

2011 Top Game Changers in Pathology

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Posted: 11/23/2011

Counting Down: Game Changers 10-2

With the end of 2011 rapidly approaching, it is time to reflect on the most outstanding papers from the *American Journal of Clinical Pathology (AJCP)* for this calendar year. As the name of the journal implies, *AJCP* covers the full spectrum of topics related to anatomic pathology and laboratory medicine. With the help of Mark Wick, MD, editor-in-chief of *AJCP*, and Philip Rogers, senior managing editor of *AJCP*, I have ranked what I consider to be the top 10 papers for 2011.

10. A Quick Halt for a Dropping Platelet Count

Pseudothrombocytopenia is an uncommon (0.1%-2% of hospitalized patients) but significant artifact induced by the anticoagulant EDTA. In one previous study,^[1] 15% of patients referred for workup of an isolated thrombocytopenia had EDTA-induced pseudothrombocytopenia. It had been reported previously that supplementing the tube of blood with an aminoglycoside could prevent pseudothrombocytopenia. The study patient in this report was a healthy 35-year-old man.^[2] The addition of amikacin to the blood sample within 60 minutes of phlebotomy completely normalized the automated platelet count in this individual, although gentamicin, aminophylline, and vitamin B6 did not.

Read the [abstract](#) for more details.

9. Identifying High-Risk HPV in Cervical Samples

Proper identification of high-risk human papillomavirus (HPV) in cervical samples is essential for proper patient management. Hybrid Capture 2 (HC2, Qiagen Inc., Valencia, California) has been a US Food and Drug Administration (FDA)-approved platform since 1995. Cervista® HPV HR (Hologic®, Madison, Wisconsin) was approved by the FDA in 2009, although one subsequent trial^[3] suggested poor clinical specificity of the Cervista assays, making the present study by Kurian and colleagues^[4] of considerable interest. The results of this study showed that there was no significant difference in prevalence rates between HC2 (7.5%) and Cervista HR (8.5%). The authors concluded that for clinical screening, Cervista HR and HC2 are comparable and should provide excellent negative predictive value for histologically relevant disease. The data did show, however, that there were 29 discordant positive results (12 with HC2 and 17 with Cervista HR), indicating that results from either assay may lead to some women with negative cytology undergoing unnecessary follow-up.

Read the [abstract](#) for more details.

8. Tracking Down an Elusive Cancer

Carcinoma of unknown primary (CUP) is an important clinical problem, representing 3%-5% of new cancer cases diagnosed each year. Pathologists routinely use immunohistochemical panels to pinpoint the tissue of origin of the cancer. This results in identification of a likely primary site in approximately 75% of patients, leaving 25% still unknown. The only FDA cleared in vitro diagnostic multivariate index assay, the Pathwork® Tissue of Origin test (Pathwork Diagnostics, Redwood City, California), measures the expression of 1550 genes in each sample and compares the resulting profile to 15 known tissue types of high incidence in metastatic solid tumors. Dumur and colleagues^[5] studied 43 cancer cases in which the complete diagnosis was determined on the basis of clinical

correlations and immunohistochemical findings and found a 97% agreement with the Pathwork results. One aim of this study was to assess a known limitation of this test, namely predicting for a tissue site not covered by the 15 tumor types used in the design of the Pathwork test. Their results gave an indeterminate result in a third of these cases, but misclassified head and neck squamous carcinoma as lung or urinary bladder cancer. This was not unexpected given a somewhat similar immunohistochemical profile, but it points to a significant limitation of this test when the tumor being analyzed is not part of the original panel of 15 cancer types used to develop the test.

[Editor's note: At the time of this writing, the December issue of AJCP, in which this study is published, had not gone to press.]

7. Preventing Coagulopathy in Patients With Massive Transfusion

Coagulopathy is a frequent occurrence in patients treated with massive transfusion. Chambers and colleagues^[6] studied the outcome of patients treated with a massive transfusion protocol (MTP) that consisted of a 1:1:1 red blood cell/plasma/ platelet administration compared with the previous protocol of 2:1 red blood cell/plasma. More than 80% of patients were noncoagulopathic at 12 hours. Of note, a 1:1:1 formula driven MTP did not affect the frequency, nature, or duration of coagulopathy according to laboratory test results when compared with patients who received the 2:1 protocol.

