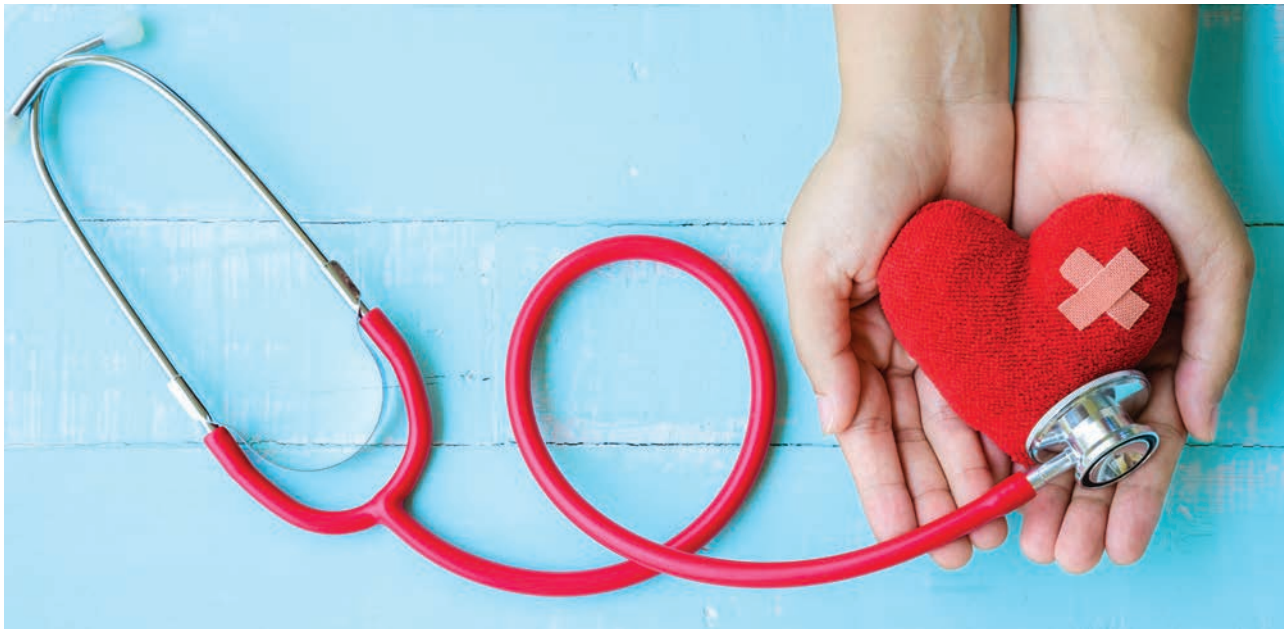

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Natriuretic peptides in heart failure

By Zivjena Vucetic, MD, PhD

Walking up the stairs had become difficult for Louise, an otherwise healthy, active, and stubborn 85-year-old retired nurse. It was spring, and Louise figured that she was deconditioned and out of shape following a particularly snowy winter that kept her from her daily walks. But when she was struggling to breathe just sitting still and sweating on a cool spring day, her family insisted that she go to the emergency department. A short while later, doctors confirmed what she suspected. Louise had had a heart attack. Her left anterior descending artery (LAD), the artery feeding the left ventricle, was 95% blocked, which had caused significant cardiac damage. Louise, like millions of others around the world, now faces a new reality—congestive heart failure.

Statistics and trends

In 2021, medical organizations worldwide convened and proposed a global definition of heart failure "as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion."[1] Simply, heart failure is characterized by inadequate cardiac output that occurs when the cardiac muscle fails to pump enough blood to keep up with the body's needs. Symptoms of heart failure include dyspnea, fatigue, weakness, atrial fibrillation, and pulmonary and peripheral edema.

According to the World Heart Federation, individuals have a 20% lifetime risk of developing heart failure, one of the world's leading causes of hospitalization.[2] Worldwide, there are an estimated 26 to 64 million individuals with heart failure.[3,4] And as the world's population ages, the burden of heart failure is increasing.[2,5] Of course, this heavy burden to human health comes with a financial strain. The global cost of heart failure is expected to rise from 30.7 billion USD in 2012 to 69.8 billion USD in 2030—nearly 40 billion USD in just 18 years.[6]

Even with proper disease management, heart failure has a high mortality rate, with a one-year mortality of up to 30% and a five-year mortality rate of up to 75%.[6] These mortality rates are even higher in low and middle income countries.[2]

Disease causes and progression

Heart failure can occur on both the left and right sides of the heart—left-side heart failure is more common and, over time, can lead to right-side heart failure.[7] Left-sided heart failure is classified into one of three groups based on left ventricular ejection fraction (EF): heart failure with reduced EF (HFrEF) when the EF is ≤40%, heart failure with mildly reduced EF (HFmrEF) when the EF is 41-49%, and heart failure with preserved EF (HFpEF) when the EF is ≥50%.[6,8] (Normal ejection fraction is 55%–65%.) Generally, in HFpEF, the cardiac muscle doesn't fully relax between beats, so it can't fill up with enough blood to pump to the body, but the percentage of what is pumped remains high. Conversely, in HFrEF, the cardiac muscle is too weak to pump out enough blood.[7] HFmrEF, a relatively new category of heart failure, is less understood but shares characteristics of both HFrEF and HFpEF.[9,10] Understanding the type of heart failure is important to understanding disease etiology.[11]

There are a variety of causes of heart failure, with coronary artery disease and heart attack being among the most common. Heart failure can arise over time, as it did in Louise's case. Reduced blood supply to her cardiac muscle led to cardiac weakening, which led to stretching and thickening of the cardiac chambers. When the heart grows in this way, it can't pump efficiently. Conversely, heart failure can occur acutely as a consequence of heart attack where heart muscle dies. In these cases, there may not be enough remaining heart muscle left to properly pump the blood. Other causes include heart valve disease, cardiac infection (myocarditis, usually of viral origin), congenital heart defects, and high blood pressure.[7] Aging, renal disease, unhealthy lifestyle choices such as poor diet, smoking and other drug use, and lack of physical exercise can also lead to weakening and stiffening of the heart.[6,7,12]

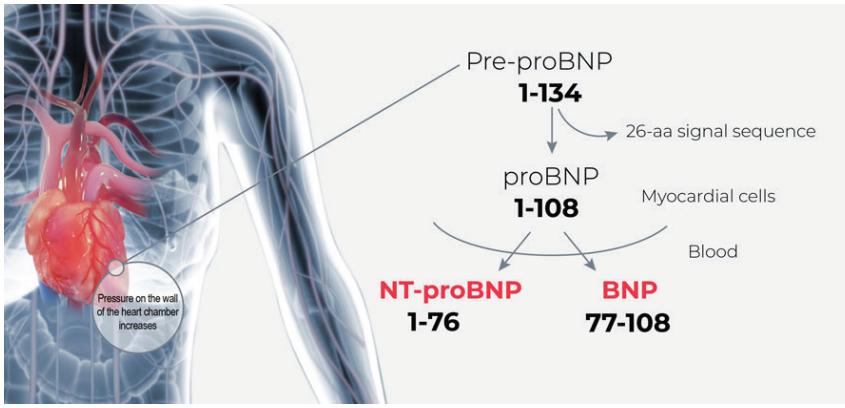

Figure 1.

Although there is an approximately even distribution between men and women,[13] heart failure may present differently between the sexes[12] with an increased prevalence of HFpEF in females and an increased prevalence of heart failure with reduced ejection fraction HFrEF in males.[12,14,15]

Clinically, heart failure presents as a syndrome with typical signs and symptoms including shortness of breath (dyspnea), fluid retention in the extremities (edema), neurologic changes such as confusion, and exhaustion coupled with an underlying cardiac cause.[11] Final diagnosis is based on symptoms, physical findings, electrocardiography and echocardiography, tests for ejection fraction, and blood tests for elevated levels of B-type natriuretic peptides (BNP and NT-proBNP).[11] Regardless of the cause, patient gender, and type of heart failure, monitoring heart failure patients assists in managing symptoms and in aiding clinicians in treatment decisions.

Natriuretic peptides as biomarkers of heart failure

B-type natriuretic peptide (BNP) is a member of a family of endocrine hormones that are well established for use as laboratory tests or biomarkers in diagnosis or exclusion of heart failure and are included in standard of care guidelines for both the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC).[16,17]

BNP is produced as a prohormone, pre-proBNP, in the myocytes of the cardiac ventricles primarily in response to increased myocardial wall stress and pressure overload that can be brought on by conditions such as heart failure.[18–20] Pre-proBNP is cleaved to the precursor peptide, proBNP108, which is subsequently cleaved to form two moieties, the biologically inert 76 amino acid amino-terminal fragment (NT-proBNP) and the biologically active 32 amino acid BNP fragment, in an equimolar ratio.[21] **(See Figure 1.)**

The biologically active BNP plays an important role in the regulation of the cardiovascular system and control of cardiac function, stimulating the kidneys to excrete sodium, which, in turn, affects blood volume and arterial pressure.[22,23] In addition to its role in cardiorenal homeostasis, BNP also reduces vascular resistance and systemic blood pressure, inhibits the renin-angiotensin-aldosterone system, impedes fibrosis, and induces myocardial relaxation.[24,25]

Elevated natriuretic peptide levels help in identifying those who require further cardiac investigation. Circulating concentrations of both BNP and NT-proBNP have been shown to exhibit clinical utility as measurable biomarkers in patients with suspected heart failure or as prognostic tools for those with existing heart failure.[26,27] Patients with higher concentrations of BNP and NT-proBNP have both higher cardiac morbidity and mortality.[28] Thus, measuring BNP and NT-proBNP can aid in the diagnosis, severity assessment, and risk stratification of patients with heart failure as well as risk stratification of patients with acute coronary syndrome.[11]

While both markers are cleared passively by various organs such as the kidneys and liver, BNP is also cleared actively by natriuretic peptide binding receptors and enzyme degradation.[23,25,29] As such, BNP has a shorter half-life than NT-proBNP—approximately 20 minutes versus approximately 60–120 minutes, respectively.

Natriuretic peptides and age

Interpreting natriuretic peptide levels must consider the whole patient. Even in healthy individuals, BNP and NT-proBNP levels increase with age and tend to be higher in women than in men.[27] Values also increase in patients with atrial fibrillation and renal disease[27,30] and decrease in those with obesity.[30]

In an acute care clinical setting, an NT-proBNP value less than 300 pg/mL and a BNP value less than 100 pg/mL are recommended to rule out acute heart failure with a high degree of certainty.[17] (Due to its longer half-life, NT-proBNP values are significantly higher than BNP levels.) Further, use of age-stratified NT-proBNP rule-in thresholds have been shown to improve specificity and positive predictive value (PPV) for diagnosis of heart failure when compared with a single cutoff value.[31–33]

Comorbidities

Heart failure is a complex medical condition that often coexists with other comorbidities. Further, symptoms of heart failure are nonspecific making heart failure diagnosis difficult. Cautious interpretation of natriuretic peptide concentrations is important in the presence of comorbidities including age, obesity, and renal disease, and conditions such as atrial fibrillation. Results should be interpreted considering the total clinical presentation of the patient, including symptoms, clinical history, data from additional tests, and other appropriate information. For example, obesity may lower NT-proBNP concentrations, while impaired renal function may raise them.[16]

Heart failure treatments

There are many facets to heart failure treatment. Lifestyle changes include changing diet to increase fiber-rich foods and lowering sugar, salt, caffeine, and alcohol intake. Adding physician-approved exercises can also improve heart failure signs and symptoms. BNP and NT-proBNP are helpful in guiding treatment of heart failure. When treatment is effective, the ventricles shrink, the muscle recovers from stretch, and lower levels of BNP are produced.

