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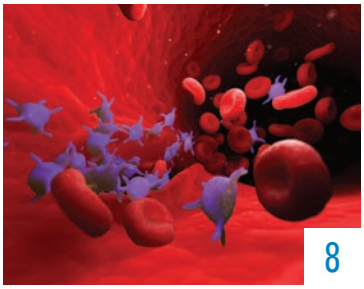
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# Laboratory developed tests

By Christina Wichmann

**Christina Wichmann**
**Editor in Chief**

In the spring 2023 Unified Agenda, published this past June in the *Federal Register*, The U.S. Food and Drug Administration (FDA) announced its plan to release a proposed rule in August 2023 that would change the way that the agency regulates laboratory developed tests (LDTs) by amending the FDA's regulations to make explicit that LDTs are devices under the Federal Food, Drug, and Cosmetic Act. The Unified Agenda provides information on regulatory and deregulatory activities under development throughout the federal government. The August date was an anticipated date and isn't binding. As of this writing, the proposed rule still hasn't been published.

For those who may not be familiar with the rulemaking process, a proposed rule is a preliminary version of a prospective federal agency regulation(s). During the proposed rule process, a federal agency seeks public comment (usually for 60 days) on its preliminary version of regulatory changes. The agency, the FDA in this case, might take these comments into account before finalizing regulatory changes and issuing the final rule.

Per the FDA, LDTs are a class of in vitro diagnostic (IVD) devices that are designed, manufactured, and used within a single laboratory. LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new strains of known infectious diseases) or are the subject of advancing scientific research (e.g., genomic testing for cancer). It is presumed that the proposed rule would add a clause or section within the FDA's IVD regulations (21 CFR 809) that would specify that LDTs are a kind of IVD, and therefore a medical device.

Since 2018, Congress has made attempts to address LDT regulation through the Verifying Accurate, Leading-Edge IVCT Development (VALID) Act. In December 2022, the VALID Act was included in the year-end omnibus spending package, but it was ultimately cut out. It looks like the FDA is going forward since Congress did not.

In recent years, the FDA has indicated its intent to regulate LDTs using a risk-based, phased-in approach due to the increasing number, significance, and complexity of LDTs. In January 2017, the FDA issued a discussion paper with a proposed framework for LDT oversight that would focus on "new and significantly modified high and moderate risk LDTs."[1] Previously marketed LDTs would be grandfathered and would not be expected to comply with most or all FDA regulatory requirements, such as premarket review, quality systems, and registration unless necessary to protect public health. This discussion paper was a follow-up to draft guidance the FDA published in 2014 where it received numerous comments from a broad range of stakeholders. This paper may still provide insight into the direction of the proposed rule, but what will be handled in law and what will be in guidance is unclear.

For readers interested in regulatory updates pertaining to clinical laboratories, our daily LABline e-newsletter provides updates, when available. When the FDA proposed rule is published, we will announce it there. You can sign up for LABline here: https://endeavor.dragonforms.com/loading.do?omedasite=MLONewPref.

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

## REFERENCES

1. Discussion paper on laboratory developed tests (LDTs). Fda.gov. Published 2017. Accessed September 11, 2023. https://www.fda.gov/media/102367/download.



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LABORATORY INNOVATOR

# Mentor, surveyor, award winner

By Christina Wichmann

**Elia M. Mears, MS MT(ASCP)SM** is a Laboratory Field Surveyor for the Laboratory Accreditation Program of The Joint Commission since 2012. Prior to her present position, she was Director of Laboratory Services at LSUHSC-Leonard J Chabert Medical Center in Houma, Louisiana. She earned her two undergraduate degrees from Duke University in Durham, North Carolina, and received her Master of Science degree from the University of St Francis in Joliet, Illinois. She also completed the Notre Dame Executive Management Program.

Ms. Mears has been an active member of AACC since 1992. She is a member of the Nutrition Division, having served as Treasurer (1998 and 1999), Chair Elect (2002 and 2003) and (2012 and 2013), Chair (2004 and 2005) and (2014 and 2015) and Secretary (2016 and 2017). She was also a member of the Personalized Medicine Division where she served as Secretary. She is presently on the Critical Point of Care Division and a member of the Southeast Section where she serves as the present Secretary-Treasurer. Ms. Mears has served in different roles in the AACC, having been on the Nominating Committee, on the Editorial Board of Clinical Lab News, on three previous Annual Meeting Organizing Committees, on the AACC Finance Committee and on the Education Core Committee. She was on the 2023 Annual Meeting Organizing Committee, and the Point of Care Certification Board. She is presently on the Clinical Lab News Board of Editors and ADLM CLS Council.

Ms. Mears has authored numerous articles in the field of nutrition and has lectured on nutritional aspects of the hospitalized patients both nationally and internationally. She was the recipient of the Nutrition Division 2001 Gary-Labbe Award for outstanding contributions in advancing Nutrition Chemistry. Most recently, she was awarded the ADLM 2023 CLS Achievement Award (formerly AACC).

**Congratulations on winning the 2023 Medical Laboratory Scientist Achievement Award from the Association for Diagnostics & Laboratory Medicine (ADLM)! Would you share professional advice and pearls of wisdom with MLO readers who are medical laboratory scientists?**

Thank you very much. It is truly an honor to have been the recipient of the AACC 2023 CLS Achievement Award, as the plaque has it written. It was awarded at a time of transition to the Association for Diagnostics and Laboratory Medicine (ADLM) and our profession now being recognized as Medical Laboratory Scientists (MLS).

I have "worn many hats" throughout my professional career and have enjoyed and learned from every role I have undertaken. I have worked at the bench, been an educator in laboratory science programs, laboratory director, each one preparing me for my next role.

It is a well-known fact that the role of the clinical laboratories and MLSs is a vital component of medicine, integral to patient care. Afterall, more than 70% of all patient diagnoses are made because of a laboratory test. Yet, there is a lack of awareness that MLSs are responsible for performing the tests and analyzing/reporting the results. As a medical profession, because we work "behind the scenes," we are hidden or under recognized. Healthcare is experiencing shortages in all professions and the medical laboratory field is no exception, with staffing shortages for a myriad of reasons. And it is getting worse, with the potential to have major implications in the healthcare industry. As MLSs, we need to advocate for our profession and engage in community outreach programs with high school students — introduce them to the role we play, help influence them into learning more about our profession, and that includes the school counselors. We can promote laboratory advocacy by joining professional societies to become a stronger voice in all aspects. We must "cultivate" our workforce.

**Through your role as a Joint Commission surveyor, how have you seen Joint Commission–accredited laboratories successfully promoting laboratory visibility in healthcare organizations?**

Yes, I have had the opportunity to see laboratories promote visibility in healthcare organizations. I have had the opportunity to survey several small organizations in which members of the C-suite are laboratory professionals; two in which the organization's administrators were MLSs. I have witnessed laboratory displays in visitor and patient waiting areas and particularly during National Laboratory Professionals Week, many set up displays for other healthcare professionals to view and learn about the laboratory. Others give laboratory tours to other healthcare professionals for them to understand what happens behind those "closed doors" and how vital lab work is to the overall care of the patient; during the tour, they have the opportunity to understand the education and professionalism involved.

In 2021, The Joint Commission and the American Society for Clinical Pathology (ASCP) joined forces to create the Leading Laboratories Program. When laboratories demonstrate to their leaders, providers, and patients a commitment to quality and excellence, the delivery of patient care is improved. This Leading Laboratory designation is awarded to Joint Commission–accredited laboratories and recognizes their leadership and team members who have prioritized high quality and safe patient care in a very effective manner. The laboratory teams are also leaders and mentors and have proven innovative practices.

The first hospital to have achieved this two-year Leading Laboratory designation was Torrance Memorial Medical Center in Torrance, California in September 2022. I had the pleasure of being one of the survey team members in May 2022 during their journey to achieve this designation. Not only were health system's outcomes, indicators, metrics, and evidence reviewed, but they had to demonstrate excellence in the four key areas of:

- Evaluating quality outcomes
- Supporting professional development
- Cultivating trusted leadership
- Promoting laboratory visibility

The second Leading Laboratory designation was achieved by Lutheran Hospital in Fort Wayne, Indiana in January 2023. Both of these organizations are examples of how a laboratory can elevate the visibility of its team to be recognized for their dedication and commitment to excellence. Perhaps this is just the start of more laboratories' quests to achieve such designation.

### Are there particular 'lessons learned' you can share through your experiences as both a Joint Commission laboratory surveyor and a hospital laboratory director?

Always stay positive. Be an advocate for the profession and be a mentor to the new MLSs in the field. Encourage them to ask questions. Do not hesitate to have conversations with them about growth opportunities "beyond the bench." It does not mean you are telling them to leave the lab, on the other hand, you are opening potential opportunities where our profession can extend in the hospital and with our background be a tremendous asset to the organization. It is an exciting career, play into its strengths. There are leadership opportunities where MLSs can grow into directorship roles and beyond. As a laboratory director, take the lead and discuss investment opportunities in training programs or be willing to serve as a clinical rotation site as the benefit can be tremendous.

As a Joint Commission laboratory surveyor, be a mentor and resource for our new surveyors. With our customers, be collaborative and share best practices observed at other organizations. Promote quality, performance improvement, and patient safety to build a safer health system for all.

### You are a long-time member of the ADLM's Nutrition Division and have authored nutritional articles in regard to caring for patients. Which types of patients should providers be ordering nutritional assessments for and what information does this lab testing provide?

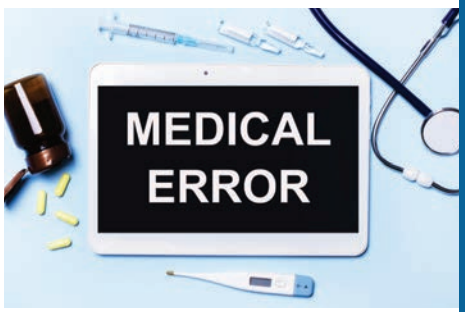
I have been a long-time member of the Nutrition Division, and I am now also a member of the Critical Point-of-Care Testing Division.

I have advocated for nutritional assessment of hospitalized patients for years. We know nutrients provide the necessary raw materials for the metabolic processes for ultimate cell survival. In the form of a well-balanced diet, these nutrients supply the energy and materials used to support cell growth and development. As such, in a state of optimal nutrition, the body repairs itself and fights disease and infection. At the other end of the spectrum, poor or inappropriate nutrition leads to the body's quick deterioration with poor outcomes. Malnutrition can be primary, arising in the absence of disease, because of lack of food due to poverty or social isolation. Secondary malnutrition or disease-related malnutrition is a result of decreased dietary intake during illness. It is this combination of reduced intake and increased requirements due to the body's catabolic state that accelerates the development of malnutrition.

There are reasons why individuals suffering from severe illness or trauma are at high risk of malnutrition, yet there is a lack of awareness and recognition of the problem. Detection of preclinical or subclinical malnutrition has the advantage of identifying and treating the condition early. Fortunately, the incidence of subclinical malnutrition is higher than symptomatic malnutrition, and easier to address. The objectives of an assessment are to identify those patients who will benefit from nutrition therapy, detect and treat the nutritional deficiency, and establish baseline values against to measure the nutrition intervention.

Patients admitted for surgical procedures, trauma patients, patients who have been or are in nursing homes, for example, are prime candidates for an assessment. But all patients should receive a nutritional assessment in order to ensure their nutritional needs are being met, particularly while hospitalized and educated upon discharge. It should be a multidisciplinary team composed of the doctor, nurse, dietician, pharmacist, and the lab.

The laboratory can provide testing parameters to detect the nutritional baselines and continue the testing to monitor improvement or the need for changes in the nutritional intervention. We know timely nutrition support can have positive impacts in patient outcomes and reduce costs. Nutrition is an aspect of patient care that can be enhanced by laboratory involvement allowing the lab the opportunity to be leaders in advancing nutrition to the forefront of patient care and improved outcomes.

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## Fast Facts

**Report highlights public health impact of serious harms from diagnostic error in U.S.**

**Using novel methods, a team from the Johns Hopkins Armstrong Institute Center for Diagnostic Excellence and partners from the Risk Management Foundation of the Harvard Medical Institutions sought to derive what is believed to be one of the first rigorous national estimate of permanent disability and death from diagnostic error.**

**≈ 795,000**

**Americans die or are permanently disabled by diagnostic error each year.**

**75%**

**of the serious harms are vascular events, infections and cancers.**

**15**

**diseases account for 50.7% of the total serious harms.**

**38.7%**

**of total serious harms are caused by stroke, sepsis, pneumonia, venous thromboembolism and lung cancer.**

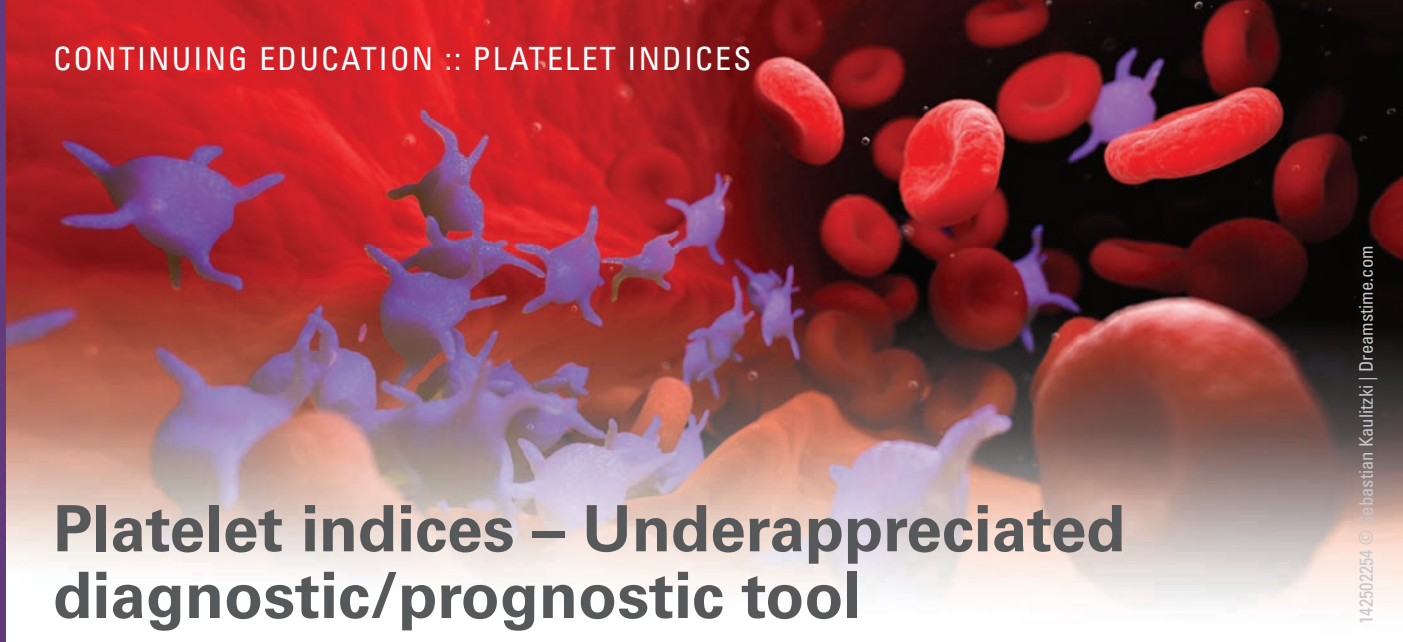
**≈ 11.1%**

**was the overall average error rate across diseases, but the rate ranges widely from 1.5% for heart attack to 62% for spinal abscess.**

**17.5%**

**of stroke cases were missed which was the top cause of serious harm from misdiagnosis.**

**Source:** https://www.hopkinsmedicine.org/news/newsroom/news-releases/report-highlights-public-health-impact-of-serious-harms-from-diagnostic-error-in-us





# Platelet indices – Underappreciated diagnostic/prognostic tool

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

The complete blood count (CBC) is a standard laboratory test performed routinely. The presence of quantitative changes in the number of blood cells and the related morphologic alterations serve as a basis for diagnosis and performing additional laboratory tests and other diagnostic assessments. Today's automated hematology instruments provide a quick and accurate way to achieve these results by incorporating state-of-the-art technology of electrical impedance, conductivity, light or fluorescence absorption, light scatter, and cytochemistry.[13,21,33,52] With these technologies, the CBC has grown from measurements of routine cell counts to performing leukocyte differentials, reticulocyte counts and indices, and platelet counts and indices. More recently, platelet indices have been examined and found to be a potentially useful tool that may provide direct and/or indirect diagnostic information, prognosis, or disease management.[11,13]

## Platelets and platelet indices

The bone marrow produces megakaryocytes that release 1,500–2,000 cytoplasmic fragments of about 3–5 µm in diameter and a volume of 4.5–11 fL. These fragments are platelets that circulate in the blood for about 7–10 days and consist of a complex of various granules, secretory vesicles, and a membranous system. Platelet enumeration and morphologic evaluation have long been a traditional part of the CBC. In a normal, healthy adult, there are 150–450 x $10^9$ platelets/L, with a total blood volume of approximately one trillion platelets and one-third residing in the spleen.[9,59] Platelet counts (PLC) are a known factor in response to various disease states. Activated platelets play a significant role in hemostasis by interacting at vascular injury sites, releasing phospholipids that activate coagulation factors. More recently, platelets have been associated with acute phase reactants in response to inflammatory conditions and can influence other cell types in dealing with various pathophysiology situations.[10] These changes in platelet morphology and proliferation kinetics are reflected in platelet indices and are now thought to be useful as a set of biomarkers for understanding and managing certain diseases or conditions. Platelet indices include the following parameters:

- Mean platelet volume (MPV): The average peripheral blood platelet size.
- Platelet Distribution Width (PDW): Reflects platelet anisocytosis, a function of platelet activation when platelets change in size and morphology.
- Platelet large cell ratio (P-LCR): The percentage of platelets that are larger than 12 fL and are metabolically and enzymatically more active.
- Immature Platelet Fraction (%IPF): Measures the percentage of young, immature platelets present, a test similar to what the reticulocyte count is to red blood cells. The %IPF often increases as the platelet count increases reflecting the early release of immature platelets (reticulated platelets) from the bone marrow. A decreased %IPF result is generally due to bone marrow suppression.
- Plateletcrit (PCT): Calculated as 'platelet count x MPV/10,000.' It is reported as a percentage reflecting the total volume occupied by platelets in peripheral blood. Similar to the PCT is the platelet mass index (PMI), calculated as the 'platelet count x (MPV/1000) fl/nL' and is thought to be a useful marker for inflammation.[12,65,72]

Published reference intervals have been shown to vary based on the analytic platform used. As with all laboratory tests, these intervals should be established by region, ethnicity, and gender. **Table 1** reflects a sample of what has been identified as general reference ranges.[2,3,26,48] Elevated or decreased platelet indices have been identified in various diseases and may provide a simple and inexpensive tool for managing them as noted in some of the following examples. See **Table 2** for a summarized list of common diseases and their effects on platelet indices.

## Cancer

Changes in platelet count numbers can vary due to the presence of cancer cells, inflammation, or chemotherapy. Higher platelet

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### LEARNING OBJECTIVES

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

1. Discuss the technologies and advancements of today's automated hematology instruments.
2. List the platelet indices that are useful in understanding certain disease states.
3. Describe the useful platelet indices in cancer, circulatory, and thrombotic diseases.
4. Describe the useful platelet indices in inflammatory concerns, metabolic concerns, infectious diseases, and other conditions.

counts as seen in breast, endometrial, ovarian, lung, colon, stomach, esophagus, renal, and kidney cancers, may reflect a more aggressive cancer.[51,73,75] Circulating platelets will adhere to the vessel endothelium wall and tumor cells. As more platelets cover tumor cells, there is resistance to the shear blood flow force, which may contribute to evading the host immune response. MPV has been thought of as a surrogate marker for activated platelets generally associated with inflammatory conditions and often present in late-stage cancers. Activated platelets release microparticles containing cytokines and growth factors. It is believed that cancers can induce interleukin-6 (IL-6; a pro-inflammatory cytokine) thus stimulating the production of thrombopoietin that in turn increases platelet production.

| Platelet Index | Term | Description | Reference Values |
|---|---|---|---|
| Platelet count | PLC | Total # platelets | 150,000 – 450,000/µL |
| Mean platelet volume | MPV | Platelet – average size | 9.6 – 13.1 fL |
| Platelet distribution width | PDW | Variation in platelet size | 9.3 – 17.3 fL |
| Plateletcrit | PCT | % fraction of platelets per total blood mass | .22% – .24% |
| Platelet large cell ratio | P-LCR | % of platelets > normal size (i.e., MPV >12 fL) | 15% – 35% |
| Immature platelet fraction | %IPF | % of circulating young platelets (reticulated platelets) | 1.3% – 9.0% |

**Table 1.** Platelet indices reference values (consolidated).
(References: Joergensen, Pogorzelska, Ali, Knight, Gibbs, Tsitsikas, Macey)

- **Breast cancer (BC):** Elevated platelet counts (PLCs) have been associated with the risk of breast cancer while low PLCs were associated with a decreased risk of BC.[20] In general, BC patients tend to have elevated platelet counts (PLC) and MPV levels. Those with metastases when compared to patients with locally invasive breast cancer had higher MPVs and PDWs. Two other platelet-related ratios that have also been evaluated are the MPV/P (mean platelet volume divided by the platelet count) and the PDW/P (platelet distribution width divided by the platelet count). Both of these indices were increased in patients with metastatic BC as opposed to patients with local BC, with results from both groups higher than the control group. These indices also correlated with tumor staging and grade. Another platelet-related marker that has been studied is the platelet-to-lymphocyte ratio (PLR). When elevated, it has been associated with poor overall survival and the risk of recurring breast cancer.[19,63]
- **Gynecological cancers:** It has been reported that women with ovarian cancer had elevated PLCs and a lower number of lymphocytes. In addition, the PDW levels were increased and were associated with poor survival.[49] In contrast, women with cervical cancer demonstrated lower MPV and PDW levels, yet PLCs and PCTs were elevated.[61] Women with endometrial cancer also showed a decreased PDW but had a significantly increased number of platelets as well as an elevated MPV and PCT.[27,29]
- **Colorectal cancer (CRC):** CRC patients have been shown to have significantly higher platelet counts (PLC), PCT, and MPVs than normal or patients with only colon adenomas. The PDW was higher in CRC patients compared to healthy controls, but lower than what was observed in colon adenoma (CA) patients. The blood tests CEA and CA19-9 are often elevated in presence of various cancers including CRC. It has been shown that the PCT and CEA results, when taken together, were more efficient in discriminating CRC patients from CA patients.[74] Further, patients with metastases had higher MPV values when compared to those without metastases.

| Some Common Disease States | Platelet Indices | |
|---|---|---|
| | Elevated | Decreased |
| Breast cancer | MPV, PDW, PLC, PLR | |
| Burkitt lymphoma | PLC, PCT | MPV, PDW, P-LCR |
| Cervical cancer | PLC, PCT | MPV, PDW |
| Cholecystitis, acute | PCT, PDW | MPV |
| Colorectal cancer | PLC, MPV, PDW, PCT | |
| COPD | MPV, PDW | |
| Dengue fever | PDW | MPV, PCT |
| Diabetes type 2 | PLC, MPV, PDW, PCR, P-LCR | PDW |
| Endometrial cancer | PLC, MPV, PCT | PDW |
| Gastric cancer | MPV | PDW |
| Hepatitis C, chronic | MPV, PDW, P-LCR | PLC |
| Hepatocellular cancer | PDW | PLC |
| IBD – Crohn's disease | PLC, PCT, PMI | MPV, PDW |
| IBD – ulcerative colitis | PLC, PCT | MPV, PDW |
| ITP | MPV, P-LCR, %IPF | PCT |
| Laryngeal cancer | PLC, PDW | |
| Lymphoproliferative cancers | | MPV, PDW |
| Lung Cancer, non-small cell | PLC, PDW | MPV, PCT |
| Malaria | PDW, P-LCR | PLC, MPV, PCT |
| Melanoma, malignant | PLC, PDW | |
| Ovarian cancer | PLC, PDW | |
| Pancreatic cancer | PLC, MPV, PDW | |
| Pre-eclampsia | MPV, PDW, P-LCR | PLC, PCT |
| Pulmonary embolism | MPV, PDW | |
| Renal cancer | PLC | MPV, MPV/PLC ratio |
| SARS-CoV-2 | MPV, PDW, P-LCR | PLC, PCT |
| Septic shock | MPV, PDW, P-LCR | PLC, PCT |
| Syphilis | PLC | MPV, PDW |

**Table 2.** A limited list of diseases and the effects on platelet indices.
PLC = platelet count; MPV = mean platelet volume; PDW = platelet distribution width; PCT= plateletcrit; P-LCR = platelet large cell ratio; PMI = platelet mass index; PLR = platelet to lymphocyte ratio

- **Gastric Cancer:** Patients with gastric cancer often show few if any symptoms before disease progression, thus early diagnosis is essential. These patients showed significantly lower PDW levels when compared to healthy controls and correlates well with the patient's age, carcinoembryonic antigen (CEA), and tumor stage. PDW appears to be a predictive factor in noting the progression and prognosis of gastric cancer. Elevated MPV has been associated with

the stage of disease and is thought to be useful in risk stratification and predicting low survival rates.[12,17,35,48]

- **Laryngeal cancer:** A common malignancy generally associated with the use of tobacco products and excessive alcohol intake. Patients with this cancer have elevated platelet counts and PDW, which were significant indicators of a poorer overall survival rate.[30,73]
- **Hepatocellular carcinoma:** These patients had high PDW levels. Patients with higher levels had a worse prognosis than those with a lower PDW.[75] Hepatocellular carcinoma patients with thrombocytopenia and an elevated MPV had a longer overall survival rate. Further, thrombocytopenia in patients with cirrhosis has been associated with morbidity and mortality and is thought to be a risk factor for hepatocellular carcinoma.[55]
- **Lymphoproliferative cancers**: A low MPV has been reported for patients with diffuse large B-cell lymphoma and may reflect a poor prognosis. With Burkitt's lymphoma, PLC and PCT were elevated while MPV, PDW, and P-LCR were decreased.[6] CLL patients with a lower MPV before starting treatment had a worse prognosis.[37] Patients with acute lymphoblastic leukemia (ALL) had lower PDW levels at diagnosis than at remission. There were no significant differences in MPV and PDW when ALL patients were compared to acute myeloid leukemia patients (AML).[1]
- **Malignant Melanoma (MM):** MM patients with thrombocytosis have been shown to have metastasis and shorter overall survival. An elevated PDW also reflects a poor prognosis and has been suggested as an independent prognostic factor in the overall survival of melanoma patients. Higher MPV levels were seen in patients with basal and squamous cell carcinomas when compared to healthy controls, yet MPV was not elevated in MM.[15,30,51]
- **Non-small cell lung cancer:** These patients showed significantly lower MPV and PCT values than the control group, but PDW and platelet counts (PLC) were elevated. PLCs and PCTs were seen to be higher in metastatic patients than for those without metastases.[12,36,47,48]
- **Pancreatic cancer:** An aggressive cancer with a poor prognosis often presenting with few if any, symptoms. The cancer markers CA19-9, CA125, and CEA are elevated generally indicating the presence of cancer but are not cancer specific. Studies have shown that the PLC, MPV, and PDW levels are also elevated in these patients compared to control groups. The PDW showed similar sensitivity and specificity with CA19-9 values suggesting that elevated CA19-9 and PDW levels may serve as significant indicators of pancreatic cancer.[34,48,67]
- **Renal cell carcinoma (RCC):** RCC studies have shown that thrombocytosis may indicate a poor prognosis for certain cancers. It has also been reported that survival times were shorter for RCC patients with low MPVs when compared to normal MPVs, thus serving as a potential prognosis predictor. Further, patients with a low MPV had a worse five-year overall survival than those with higher MPV levels and a greater risk of death. When evaluating the MPV/PLC ratio, decreased values projected a higher risk of disease progression and poor overall survival.[31,36,71]

## Circulatory concerns

According to the Centers for Disease Control and Prevention (CDC), one person dies from cardiovascular disease (CVD) every 34 seconds in the United States each year. CVDs are a group of disorders presenting as four main types: coronary heart disease, stroke, peripheral arterial disease, and aortic disease. It is well known that platelets play a pivotal role in CVDs with the secretion of substances that enhance coagulation, inflammation, thrombosis, and arteriosclerosis.