Medications such as angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and diuretics may be prescribed to dilate blood vessels, slow heart rate, and reduce fluid, respectively. A newer class of heart failure medicines, Angiotensin Receptor-Neprilysin Inhibitor (ARNi) drugs, is a combination of two drugs—one that blocks angiotensin II and one that breaks down BNP. ARNi drug therapy is designed to dilate blood vessels (angiotensin receptor blocker) and reduce work on the heart (neprilysin inhibitor that aids in sodium removal and blood vessel dilation). Early

in ARNi therapy, BNP levels have been shown to increase,[34,35] which may make NT-proBNP monitoring more useful in these patients.[35]

Depending on the severity and etiology of the heart failure, a surgical procedure may be required. Removing arterial blockage and repairing damaged heart valves can improve blood flow within the heart and around the body. Implantable devices, pacemakers and defibrillators, can help with cardiac resynchronization, pacing the heart, and ensuring that dangerous cardiac rhythms are corrected. In situations where the heart damage is severe, patients may require heart transplant. When necessary, ventricular assist devices, mechanical pumping devices, may be used to help pump blood in those awaiting heart transplant.

Closing

It's been eight years since Louise's heart attack. With a change in lifestyle, improvement to diet and exercise, and regular monitoring of her natriuretic peptide levels and pacemaker battery level, she is now an active 93-year-old living her life to the fullest.

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Molecular testing ushers in a new era of rapid diagnostics for pharyngitis

By Jane M. Caldwell, PhD, Bobby L. Boyanton Jr., MD

Acute pharyngitis "sore throat" is an inflammatory condition of the pharynx and/or tonsils commonly observed in both adults and children. Viruses are primarily responsible, but bacteria are also implicated. Infection with beta-hemolytic *Streptococcus pyogenes*, or Group A streptococcus (GAS), accounts for 5%–15% and 20%–30% of infections in adults and children worldwide, respectively. Acute pharyngitis is one of the most common reasons for primary care visits[1] and is the most common diagnosis linked to antibiotic use in school-aged children.[2] Antibiotics are ineffective against viral pharyngitis and do not shorten illness duration or improve patient outcomes. Because throat culture takes up to 48 hours to produce actionable results, clinicians may preemptively prescribe antibiotics "just in case" the infection is due to GAS. This practice leads to unnecessary antibiotic use and the promotion of bacterial resistance. According to a recent study, it is estimated that nearly half of antibiotic prescriptions for pharyngitis are unnecessary because most infections are of viral origin.[3] This practice also wastes healthcare resources and unnecessarily subjects patients to antibiotic-associated side effects. Moreover, other pathogenic bacteria may be responsible for the infection and these may not be responsive to conventional GAS therapy. Rapid, accurate, and reliable testing solutions are needed to provide timely patient information during the clinician office visit. State-of-the-art nucleic acid amplification tests (NAAT) can fulfill this need and have the potential to improve antimicrobial stewardship.[3] This article will address the complexities of acute pharyngitis diagnosis and treatment and summarize emerging clinical data pointing to the advantages of NAAT over present testing recommendations.

Present testing guidelines for pharyngitis

Current guidelines for the diagnosis and management of GAS pharyngitis were released by the Infectious Diseases Society of America (IDSA) in 2012.[4] For children ≥ 3 years of age, testing should consist of a rapid antigen detection test (RADT) or throat culture.[4] Due to variable sensitivity of RADTs, throat culture is recommended for children and adolescents with a negative RADT. Due to the high specificity of RADTs, throat culture is not recommended for a positive RADT.[4] Furthermore, the IDSA advises against routine GAS testing for patients <3 years of age as the incidence of GAS pharyngitis and rheumatic fever are rare in this population.[4,5] The IDSA also advises against GAS testing in individuals without pharyngitis or pharyngitis associated with viral symptoms to prevent false positive results due to GAS colonization.[4,5] Viral symptoms include cough, runny nose, hoarseness, oral ulcers, conjunctivitis, and/or diarrhea.[4] Testing outside of these recommendations leads to spurious test results, misdiagnoses, medication side effects, and promotion of antibiotic resistance.[6-10] Nearly three decades ago, it was noted that approximately 70% of patients with sore throats seen in the primary care setting received antibiotic prescriptions.[11] Recently, a retrospective cohort study found that nearly 40% of pediatric patients tested for GAS were not compliant with IDSA guidelines.[5] This translated into greater return rates for patients, misdiagnoses, inappropriate antibiotic use, allergic reactions and loss of school days.[5]

Antigen and culture testing

The gold standard test for pharyngitis, developed over 70 years ago, is throat culture for the isolation of beta-hemolytic GAS

Table 1: Performance of CLIA-waived NAATs for Detection of GAS vs. Culture Reference Method

Reference	Technology	TAT (minutes)	Sensitivity (%)	Specificity (%)
Faron (2015)[24]	iNAA	60	98.3	93.2
Cohen (2015)[25]	iNAA	8-10	96.0	94.6
Ralph (2018)[26]	PCR	18-25	100.0	79.3
Parker (2019)[7]	PCR*	18-25	100.0	97.4
Ferrieri (2021)[27]	PCR	18-25	100.0	83.5
Taylor (2021)[28]	PCR	18-25	100.0	90.4

TAT, turn-around time; **PCR,** real-time polymerase chain reaction; **iNAA,** isothermal nucleic acid ampification
*Two different PCR tests were utilized and yielded identical performance

on sheep blood agar.[12,13] Culture has a turnaround time of 24 to 48 hours, which markedly delays timely diagnosis and patient management. Despite being the gold standard, culture is not without limitations. The quality of specimen collection is critical for optimal test results. A study investigating dual throat swab collection found that utilization of a single swab would have missed 9% to 12% of positives.[14] Following specimen collection, throat swabs should be placed into transport media (e.g., Amies) and expeditiously delivered to the laboratory. Transportation delays >24 hours decrease bacteria viability and increase the chance of false negative test results. Technical expertise is required of laboratory personnel to appropriately cultivate and identify GAS. More importantly, culture does not have the ability to distinguish between infection and colonization. As such, cultivating GAS should never clinically equate to active infection.

Rapid antigen diagnostic tests (RADTs) for GAS were developed over 40 years ago for use at the point-of-care (POC) or within clinical laboratories.[15] Various RADT formats are available for use, including latex agglutination, lateral flow immunoassay, and optical immunoassay.[13] GAS RADT specificity is approximately 95%. As such, culture for positive RADTs is not warranted. However, GAS RADT sensitivity is insufficient for stand-alone testing. Systemic reviews and meta-analyses estimate the GAS RADT pooled sensitivity at 85% (range 70%–90%).[4,16-18] As such, culture is recommended for children and adolescents with a negative RADT result. RADTs also have limitations. A poorly collected sample may contain suboptimal quantities of GAS, which decreases test sensitivity and leads to false negative test results. Some RADTs allow the throat swab to be placed into liquid transport media so that culture can be performed if the RADT is negative. This workflow dilutes the concentration of GAS leading to decreased test sensitivity and false negative RADT results. RADTs rely upon the operator to observe and properly interpret the presence/absence of agglutination, color changes, and/or the presence of detection lines in test strips.[13] These human-related tasks introduce intra- and inter-operator bias and inconsistent test results. Bias is further compounded when considering each operator's visual acuity and degree of color blindness (if present), and the quality of ambient lighting where testing is performed. Some manufacturers have employed optical reading devices to mitigate human interpretative bias. An overlooked limitation of RADTs is their inability to distinguish between colonization and active or past infection. By design, RADTs detect one or more GAS-specific bacterial proteins. A mere positive result does not always equate to active infection. Lastly, at present, commercially available pharyngitis RADTs only detect GAS.

Molecular testing — Technological advancements and supporting clinical data

Molecular testing solutions have undergone significant improvements over the last few decades. Initially, such testing used a chemiluminescent-labeled DNA probe directed at a GAS-specific ribosomal RNA (rRNA) sequence. When compared to culture, this test yielded excellent sensitivity (95%) and specificity (100%).[19] However, slow turnaround times and technical limitations, precluded its use into the POC setting. The next decade witnessed the transition from manual to semi- or fully automated DNA extraction and nucleic acid amplification technologies. Although not suitable for the POC setting, these moderate-to-high complexity tests replaced culture for negative RADTs, greatly reducing the turnaround time for definitive results. A study of 2,050 patients in an urgent care setting with negative GAS RADT results demonstrated excellent test sensitivity (91.4%) and specificity (98.5%) for an isothermal amplification test when compared to culture. The authors' highlighted the ability to use this test as a quicker alternative to culture for negative GAS RADTs.[20] A study of 161 patients with negative GAS RADT results showed exceptional test sensitivity (100%) and specificity (100%) of a PCR test when compared to culture. The turnaround time of PCR was 18.1 hours compared to 45.0 hours for culture.[21] In the last decade, further nucleic acid extraction and amplification technology advancements have provided a definitive path to enter the POC arena. These include both rapid real-time PCR and isothermal nucleic acid amplification (iNAA) technologies. In general, iNAA yields faster, more cost-effective test results by negating the need for iterative heating and cooling on an expensive thermocycler — a requirement of real-time PCR. Presently, commercially available iNAA technologies amplify and detect one or two nucleic acid targets. In contrast, high-level multiplexing (≥4 targets) is already available with real-time PCR. Improved multiplexing capabilities is possible with iNAA,22,23 and will likely be a requisite to meet the growing demands of the rapidly expanding molecular POC testing market.

To date, several NAATs have received FDA-approval and CLIA-waived status allowing their use in the POC setting (**Table 1**). Two recent studies (1,673 symptomatic patients) demonstrated excellent test sensitivity (>96%) and specificity (>93%) for two different iNAA assays when compared to culture.[24,25] A smaller study (145 symptomatic patients) demonstrated excellent test

Table 2: Non-Group A Streptococal Bacterial Associated with Pharyngitis

Microorganism	Typical Patient Demographics	Associated Disease(s)
Atypical Bacteria[4,35]		
Chlamydia pneumoniae ***Mycoplasma pneumoniae***	All ages but most common 5-20 years	Pharyngitis, pneumonia, bronchitis
Groups C/G Streptococci[12,21,31,33]		
Streptococcus dysgalactiae ***Streptococcus equisimilis*** ***Streptococcus equi*** ***Streptococcus zooepidemicus***	College students and adults; epidemic food-borne pharyngitis due to the consumption of unpasteurized milk products, goat cheese, pork or contact with horses; outbreaks in families and school-aged children	Pharyngitis, pharyngotonsillitis
Other Bacteria[4]		
Arcanobacterium haemolyticum	Teenagers and young adults	Pharyngitis, scarlantiniform rash
Corynebacterium diphtheriae	Unvaccinated individuals; children and older adults living in endemic areas	Pharyngitis, diphtheria
Fusobacterium necrophorum	Adolescents and young adults	Recurrent/persistent pharyngitis, Lemierre's syndrome, peritonsillar abscess
Neisseria gonorrhoeae	Sexually active persons; sexual abuse	Pharyngitis, pharyngotonsillitis

sensitivity (100%) and good specificity (79.3%) of a real-time PCR test when compared to culture. Lower molecular test specificity was due to increased detection of GAS that was likely below culture detection threshold.[26] Three additional studies (648 symptomatic patients) demonstrated excellent test sensitivity (100%) and good-to-excellent specificity (83.5%–97.4%) of rapid real-time PCR when compared to culture.[7,27-28] To expedite accurate diagnosis and reduce unnecessary antibiotic use, the authors recommended replacing RADTs and culture with molecular tests.[7] Another group recently recommended that rapid real-time PCR be used as first-line testing for GAS.[28] Authors of a recent study, whose laboratories collectively served two pediatric hospitals and eight urgent care centers, noted that molecular testing provided definitive results in a timely manner without the need for back-up culture.[29] These tests offer turnaround times ranging from 8 to 60 minutes, and test sensitivity and specificity equivalent to and exceeding that of culture and RADTs, respectively. Prior to deployment in the POC setting, these molecular solutions should be vetted with appropriate stakeholders to ensure turnaround time constraints will not adversely affect staffing and patient flow.

Molecular testing considerations and concerns

Several issues need consideration prior to adopting NAATs. First, DNA is a highly stable chemical structure and its presence in the testing environment may lead to false positive test results. Adherence to proper specimen handling, unidirectional workflow, frequent glove changes, and environmental decontamination protocols can essentially eliminate this possibility. The incorporation of negative controls into the testing process can also facilitate detection of DNA contamination. Second, DNA polymerases, the enzymes that amplify DNA, are susceptible to interfering substances that may inhibit the nucleic acid amplification reaction. As such, internal amplification controls must be incorporated into the test system to verify that each test performed as expected. In response, manufacturers have developed fail-safe systems using cassettes with minimal pipetting and operator input to reduce human error. Remote instrument monitoring via the internet by laboratory staff and field service engineers is a reality and aids in the real-time monitoring of test and instrument performance. Despite these technological advancements, other challenges still face molecular testing. Due to improved sensitivity over culture, it may be difficult to distinguish colonization from infection. This is relevant in cases of acute pharyngitis where an individual's clinical signs and symptoms favor a viral etiology.[13] The GAS colonization rate can reach 20%–25% in asymptomatic patient populations. Therefore, molecular tests for GAS should only be used on individuals with clinical signs and symptoms supporting a bacterial infection. Another challenge for NAATs is the inability to distinguish between viable from non-viable bacteria or active from resolved infection. In one study, 20% of patients adequately treated for GAS still tested positive by NAAT between 14–18 days after the initial diagnosis.[30] Likewise, NAATs should not be used as a "test-of-cure," especially within the first 14 days after completion of therapy. If clinically indicated, "test-of-cure" should be performed by culture.

Currently, the IDSA guidelines focus upon the diagnosis and treatment of GAS to prevent extension of infection into the head and neck region and prevent immune-mediated complications (rheumatic fever or kidney damage). However, other pathogenic bacteria may be responsible (**Table 2**). Certain beta-hemolytic groups C/G streptococci are considered pathogenic and are detected in 3%–22% of pharyngitis cases;[31-33] these include *S. equi*, *S. dysgalactiae*, *S. equisimilis*, and *S. zooepidemicus*.[12,21,32] *Streptococcus dysgalactiae* is second only to GAS for prevalence in patients symptomatic for pharyngitis (0.85% in patients younger than 15 years and 2.18% of patients older than 15 years; n = 1799).[33] These organisms are primarily seen in college

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students and adults, and associated with epidemic food-borne pharyngitis.[4,34] However, if left untreated, these have not been definitively linked to rheumatic fever or kidney damage.[4] Non-streptococcal bacteria have also been implicated in pharyngitis, including *Fusobacterium necrophorum, Arcanobacterium haemolyticum, Corynebacterium diphtheriae, Neisseria gonorrheae, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*.[4,35] Despite having clinical signs/symptoms similar to GAS and available antibiotic therapy, infections due to Groups C/G streptococci and other non-GAS organisms are not frequently tested at the POC (**Table 2**). Currently, CLIA-waived NAATs for Groups C/G streptococci do not exist. Few CLIA moderate-to-high complexity NAATs are currently available, which largely precludes their use at POC; two of these generate test results in 25 or 60 minutes.[36] Non-streptococcus organisms are only detected in laboratories using specialized cultivation, biochemical, latex agglutination, and/or mass spectrometry-based identification techniques. Development of POC multiplex assays for GAS and non-GAS pathogens could improve patient outcomes.

Cost and reimbursement are additional considerations. Molecular tests are more expensive than RADTs and culture; however, they do not require expensive, skilled labor. Generally, molecular reimbursement is proportionally higher than RADT and culture. Net revenue, reimbursement minus expense, for NAATs generally provides a viable financial path for molecular testing implementation. Molecular also offers rapid, definitive answers that enhance patient management and provides opportunities to improve antibiotic stewardship.[3] Evidence suggests molecular testing results in lower antibiotic usage in individuals with acute pharyngitis.[6,8] Likewise, appropriate antibiotic prescribing was enhanced with molecular POC (97.1%) vs. RADT and culture (87.5%).[8]

Summary

Molecular testing has sufficiently advanced to provide accurate, rapid, and reliable results for the diagnosis of GAS pharyngitis at POC. These user-friendly testing solutions have the potential to improve workflow efficiency, patient satisfaction, clinical outcomes, antibiotic stewardship initiatives, and lower healthcare costs by reducing wait times, return visits, and follow-up calls. In a recent commentary in *Clinical Microbiology and Infection*, the authors summarized as follows, "[Rapid molecular] tests are here to stay. They are being used now, and they will be used more frequently as clinicians become comfortable with molecular testing for GAS and many other infectious diseases. Published data for the diagnostic accuracy of these tests is growing but it is important that the appropriate clinical context and setting to perform these tests be considered and evaluated."[14] The final frontier for widespread POC molecular testing deployment is speed. The majority of healthcare professionals working in busy outpatient clinics define "rapid" as ≤ 15 minutes (author's professional opinion); a metric critical for patient management and clinic operational efficiency. Today, a handful of manufacturers offer FDA-approved, CLIA-waived rapid POC molecular testing solutions. Of these, only one generates results in ≤ 10 minutes. Over the next few years, additional POC molecular technological advancements will facilitate enhanced multiplexing capabilities in conjunction with test result generation in 5–10 minutes. We are now entering the ultra-rapid NAAT era.

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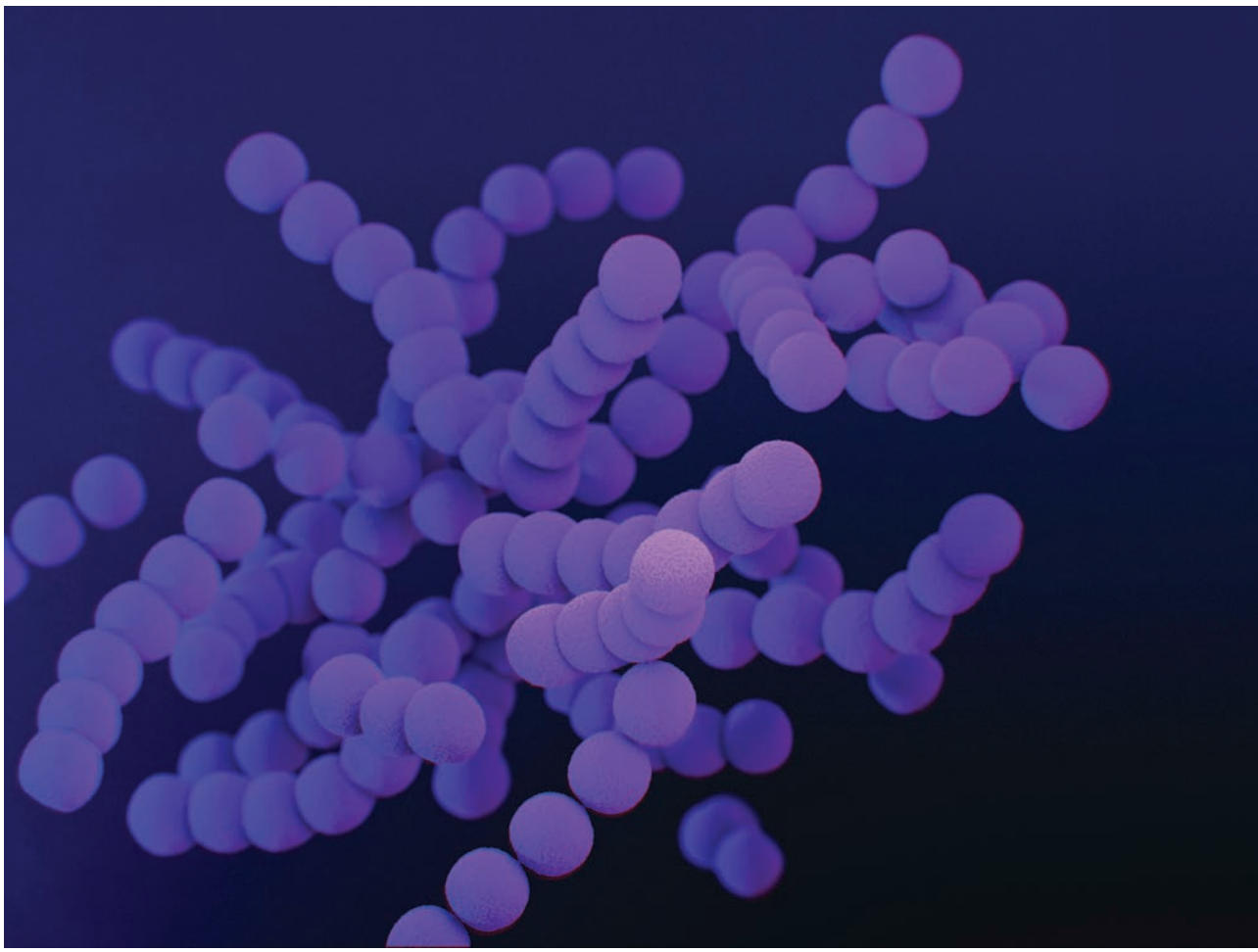

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Group B streptococcus: Beyond pregnancy and neonatal infections

By Nicholas M. Moore, PhD, D(ABMM), MLS(ASCP)cm

Streptococcus agalactiae, also known as Group B streptococcus (GBS), is a gram-positive coccus that was first differentiated from other beta-hemolytic streptococcal species by renowned microbiologist Rebecca Lancefield, PhD, in the early 1930s.[1] Her seminal work established the Lancefield grouping based on an immunologic reaction of carbohydrate antigens expressed on the bacterial cell wall. Serogrouping of the C-carbohydrate expressed by beta-hemolytic streptococci has remained useful for rapid identification and patient management even in the era of advanced identification methods, e.g., matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF).

Upon its first recognition in 1917, GBS has remained a significant cause of bovine mastitis in cattle.[2] Despite being initially regarded as an animal pathogen, it can cause a variety of infections in human hosts. GBS easily colonizes the genitourinary and gastrointestinal tracts in humans. It can also colonize the upper respiratory tract, but to a lesser extent.

In 1996, the Centers for Disease Control and Prevention (CDC), in collaboration with key stakeholders and several professional societies published the first guidelines on preventing GBS disease. These guidelines were subsequently updated in 2002 and again in 2010.[3] As a result of screening and intervention, the incidence of GBS disease declined substantially.[4] In 2019, the CDC assigned ownership of guideline components to three professional organizations: The American Academy of Obstetrics and Gynecology (ACOG) and the American Academy of Pediatrics are responsible for guidelines related to the prophylaxis and treatment of GBS in pregnant women and newborns, respectively, while the American Society for Microbiology (ASM) is charged with updating guidelines and best-practices related to the detection and identification of GBS.[5-7]

Epidemiology of Group B streptococcal infections in the United States

In many state public health jurisdictions, reporting of GBS infections is not required. Beginning in the late 1990s, the CDC began active surveillance for GBS through the Active Bacterial Core surveillance (ABCs) network.[8] The ABCs is a multistate, population-based surveillance system for invasive bacterial pathogens, including GBS. The ABCs are an integral component of the Emerging Infections Program[9] within the Division of