- **Acute myocardial infarction** (AMI) patients had an elevated MPV when compared to non-AMI patients and have been associated with increased mortality following an MI or with angioplasty with recurring stenosis. It has been suggested that the MPV may serve as a useful prognosticator in patients with CVD and has been linked to other cardiovascular risk factors such as smoking, diabetes, obesity, hypertension, and hyperlipidemia.[14]
- **Acute mesenteric ischemia** is a syndrome due to an embolism or mesenteric venous thrombosis resulting in narrowing or blocked blood vessels. The MPV is significantly higher in such patients and may serve as a prognostic indicator. Those patients with the highest MPV values were less likely to survive vascular damage to the liver and kidneys.[10] Acute ischemic stroke (AIS) is due to thrombotic and embolic mechanisms. AIS patients, after undergoing thrombolytic therapy, experienced higher MPV levels. In one study, there was a correlation between worse outcomes at three months and elevated MPV. Lower MPV levels at hospital admission predicted a good outcome.[70]
- **Pulmonary embolism** (PE) occurs when a blood clot (usually from the leg) travels to a lung artery. Traditionally, clinical manifestations of a pulmonary embolism may be non-specific and are the third most common cause of cardiovascular death. These patients demonstrate higher MPV and PDW values. Studies have shown there is a positive correlation between MPV and the increased risk of PE. Platelet counts, while in the normal range, tended to be significantly lower in the more severe PE cases than in other cases. Elevated MPV and PDW combined with the D-Dimer test provide a strong indication of pulmonary embolism.[23,32]

## Other thrombotic-related concerns

Other thrombotic concerns include thrombocytosis and thrombocytopenia and have been associated with various medical issues as potential risk factors. In one study of surgical patients, those with thrombocytosis (platelet counts > 450 x 109/L) had a high number of post-operative issues such as failed wound healing, increased hospital readmissions, and return to the operating room, while those patients with thrombocytopenia (platelet counts below 150 x 109/L) were at risk with minor complications, post-operative anemia requiring transfusion and some with cardiac events.[28] The presence of thrombocytosis and IL-6 reflect an inflammatory response that often accompanies many cancers. Hypercoagulability and malignancies can result in thromboembolisms a common cause of death in cancer patients.[12]

Thrombocytopenia is due to either 1) platelet destruction/consumption as seen in immune thrombocytopenic purpura (ITP), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP); or 2) hypoproductive thrombocytopenias with outright bone marrow failure generally due to chemotherapy-induced bone marrow toxicity.

- **ITP** is an autoimmune problem that attacks and destroys platelets in error. In hyperdestructive/consumptive thrombocytopenia, the MPV, P-LCR, and %IPF are elevated and significantly higher than in patients with hypoproductive thrombocytopenia. As expected, the plateletcrit (PCT) is low due to significantly fewer platelets.[24]
- **Differentiating ITP** from hypoproductive thrombocytopenia may avoid the need for a bone marrow aspiration.[43,44] In

evaluating PIs, the immature platelet fraction (%IPF) values were particularly high in those patients with hyperdestructive/consumptive thrombocytopenia when compared to those with hypoproductive thrombocytopenia.[24] When compared to controls and patients with myelodysplastic syndrome (a hypoproductive thrombocytopenic condition), ITP patients had significantly lower PLCs and a lower PCT. However, the ITP patients had higher MPV levels than the control group. The PDW for the ITP patients was lower than that of the MDS group, but still significantly higher than the controls.[60] In a similar study, the MPV, PDW, and P-LCR values were significantly higher in ITP patients than in those with hypoproductive thrombocytopenia. In general, MPV, PDW, P-LCR, and %IPF levels tend to be elevated in ITP patients when compared to healthy controls, yet the hypoproductive thrombocytopenia patients did not show this.[44]

## Inflammatory-related concerns

Inflammatory conditions can initiate platelet activation causing morphological changes in the platelets such as swelling and pseudopodia (platelet anisocytosis) and may mark activation of aggregation activity. These changes are usually reflected in increased MPV and PDW.

- **Cholecystitis** most often occurs when the cystic duct of the gallbladder is blocked resulting in the accumulation of gallstones and is typically diagnosed using ultrasonography in addition to other laboratory tests (CRP, ESR, and WBC). Patients with acute cholecystitis have been shown to have significantly lower MPV values yet their PDW and PCT values were significantly higher when compared to a control group, thus these tests may be of value in the early diagnosis of cholecystitis.[10]
- **Inflammatory Bowel Disease** (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). Patients with IBD can develop arterial and venous thrombotic events, ultimately resulting in platelet activation. Active UC patients tend to have significantly higher PLCs but lower PDW values when compared to inactive UC patients and controls. The PCT was also significantly higher while the MPV was lower. Crohn's Disease (CD) patients have higher PLCs, yet significantly lower PDW values when compared to controls. These patients also had an increased plateletcrit (PCT) and platelet mass index (PMI) compared to the controls. When comparing the CD group with the UC group, the PDW values were significantly lower for the CD group. The MPV was lower in the UC and CD groups compared to the controls. Further, active UC (AUC) patients showed significantly higher PLC and lower PDW when compared to inactive UC patients. When AUC patients were compared to healthy subjects, PCTs were significantly higher while the MPV was significantly lower. Active CD patients showed significantly elevated PLC, PCT, and PMI mean values than inactive CD patients and healthy controls.[18]

## Metabolic concerns

- **Diabetes** affects 34.2 million people in the United States, with up to 88 million in the pre-diabetic stage according to the CDC. Type II diabetes is characterized by hyperglycemia, hypertension, dyslipidemia, impaired fibrinolysis, and elevated pro-coagulation factors. These factors contribute to greater platelet activity and potential diabetic angiopathy. Studies have shown that the PCT may be only slightly higher, but the MPV, PDW, PLC, and P-LCR tend to be elevated compared to non-diabetic individuals.[46,58,69] PIs have also been shown to correlate with hemoglobin A1c levels.[46] In these studies, the PDW was significantly higher in diabetics with complications than those without. Thus, platelet indices may be useful in predicting and monitoring diabetic patients.<b style="font-size: 14px;">

## Infectious diseases

Infectious diseases can cause hematological changes including platelets, which have historically been associated with coagulation and hemostasis. Acute infections can inhibit megakaryopoiesis, however, chronic infections tend to stimulate the production of inflammatory cytokines (IL-1, IL-6, and TNF alpha), which in turn activate megakaryopoiesis, resulting in the early release of large, young platelets.

- **Chronic hepatitis C virus (HCV)** patients often develop hepatic fibrosis, cirrhosis, and complications of end-stage liver disease. Platelet parameters from these patients have been shown to correlate with the stage of the disease. Patients with advanced fibrosis demonstrated significantly lower platelet counts while the MPV, PDW, and P-LCR were all elevated.[57]
- **Malaria** is a blood parasitic disease, a result of protozoan infection via a mosquito vector. A decreased platelet count is the most frequent complication of malaria most likely due to sequestration. The PLC, MPV, and PCT are decreased when compared to healthy adults. The PDW and P-LCR are increased when compared to healthy individuals. It has been reported that the P-LCR and PCT are sensitive and specific markers in the diagnosis and prognosis of severe malaria infections. As the PLC and PCT decrease, increased levels of parasitemia are observed thus they may serve as useful markers for disease progression. Because these changes in platelet parameters are thought to reflect higher levels of parasitemia, platelet degranulation occurs resulting in the release of platelet factor 4, which is thought to kill malarial parasites.[7,61]
- **Dengue fever** is a mosquito-borne viral disease that is generally found mostly in tropical/subtropical areas. Along with typical symptoms of fever, rash, muscle aches, and joint pain, patients with dengue fever may also have abnormal platelet indices. Low MPV and PCT are observed along with an elevated PDW. As with malaria, disease severity can be reflected in platelet indices changes.[39]
- In a **syphilis** study with over 2,000 patients with primary and secondary syphilis, there was significant thrombocytosis and decreased MPV and PDW when compared to healthy individuals. When treated, these abnormalities were resolved. The elevated platelet count was shown to correlate with other syphilis markers such as RPR, cerebral spinal fluid-WBC, CSF-protein, and CSF-VDRL. In contrast, decreased MPV and PDW were negatively associated with these parameters.[25]
- **SARS-CoV-2 (COVID-19)** studies have indicated a relationship between platelet indices and COVID-19-positive patients. In critically ill COVID-19 patients, elevated D-dimers were present along with a prolonged prothrombin time (PT) and a modest decrease in platelets. Viral infections have been known to cause platelet activation thus releasing chemokines, which cause changes in platelet indices. COVID-19 patients showed significantly higher MPV, P-LCR, and PDW levels when compared to COVID-19-negative patients. Further, platelet counts (PLCs) and plateletcrits (PCTs) were lower than those of COVID-19-negative patients, though not at a significant

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**Table 3**. Hematology anlyzers and platelet indices
(Source CAP Today, 2022) https://www.captodayonline.com/2022/ProductGuides/10-22_CAPTODAY_Hematology.pdf

level. In another study with COVID-positive children, the PCT was lower when compared to other respiratory infections, though again, not at a significant level. In this same group, the MPV and the PDW were significantly higher than in the control group.[16] A small number of COVID-positive patients showed an increased %IPF when compared to normal. In another study, the platelet-to-lymphocyte ratio (PLR) was shown to be elevated.[40,50]

- **Septic shock** is a life-threatening condition when blood pressure drops precipitously after a bacterial, fungal, or viral infection. Studies have shown that patients with septic shock who did not survive had increasing MPV, PDW, and P-LCR levels while the PLC and PCT were decreased. P-LCR correlated to the MPV in septic shock patients. The bone marrow may release younger, larger platelets due to stress-induced platelet destruction, which also results in decreased PLCs.[19,56]

## Other concerns

- **Pre-eclampsia** (PE) is a serious complication in 3–8% of pregnancies characterized by high blood pressure and proteinuria often leading to maternal morbidity and even mortality. In addition, 5%–10% of women with uncomplicated pregnancies may have a decreased PLC of <150,000/µL, with about 70%–80% having a continuous drop in platelets (gestational thrombocytopenia; PLC<70,000/µL). This type of thrombocytopenia is similar to ITP and is not always readily differentiated. The PCT was significantly decreased in women with severe and mild pre-eclampsia when compared to a control group. The platelet count (PLC) significantly decreases as the degree of severity of pre-eclampsia progresses.[4,52,64] The MPV, PDW, and P-LCR are elevated in severe PE as opposed to mild PE and control groups. These changes in MPV and PDW correlated with increases in blood pressure and thus may be useful in the early detection of pre-eclampsia and its severity.[65] In healthy individuals, the MPV and PDW are proportionally related, however, in preterm labor, the MPV has been noted to decrease as the PDW increases.[48] Of interest, patients experiencing a missed abortion showed elevated PLC, PCT, and PMI, while those with recurrent miscarriages showed elevated PDW.[8,66]
- **Chronic obstructive pulmonary disease** (COPD) is an inflammatory condition that is complicated by various comorbidities including pulmonary hypertension (PH). Platelets are thought to be part of the pathogenesis and the progressive nature of COPD. Platelet activation in COPD patients results in an elevated MPV and correlates with a greater incidence of advanced disease state and was particularly higher with those patients that had PH.[42] Overlap syndrome (OS) involves the existence of COPD and obstructive sleep apnea syndrome causing platelet activation. Subsequently, both the MPV and PDW are elevated in such patients when compared to healthy controls.[5]

## Discussion

Platelets play an important part in coagulation and hemostasis but also in inflammation, immunity, malignancy, and organ regeneration.[55] Platelet counts certainly provide significant information in the diagnosis and treatment of patients, advances in technology have allowed for closer scrutiny revealing other associated properties of platelets. As platelet numbers increase or decrease as a function of a clinical condition and when activated, platelet indices may also play a part in supporting a diagnosis or prognosis. For example, the PDW may be a more sensitive indicator of platelet activation than the MPV, yet together, as been shown, they can serve as indicators of patient morbidity and mortality.[12] Of interest, elevated plateletcrits (PCTs) have been noted to appear three or more years prior to the diagnosis for some cancers, and for lung cancer, up to ten years before diagnosis.[20,31,36]

Platelets normally circulate in a resting state but upon stimulation, become activated. When activated, conformational changes within platelet glycoprotein IIb/IIIa promote fibrinogen binding that then acts as a bridge for platelet-to-platelet contact resulting in aggregation. Platelet surfaces have receptors for adhesive glycoproteins and are integral in maintaining healthy hemostasis by adhering to damaged blood vessels, aggregating, and enhancing thrombin production. Stimulated platelets undergo morphologic changes, swell, and degranulate. Measurements of platelets that undergo these various changes are reflected in platelet indices (PI).

Platelet indices are often part of an automated CBC, thus readily available and inexpensive to obtain. **Table 3** lists some hematology analyzers that can evaluate various platelet indices. As with other laboratory measurements, variation of normal PI intervals may be dependent on race, age, gender, smoking, alcohol consumption, and physical activity requiring each laboratory to establish reference ranges. Other considerations when measuring platelets and platelet indices are the presence of other cell types, cell fragments, platelet clumps, improper detection of large platelets, and micro red blood cells that may be counted as 'large' platelets. Because platelets are fragile, blood collection utilizing minimal tourniquet pressure and maintaining the specimen at room temperature are optimal practices for platelet analyses. Any delay in analyzing the specimen (must be processed within 120 minutes) can affect changes. The type of anticoagulant used to collect blood may also have an effect.[68] In addition, due to variations in the analytical methodology used, there is also a need to establish harmonization and standardization to ensure accurate data interpretation that can be applied to clinical relevance.[11,48,54]

Chronic infections can stimulate cytokine (IL-1, IL-6, TNF alpha) production thus activating megakaryopoiesis and releasing younger and larger platelets into the blood resulting in an elevated MPV. These larger platelets (high MVP) have more granules, which are

released within the first 24–36 hours, thus more metabolically active.[68] In acute infections, the production of megakaryocytes can be inhibited. Often acute infections result in the destruction of large and active platelets at the inflammatory site(s), thus the MPV may be lower. These changes in the platelet indices have also been noted in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and atherosclerosis.[8,26]

Breast, lung, colon, esophageal, gastric, renal transitional cell, gynecological, melanoma, and glioblastoma cancers have been associated with thrombocytosis. It has been proposed that cancer cells may activate platelets resulting in thrombocytosis. and subsequently, may play a role in promoting tumor growth, angiogenesis, metastasis, and cancer-associated thrombosis. Further, it has been suggested that anti-platelet drugs may mitigate such activities.[41] As platelet numbers increase or decrease, platelet indices can also change and thus serve as indicators of disease presence or progression. For example, metastatic colorectal cancer shows significantly higher MPVs than those patients without metastatic cancer. Elevated MPV values in gastric cancer patients decreased with tumor resection. Patients with thyroid cancer had higher MPV levels than those with benign goiter or normal controls.[36] Changes in the MPV have also been observed in patients with septic shock, appendicitis, pancreatitis, and infective endocarditis.[19]

Platelet indices in themselves, are not uniquely diagnostic but may serve as an adjunct to the early evaluation of various patient conditions. It should be noted that most of the studies cited had certain limitations such as the use of different testing methodologies or noting how blood was collected and stored. Some studies were retrospective with some conflicting reports. Nonetheless, it appears that measuring platelet indices can be useful in following patients. It is inexpensively done as part of a routine CBC and in some cases may obviate the need for further and more expensive testing. More prospective studies of platelet indices are needed to establish consistent normal reference intervals and to further explore how PIs can be used in predicting various patient outcomes including the risk of death as they relate to cancers, infections, inflammation, diabetes, thrombotic concerns, and other serious medical disorders. Identifying abnormal platelet indices could play a useful role in confirming, monitoring, and/or predicting certain disease outcomes.

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*References continued online at https://mlo-online.com/53069909*

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# Platelet indices – Underappreciated diagnostic/prognostic tool

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## TEST QUESTIONS

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1. **Today's automated hematology instruments incorporate the following technologies**
   - A. Cytochemistry, light scatter, and electrical impedance only
   - B. Electrical impedance, conductivity, light/fluorescence absorption
   - C. Light scatter and cytochemistry
   - D. Both B. and C.
2. **Recently it has been found that _____ _____ can be useful in understanding many pathophysiological conditions.**
   - A. RBC count
   - B. Platelet indices
   - C. Platelet function
   - D. None of the above
3. **Which parameters are included in platelet indices?**
   - A. MPV, PMI, PCT, %IPF, P-LCR, and PDW
   - B. PDW, PMI, PCT, and MPV
   - C. PDW, %IPF, PMI, and PCT
   - D. MPV and PDW
4. **Thrombocytosis has been noted in the following cancers except**
   - A. Colorectal cancer
   - B. Ovarian cancer
   - C. Renal cell carcinoma
   - D. Basal cell carcinoma
5. **Ovarian, endometrial, gastric, and non-small cell lung cancer all show elevated MPV levels.**
   - A. True
   - B. False
6. **There are no significant differences in _____ and _____ in ALL and AML patients.**
   - A. MPV; PCT
   - B. PCT; PDW
   - C. MPV; PDW
   - D. PDW; PLC
7. **_____ _____ has shown similar sensitivity and specificity with CA19-9 and PDW levels.**
   - A. Malignant melanoma
   - B. Hepatocellular carcinoma
   - C. Pancreatic cancer
   - D. Gastric cancer
8. **Cardiovascular disease plays a pivotal role in the secretion of substances that enhance**
   - A. Inflammation and thrombosis
   - B. Arteriosclerosis
   - C. Coagulation
   - D. All of the above
9. **The _____ value for AMI, AIS and PE patients serves as a good use of risks and outcomes for the patient.**
   - A. MPV
   - B. PCT
   - C. PDW
   - D. P-LCR
10. **When comparing post-operative patients who had thrombocytosis versus thrombocytopenia, there have been different associated risk factors identified with each.**
    - A. True
    - B. False
11. **Which platelet indices tend to be elevated in ITP patients when compared to healthy controls?**
    - A. PCT, PMI, and MPV
    - B. MPV, PDW, P-LCR, and %IPF
    - C. MPV, PDW, and PCT
    - D. P-LCR, %IPF, PMI, and PCT
12. **As an early indicator of cholecystitis, patients have been shown to have a lower _____, but higher _____and _____ compared to a control group.**
    - A. PCT; MPV; PDW
    - B. PDW; P-LCR; PCT
    - C. P-LCR; PCT; %IPF
    - D. MPV; PDW; PCT
13. **Which disease event results in the activation of platelets?**
    - A. Dengue fever
    - B. Inflammatory bowel disease
    - C. ITP
    - D. None of the above
14. **In diabetes, platelet indices have shown to correlate with**
    - A. Random glucose levels
    - B. BUN/Creatinine levels
    - C. A1c levels
    - D. Total cholesterol levels
15. **Acute infectious diseases tend to stimulate the production of inflammatory cytokines, which activate megakaryopoiesis.**
    - A. True
    - B. False
16. **Which platelet factor is thought to kill malarial parasites?**
    - A. 2
    - B. 3
    - C. 4
    - D. 6
17. **In syphilis, which parameter correlates with other markers of the infection?**
    - A. Elevated platelet count
    - B. Decreased platelet count
    - C. Increased MPV
    - D. Increased PDW
18. **In _____, the bone marrow may release younger, larger platelets which results in decreased platelet counts.**
    - A. COVID-19
    - B. Dengue fever
    - C. Syphilis
    - D. Septic shock
19. **Pre-eclampsia presents a thrombocytopenia that is similar to**
    - A. Septic shock
    - B. ITP
    - C. Diabetes
    - D. Malaria
20. **In COPD, platelet activation correlates with a greater incidence of advanced disease state and which of the higher parameters than those with pulmonary hypertension?**
    - A. P-LCR
    - B. PDW
    - C. MPV
    - D. PCT

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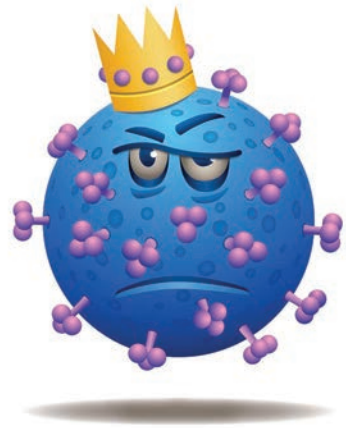

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# Addressing STI challenges: A diagnostic update on the current landscape and future strategies

By Chibuzor M. Babalola, MD, MPH; Jeffrey D. Klausner, MD, MPH; Andy Liu, BS

The relentless rise in curable bacterial sexually transmitted infections (STIs) across the United States is an urgent public health crisis.[1] In the latest report from the Centers for Disease Control and Prevention (CDC) in 2021, there was a staggering number of cases, including over 1.6 million new cases of *Chlamydia trachomatis*, 700,000 for *Neisseria gonorrhoeae*, and 170,000 for syphilis. This represents a continued increase in *C. trachomatis* and *N. gonorrhoeae* infections, and a notable 32% increase in syphilis cases compared to the preceding year.[1,2]

In addition to the increases in reported STIs, antimicrobial resistance is also growing.[2] Nearly half of *N. gonorrhoeae* infections were antimicrobial resistant in 2021, signaling a critical challenge.[2] Moreover, the emergence of resistance in infections like *Mycoplasma genitalium* has raised additional concerns.[3,4] Although not recommended for routinely screening, *M. genitalium* is prevalent in 15% to 40% of cases of persistent or recurrent urethritis.[3,4] Estimates point to around three million prevalent cases of *M. genitalium* in the United States.[5]

Effective management of the STI epidemic will require the adoption of innovative and accurate diagnostic tools that are practical, rapid, and available at or near the point of care. Improved diagnostics will not only expedite STI detection and treatment, but also detect drug resistance in real time to promptly guide therapy and foster antimicrobial stewardship.

## Diagnostic landscape

### *Chlamydia trachomatis and Neisseria gonorrhoeae*

Molecular technology has significantly transformed the field of STI diagnostics. Today, rapid point-of-care assays based on nucleic acid amplification tests (NAATs) are available for the detection of *C. trachomatis* and *N. gonorrhoeae* and increasingly recognized as gold standard assays due to their performance profiles, with sensitivities and specificities exceeding 95%.[6] A noteworthy development lies in newer molecular diagnostic technologies, which are designed as combination assays, allowing for the detection of multiple pathogens to potentially enhance case management.[7]

Three point-of-care Food and Drug Administration (FDA)–cleared devices are currently available for the simultaneous detection of *C. trachomatis and N. gonorrhoeae*. These polymerase chain reaction (PCR)-based tests amplify target pathogen genomic DNA to provide results within 30 to 90 minutes, without requiring user calibration. The characteristics and performance of the FDA-approved molecular point-of-care *C. trachomatis/N. gonorrhoeae* tests are highlighted in **Table 1**. Some have received a Clinical Laboratory Improvement Amendments (CLIA) waiver.[8-11]

### *Mycoplasma genitalium*

Although *M. genitalium* screening is not routine in the United States, CDC guidelines now recommend for testing in cases of

| FDA Approval | Operational Characteristics | Time to results | Specimen Type | C. trachomatis performance | N. gonorrhoeae performance |
|---|---|---|---|---|---|
| Jan 2013* | • Cartridge-based.<br>• Table-top instrument.<br>• No manual calibration.<br>• Requires electricity.<br>• Molecular targets: Two conserved chromosomal targets for N. gonorrhoeae (NG2, NG4) and one for C. trachomatis (CT1). | 90 minutes | Patient and clinician collected urogenital swabs and urine in males and females. | Sensitivity: 92.5% to 96.1%<br>Specificity: 99.1% to 99.3% | Sensitivity: 92.5% to 96.1%<br>Specificity: 97.3% to 100% |
| May 2019† | | | Extragenital swabs: Pharynx and Rectum | Sensitivity: 95.9% (Pharynx) 86.6% (Rectum)<br>Specificity: 99.7% (Pharynx) 99.4% (Rectum) | Sensitivity: 94.7% (Pharynx) 91.2% (Rectum)<br>Specificity: 98.8% (Pharynx) 99.6% (Rectum) |
| April 2021 | • Cartridge-based.<br>• Table-top instrument.<br>• No manual calibration required.<br>• Requires electricity.<br>• Molecular targets: Two genomic DNA targets for N. gonorrhoeae and one for C. trachomatis. | 30 minutes | Female vaginal swab (clinician collected or patient-collected in a clinical setting) and male urine | Sensitivity: 92.5% to 96.1%<br>Specificity: 99.1% to 99.3% | Sensitivity: 92.5% to 96.1%<br>Specificity: 97.3% to 100% |
| August 2021<br>2nd generation in March 2023 | • Palm-held single-use.<br>• Power adapter is available.<br>• Visual interpretation.<br>• Molecular targets: N. gonorrhoeae genomic DNA and C. trachomatis cryptic plasmid DNA | 30 minutes | Patient-collected vaginal swab | Sensitivity: 96.4% to 97.9%<br>Specificity: 96.8% to 98.8% | Sensitivity: 95.0% to 100%<br>Specificity: 99.0% to 99.1% |

**Table 1**. Characteristics of the FDA-approved point-of-care NAATs for C. trachomatis/N. gonorrhoeae detection.

NAAT, Nucleic Acid Amplification Test.
*Categorized as "moderate complexity" under the Clinical Laboratory Improvement Amendment.
†Yet to receive Clinical Laboratory Improvement Amendments - waiver.

recurrent or persistent urethritis or cervicitis.[3,4] Rapid point-of-care *M. genitalium* tests are not available in the United States, but two automated high-throughput laboratory-based NAATs have FDA clearance for detecting *M. genitalium* in male and female specimens, including urine and self-collected vaginal swabs.

The first assay uses transcription-mediated amplification and hybridization protection assay technologies to detect the 16s rRNA of *M. genitalium*.[12] The second, recently FDA-cleared in 2022, is a reverse transcriptase PCR, four-in-one multiplex test to simultaneously detect *C. trachomatis, N. gonorrhoeae, Trichomonas vaginalis, and M. genitalium* DNA.[13]

## Key points

- Improved diagnostics will play a crucial role in combatting the STI epidemic.
- Molecular advancements and rapid assays enhance STI management.
- The threat of resistance requires ongoing surveillance and innovative technologies.
- Diagnostic stewardship is vital for advancing antimicrobial stewardship efforts.