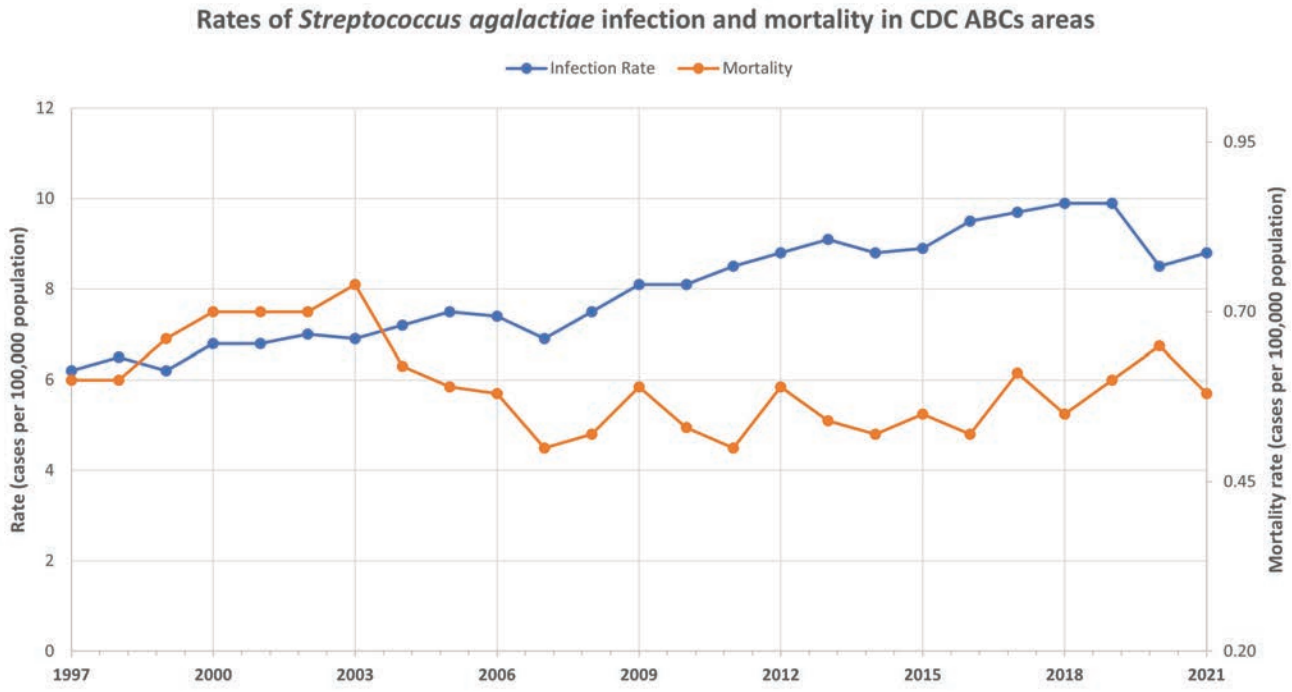

Figure 1.

Preparedness and Emerging Infections. This program spans six states and four multi-county areas in additional states covering a population of nearly 45 million people.

Since the ABCs began tracking GBS in 1997, the overall rate of GBS has increased 42% from 6.2 per 100,000 to 8.8 per 100,000 in 2021, the last year of data currently available. Despite the increase in number of cases, the mortality rate has remained stable during this time period (**Figure 1**).

Group B streptococcal infection in pregnant women

GBS can manifest in a variety of clinical syndromes in pregnant women, including urinary tract infections, post-operative caesarean wound infections, endometritis, and bacteremia. Fulminant infections, including meningitis and endocarditis have also been reported, though these are rare.

Urinary tract infections are most commonly reported during pregnancy. GBS can cause uncomplicated cystitis

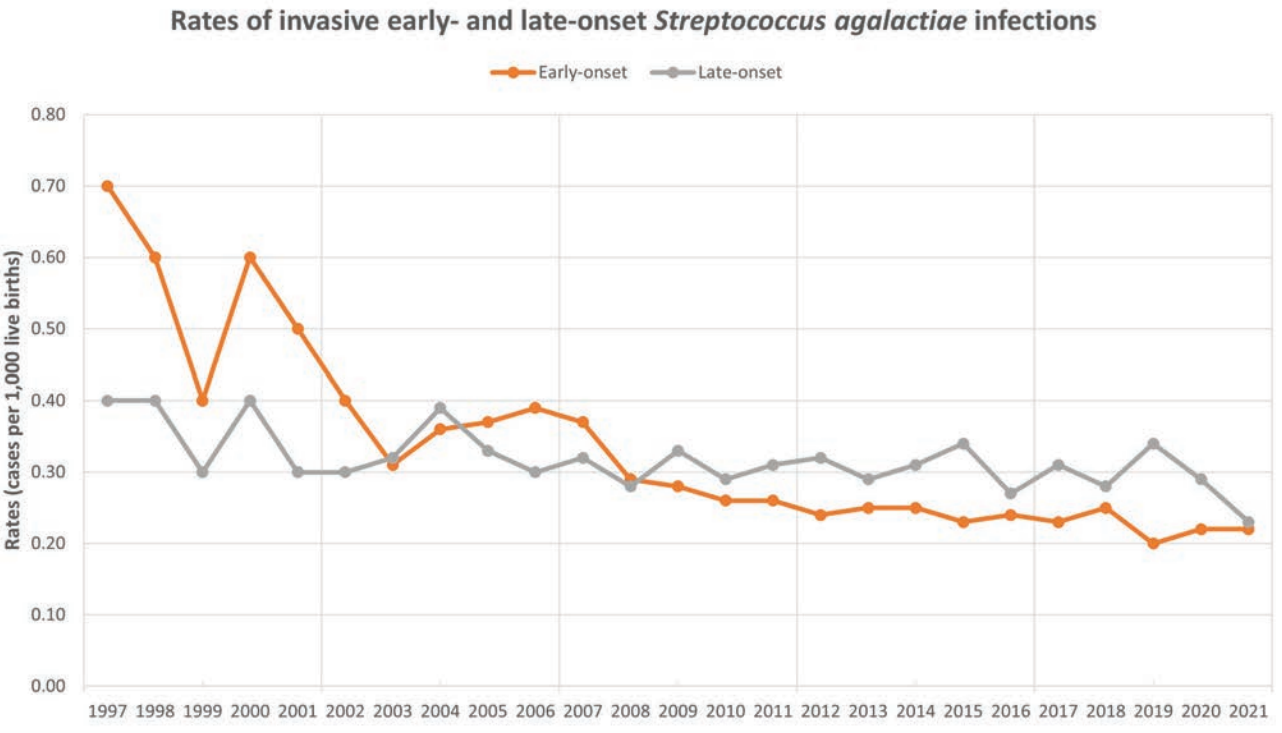

Figure 2.

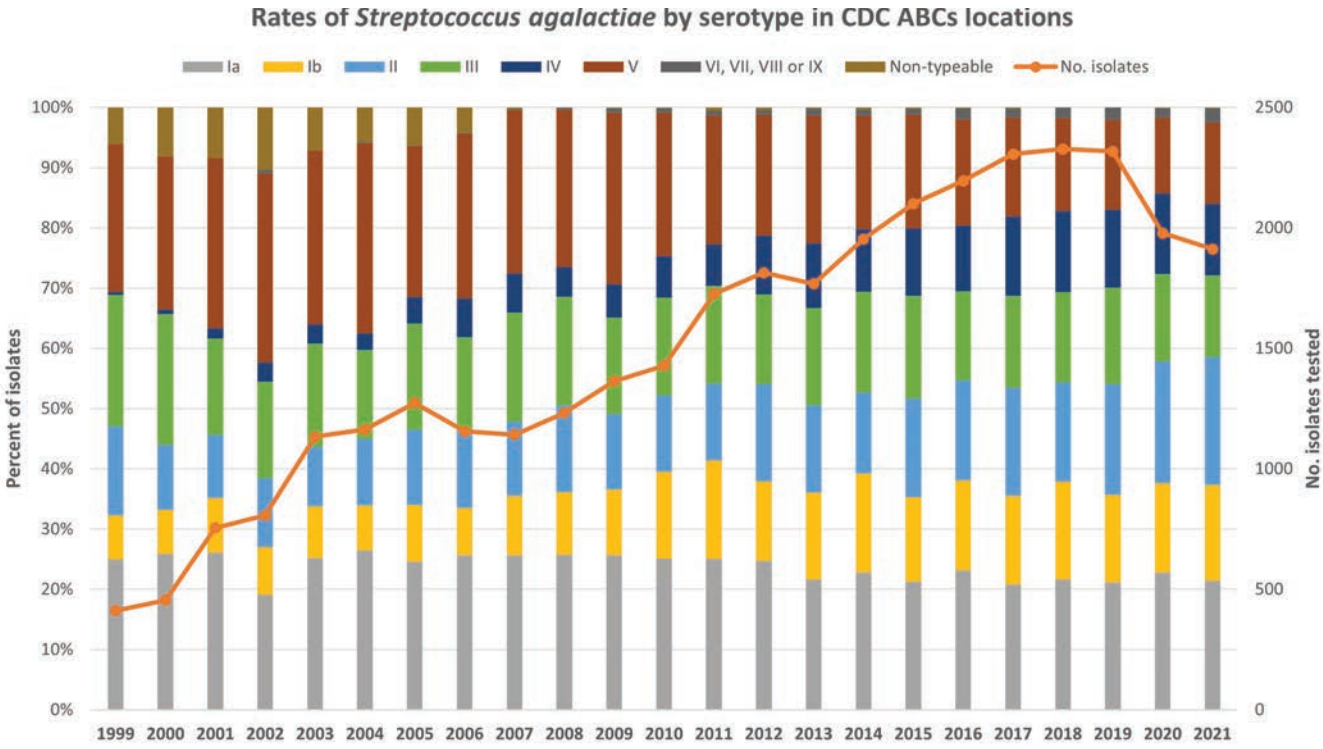

Figure 3.

and pyelonephritis. Asymptomatic colonization with GBS during pregnancy is a risk factor for later infections as well as infections in the neonate following birth. In one retrospective cohort study, untreated GBS bacteriuria had an odds ratio of 7.2 (95% confidence interval 2.4 to 21.2) for developing chorioamnionitis, and increasing colony counts of GBS reported in culture was also associated with increasing grade of chorioamnionitis.[10]

Other complications of GBS carriage during pregnancy includes endometritis and bacteremia. One retrospective cross-sectional study of more than 7,922 pregnant women indicated that postpartum endometritis was 1.8 times more likely in women colonized with GBS.[11] Bacteremia due to GBS remains a concern in peripartum individuals. In a large retrospective cohort from 2009–2016, GBS was isolated from positive blood cultures in 11% of cases.[12] Other infections may include meningitis, endocarditis, abdominal abscess, and necrotizing fasciitis, though these are rare peripartum complications.

Group B streptococcal infection in neonates

In the 1970s, GBS emerged as the leading cause of morbidity and mortality among neonates. In the United States, the reported case fatality rates reached nearly 50%.[13,14] GBS in neonates is acquired *in utero* resulting from intraamniotic infection or rupture of membranes, as well during birth as a result of passing through the vagina. Worldwide, the reported incident rate of GBS is 0.5 per 1,000 live births.[15]

GBS disease can be classified based on disease onset as either early-onset or late-onset disease. Combined, the incidence rate for GBS disease is approximately 0.5 per 1,000 live births (**Figure 2**). Early-onset disease of GBS is defined as the identification and/or isolation of *S. agalactiae* from blood, cerebrospinal fluid (CSF), or another sterile site from birth through six days of age.[16] More than 95% of early-onset GBS and 97% of late-onset GBS in the United States are due to serotypes Ia, Ib, II, III, IV, and V.[17] Neonates that develop early-onset GBS disease typically present with sepsis (80-85% of cases), pneumonia (approximately 10% of cases), and meningitis (5-10% of cases).

GBS in neonates is acquired in utero resulting from intraamniotic infection or rupture of membranes, as well during birth as a result of passing through the vagina.

Late-onset GBS disease is defined as disease occurring at four to five weeks of age. Patients typically present with bacteremia (65% of cases) and meningitis (25% to 35% of cases). Late-onset disease can be further broken down into late, late-onset GBS disease, which occurs in infants older than three months of age. Typically, infants who develop late, late-onset GBS were born pre-term before 28 weeks of gestation or have a history of immunodeficiency.[18,19] Other manifestations of late-onset disease can include pneumonia, septic arthritis, and osteomyelitis.[20]

The ABCs surveillance network also performs additional characterization of GBS isolates from selected surveillance areas using whole genome sequencing. Performing whole genome sequencing allows epidemiologists to determine capsular serotypes, multi-locus sequence typing, and phylogenetic clustering to identify transmission events. During the 22 years with data available, serotypes for 32,808 isolates have been determined. There are slight variations in the proportion of serotypes year over year, but notably serotype Ia has remained fairly stable, representing approximately 20% of isolates each

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year of the program. Some serotypes have seen increases over time (serotype II) whereas others have decreased in recent years (serotype V, non-typable isolates) (**Figure 3**).