### *Resistance-guided therapy*

*N. gonorrhoeae* and *M. genitalium* are of concern due to their increasing resistance to antibiotics.[3] Both STIs are on the CDC's resistant threat watchlist.[14] Over time, *N. gonorrhoeae* has quickly developed resistance to nearly all antibiotics used in its treatment. The CDC's Gonococcal Isolate Surveillance Project monitors antimicrobial susceptibility in about 3% of urethral isolates in the United States and of the isolates sampled in 2021, around half showed high minimum inhibitory concentrations (MIC) to at least one antibiotic.[3,15] However, it is worth noting that all cases still respond to injectable ceftriaxone, an antibiotic from the cephalosporin class and the current recommended treatment for uncomplicated *N. gonorrhoeae* infection.[2]

While there is yet to be a standardized laboratory criterion for cephalosporin resistance in *N. gonorrhoeae,* reduced susceptibility is generally considered when MICs exceed 0.5 µg/ml. Notably, there have been identified cases of isolates with decreased susceptibility to ceftriaxone (MIC: 1.5-4.0 µg/ml) in East Asia and Europe.[3,15]

Laboratorians and healthcare providers are urged to stay vigilant and report instances of cephalosporin resistance or treatment failure to the CDC. Clinical laboratories should also send specimens to the CDC for further analysis. When *N. gonorrhoeae* treatment failure is suspected, culture and antimicrobial susceptibility testing are still the standard assessment. Agar dilution is the preferred method for susceptibility testing, although qualitative MIC determination using the Etest is acceptable.[3,15]

To improve treatment decisions and slow the spread of antimicrobial resistance, there is an urgent need for molecular assays that can identify genetic mutations that predict antibiotic resistance in *N. gonorrhoeae* in real time. Utilizing a resistance-guided therapy approach for *N. gonorrhoeae* may facilitate the use of alternative antibiotics such as ciprofloxacin in susceptible strains, which may decrease the selective pressure for resistance to cephalosporins.[16]

While there are various mutations that are associated with ciprofloxacin resistance in *N. gonorrhoeae*, it is the absence of a single mutation at the serine 91 codon of the gyrase A (*gyrA*) gene that confers susceptibility to ciprofloxacin.[17] As such, real-time PCR-based molecular assays have been developed to predict gonococcal susceptibility to ciprofloxacin, which have been implemented in clinical practice.[17,18] In a multicenter clinical trial assessing resistance-guided therapy through *gyrA* genotyping, a treatment efficacy rate of 100% (1-sided 95% confidence interval [CI], 97.5%–100%) for ciprofloxacin was observed when *gyrA* genotyping predicted susceptibility to ciprofloxacin.[16] In the latest STI Treatment Guidelines, the CDC recommends the use of *gyrA* testing to detect ciprofloxacin susceptibility and to treat with a single oral dose of ciprofloxacin 500 mg among persons with predicted susceptible strains.[15]

Multiple mutations in *pen*A and non-*pen*A genes have been identified as potential markers of *N. gonorrhoeae* resistance to cephalosporins. *Pen*A mosaicism has been linked to ceftriaxone resistance, but not all strains conform to this pattern. Non-*pen*A mutations, including *pon*A (L421P), *pen*B (G120/A121), and *mtr*R (–35delA), are also crucial markers, particularly among non-mosaic strains. Several assays are under development, each with varying sensitivity and specificity.[15] In a study from Canada, an assay that targeted three or more mutations for detection had 98.3% sensitivity but low specificity (66.7%).[19] The most effective mutation combination is yet to be determined. Geographic variation and heterogeneity in molecular markers introduce further complexity, with some mutations being more prevalent in certain regions. Precision could be improved by tailoring assays to the local epidemiology and by increasing genomic surveillance. Future work should evaluate assays in diverse scenarios.[18]

In 2016, a study found high prevalence of macrolide-resistant *M. genitalium* (51% from females and 42% from males).[20] Increasing resistance in *M. genitalium* has led to recommendations that a positive *M. genitalium* result should be routinely followed by a test for resistance.[3,21] Currently, laboratory sequencing methods like Sanger sequencing and pyrosequencing can identify single base macrolide-resistance-mediating mutations at positions 2058/2059 of the *M. genitalium* 23S rRNA gene.[21,22] Rapid diagnostic tests that detect *M. genitalium* resistant mutations to macrolide antibiotics are already available in Europe. Their evaluation is still ongoing in the United States and will represent a pivotal step toward effective management of resistance in the context of *M. genitalium* infections.[3,4]

| FDA Approval | Test Antigens & Time to results | Specimen Type | Sensitivity | Specificity |
|---|---|---|---|---|
| December 2014 | • Antihuman immunoglobulins gold conjugate and highly purified T. pallidum recombinant proteins (TP-15, TP-17, TP44)<br>• Results in 10-15 minutes | fingerstick whole blood, venous whole blood, serum, plasma | 98.0%<br>(95%CI: 95.0-99.2) | 97.2%<br>(95%CI: 94.0-98.7) |
| February 2023 | • A recombinant T. pallidum antigen and Protein A (for test control)<br>• Results in 10-25 minutes | | 94.7%<br>(95%CI: 89.0-97.6) | 95.5%<br>(95%CI: 94.2-96.6) |

**Table 2.** Characteristics of the FDA-approved point-of-care syphilis treponemal antibody tests.

| FDA Clearance | Specimen Type | Test Turnaround Time | Quantitative Titer Range | Sensitivity | Specificity |
|---|---|---|---|---|---|
| November 2015 | serum | 192 tests per 90 minutes | 1:1 to 1:256 | 95.5% (95%CI: 77.2-99.9) | 99.9% (95% CI: 99.3-100) |
| May 2017 | serum, heparinized plasma, EDTA plasma | 100 tests per hour | 1:4 to 1:64 | 92.5% (95%CI: 87.3-95.6) | 97.9% (95%CI: 96.7-98.6) |
| June 2018 | serum, plasma | 190 tests per hour | 1:1 to 1:2048 | 99.1% (95%CI: 95.2-99.9 | 99.9% (95%CI: 99.4-100) |

**Table 3**. Characteristics of the FDA-cleared automated RPR syphilis tests.
*All tests detect antibodies to non-treponemal reagin (cardiolipin and lecithin).

### *Syphilis*

The bedrock of syphilis diagnosis still lies in serologic testing.[23] Both treponemal tests (detecting IgG or IgM antibodies against *Treponema pallidum*) and nontreponemal tests (identifying non-specific antigens, such as cardiolipin produced in response to an active infection) are essential for screening and confirming diagnosis of an active infection.[23] Gaps in completing the testing-to-treatment cascade have contributed to the surge in syphilis cases in the United States.[1] Rapid point-of-care serologic treponemal tests may bridge these gaps.

Commercially available today are two FDA-cleared rapid point-of-care treponemal tests with good performance (see test characteristics in **Table 2**).[24-26] The first, receiving CLIA waived status in 2014, employs lateral flow to detect treponemal antibodies by binding to recombinant *T. pallidum* proteins to generate a visual band that indicates a reactive result.[25,26] The second test, recently achieving its CLIA waiver in 2023, uses a proprietary dual immune-chromatographic path platform to simultaneously detect antibodies against HIV types 1 and 2 and *T. pallidum* (for syphilis). It employs a microreader for results.[26] Treponemal antibodies in an infected sample bind the recombinant *T. pallidum* antigens integrated into both assays (**Table 2**).

Rapid point-of-care treponemal tests could facilitate reflex confirmatory non-treponemal testing in the reverse syphilis testing algorithm to guide timely treatment decisions. The manual Rapid Plasma Reagin or Venereal Disease Research Laboratory tests are the standard for non-treponemal serology. Recently, three FDA-cleared, fully automated RPR tests have been introduced in the United States.[27-33] One automated platform detects treponemal and nontreponemal antibodies using a *T. pallidum* fusion protein (rTP47/rTP17) and cardiolipin coated fluoromagnetic beads, while the other two automated platforms are based on the manual RPR test and utilize proprietary hardware and software tools to collect and analyze the RPR test results **(Table 3)**.[27-33] While these automated RPR instruments can shorten processing times and reduce staff workloads and interpretation errors, more studies are necessary to better understand the performance of these devices to guide the implementation of these tests across laboratories.[27] Lastly, a rapid point-of-care assay that can accurately and simultaneously detect treponemal and non-treponemal antibodies is likely to be available in the near future.[34,35]

## Diagnostic stewardship

Antimicrobial stewardship is a strategy against antimicrobial resistance and a priority in mitigating resistant sexually transmitted pathogens as well as other infectious diseases. Stewardship focuses on preventing antibiotic overuse, misuse, and abuse.[36] Delayed STI results resulting in empiric therapy has been a major contributor to antimicrobial resistance in STIs.[37] As such, accurate rapid diagnostics can overcome obstacles in timely diagnosis and counteract the rise of antimicrobial resistance. Furthermore, rapid diagnostics that afford real-time, resistance-guided therapy could also streamline antimicrobial use in STIs.

Meanwhile, the concept of "diagnostic stewardship" is worth highlighting. Recently introduced in the domain of antimicrobial stewardship, diagnostic stewardship aims to ensure that the right test is administered to the right patient at the right time.[38] As modern molecular diagnostic technologies advance into multiple target combination assays, cautiousness is advised, to prevent overdiagnosis and overtreatment, which could undermine the primary purpose of antimicrobial stewardship.

## Conclusion

The STI crisis and growing antimicrobial resistance underscore the need for accurate, clinically actionable diagnostics. Advancements in molecular diagnostics offer rapid STI testing, while serologic tests remain pivotal for syphilis. Addressing resistance requires ongoing surveillance and the implementation of assays for detecting resistance mutations. Embracing diagnostic stewardship together with innovative technologies will ensure timely interventions and effective antimicrobial use.

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# Infective endocarditis: Increased prevalence or improved diagnostics?

By Diane C. Halstead, PhD, MASCP, D(ABMM), F(AAM); Sabine R. O'Laughlin, MD, FACP

The incidence of infective endocarditis (IE), an infection of the heart endothelium, ranges between 5 to 7.9 cases per 100,000 individuals per year in the United States.[1] If not diagnosed and treated promptly, organisms causing IE can damage or destroy heart valves leading to life-threatening complications and mortality. Diagnosis is challenging without a high index of suspicion based on patient history and presentation traditionally followed by blood cultures, imaging, serological, and molecular studies. A notable number of IE cases have been caused by fastidious, culture-negative organisms including *Bartonella* spp. Communication with laboratory staff regarding the physician's suspected diagnosis along with the use of molecular testing can maximize the number of confirmed cases of *Bartonella*.

## Case description

This case describes an immunocompetent, well-developed, and alert adult male with a history of progressive weakness, persistent fever at 39°C max, shortness of breath, abdominal pain, weight loss, fatigue, painless hematuria, and anemia — symptoms compatible with subacute native valve endocarditis.[2] The patient had a history of hypertension and hypercholesterolemia but denies any preexisting heart or lung disease. Maternal family history was positive for heart disease. Physical examination of his abdomen was remarkable for left upper quadrant/flank area tenderness and splenomegaly with a wedge infarct confirmed by computed tomography (CT). An upper gastrointestinal endoscopy and colonoscopy were unremarkable and therefore an unlikely cause of anemia. Microscopic review of bone marrow showed no pathological findings.

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Baseline studies included an elevated erythrocyte sedimentation rate of 61 mm/hour and complete blood count (hemoglobin 8.5 g/dL and hematocrit 25.1%) and differential blood count within normal limits. Blood cultures incubated for five days at 35°C and urine culture showed no growth. Urinalysis showed moderate blood and nineteen red blood cells per high power field. Serology tests were negative for syphilis, EBV, hepatitis B and C, leptospirosis, autoimmunity, and Lyme disease. Indirect immunofluorescent antibody (IFA) tests were positive for *Bartonella henselae* IgG >1:512 (reference negative < 1:64) and IgM negative (reference negative <1:20); *Bartonella quintana* was IgG negative (reference negative <1:64) and IgM negative 1:80 (reference negative <20) by.

A transesophageal echocardiogram (TEE) showed evidence of a highly mobile vegetation on the left cusp of the aortic valve associated with moderate-to-severe regurgitation consistent with infective endocarditis (IE). The patient was scheduled for an aortic value replacement with a mechanical valve prosthesis. At surgery, the patient's valve showed evidence of granulation tissue and associated inflammation consistent with IE. The left coronary flap (cusp) was damaged and found to have a large vegetation that was excised and sent to the laboratory for histopathology and culture. The immunohistochemical analysis, modified Warthin-Starry silver-stained sample and conventional bacterial culture were negative. Remaining paraffin-embedded tissue was sent for a polymerase chain reaction (PCR) test designed to differentiate the most common species of *Bartonella*. Post-amplification melt curve analysis of the PCR product confirmed the presence of *B. henselae*.

## Case discussion

Infective endocarditis occurs when organisms attach to one or more heart valves or endocardial tissue and cause infection. If not treated promptly, these organisms can damage or destroy heart valves leading to life-threatening complications. There are at least 45 Bartonella spp. with worldwide distribution, 13 proven or likely to be human pathogens.[2] Although *Staphylococcus aureus*, coagulase-negative staphylococcus, viridans streptococci, and enterococci are common causes of IE, other fastidious organisms including *Bartonella quintana* and *Bartonella henselae* cause a small but notable number of IE cases.

Members of the genus *Bartonella* (formerly *Rochalimaea*) characteristically are small, fastidious, aerobic intracellular Gram-negative bacilli targeting RBCs and endothelial cells of blood and lymphatic vessels. *B. quintana* causes trench fever primarily in homeless persons and chronic alcoholics infested with human body lice that serve as a reservoir and vector for the pathogen. In contrast, *B. henselae* is well known as the causative agent of cat scratch disease (CSD) due to exposure through a cat lick, scratch, bite, or arthropod vector, the cat flea. However, the patient did not have a history of valvular disease, nor did he report a cat exposure. The major risk factors for *B. henselae* IE include preexisting valvular disease and contact with cats, an asymptomatic zoonotic reservoir with chronic bacteremia.

To establish a diagnosis of IE, the Modified Duke Criteria were used, based on pathological and clinical major and minor criteria.[3,4] This patient had two major criteria (vegetation and regurgitation plus endocardial involvement confirmed by surgery) and one minor criteria (fever >=38°C) meeting the criteria for

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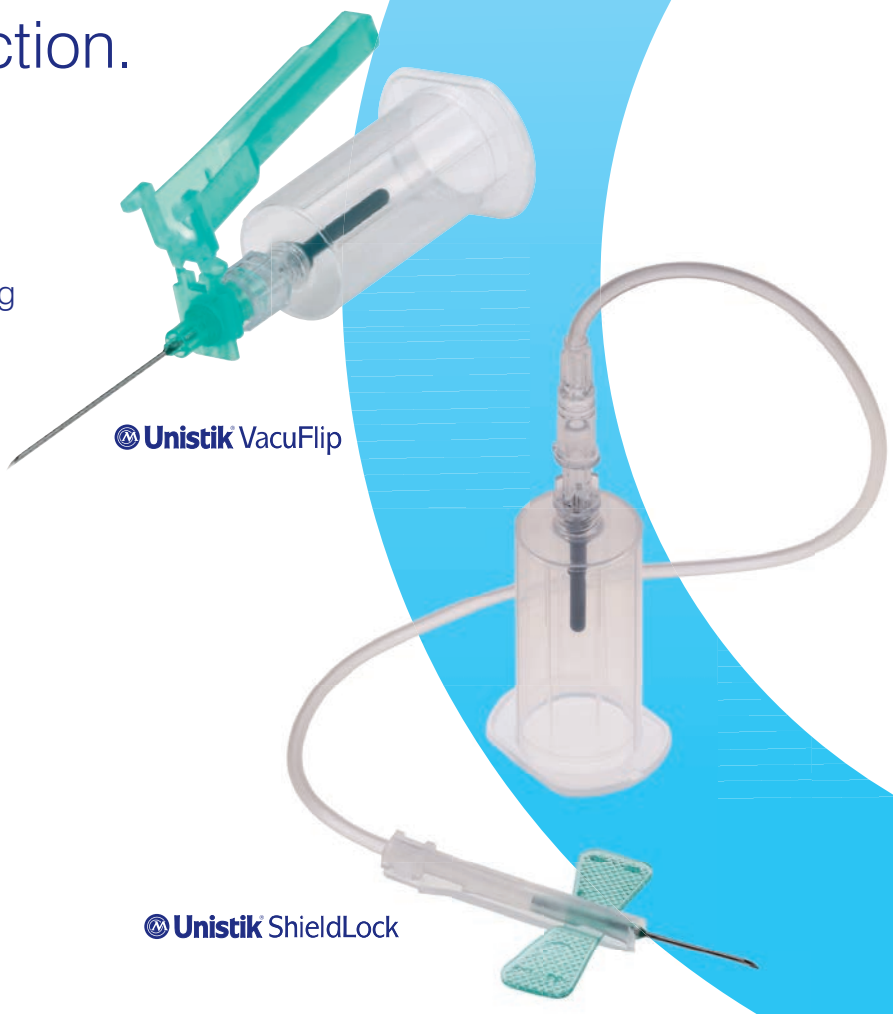


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an active infection causing IE. The role of the laboratory is paramount in determining the offending agent since patients infected with other organisms known to cause IE can exhibit similar clinical manifestations.[2] At least 2–3 blood culture sets from separate venipunctures with a maximum recommended blood volume per bottle and serology tests for IgG and IgM antibodies directed against the suspected agent should be included in the initial battery of tests. In addition, excised valvular tissue taken during surgery should be submitted for histopathology examination and culture.