Group B streptococcal infection in nonpregnant persons

Infections due to GBS in nonpregnant persons is high. In the United States, the incidence among all persons was estimated to be 11 cases per 100,000 persons in 2016.[21] The incidence for GBS is higher among older adults.[22] Some studies have tried to identify specific risk factors for GBS infection. Diabetes is a commonly reported underlying medical condition in patients with GBS disease.

A variety of infection types have been described in the medical literature from retrospective cohort and case-control studies. Many times, cases of GBS in nonpregnant persons are classified as nosocomial. Skin and soft tissue infections, bacteremia, urinary tract infections, pneumonia, meningitis, septic arthritis, endocarditis have all been described in patients. Therefore, isolation and identification of GBS from any normally sterile site is significant and should be reported.

Laboratory surveillance for GBS

Laboratory testing remains a crucial component for rapid detection of GBS maternal colonization. The ACOG recommends performing universal GBS screening between 36 0/7 and 37 6/7 weeks of gestation. All women whose vaginal–rectal cultures at 36 0/7–37 6/7 weeks of gestation are positive should receive appropriate intrapartum antibiotic prophylaxis.[3] Cultures for GBS most accurately predict colonization status at birth if done within five weeks prior to delivery. Changing the interval from 35–37 weeks to 36 0/7 as the baseline was done to ensure more accurate results for the nearly 7% of births that occur after 31 weeks of gestation.[23]

> Testing for GBS colonization can be done by culture method or by using nucleic acid amplification testing (NAAT), e.g., PCR.

It is recommended to use a single-flocked swab and obtain a specimen first from the lower vagina and then from the rectum without the use of a speculum. Use of a single swab to sample both anatomic locations has been shown to increase sensitivity for detecting GBS.[24] Flocked swabs release microorganisms more effectively, thereby increasing GBS detection and recovery compared to traditional fiber swabs.[25] Specimens should be transported to the laboratory and processed within 24 hours of collection, especially when culture methods are used. Amies transport medium or ESwab transport systems are preferred over sending a dry swab to the lab in a sterile container. Additionally, it is recommended to hold specimens refrigerated at 4–8°C if there is a delay in sending to the testing laboratory. Culturing specimens greater than 24 hours may yield a false-negative result. Specimens not processed within 24 hours should be rejected and recollection is recommended.

Testing for GBS colonization can be done by culture method or by using nucleic acid amplification testing (NAAT), e.g., PCR. Direct plating of swabs onto culture media may be performed in some labs, to reduce time to detection, but it should not be the sole means of screening for GBS carriage. Use of liquid broth media is recommended, and may include nonselective, selective, and differential broth media types to aid in the recovery of GBS. Nonselective broths, when used, can overgrow other vaginal or gastrointestinal microbiota making detection a challenge. Selective media can result in a 2.5-fold increase in detection of GBS compared to use of non-selective broth.[26] Some differential broths, such as Carrot Broth, support pigment production by hemolytic GBS strains. When positive, these samples can be reliably reported based on pigment observation. The pigment production is highly specific for presence of GBS and is sensitive for hemolytic strains. However, non-beta-hemolytic GBS strains are not detected by this method.[27] Sub-culture of pigment-negative broth culture is still recommended.

Several NAAT test manufacturers are approved for testing following a broth enrichment step and do not require culture confirmation of negative results. The main limitation of NAAT-based testing approaches is the lack of recovery of an isolate for antimicrobial susceptibility testing.

The recommended intrapartum antimicrobial prophylaxis is penicillin or cefazolin; therefore, AST is warranted for women who have a documented penicillin allergy. Though clindamycin is the recommended alternative,[3] rates of clindamycin resistance in GBS have been increasing from 20.2% in 2006 to 49.1% in 2021 based on data from the CDC.[8]

Conclusions regarding GBS disease and surveillance testing

Even though recommendations regarding testing and administration of intrapartum antimicrobial prophylaxis have been in use for more than 25 years, neonatal disease due to GBS remains a significant cause of morbidity and mortality. Clinical microbiology laboratories are required to perform screening for GBS among pregnant women. The timing of when screening cultures should be collected has evolved, in part due to the awareness that colonization with GBS can be intermittent. Performing NAAT following a broth enrichment step increases sensitivity for GBS detection. Though culture remains an important component for ensuring appropriate antimicrobial agent selection among women with a penicillin allergy.

> The ACOG recommends performing universal GBS screening between 36 0/7 and 37 6/7 weeks of gestation.

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Lab analytics: Five ways to grow your lab using real-time data

By Jonathon Northover, JD

Under constant pressure to cut costs and perform more efficiently as reimbursements decline, laboratories are often promised that they can stay afloat and even thrive if only they would deploy some form of analytics. However, analytics is a catch-all term that might mean operational, clinical, or financial analytics using retrospective, real-time, or even predictive methodologies. Beyond a promise, are any of these supported with real-world 'proof' of what actually works?

While varied combinations of the above can all be helpful, this is the story of how real-time operational analytics, specifically, has been hugely beneficial for clinical reference laboratories in the United States.

Sam Kabbani is a clinical laboratory expert in southern California who successfully uses real-world analytics to predict business growth. Sam has been an owner/operator of clinical laboratories for over 30 years. Sam manages seven laboratories in his region and is the owner of four of them. His labs service more than 200 physician and nursing home clients. As a consultant, he has helped many other laboratory clients with his insight and expertise over the past few decades.

Finding growth in an unpredictable, constantly changing environment

For long-term success, Sam advises that lab professionals take a predictive view of the market to adapt quickly. Only then can they thrive. This has been a key lesson for him. In addition, growth cannot be maintained without making constant, informed changes to one's business. Though Sam can access all his data in real time, he needed insights into this data to make sure his changes were truly informed. Without those insights, he said, "you are just experimenting."

"I've looked at several solutions to address this. Nothing was able to help. They were either too expensive, had gaps in functionality, were difficult to use, or were a combination of all of those factors," Sam said. "But, as soon as I saw this particular performance metrics software,[1] I wanted to use it. It provides exactly what I need — the ability to change my business to directly impact growth on multiple levels. When I started using it, I realized it's even more helpful than I thought it would be. Now, I could not manage my labs without it."

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Through his laboratory information system and performance metrics software,[1,2] Sam has discovered five ways to improve the bottom line and grow a lab using real-time operational analytics.

1. Identifying profitable tests

Sam can more clearly determine which of his test offerings are most profitable. He currently has an operational view that shows his profit per panel, which rolls up his profits per test alongside volumes. "With a view into my revenues versus costs per test, I can see at a glance where my profits are. It's uncovered where I can focus on performing more high-margin tests—not just high-volume tests. This can affect my bottom line directly by up to 15% where previously we were leaving that money on the table," Sam said.

2. Identifying revenue loss or neutrality

"Prior to my current laboratory information system, I always wanted to know which of my clients would I be able to support steadily at a good profit for my business, versus which clients are too high cost to support. In some scenarios this is crucial, as both my lab and their practice are better served by an increase in volume or by them sending their samples to a different lab. This way, I avoid the opportunity cost of testing samples at a loss while I could have been testing different samples at a profit," Sam said.

One way to do this is with a monthly panel trends view, which enables Sam to identify two main areas of avoiding losses that can mount up:

- For example, Sam quickly identified one client that was requesting his mobile phlebotomy team to perform home collections for their patients. "However, based on the small number of patients they supported at their location and the cost to me of sending out my team to perform the collections, I could show them that it wasn't worth it."
- Sam was also able to quickly identify when volume from a specific client suddenly decreased. "This enabled me to go to my sales team and find out why, so that I can preemptively address any issues to prevent that work continuing to decrease."

3. Improving client relationships

"With my performance metrics software, I have not only boosted my credibility but also been able provide insights into the business of my clients as a trusted partner. This creates additional loyalty to our services and ensures we continue to win business in the area. Do not underestimate the importance of this," Sam said.

For example, the daily panel count view enables Sam to renegotiate contracts with some of his clients by helping answer questions such as:

- Which clients are ordering STATS (since, as with most labs, we charge a STAT fee)?
- Should I provide a service on Sundays? With my operational analytics tool, I can compare volume from that client over several Sundays. If it is consistently low volume, I can reset the contract to offer an on-call Sunday service instead of being available 24/7.
- Which clients should I make a top priority based on the revenue I am receiving?

Insight into turnaround times has also enabled Sam to quickly respond to client questions. For example, a physician client may inquire as to where an opiate result on a specific patient currently stands. With his performance metrics software, Sam can quickly view turnaround time by test by filtering to his opiates panels and then the specific test. "My turnaround time view might then show that the sample took three days to arrive. Even still, perhaps the receive-to-run time was still too long. I can then look into the sample tracking to determine why there was a bottleneck."

4. Reducing staffing costs

Adjusting staffing to match a constantly changing throughput of samples is very difficult for any lab. A careful balance must be struck: if a lab is overstaffed, there may not be enough business to pay the team; whereas, if a lab is understaffed, the lab cannot provide high-quality service to its clients and risks losing their business. Either way, it is a financial loss.

"My performance metrics software has shown me the patterns in my changing levels of throughput and allows me to predictably balance my staffing to match that throughput. Now, my staffing costs are directly related to how much business I am generating. I am not under- or overstaffed at any given point; and therefore, I am never losing money and am optimally supporting my profitability," Sam said.

The Lab Tech Productivity view has enabled Sam to see how he should predictively change staffing levels based on throughput volume needs. For example, for upcoming days, weeks, and months, Sam has been able to make changes such as:

- Reducing the cost of techs working specific benches at low-peak times (some days at 8 pm he may be running insufficient samples to justify a tech, such as in microbiology).
- Increasing staff based on high volumes at predictable patterns during certain days and times (hematology tends to be bombarded on Friday and Saturday evenings).

The Orders by User (Staff) view shows productivity. Sam can see, for example, how many samples are being collected by which courier phlebotomist and obtain a better understanding of the precise dollar value each phlebotomist is adding to the lab. Are they going out for six hours and returning with 100 samples or 10 samples? "When there are differences, I can review the routes and distances but also determine whether retraining is needed to redress the balance of performance across my team. I can also see who has been the most productive within a given time period," Sam said.

5. Winning new business

With these analytics, Sam can demonstrate that he has a proactive handle on his operations. "I can demonstrate my lab's performance over time, showing how I consistently hit turnaround time targets as advertised. With this information, I instill confidence in potential and existing clients, and I am able to win new business more effectively."

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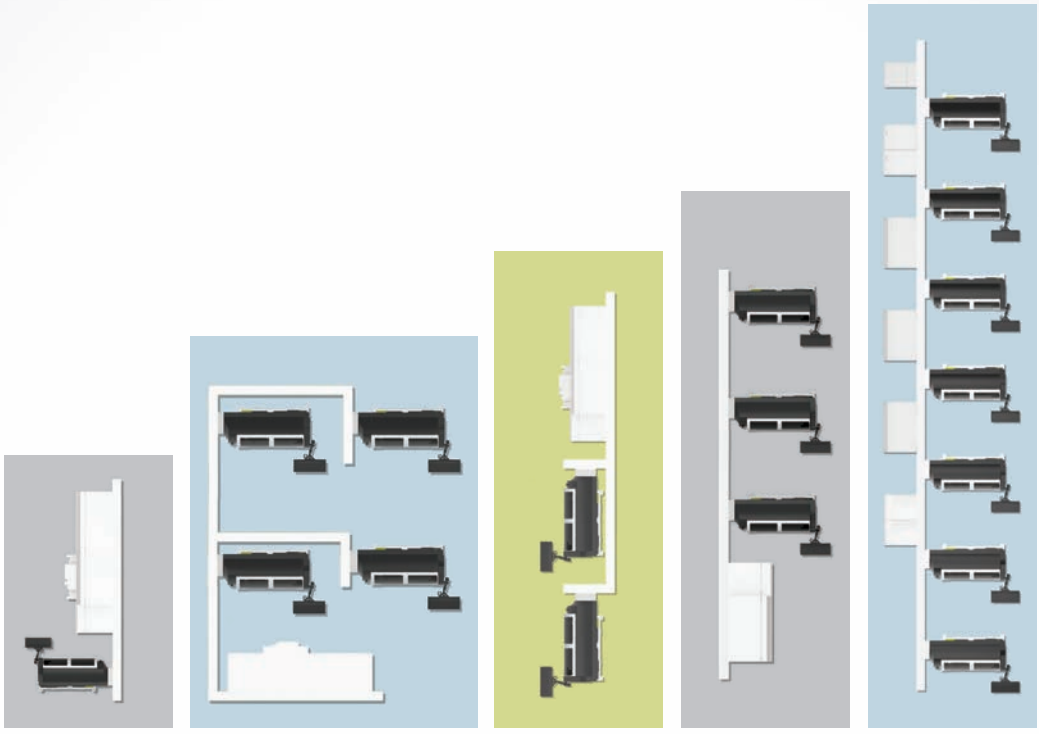

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Cause Analysis: The five whys method

By Carlyn Mathews

Although CLIA includes brief requirements for corrective actions, it does not include a requirement for cause analysis (also referred to as root cause analysis). However, a core element of the ISO management system requirements that form the basis for ISO 15189 is corrective action, starting with cause analysis. The standard is designed to place planned, thoughtful consideration and investigation into how the nonconformance occurred and dig deeper into the issue and determine how to prevent future recurrence. In addition, a cause analysis can also prevent deficiencies that have yet to occur. Oftentimes, a single issue can be the cause of multiple nonconformities, and therefore, solving one issue will reduce the risk of another occurring.

Properly identifying the problem through cause analysis is critical not only to achieve and maintain ISO 15189 accreditation, but also to maintain high-quality patient care.

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A top-down approach

Cause analysis takes a top-down approach by first identifying the deficiency then taking small steps to dig deeper and determine the root of the nonconformity. One of the best ways to do this is using a method called "the 5 Whys." As the name suggests, the process involves identifying a problem statement and asking yourself "why" a multitude of times until the cause can be identified. The answer to each question should parrot the problem statement before it for logical transitions and a clear line of thought.

Take, for example, internal quality control materials failed to fall within the defined range of acceptability. ISO 15189 requires labs to ensure the validity of examination results in clause 7.3.7.2, stating, "When internal QC defined acceptability criteria are not fulfilled and indicate results are likely to contain clinically significant errors, the results shall be rejected and relevant patient samples re-examined after the error has been corrected."

In this case, the problem statement would read, "The internal quality control materials failed to fall within the defined range of acceptability, causing a rejection of results and the need for another test to be performed. Now, it's time to start asking 'why?'.

Why 1: Why did the quality control materials fail to fall within the acceptable range?

Answer 1: The quality control materials failed to fall within the acceptable range because the test was performed incorrectly by the technician.

Why 2: Why did the technician perform the test incorrectly?

Answer 2: The technician performed the test incorrectly because they missed a crucial step in the method.

Why 3: Why did the technician miss a step in the test method?

Answer 3: The technician missed a step because they weren't provided the proper training on the test method.

Why 4: Why did the technician not receive proper training on the test method?

Answer 4: The technician did not receive proper training on the test method because it was not documented in the training documents.

Why 5: Why was this test method not documented in the training documents?

Answer 5: The test method was not documented in the training documents because it was added to the scope of accreditation before the scheduled review of training documents.

Resolution: When adding new methods to the scope of accreditation, document an additional step to incorporate the method into the training documents.

Conclusion

While basic, this is a common example of how deficiencies can happen in the laboratory and how to properly determine the core of the issue. Depending on the complexity of the nonconformity, you may only need to ask "why" three or four times before finding the cause. In other cases, you may need to ask "why" seven or eight times before you reach the true cause. Once the source of the problem and the resolution are properly determined, the corrective action can take place.

The answers to your questions may not always be obvious, so take the necessary time to thoroughly investigate. A comprehensive cause analysis will inevitably save you time in the future that may have been spent resolving related issues. It will also reduce risk in the laboratory and ensure that patients and their doctors continue to receive high-quality laboratory results that they can use to confidently make medical decisions.

Carlyn Mathews is the Clinical Program Manager at **A2LA**, one of the largest accreditation bodies in the world and the only independent, internationally recognized accreditation body in the United States that offers a full range of comprehensive conformity assessment accreditation services. Carlyn works closely with clinical laboratories to help them achieve and maintain accreditation to federal and global standards.

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Integrating pharmacogenomics into the standard of care in the United States

By Tricia Kenny

The practice of pharmacology has been around for thousands of years, starting with Pythagoras' observations of how fava beans directly impacted the prevalence of hemolytic anemia, a blood disorder that causes weakness and fatigue, in individuals that consumed them.[1] In the millennia following, researchers continued to explore what caused certain reactions with early treatments. In the 1950s, the idea of testing for how individuals react to different drugs started to formalize into a substantial clinical application.[2] The emergence of genomic technologies including genotyping decades later helped formalize the process and the term pharmacogenomics was coined to help define the burgeoning area of study.[3]

Pharmacogenomics (PGx) is used to understand how variations in key areas of an individual's DNA may impact efficacy of a medication, dosage considerations, as well as exploring potential adverse drug reactions (ADRs). Ideally, this is performed in advance of prescribing medication so that the physician or the pharmacist can streamline medication selection, reduce trial-and-error, and minimize ADRs. Alternatively, it is done to help explain why a medication is not working or causing an ADR and get the individual back on the best therapeutic path. A wide-reaching PGx study showed that 100 percent of individuals assessed had at least one gene that was known to impact medication outcomes, while 66 percent of the same population had genetic risks detected for medicines that they were already prescribed to take.[4] The data exemplified how almost everybody receiving treatment have the potential to be impacted by not receiving PGx assessments and could benefit from such testing/assessments.

What is holding back PGx as standard of care

PGx is not a widely adopted practice despite the benefits it could provide, for two core reasons: an unclear path to reimbursement including demonstrated longer term economic value and its lack of broad utilization among clinicians (and subsequently, patients). Although there are extensive findings demonstrating the clinical utility of PGx testing to impact better health outcomes, reimbursement of these tests is only recently becoming available through real-world implementation studies demonstrating economic value to payers.

In addition to economic drivers, utilization of PGx testing to assist with medication prescribing and its benefit is still in its infancy. Despite being easy to implement within molecular testing laboratories, there are very few clinicians who truly understand how to utilize PGx for medication management. Since clinicians who can order tests often do not know how to interpret the results, the demand of testing is still relatively low. With stakeholders across the healthcare delivery chain unaware of the value or the new means of economic viability, widespread adoption across a meaningful scope has been challenging.

Bringing PGx forward

Illustrating how PGx can help provide better health outcomes while saving time and costs for the healthcare system and payers is key in bringing it to the mainstream. Researchers and test manufacturers have an obligation to continue presenting the data that show how PGx can help advance care across different disease areas. In addition, technology providers would need to educate laboratory technicians and clinicians how to interpret the results that are found with such testing. Areas where PGx research is showing promise, as well as returns already, include oncology, cardiology, pain management, peri- and post-operative care, mental health, geriatric care, and many more.

Oncology: Oncologists can utilize PGx to help assess patients to determine which chemotherapies will be most effective, and the medication dosage patients can tolerate. These care improve-

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The quality of treatment starts with diagnosis.

ments are critical in a disease state where speed, efficiency, and accuracy are key.[5] These benefits are clear when applied at the point-of-care or during the prescription stage, but they have also been shown to potentially provide benefits later in the care journey for people living with cancer, in terms of treating residual effects of the disease or in limiting potential negative after effects.[6]

Analyzing even two genes can help to make a big difference in how individuals are treated, and how much those treatments help them, as has already been shown in the clinic.[7] Recent studies of people with non-Hodgkin's lymphoma taking rituximab demonstrated that people with the FcγRIIIA genotype, determined by a single nucleotide polymorphism (SNP) at residue 158, had a considerable increased reaction than those without that genotype. Other cancer researchers have shown an understanding of how different genes, such as TPMT, UGT1A1 an DPYD, work with the toxicity of different drugs and treatment-limiting tolerabilities and have already shown those benefits at the bedside.[8]

Pain: Hundreds of millions of people struggle with various degrees of pain, and are forced to manage it with medication, costing almost six hundred billion dollars every year.[9] PGx can help find pain management therapies that work with a specific genetic makeup to avoid drugs that will be damaging to them in the long run and can potentially identify individuals that are susceptible to opioid-addiction.[10] Already, particular CYP2D6 gene variants have been identified that impact codeine and tramadol prescriptions and their ability to have a positive or negative impact on patients.[11] The OPRM1 and COMT genes are just among the many others that are currently being assessed to find out how they impact future opioid dosages.

Mental health: For individuals struggling with a variety of mental illnesses, such as depression, having to go through a trial-and-error approach through ineffective drugs can be a massive struggle. Some people can take months, if not years, to find an antidepressant to work for them, building up costs and causing additional issues by having persistent depression.[12] Each medication that they try can take four to six weeks alone to fully understand whether or not it will have a clinical benefit or if it will even be tolerable. PGx would provide the opportunity to find a treatment that would be most effective in the first instance, cutting out not only wasted time, but wasted money as well; this doesn't even begin to explore how much of a toll different side effects can have during those trial periods.[13] In a recent study, pharmacogenomic testing was shown to potentially save almost $4,000 annually for people living with depression.[14]

Advancements already made

Therapeutic areas, such as neurological diseases, cardiovascular disease, respiratory illnesses, autoimmune disorders, and more can find similar benefits if PGx is applied on a broader scale, which is already beginning to be proven. A team of researchers, led by Dr. Phil Empey from University of Pittsburgh School of Pharmacy, launched the Pharmacogenomics-guided Care to Improve the Safety and Effectiveness of Medications (PreCISE-Rx) program in 2015, which created a streamlined process for testing individuals as soon as they arrived at the University of Pittsburgh Medical Center (UPMC) and added any gene–drug reaction findings to their electronic health records.[15] The program has already tested thousands of patients and has made this sort of testing routine in their approach to care.

Overall health is improved when people find the treatments that can address their medical issue through PGx. Clinicians can save time by reducing the need to revisit with patients to discuss new treatment alternatives, and the clinician/patient relationship is improved by building trust through more successful initial treatments. Money can be saved for patients and the industry at large with therapeutics not being given to individuals who will not tolerate or will not react positively to them. The applications of PGx are far reaching and more can be learned in the future.

Research already conducted has shown that over 85 percent of neurological PGx case studies, including depression and schizophrenia, assessed showed cost savings, specifically in studies that assessed CYP2D6 and CYP2C19 drug-gene interactions, showing how the long-held promise has already started to reap benefits.[16]

Many independent organizations and working groups have formed to help bring PGx into the standard of care as well. The STRIPE Collaborative Community was formed in 2020 to bring together members of the PGx community, as well as the FDA, to address challenges the industry is facing to make precision medicine mainstream. The PharmacogeneVariation (PharmVar) Consortium and PharmGKB are different public databases that seek to share information on drug and gene variants to help those working in the field. The Clinical Pharmacogenetics Implementation Consortium (CPIC) publishes peer-reviewed guidelines to facilitate the translation of PGx data into actionable prescription algorithms. All of these groups working together in recent years has advanced the space and helped to democratize data for those that could benefit from it.