Although *Bartonella* species can grow on cell-free media containing heme at 35–37°C with 5% supplemental $CO_2$, e.g., chocolate agar, they may take at least 2–3 weeks to grow.[2,3] By default, approximately 20% of cultures are positive due to the fastidious nature of *Bartonella*, lack of communication in alerting the laboratory of the suspected diagnosis, or empiric antibiotic therapy prior to culture.[2,5,6]

The IFA, considered a reference method for supporting a diagnosis of *Bartonella*, was positive for *B. henselae* IgG >1:512. Although *B. quintana* IgG was negative, the significance of a positive IgM 1:80 is unknown. That said, cross-reactive antibodies do occur between *B. hensalae* and *B. quintana*, as well as between *Bartonella* spp. and *Chlamydia* spp. and *Coxiella burnetii* that cause IE.[3,5,6] Another serological test, Western blotting has been used to confirm a diagnosis of *Bartonella* for patients with a negative *Bartonella* IFA but positive PCR and clinical findings.[7] *B. henselae IE* can also masquerade as small vessel vasculitis (SVV) with a similar presentation, e.g., fever, fatigue, renal and valvular involvement. If suspected, *B. henselae* IE may be differentiated from SVV by low complement 3 and antineutrophil cytoplasmic antibodies (ANCA).[8] Echocardiography plays a key role in identifying patients who have negative blood cultures but present with signs and symptoms of IE and require surgery and valve replacement. When a valve is damaged, blood leaks back into the left ventricle, causes regurgitation, prevents the heart from efficiently pumping blood to the rest of the body, and results in fatigue and shortness of breath as seen in this patient. Although the use of platelet lymphocyte ratios have shown prognostic value in cardiovascular conditions, there is limited data regarding its predictive role in patients with IE.

Since laboratory diagnosis of *Bartonella* IE using traditional culture techniques remains challenging, post-amplification melt curve analysis of the PCR product from infected tissue was used to confirm the presence of *B. henselae*. Other methods that have been used include serum PCR since this sample is often readily available and a riboflavin synthase-encoding ribC gene along with a one-step procedure to prevent amplicon carryover and a thermal cycler to differentiate *Bartonella* species and shorten the delay in diagnosis before valvular surgery.[9] Even though there are no in vitro antibiotic susceptibility test breakpoints because of the fastidious nature of *Bartonella*, knowing the etiology provided direction in selecting optimal therapy with IV vancomycin, ceftriaxone and gentamicin, metoprolol beta-blocker, and warfarin anticoagulant for this patient.[2,3]

## Conclusion

A literature search of publications over the past 10 years suggests that there has been a significant increase in the number of cases of IE caused by *B. henselae*. This increase may reflect an improved recognition of *Bartonella* causing IE and the use of molecular tests with greater sensitivity and specificity in identifying *Bartonella*. Clinicians in turn may be more enthusiastic in ordering tests that provide more timely and reliable results for successful patient outcomes.[6] Of note, improvements in diagnosis, management, and treatment of patients with IE have also been attributed to the use of early interventions with a multidisciplinary team including specialists in cardiology, infectious diseases, imaging, surgery, and improved communication with laboratory staff regarding their suspected diagnosis to maximize the number of confirmed cases of *Bartonella*.[10]

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# Fanconi anemia: A diagnostic approach to diagnosis and treatment

By Floyd Josephat, Ed.D., MLS(ASCP) and Morgan Duke

Fanconi anemia (FA), also known as inherited aplastic anemia, is a disease that causes bone marrow failure and many physical abnormalities. FA is a rare, fatal disease that affects 1 out of 136,000 newborns and usually results in death before age ten if undiagnosed.[1] FA is caused by a genetic mutation in a DNA repair pathway. As a result of this mutation, cell death increases in the bone marrow, which causes a decrease in red blood cells, white blood cells, and platelets. These cells help transport oxygen, fight infections, and clot blood. Therefore, without these cells, serious complications occur.

According to the National Heart, Lung, and Blood Institute, anemia is any condition leading to a shortage of red blood cells.[2] There are different types of anemia, some not life threatening and some that are very serious. Fanconi anemia is a type of serious anemia that is chronic and has a strong genetic component. It is like DBA, Diamond-Blakfan anemia, and usually present with similar symptoms. One of the symptoms of DBA and FA is a failure of the bone marrow to produce an adequate supply of red blood cells due to bone marrow failure. This shortage causes the anemic state in patients and leads to an overall depletion of oxygen throughout the body.[3] In addition, FA patients can experience some physical abnormalities that are sometimes associated with this disorder. Fanconi anemia is caused by FA complementation gene (FANC) mutations that significantly reduce genomic stability.[4] There are 23 FANC genes found to be involved in DNA repair, and most are inherited recessively. Only two are X-linked or autosomal dominant: FANCB and FANCR.[1]

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## Diagnostic criteria

As previously stated, FA is only suspected after the development of pancytopenia, so the disease is far along when detected. Therefore, it is recommended to screen all children, or all young adults diagnosed with aplastic or hypoplastic anemia for FA.[5] However, if parents undergo genetic testing and both are carriers of the FA gene, testing can be performed on the fetus. According to Soulier, "increases of fetal hemoglobin, serum alpha-fetoprotein, and macrocytosis are commonly noted in FA."[5] An increase in fetal hemoglobin is evident of excessive destruction of red blood cells, while alpha-fetoprotein helps indicate any chromosomal abnormalities, which are both characteristics of FA. Fetal hemoglobin and serum alpha-fetoprotein tests can be performed while the individual is pregnant or after birth. The primary genetic test for FA is a chromosomal breakage test. A chromosomal breakage blood test elicits the sensitivity of FA cells to DNA cross-links by exposing them to chemical cross-linking agents such as diepoxybutane. Since FA cells cannot break down these cross-links, the chromosomes will break, resulting in a positive chromosomal breakage test.[5] Along with a positive chromosomal breakage test, a complete blood count (CBC) and bone marrow aspiration or biopsy can be performed to get a more precise diagnosis. If an individual has FA, pancytopenia will be seen on the CBC, and hypocellular bone marrow will be found on a bone marrow biopsy.[1]

## Laboratory diagnosis

When assessing patients with FA, the hematology test and its values can be very helpful. Initial screening test results can help alert the pathologist that a bone marrow test may be needed to even assess the patient further. One example could be a low cell count on any of the following: white blood cell, red blood cell, platelets, etc. If leukopenia or thrombocytopenia is seen, then the pathologist may check for bone marrow failure or some other disease. The red blood cell morphology is often macrocytosis in several Fanconi patients with an average mean corpuscular volume (MCV) value of 105 fL. The CBC differential is usually normal.

## Prognosis and treatment

The prognosis for individuals with FA is very poor. FA patients are highly susceptible to cancer and often develop acute myeloid leukemia (AML).[4] The cause of death in patients with FA is usually bone marrow failure or malignancy.

Due to increased cell death, blood transfusions are a great supportive therapy for FA patients.[1] A more long-term treatment, if successful, is a stem cell transplant. However, this procedure is invasive, so it is reserved as a last option. A new technique that could be beneficial is the correction of CD34+ in affected cells by gene therapy.[1] CD34+ is a cell marker of hematopoietic stem cells, so correcting these mutated markers would fix the pancytopenia in FA patients.

## Case study presentation

A 12-year-old boy presented with pallor and fatigue for the past month at the hospital. Upon inspection, he had moderate pallor, multiple light brown birthmarks, a palpable liver, and short stature for his age group. He had hypoplasia of the left thumb and a total absence of his right thumb.[6] His family history was normal, as his parents and siblings were healthy. A CBC and differential were performed (**Table** 1), and hypocellular marrow was shown on a bone marrow biopsy. Fanconi anemia was suspected, so a chromosomal breakage test was performed, and it was positive. The positive chromosomal breakage test resulted in a FA diagnosis.[6]

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| RBC | 3x10^12/L | 4.5-5.5 x10^12/L | Low |
| Hct | 33% | 42-52% | Low |
| MCV | 105 fL | 80-100 fL | High |
| MCHC | 32 g/dL | 32-36 g/dL | Normal |
| WBC | 3.5x10^9/L | 4.5-11.5 x10^9/L | Low |
| Neutrophil | 42% | 50-70% | Low |
| Lymphocyte | 39% | 18-42% | Normal |
| Monocyte | 2% | 2-11% | Normal |
| Eosinophil | 0% | 1-3% | Low |
| Platelets | 100x10^9/L | 150-450 x10^9/L | Low |
| RBC Morph | Macrocytosis | Normal | Abnormal |

**Table 1.** Patient's CBC and Diff results.

## Conclusion

Fanconi anemia is a rare but deadly anemia that is caused by a genetic mutation. The mutation of the FANCA gene interferes with an important DNA repair pathway concerning interstrand cross-links. The toxic buildup of these links results in poor growth, hypocellular bone marrow, and pancytopenia. Diagnosis is often late in the development of FA, limiting the treatment available for these individuals. Further study into FA, specifically into the early stages of disease development, would aid in early diagnosis and help improve patients' quality of life.

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# Overcoming data management challenges with an all-in-one LIMS

By Jaswant S. Tony

Although automation is key to achieving greater efficiency and accuracy for medical laboratories, many find that laboratory information management system (LIMS) or electronic health record (EHR) interoperability and data integration are stumbling blocks to implementing electronic processes, according to a *Medical Laboratory Observer* industry survey earlier this year.[1] Labs may encounter integration challenges from acquiring a series of incompatible data processing systems unique to each function or department over the years. The lack of standardization makes electronic data transfer between systems difficult if not impossible.

Switching to an all-in-one LIMS platform that seamlessly connects the lab's clinical, financial, and administrative functions, plus offers EHR integration with providers' offices, can eliminate these barriers.

## Lack of interoperability and integration causes headaches

For clarification, interoperability is when two systems speak the same language. This differs from integration, which refers to translating data between systems. Since software may not originally be designed to communicate with other systems, integration is used to connect a new module to a legacy installation. If a lab utilizes software specific to each department, there may be disconnects in handing off data due to limited or no integration between systems. Accessioning, test processing, and analysis may be handled by one application, but results reporting may be done by another if laboratorians prefer a different format or to meet billing and insurance requirements.

The lack of interoperability and data integration across laboratory systems leads to more human data manipulation, which can increase the chance of errors. Lab managers must rely on technicians to relay data output from analytical instruments to the next workflow operation. When data is manually copied from one software system to another, there is a higher risk of transferring the data incorrectly, generating the wrong output, and a flawed report. In addition to producing inaccurate reports, manual data input lengthens results turnaround times (TATs). Healthcare providers (HCPs) may experience delays in receiving important patient test results, potentially impacting follow-up care. Also, entering lab data by hand is time consuming and requires more dedicated labor. Given the ongoing industry shortages of qualified personnel, labs may be limited in the number of orders they can process, which constrains revenue and business growth.

Diagnostic labs must collect and submit information such as test requisitions, lab reports, and patient medical notes to receive reimbursement from the Centers for Medicare & Medicaid Service (CMS) or private insurance.[2] If the LIMS and revenue management software are not integrated, there can be significant lost revenue if charges are unbilled. Additionally, maintaining regulatory compliance and updating system security can be more difficult if the LIMS is unable to communicate with other laboratory systems.

## Advantages of a fully integrated LIMS

So how can an LIMS that offers greater interoperability or data integration benefit clinical laboratories?

A modern LIMS, accessed through a single portal, allows labs to manage all their data in one place. It simplifies data exchange among test processing, report generation, billing, insurance, accounting, and other functions. Data is stored in one central location and is accessible to all departments. The platform automates many laboratory processes and aids in streamlining workflows. In addition, a more open system can easily interface with other types of previously installed software.

Ensuring repeatability and consistency of test data is a major challenge for clinical laboratories.

Mistakes can occur when data files are manually pulled from analyzers and copied into a formatted report, which is

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uploaded to a database. A fully integrated LIMS automatically takes data readouts from instruments and enters them directly into the lab's central data system without making any changes. Directly integrating facility instrumentation provides real-time data importing and analysis.

An LIMS with advanced features can also process the data to make it more readable for the technician, clinician, or medical director. Though diagnostic tests generate vast amounts of data, clinicians need to focus on only a few key values. The LIMS can identify and highlight the most important data for targeted review by clinicians. This makes it easier to interpret and build an accurate report quickly. Thus, a fully integrated LIMS platform helps labs achieve process standardization for improved data quality, consistency, and ease of use.

A higher level of integration and connectivity enables more efficient test processing and faster TATs. Labs can deliver results much faster to physicians and their patients as well as increase daily test volumes. Predictable interoperability and integration throughout the lab can also ease staff overwork and significantly boost productivity. Less manual data transfer frees laboratorians to perform higher-value clinical work such as complex tests, data analysis, or results interpretation. Given ongoing industry staff shortages, reduced workloads and stress means less burnout, more job satisfaction, and better employee retention.