Raising awareness

Test manufacturers have already been working to make the bold promise of making PGx more of a reality. Considerable leaps have been made especially following the advancement of and investments in diagnostics during the COVID-19 pandemic. Infrastructure that was widely distributed and implemented during the peak of the pandemic helped improve diagnostic technology accessibility by labs around the United States; those same platforms and personnel can now be used to run PGx tests. The evolution of leveraging relationships developed during the pandemic and offering new molecular tests can help replace testing revenues as COVID-19 testing volumes, as well as the test demand for other infectious diseases, decline.

Additionally, technology has advanced in the ability to identify and assess genes on a larger scale, accelerating research. Elements like artificial intelligence have brought this even further along, allowing for automated assessments of genes. That improvement in machine learning, paired with the advancements made in diagnostic tools that help to pair personalized treatments with the right individuals has put PGx in a better place than ever to have real, concrete applications in the medical world.

Increased awareness of the benefits of PGx testing could lead to a general uptick in demand. Laboratorians and technology providers are in a great position to help clinicians to understand when and how to order PGx testing, and downstream interpretation of results. It has been shown that clinicians don't have the time alone to teach themselves how to implement PGx, so utilizing the investment made in diagnostics over the past few pandemic-riddled years from both industry and governments, can help to get everyone up to the same level.[17] All of these groups working together in tandem to call for the benefits that PGx provides could help drive demand, and in turn, help accelerate its adoption across the industry.

Key takeaways

Pharmacogenomics has moved quickly in recent years to become a viable piece of the overall healthcare puzzle, serving to identify

effective treatments by figuring out which therapy could work best with each individual based on their individual genomic makeup. The field has been growing and can be a key element in bringing personalized care on to a broader scale.

PGx can lead to better overall quality of care by making sure that medications are prescribed with the specific individual in mind rather than guessing what may work best under the "standard of care" paradigm. It can help reduce costs and time wasted among hospitals, pharmacies, and healthcare providers by cutting down on outpatient visits used for trial-and-error approaches to find a medication that will be effective and on emergency room visits and hospital stays due to adverse drug reactions.[18] Patients are helped through reduced amount of time for medical visits, struggling with specific diseases, and possible side effects of drugs they struggle to tolerate. Overall, PGx has the potential to greatly reduce costs for the healthcare system, patients, insurers, and patients' employers.

Test manufacturers have continued to improve their diagnostics, helping make them easier to implement at a lower cost per sample than they were before. This is profitable to testing laboratories and can help provide economic value to the payers as well. In turn, those working within the different stages of the health delivery system have an obligation to learn more about tools that are readily available now in order to help them provide a better overall experience, reduce disparities in care, and save time. Personalized care has long held substantial promise, and now, that promise can be fulfilled. The next big step is for the industry and the medical community to come together to help see this through.

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Diversity, equity, inclusion — Managing and leading today's diverse laboratory workforce

By Anthony Kurec MS, MASCP, MLT(ASCP), H, DLM

Laboratory workforce shortages have been a concern for many years. During this COVID era, there has especially been an impactful change as seen in all aspects of healthcare as well as many other industries that support it.[1] In part, this reflects the 'Great Resignation' phenomena seen not only in the United States but in Europe and Asia. In 2021, over 47 million Americans quit their jobs, and in the last six months of 2021, almost 2.8 million healthcare workers resigned.[2,3]

In addition, social media has spawned a type of movement known as 'Quiet Quitting' referring to a growing number of workers who put in the least amount of effort, working no more than the minimally required number of hours, and expressing little or no enthusiasm for the job. It is estimated that over 50% of the U.S. workforce appear to be disengaged with their job with a particularly high number of Gen Zs and younger Millennials (less than 35 years old) making up this contingency.[4] A significant shift in priorities has occurred during this pandemic era resulting in a kind of worker clarity that will not accept traditional organizational practices that do not align with today's thinking where many feel that they don't "fit in."[5]

Multicultural workforce

Multicultural workforce is a term that has most often been associated with racial or ethnic differences. Today's workplace environment reflects a greater diversity of staff and patients yet preconceived inequities still remain. Our interactions with each other are broadly based on how we were raised, what we have learned from our parents, and the environment that we grew up in as we approached adulthood, regarding race, nationality, gender, religion, social groups, and/or other unique associations.[6]

During this COVID era, the difficulties in retaining staff have led to a closer examination of what is currently referred to as Diversity, Equity, and Inclusion (DEI) practices and their impact on hiring and managing staff. DEI can be viewed as a three-legged stool that supports the work environment and its workforce, something laboratory leaders need to examine, understand, and implement (**Figure 1**). While good laboratory leaders learn and become proficient in utilizing technical and managerial skills, great laboratory leaders possess certain innate skills that will cultivate a positive and inclusive work culture.

Figure 1.

Leg 1 — diversity

A diverse workforce reflects multiple persons and personalities, with different backgrounds, identities, and demographics.[7] Diversity can serve as a metric in that each of the following can be counted and used as a base for developing and expanding diversity. Diversity discussions must not be limited to just that of race, ethnicity, or gender but also can include religion, sexual orientation, socioeconomic status, and age.

Diversity should also recognize situations that may arise due to differences in political or national

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views (e.g., Republicans versus Democrats), educational background differences (e.g., Syracuse University versus Georgetown University), physical differences (e.g., morbidly obese, 'little person'), and those with mental health situations (e.g., anxiety, ADHD). In any given collection of people, any one or more of these areas when viewed to be a deficit or other limiting factor in job performance can result in a disproportionate, divisive, and unhealthy workforce. Therefore, it is incumbent upon laboratory leaders to recognize and work with staff in building an inclusive workforce that recognizes and accepts these differences.

Leg 2 — equity

Though a laboratory may have a diverse workforce, equity is an essential step in promoting fair access to opportunities, resources, and professional success. In other words, all employees are treated, evaluated, and supported in the same manner regardless of their 'uniqueness.' Studies have shown that employees who are treated fairly are almost ten times more likely to want to work, six times more prideful in their work, and five times more likely to be retained.[8]

Leg 3 — inclusion

Inclusion involves actions taken to understand and accept certain strengths and identities that contribute to better engaging employees in ways that make them feel and want to be part of a team. That is, they become part of the inner circle and actively make meaningful contributions. In a study by the Society for Human Resource Management,[9] eighty-four percent of respondents felt that managers were poorly trained causing unnecessary work and stress. Five skills were also identified (**Figure 2**) as ways that managers could work to improve the workplace environment, which includes cultivating a positive and inclusive team.

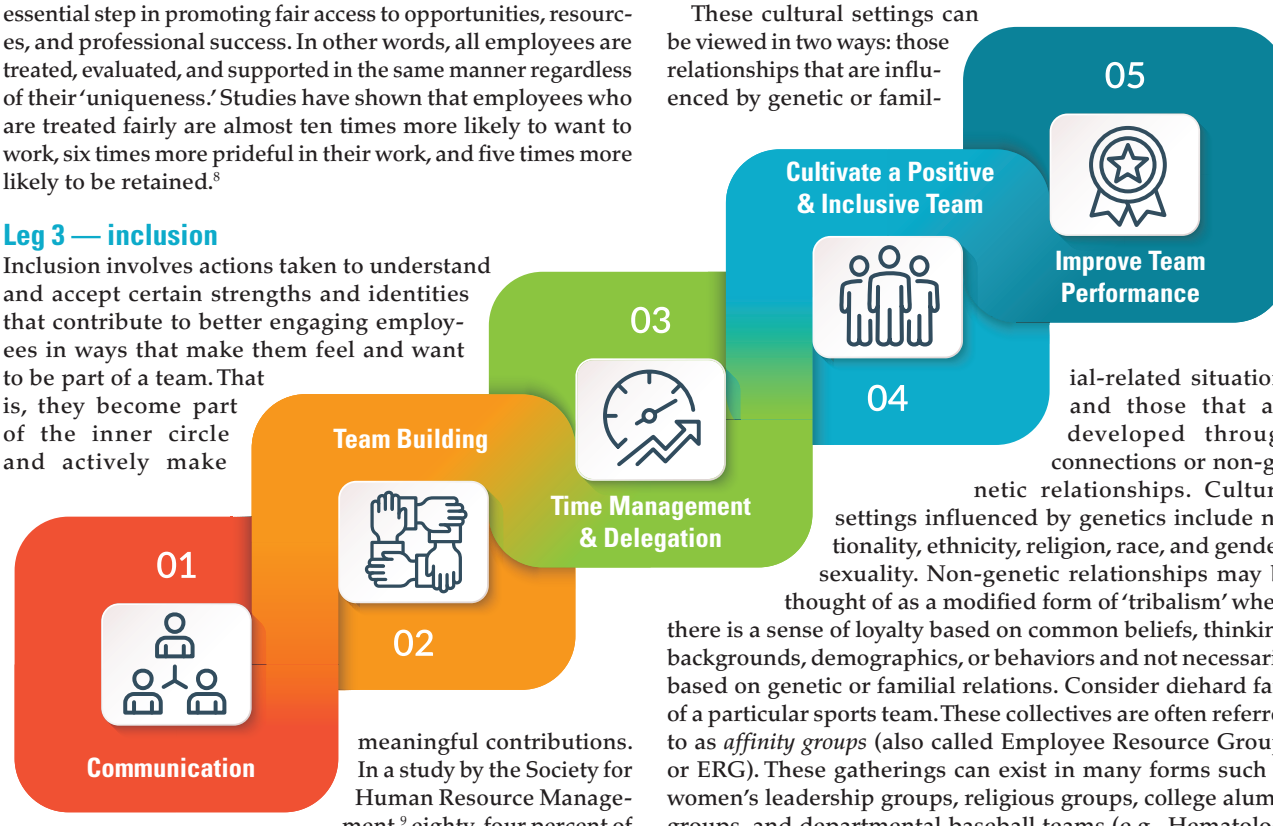

Figure 2. Five management skills to improve the work environment.

'The Three Qs'

How do leaders learn and implement DEI? Looking at the 'three Qs' may be a good way to start. IQ, or Intelligence Quotient, serves as a key component in management for being smart enough to recognize and embrace needed changes.

EQ or Emotional Quotient (also called Emotional Intelligence) is a leader's ability to understand, manage, and evaluate their own emotions when dealing with stressful situations while attempting to recognize and influence the emotions of others involved.[10] Empathy is the key ingredient to EQ. This directly relates to understanding what commonalities we share and what makes each person different. **Figure 3** shows the four key components of EQ. Laboratory Leaders with a high EQ set the tone for a well-functioning and engaged laboratory. To gauge one's own EQ several tests are available.[11] **Table 1** provides some suggestions for enhancing one's EQ.

The third Q is Cultural Quotient (CQ; also known as Cultural Intelligence). Approximately 70 percent of international businesses fail due to a lack of understanding of cultural differences.[12] **Figure 4** shows the three components of CQ. With respect to DEI initiatives, this may be the most important Q in that a leader with a high CQ readily recognizes, relates to, and effectively works with others in various cross-cultural settings. A leader with a high CQ makes every effort to understand different beliefs, thoughts, activities, behaviors, and experiences that may be present in a diverse work environment.[13] A short evaluation of CQ is provided in Earley & Mosakowski, 2004.[14]

These cultural settings can be viewed in two ways: those relationships that are influenced by genetic or familial-related situations and those that are developed through connections or non-genetic relationships. Cultural settings influenced by genetics include nationality, ethnicity, religion, race, and gender/sexuality. Non-genetic relationships may be thought of as a modified form of 'tribalism' where there is a sense of loyalty based on common beliefs, thinking, backgrounds, demographics, or behaviors and not necessarily based on genetic or familial relations. Consider diehard fans of a particular sports team. These collectives are often referred to as *affinity groups* (also called Employee Resource Groups or ERG). These gatherings can exist in many forms such as women's leadership groups, religious groups, college alumni groups, and departmental baseball teams (e.g., Hematology versus Blood Bank), resulting in individuals who 'look, talk, and act like me.' These commonalities serve as a rallying point that leads to improved communication and cooperation among laboratory staff, other hospital staff, and even patients.