Improving revenue is another advantage. A platform that integrates the lab's clinical and financial operations with client EHRs automates data collection and bill processing to improve insurance reimbursements. With shrinking test fee margins, measures to capture additional revenue take on greater importance. And as the coronavirus pandemic wanes, labs are expanding test menus to diversify beyond COVID-19 testing and attract new customers. They are seeking to repurpose molecular analyzers for other applications.[3] More extensive integration of lab systems will be needed to manage a much broader range of diagnostic data.

## Integration creates a laboratory–physician partnership

An all-in-one LIMS can help labs resolve their own electronic communication issues, but laboratory integration with HCPs in private medical offices, hospitals, and imaging centers benefits those organizations as well.

The LIMS can be directly integrated with patient EHRs located in HCP offices that utilize the lab's diagnostic services. Such an interface enables faster exchange of bidirectional data: physicians administer patient tests, submit them to the lab for processing, then receive reports electronically. Faxing back-and-forth is no longer needed, eliminating paper documents, saving administrative time, and speeding results delivery.

An LIMS platform that communicates seamlessly between the lab, doctor's office, and patients allows better management of patient information. By incorporating telehealth and other digital systems, it fosters closer connections to the point-of-care (POC). LIMS integration creates a partnership between medical laboratories and physicians that offers competitive advantages for both.

## Cloud-based systems: A complete solution

Whether upgrading or purchasing new, medical laboratories should consider a cloud-based, SaaS LIMS that offers flexibility, scalability, and ease of integration with other laboratory equipment. These systems can transfer large files at high speed across lab locations or to external collaborators. They can also be installed quickly, do not require an up-front investment, and have low maintenance costs.

Cloud-based models provide automatic updates to ensure the lab maintains compliance with important regulatory, data security, and privacy standards such as HIPAA, HITRUST, and NIST.

## Up next: Machine learning and artificial intelligence

Already revolutionizing other industries, machine learning and artificial intelligence (AI) are finding their way into laboratory software. Their use in an LIMS can address interoperability and integration barriers that arise when a lab utilizes a mix of legacy systems or each lab within a health system has a different LIMS. Non-standardization limits interoperability between systems and requires the use of machine learning to function.

Some cloud-based LIMS currently incorporate machine learning. They retain historical data from previous diagnostic tests, analyze the data, highlight trends, and make recommendations on what the data may be indicating. Although, the use of AI in LIMS is still under development.

## Conclusion

Adopting an all-inclusive LIMS platform can overcome the significant interoperability and integration challenges faced by diagnostic laboratories. Cloud-based, SaaS systems can help them improve the quality and consistency of test results, boost productivity, expand testing capabilities and volume capacity, increase reimbursements, and reduce costs. And system integration with their medical practice clients helps HCPs provide better patient care at lower cost. As clinical laboratories plan for the future, advancing digital connectivity both internally across operations and externally with HCP clients and business partners will ensure their competitiveness and long-term sustainability in today's evolving healthcare services market.

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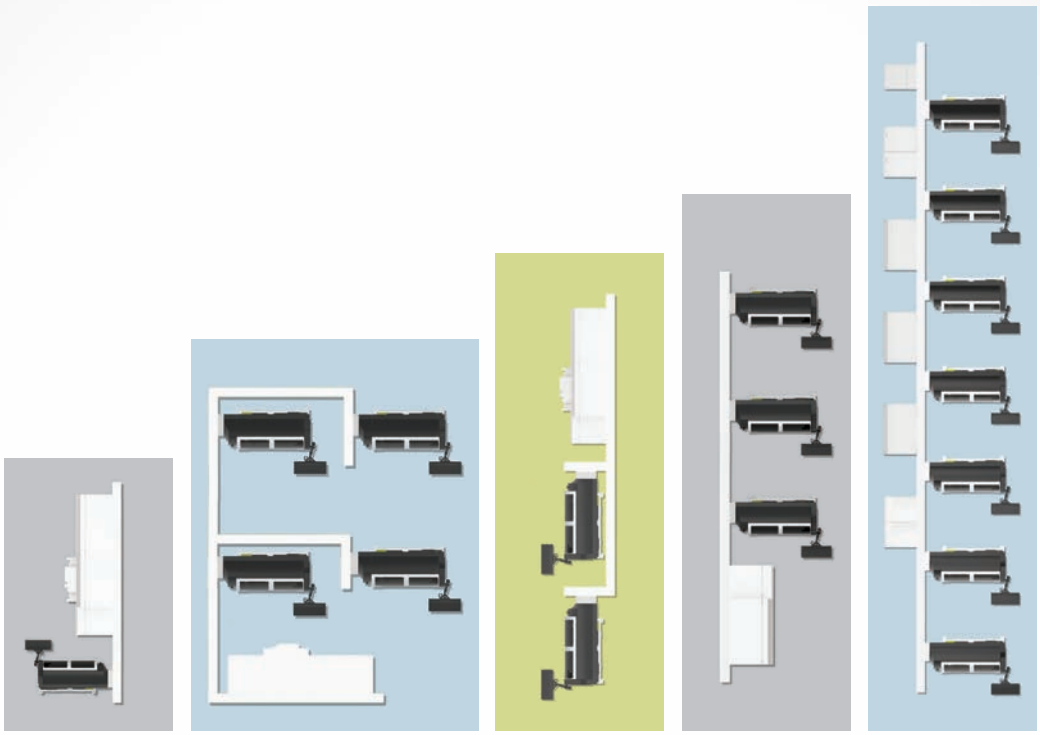

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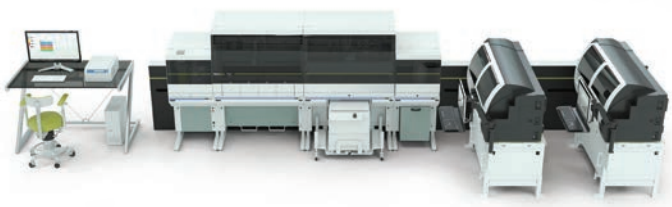

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# The path forward in addressing healthcare inequity requires cutting-edge technology

By Laura Dalton, DO, MBA

Sadly, the current reality of healthcare for millions of people in the United States looks bleak. In 2022, there were 30 million Americans who had no health insurance, and more than 85 million were enrolled in Medicaid.[1,2] Lack of insurance or finding clinicians that accept subsidized coverage can dissuade patients from receiving medical care.

People of color and diverse backgrounds have faced longstanding disparities in health coverage that contribute to inequalities in health. The ongoing gaps in coverage for this community have wide-ranging implications for people's access to care, and ultimately, leading to unnecessary illness. According to a recent Harris survey,[3] about 1 in 10 Hispanic and Black women say they have never had an OB/GYN visit for routine care and similar proportions say they have never had a Pap test. And according to the Centers for Disease Control and Prevention (CDC), in 2021, the maternal mortality rate for non-Hispanic Black women was 69.9 deaths per 100,000 live births, 2.6 times the rate for non-Hispanic white women.[4]

While patients get annual wellness visits so providers can assess their overall health and detect any concerns, studies confirm that patients who regularly see a clinician tend to be healthier than those who do not schedule routine visits.[5,6] But this only works if patients can access the care they need despite economic barriers or lack of resources. Even before the pandemic disrupted the foundations of the healthcare system, many Americans struggled to access the care they needed. But now, the struggle has intensified due to healthcare facilities being understaffed and flooded with patients catching up on appointments they put off over the last three years. Providers and lab technicians are being stretched thin as they manage the sudden influx of testing.[7] There is no doubt that systems need to be improved for all. That is where technology can come in; it can enhance testing in every way — from accuracy, speed, and accessibility.

Many healthcare systems, including Planned Parenthood, are currently facing demanding healthcare conditions in 2023, such as economic pressure, labor shortages, an influx of patients, and lingering effects from COVID-19. Clinicians and staff shortages brought on by the pandemic have drastically changed how healthcare institutions operate and handle resources. It is especially felt in non-profit organizations like ours that serve as a crucial part of patients' safety nets.

With new technology from our partnership with BD, Planned Parenthood Mar Monte will now further deliver high-impact results for its patients, most of whom are 200% below the poverty level. This new system for sexually transmitted infection (STI) testing processes tests at a significantly faster rate and at a higher volume than our lab's previous technology — an important step in providing health equity for our patients. The automation, moderate complexity, and faster turnaround time offered with this new technology help providers do their job better by getting results to people in a more timely manner before their symptoms lead to worse disease.

Additionally, we are preparing our system to include an HPV analytical instrument that automates HPV tests that individually identifies HPV 31, a high-risk genotype, allowing for a more precise, accurate way to measure a woman's risk for developing cervical precancer and cancer compared to an assay with partial genotyping.[8]

As we look ahead, healthcare providers, payers, and medical technology companies need to be truly committed to health equity as a strategic imperative. We need more medical technology companies joining BD in creating systems that help organizations like ours with overburdened clinicians and lab techs. Investing in medical technology solutions like this provides faster and more cost-effective ways to improve patient outcomes, which can help ease the pressure on healthcare systems by reducing the burden on lab teams by providing a higher volume of results in less time. A greater shift toward more medical technology eases the pressure on the entire healthcare system, creating a better future for both patients and providers. Clinicians deserve the best tools to help do their jobs better – better technologies provide clinicians and patients with more precise test results, leading to better patient care. The glue that holds our healthcare system together is coming perilously close to dissolving. And if we have any hope of saving it, we must collectively find new ways of providing healthcare staff with the resources needed to deliver gold-standard care for all. It's time to think boldly and reimagine the status quo.

*Just recently, Planned Parenthood Mar Monte installed a BD COR™ PX/MX System for sexually transmitted infection (STI) testing. Planned Parenthood Mar Monte will be expanding its system to include BD COR™ GX instrument, an HPV analytical instrument that automates the BD Onclarity™ HPV Assay, the only FDA approved HPV test that individually identifies HPV 31, a high-risk genotype.*

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**Laura Dalton, DO, MBA** is Chief Medical Operating Officer, **Planned Parenthood Mar Monte**.

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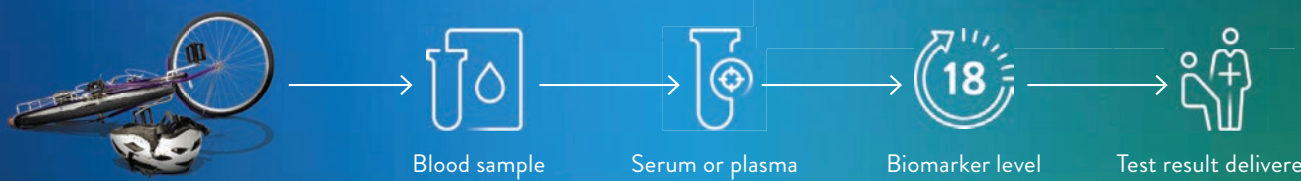
## IT'S A GAME CHANGING TOOL TO EVALUATE CONCUSSIONS.

## IT'S THE POTENTIAL TO RULE OUT UNNECESSARY CT SCANS.[1]

## IT'S REAL LIFE.

### ALINITY i TBI TEST PATHWAY




Patient presents to ER with suspected mTBI

Blood sample collected within 12 hours of injury

Serum or plasma sample prepared, test run

Biomarker level read out within 18 minutes

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1. Alinity i TBI [package insert] 802673R01. Instructions for use. Abbott Diagnostics. May 2023.
2. Michelson EA, Huff JS, Loparo M, et al. Emergency department time course for mild traumatic brain injury workup. *West J Emerg Med*. 2018;19(4): 635-640. doi:10.5811/westjem.2018.5.37293




Abbott

# Advances in digital pathology

## Automating H&E image-based detection and prognostic evaluation of breast cancers hold promise

By Satabhisa Mukhopadhyay, PhD

Cell cycle deregulation influences many cancers.[1] Although in the current standard of care (SOC), clinicopathological factors and events at the molecular level largely determine diagnostic, therapeutic, and patient management pathways in cancer, the patient-to-patient variability in therapy response, as well as in cancer remission and recurrence, can be further influenced by the degree of deregulation of key cell cycle events. This can potentially introduce considerable unknown variability from person to person. On top of that, these deregulation profiles on their own, as well as how the tumor microenvironment interacts with them, can potentially introduce unknown variability within a tumor and/or across different tumors in a patient. This, in turn, can manifest as intra- and/or inter-tumor heterogeneity.

For example, in breast cancers, clinicopathological factors such as tumor subtype, hormone receptor status (estrogen receptor (ER) and progesterone receptor (PR)), HER2 status, nodal status, tumor stage, patient's age, general health, menopausal status, inherited breast cancer genes such as mutations in BRCA1 and BRCA2 decide the treatment plan.[2] There are other molecular tests, such as certain multi-gene panels, that can be used additionally if they meet the appropriate conditions.[2]

At the level of molecular biomarkers, there are some prognostic or predictive molecular tests that have successfully incorporated some of the cell cycle deregulation components at the protein or gene levels. For example, tests that incorporate p53 gene deregulation are used in breast and bone cancers, leukemia, and sarcoma if certain other conditions based on family history, symptoms, and previous cancer diagnoses are met. In breast cancer, the multi-gene panels mentioned above and, in general, other similar genomic tests have had some success by partially incorporating cell-cycle-driven gene components among many other components, such as proliferative components throughout the cell cycle (which is correlated with the Ki67 expression profile as well), G2M checkpoints, DNA repair pathways, PI3K/AKT/mTOR pathways, on top of incorporating ER, PR, and HER2 profiles.[3,4] Note that ER, PR, and HER2 profiles in a tumor are also tied to key drivers of cell cycle G1/S phase.[5-7]

However, a substantial opportunity exists for inter- and intra-person variability and intra- and/or inter-tumor heterogeneity to influence the landscape of therapy response, recurrence, and remission in breast cancer, and across a spectrum of other cancers.[8-10] On the other hand, most of the neoadjuvant and adjuvant targeted therapies across chemotherapy, immunotherapy, and other targeted therapies (small molecules or monoclonal antibodies) used in the current standard of care across multiple cancers are agents that are designed to precisely target the cell cycle.[1] For example, **Table 1** refers to various commonly used neoadjuvant chemotherapy and adjuvant lines of chemotherapy in breast and other cancers. All of them precisely target certain events specific to various phases of the cell cycle. From the molecular point of view, tests measuring mutations or deficiencies in DNA damage and repair pathways such as BRCA mutational status, homologous recombination deficiency (HRD) status, etc. are natural candidates who could possibly explain sensitivity to some of these agents, such as sensitivity towards platinum-based chemotherapy in advanced ovarian cancer.[11] Thus, they can help guide cohort selection.