Laboratory leadership and DEI

Because an organization may be considered diverse, it does not necessarily reflect equity and/or inclusion. In a study by

1) **L**isten more than talk
2) **E**quip staff with appropriate tools and resources to do their jobs
3) **A**ppreciate staff by investing time and effort in them
4) **D**evelop opportunities for staff to grow and advance in their careers
5) **E**nlist support from others, especially senior staff, to accomplish goals
6) **R**elationship building ensures team engagement
7) **S**erve YOUR staff instead of waiting to be served

Table 1. Seven steps for L.E.A.D.E.R.S to enhance their EQ. (Modified Loblack 2021).[19]

McKinsey & Co., about $8 billion was spent on diversity training. More than half of the employees surveyed agreed that diversity efforts were acceptable, while 61 percent felt that inclusion efforts were less than acceptable.[15]

Equality does not necessarily mean equity. As seen in **Figure 5**, there is equal access to viewing a ball game over the fence, but not equal opportunity to participate. Equity allows for adjustments to be made so all enjoy the game. Similarly, employees may be equally presented with better positions, salary increases, more responsibilities, and education opportunities, but successfully obtaining access to them may be limited and can only be achieved through true equity practices. It should be noted that without equity, diversity and inclusion may not be achievable or sustainable.

This is reflected in inclusion options. Individuals that have been previously excluded from participation in certain opportunities may eventually be allowed to be peripherally integrated 'around' the inner circle, but never truly part of the inner circle. Implementing inclusion practices allows these individuals to be part of the 'inner circle.' They then can actively be involved and participate in developing policies and other opportunities within the organization.

Figure 3. The Four core compentencies of EQ (Landry, 2019).[10]

Potential fixes to ensuring DEI

Initiating DEI practices requires buy-in from the top levels of management who provide opportunities for meaningful conversations that identify accountability and actionable items. Consider some of the following suggestions:[7]

- Understanding and implementing DEI ensures that anti-discrimination laws are followed. According to the EEOC (Equal Employment Opportunity Commission), over sixty-one thousand workplace discrimination charges were filed in 2021 ranging from discrimination due to disabilities to improper use of genetic information.[16]
- Senior laboratory leaders should review their hiring practices by ensuring an appropriately written job description that would otherwise unfairly eliminate a candidate. It should also clearly identify physical/mental requirements to do the job with consideration of providing procedural accommodations if necessary (e.g., phone assistive listening device for the hearing impaired).
- Advertise job opportunities that increase visibility and do not limit access to minorities or other underrepresented entities (women, people with disabilities, etc.). Social media has a number of platforms that readily accomplish this.[17]
- Use clear and concise language when speaking and writing. Avoid jargon, slang, idioms, or gender-slanted terms (he versus she, "an opportunity for working moms," etc.).
- Actively listen and paraphrase to ensure you understand what is said to you.
- Use of salary history, previous employment absenteeism, or past criminal background has raised some legal discrimination issues; consult your Human Resource Department.
- When creating a hiring team, consider its diversity.
- Use a pre-set list of interview questions that are used for every candidate.
- Do not assume that a culturally different person is typical of that culture or group.
- Recognize your unintentional biases (microaggressions or stereotyping) that might eliminate a candidate or minimize a worker (i.e., names, attire, smoker, tattoos, etc.).

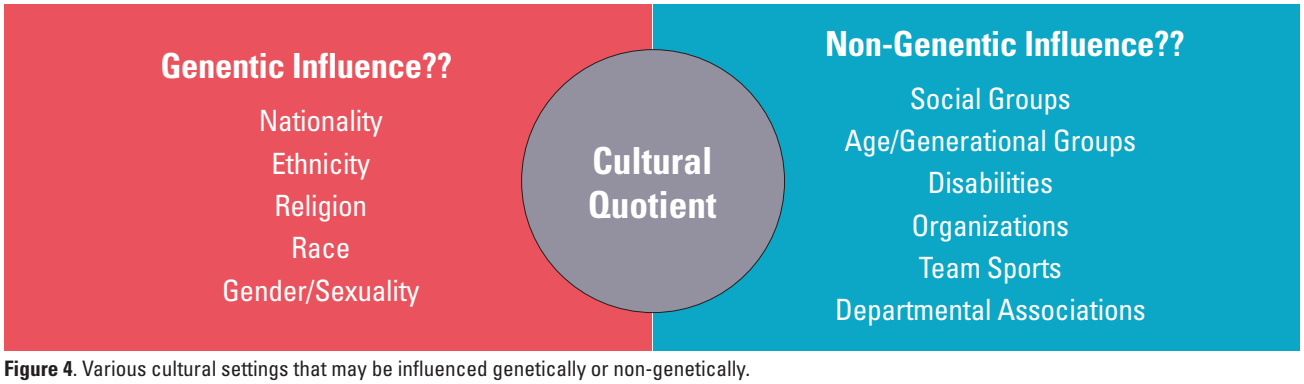

Figure 4. Various cultural settings that may be influenced genetically or non-genetically.

- Be aware of culturally acceptable body language (hand gestures, touching, eye contact, personal space, etc.).
- Develop and advertise your DEI-based hiring policy that promotes fair practices.
- Educate yourself about cultural differences (i.e., food, modesty issues, religious holidays/traditions, etc.).

iam2mai/iStock / Getty Images

Figure 5. Equality vs. Equity

Summary

Understanding and implementing DEI policies can be challenging yet becomes an important part in hiring, training, and retaining staff. It has been reported that companies that have a well-developed DEI program are 43 percent more likely to see higher profits. Executive team gender diversity has shown a 25 percent increased profitability and was more likely to outperform other companies by 30 percent. Management teams that are racially diverse tend to work more effectively than those that are not. And finally, three in four employees and job seekers value a diverse workplace, thus potentially improving recruiting and retention opportunities.[7]

Over the past several decades, diversity and affirmative action efforts have had limited impact focusing on only a few issues (race, religion, and sometimes gender). In a study by the American Hospital Association, as many as a third of hospital patients are minorities, yet only 14 percent are on hospital boards, 12 percent are in executive leadership positions, and 17 percent are in first- and mid-level management.[18] Of note, Millennials and Gen Zs are more fluid in their interpretations and see lifestyle choices, experiences, and ideas are more relevant, thus creating a greater level of flexibility in workforce practices.

So how diverse is the laboratory? There are approximately 57,000 medical laboratory scientists, 65,000 medical laboratory technicians, and over 152,000 phlebotomists at an average age of about 43 years. Gender distribution is about two-thirds female and one-third male, yet there are more male laboratory managers (58%) than females (42%). Racial distribution is White (56%), Hispanic/Latino (16%), Asian (13%), and Black/African-American (12%). Of note, women earned 100% of what men do. And finally, about 12% identify as LGBTQ+.[2]

It is really easy to judge people based on their differences, but it takes effort to learn and understand, and accept these differences. Laboratory leaders can then build a balanced and functional workforce that works well together and is highly productive. It is equally important to remember that when patients, staff, and the general public see healthcare workers that look, act, and talk like them, there will be a greater sense of connectivity, acceptance, and understanding that promotes better patient care and a healthier work environment.

"Like a string of beads, it is our unique differences and intricacies that make us so appealing and attractive. We would not be as beautiful if we were all the same. It's the contrast and asymmetry that makes us worthwhile."–Lindsey Lunsford, M.E.M., Second edition DEI Fellow

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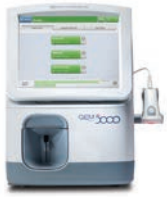

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Rapid, comprehensive clinical chemistry testing

Delivering consistent high-quality results, the RX imola is ideal for medium to high throughput laboratories. Capable of performing 400 photometric tests and 560 tests per hour including ISE, the RX imola comprises the RX series test menu and excels in performance and functionality to provide rapid, comprehensive testing.

Randox

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LABORATORY INNOVATOR

API's first employee

By Christina Wichmann

Sue Harmer, MT(ASCP) has been named the new President of the American Proficiency Institute (API). Sue started working for API as its first employee 30 years ago when it operated out of a small room on Traverse City, Michigan's main street. Hired for her experience in chemistry, hematology, and blood banking, Sue quickly rose to managing operations for the organization. Fast forward to 2023, she now leads one of the largest global proficiency testing providers. Certified as a medical laboratory scientist, Sue previously worked in hospital laboratories in Washington state. A graduate of Ferris State University, she serves as a liaison to the ASCP/API Editorial Advisory Board, and has co-authored studies on proficiency testing.

You were hired 30 years ago as the American Proficiency Institute's first employee! What are some of your favorite projects you have worked on?

Thirty years is a long time, so I have several favorites to share. From the beginning, I was tasked with setting up the shipping process. I had to work with our software developers to help define a process that would pull each of the unique proficiency products that a laboratory ordered into a kit and resolve how to make an assembly process for many thousands of those kits happen over a two-day period. As a medical technologist, it was embedded in me to follow quality processes and ensure the accuracy of this process! It was interesting and challenging to apply that skill set to a different scenario.

I also had the opportunity to develop a proficiency testing program for laboratories in the food industry. Developing proficiency testing for an adjacent industry gave me an opportunity to learn about food microbiology and gain an appreciation of the important role proficiency testing plays in quality improvement across all laboratory sectors.

Frankly, the overall running of a proficiency testing program is one big, continuous, favorite project! From developing new products for the API portfolio to sourcing material to figuring out system logistics, it's all a wonderful challenge.

If a laboratory receives an unsatisfactory proficiency testing result, what steps should it take to determine the cause of the problem?

The API "Corrective Action Checklist" is a great place to start. A laboratory follows the checklist to determine the possible cause of the problem. It begins with a review of the proficiency testing results to rule out a clerical or transcription error and continues with a retrospective look at the testing method used, units reported, and rechecking the sample identification. To determine if specimen handling errors were involved, the checklist suggests examining how samples were received and managed. Other items covered in the checklist include a review of quality control data, maintenance logs, instruments, and reagents, in addition to calibration verification.

Remember, it's important to include testing personnel and the laboratory's medical director in this review and to document fully the findings.

Have laboratory automation and new technologies posed any challenges to proficiency testing? Any advice for overcoming these challenges?

Sure, but in a positive way. As laboratory information systems developed and laboratories used those systems to report out their patient results, we knew we needed to adapt. Proficiency testing processes needed to align better with a patient testing scenario. For us, it led to the birth of API DataDirect, where a laboratory's LIS will run a report and create a data file, which is then uploaded to the API website. No more manual entry, and clerical errors are eliminated — a win for technology and the laboratory.

I find that you always need to adapt. From the beginning of my time at API, we saw the need to innovate by offering liquid chemistry samples and blood cell photographs. Now we have molecular technologies and other advancements that require new solutions. I find it exciting and refreshing to innovate.

Could you describe the characteristics of the most successful labs in your proficiency testing program?

Consistently successful proficiency testing exposes good laboratory practices — a goal for all laboratories to pursue! Proficiency testing demonstrates the accuracy and reliability of a laboratory.

The most successful laboratories are educated about CLIA requirements and understand the principles behind them. They invest time in personnel training and competency and are disciplined about instrument maintenance, controls, and laboratory practices like proper reagent storage and sample handling. Good laboratories thoroughly document their policies and procedures and keep them up to date.

The laboratories that get the most value out of proficiency testing are engaged in the process and use it as one of many laboratory quality tools. We enjoy helping laboratories see the value of proficiency testing not just as a requirement, but as an important part of their overall quality practices.

Are there any new API projects in development that you can share with MLO readers?

API continually makes adjustments and improvements to its proficiency testing products and services. We often reach out to laboratories to ask what they would like to see and what would be useful to them. From improving the API DataDashboard (where proficiency testing performance may be reviewed at-a-glance) to updating our website, new projects are always at the forefront.

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