However, a more precise therapy response measurement covering the aspect of patient-to-patient and interpatient variability could potentially come from the cell cycle S, S/G2, and M phase-specific surrogate biomarkers and presumably an envelope biomarker collectively encompassing these components. Needless to say, if such cell cycle–targeted surrogate biomarkers, with or without immune interactions, are able to predict clear therapy response signatures in terms of predicting pathologic complete response (pCR) or residual cancer burden (RCB) post-neoadjuvant therapy, it would dramatically impact the efficiency of novel biomarkers in cancer and hopefully facilitate, to some extent, regulatory and payor considerations around their development endeavor.

With the advent of digitization of tissue slides, the use of digital pathology workflows and PAC (picture archiving and communication) systems has started to become more commonplace beyond radiology. This year, the American Medical Association (AMA) CPT Editorial Panel published 13 new add-on category III

| Chemotherapy Class | Target | Agents | Cell cycle phase implicated | Biomarkers, Regulatory, Payor and other Considerations |
|---|---|---|---|---|
| Alkylating agent | DNA inter stand crosslinks | Cisplatin, Carboplatin | S/G2 | a. Tests measuring mutation or deficiencies in DNA damage and repair pathway such as BRCA mutational status, HRD etc. could be implicated.<br><br>b. A more precise therapy response measurement could potentially come from cell cycle S, S/G2, and M phase specific surrogate biomarkers and an envelope biomarker collectively encompassing these components. |
| Alkylating agent | DNA inter stand crosslinks | Cyclophosphamide | S/G2 | |
| Anthracycline | Topoisomerase II | Doxorubicin, Epirubicin | S | |
| Taxane | Tubulin | Docetaxel, Paclitaxel | M | |
| Antimetabolite | Gemcitabine | Nucleoside analogue and ribonucleotide reductase | S | |
| Antimetabolite | 5-Fluorouracil | Thymidylate Synthase | S | |
| Antimetabolite | Methotrexate | Dihydrofolate reductase | S | |

**Table 1.** Targeted chemotherapies in the current SOC and the associated cell cycle phases.

temporary CPT codes (0751T–0763T) for digital pathology digitization procedures, which can be used to report additional clinical staff work and service requirements associated with digitizing glass slides for primary diagnosis.[12] This has created enthusiasm for adopting digital pathology workflows.

As a next step in digital pathology, a natural question can arise around how "digitally extracted" biomarkers from hematoxylin and eosin (H&E) whole slide images (WSIs) can support prognostication and therapy response prediction. In particular, how could an automated digital pathology workflow possibly support the development of cell cycle and immune interaction-targeted surrogate biomarkers generated from H&E WSIs, and how could they achieve a viable reimbursement pathway?

At present, the majority of the available digital pathology diagnostic tools, primarily based on standard artificial intelligence/machine learning (AI/ML) methods and data-driven learning combining digital pathology and clinical data, are either being developed or deployed for research use only (RUO) to identify cell-type-specific or tissue segmentation–specific diagnostic features. In the oncology space, the potential clinical application of these solutions is currently limited to immunohistochemistry (IHC) scoring and cell-type-based scoring of immune compartments.[13] There is currently no reimbursement code available for these solutions. Hopefully, new digital pathology add-on codes will be available in this category in the near future.

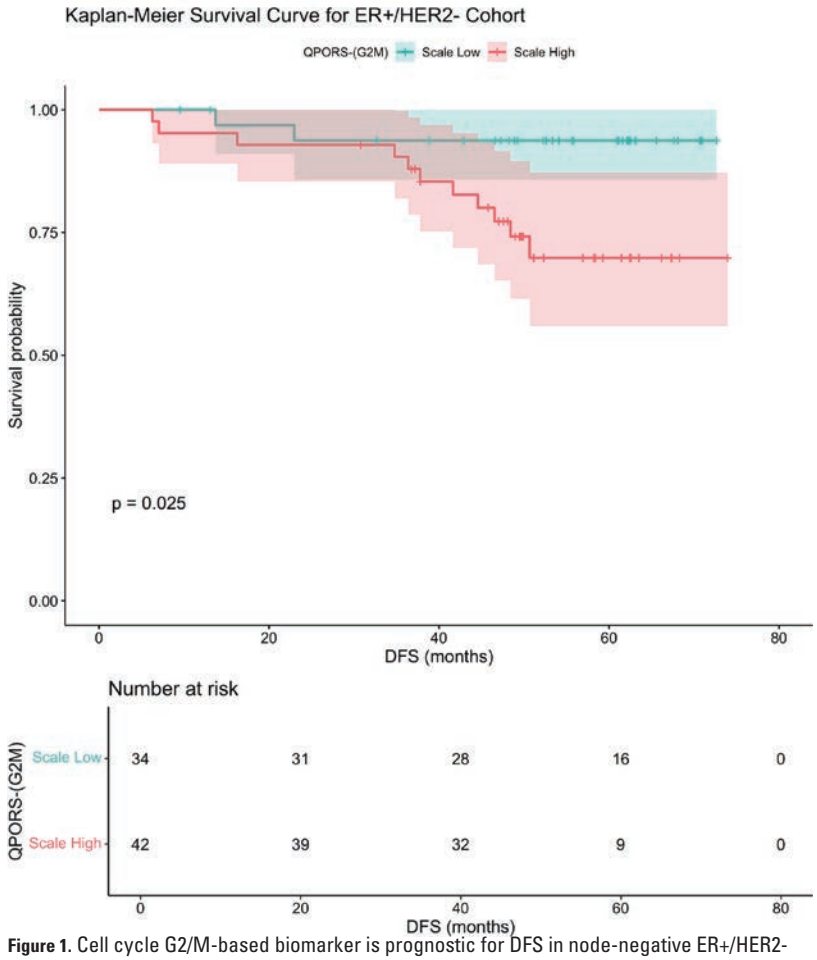


**Figure 1.** Cell cycle G2/M-based biomarker is prognostic for DFS in node-negative ER+/HER2- breast cancer patients over a 5-year median follow-up period.

Beyond the scope of any standard AI/ML tools, a tumor biology-driven computational digital pathology solution would be very effective if it could extract cell cycle deregulation signatures directly from the digital images of biopsy, resection, or cytology specimens, and if possible, from the routine H&E-stained specimens alone.[9,14,15] The simplistic analytical ability of such a solution to quantify these deformations from the digital WSIs of H&E-stained tissues alone can bring forward novel collective information independent of routine clinicopathological factors, a key ingredient in predicting therapy response. Such collective information can be even more relevant for large or heterogeneous tumors, where therapy response is likely driven by competitions between different clonal populations and an overall knowledge of the tumor might be necessary.

For example, using a statistical physics and tumor biology-based computational methodology, the cell-cycle G2/M deregulation-based biomarker extracted from the digital WSIs of H&E-stained ER+/HER2- breast cancer excisions was prognostic for disease-free survival for node-negative patients over a 5-year median follow-up period ($p = 0.025$, $n = 76$).[14] Moreover, the biomarker could predict 20% more recurrences in a low-risk population designated by a standard of care test. All the samples in this case were drawn from pre-treatment excisions, and the biomarker primarily represented malignant cell cycle deregulations coming from cell cycle G2/M perturbations (see **Figure 1**).

Such a solution could potentially be a very useful tool for developing pan-cancer biomarkers that are prognostic of progression-free or disease-free survival and are capable of predicting tumor recurrences. More importantly, such a solution can possibly provide biological insight to tumor recurrence and resistance to therapy for a wide variety of treatment pathways.

This type of computational digital pathology platform (with appropriate regulatory clearance) can simultaneously be used as an adjunct for reporting selected routine reflex tests (such as ER, PR, HER2, and Ki67 status in breast cancer.[9,15,16] With the ability of this category of solutions to generate routine reflex tests from standard digital inputs (H&E WSIs) and deliver them in the standard reporting format following the current SOC, it is possible some existing CPT codes could be leveraged under proper allowance from appropriate authorities, such as the AMA. However, the whole new nature of these solutions, expanding to predictive and prognostic tests, might demand new CPT codes or other reimbursement pathways.

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*Continued on page 40*

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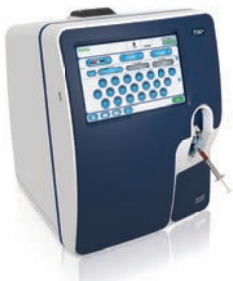
**hc1**



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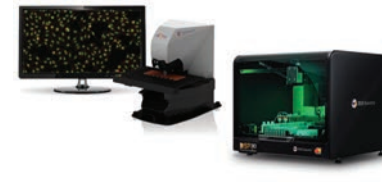

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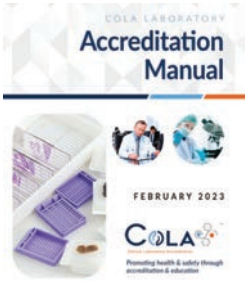


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*Continued from page 35*

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**Satabhisa Mukhopadhyay, PhD**, is founder and chief scientist at **4D Path**, where she brings her years of innovative cross-disciplinary research and leadership. Satabhisa is a physicist by training, receiving her PhD in Theoretical Physics from Rutgers University and MS in applied Mathematics from the University of Cambridge. She has years of research experience in biomedical science, cancer cell biology, and pharmacology at MIT and Harvard Medical School. Her research interest always evolved around developing machine learning and statistical physics-based models to build methodologies that directly address real life translational questions, especially on cancer drug resistance, at systems level.

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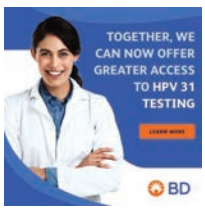


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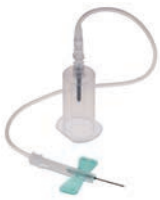

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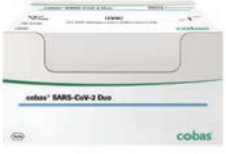
## High Throughput Qualitative & Quantitative SARS-CoV-2 results




Labs looking for more than just detection can use an assay with viral load information that's calibrated with WHO International standards. Discover the latest innovation from the first to bring you high-throughput gold standard PCR testing methodologies.

**Roche Diagnostics**

## OSOM® Ultra Plus Flu A&B Test

Differentiate between influenza type A and B in just 10 minutes with minimal hands-on time, a simplified workflow, and two complimentary tests for external quality testing. The test's high sensitivity and specificity allows for accurate diagnostic testing.

**SEKISUI Diagnostics**

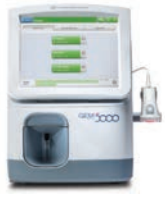
## Over 1 in 2 concussions are ignored

CONCUSSION AWARENESS NOW

It's got to change. That's why we've assembled leading minds from the front lines of concussion research, treatment and advocacy. Help us spread the word and together, we can set a new standard.

**Abbott Diagnostics**

## GEM Premier™ 5000



GEM® Premier™ 5000 blood gas system with iQM®2 assures quality before, during and after every sample in lab and POC testing—for improved patient care. All-in-one, multi-use cartridge offers advanced simplicity.

**Werfen – Acute Care**

## ACL TOP® Family 50 Series

ACL TOP® Family 50 Series Hemostasis Testing systems offer the most advanced automation, quality management, and routine to specialty assays for mid- to high-volume clinical laboratories, including those with lab automation tracks.

**Werfen - Hemostasis**

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Join QuidelOrtho at the 2023 AABB Annual meeting, October 14-17 for the latest innovations at booth #405. Register for demos and ask the experts workshop.

**QuidelOrtho**

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"If we as organizations want to call ourselves healthcare organizations, we have to be involved in more than just the delivery of medical care after someone gets sick."

**MICHAEL DOWLING**
President and CEO,
Northwell Health, USA

"Sometimes things are not in the budget but sometimes we have to figure out how to do it, particularly if it is going to make a huge difference for patients."

**QUINT STUDER**
Co-Founder, Healthcare Plus Solutions Group, USA

"We have opportunities to develop appropriate clinical algorithms that can help ensure that patients get the care that they need"

**OCTAVIA PECK-PALMER**
Division Director, Clinical Chemistry,
Associate Professor of Pathology,
University of Pittsburgh
School of Medicine, USA

"Many of us have the ideas, the plans and the scientific knowledge, but we need to be able to ensure that it aligns with what people are able to do."

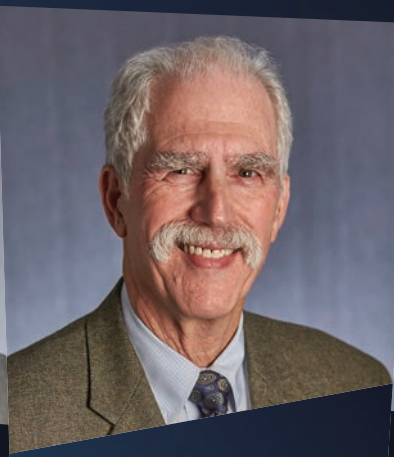
**YIN LING WOO**
Professor of Obstetrics and Gynaecology, Consultant Gynaecological Oncologist,
University of Malaya,
University Malaya
Medical Centre, Malaysia

"Every voice matters as we collaborate to improve the health of individuals and populations around the world."

**CHRISTINA CARABALLO**
Vice President, Informatics,
HIMSS, USA

"We have to completely reimagine what is the role of the clinical lab, not at a test level, but in the longitudinal way of data that gives us a meaningful way to predict risk."

**KHOSROW SHOTORBANI**
President, Executive Director,
Project Santa Fe Foundation, USA
Founder and CEO,
Lab 2.0 Strategic Services, USA



"Together, we can address diagnostic error which the NASEM reports to not only be possible, but a moral, professional, and public health imperative."

**PAUL EPNER**
Vice-Chair,
Sepsis Alliance, USA

"Through the use of a new biomarker, multiple health systems were able to save and mitigate downstream costs while improving health for the entire ecosystem."

**TRICIA RAVALICO**
Director, Scientific Leadership and Education, Core Diagnostics,
Abbott, USA

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