Read the [abstract](#) for more details.

6. Evidence That H1N1 Contributes Directly to MODS

Influenza A (H1N1) can cause significant morbidity and mortality. Although acute lung injury is the hallmark of the disease, multiple organ system dysfunction (MODS) can develop and lead to death. Carmona and colleagues^[7] studied the autopsy material from 5 patients who died during the 2009 H1N1 pandemic. Although all 5 patients showed (as expected) influenza viral particles in the lung by immunohistochemistry, surprisingly, 4 patients also showed viral particles in macrophages within glomeruli. As reported, this was the first paper to show the presence of H1N1 virus in the kidneys of individuals who died in this pandemic. A number of patients who died in this pandemic had MODS that caused or significantly contributed to death. Although the MODS could have been secondary to a systemic inflammatory response syndrome, given the findings of this study, direct viral injury to the kidneys is a possibility that necessitates further study.

Read the [abstract](#) for more details.

5. Innovative Technique for EGFR and KRAS Testing

EGFR mutations occur in 10%-15% of unselected non-small cell lung carcinomas and their presence predicts response to *EGFR* tyrosine kinase inhibitors. *KRAS* mutations (mutually exclusive to *EGFR* mutations) on the other hand signify resistance to the same treatment. A common problem in the modern era of diagnosis is that the tumor sample (frequently a cytologic specimen) may be quite small and may not provide enough material for traditional molecular testing. Betz and colleagues^[8] describe a novel technique to scrape individual tumor cells from Romanowsky-stained cytology smears for this molecular testing. They were able to show successful testing for *EGFR* and *KRAS* mutations by this method, a very important advance, especially when the cell blocks contain insufficient cellularity for testing.

Read the [abstract](#) for more details.

4. Instantaneous Delivery of Critical Laboratory Results

A critical laboratory result (too high or too low) has an impact on patient safety and must be rectified by swift medical

intervention. Failure to communicate critical results in a timely manner and/or to the right person has huge implications for patient care. The question has arisen whether cell phone texting is a mechanism by which critical laboratory results can be disseminated in an expedited manner.

During the 1-year study period, Saw and colleagues^[9] assessed 18,525 critical laboratory results (0.44% of reported results) reported by text message. In the period before the study, the mean and median response times for critical laboratory results reporting were 14.6 and 7.3 minutes, respectively. During the study period, those times decreased to 4.7 and 2.0 minutes, respectively. Cell phone text messaging is a very attractive candidate for distribution of critical results because the software application is widely familiar, communications are 2-way and almost instantaneous, exchanges are captured in an electronic audit trail, and cell phones are essentially universal, negating the need for an additional device.

Read the [abstract](#) for more details.

3. A Novel Biomarker in HCC

Hepatocellular carcinoma (HCC) is the most common cancer in the world. Alpha-fetoprotein is a useful biomarker for HCC, but its predictive value is limited by the fact that only 40% of patients with proven HCC have elevated serum levels of this marker. Midkine is a novel biomarker that is a member of a highly conserved and developmentally regulated gene family and has been shown to be upregulated in neuroblastoma and cancers of the gastrointestinal tract, urinary bladder, breast, and liver. Hung and colleagues^[10] studied 285 patients prospectively, 144 whose HCC was in complete remission and 141 who were at risk for de novo HCC developing. The rising rate of serum midkine was inversely correlated with remaining days of survival in patients with HCC, but the serum level of midkine was not able to detect emergence of HCC in those at risk for HCC or to detect relapse in patients with a history of HCC. Therefore, serum midkine levels should be used to monitor progression of known HCC because a steep rise in this marker heralds the end of life.

Read the [abstract](#) for more details.

2. Link Discovered Between *Chlamydia psittaci* and Lung MALT Lymphomas

Extranodal mucosa-associated lymphoid tissue (MALT) lymphoma is the second most common type of indolent non-Hodgkin lymphoma. The most common location for MALT lymphoma is in the gastrointestinal tract, with most cases occurring in the stomach and linked to *Helicobacter pylori* infection. Other organisms have been associated with MALT lymphomas outside of the gastrointestinal tract. One such organism, *Chlamydia psittaci*, has been identified as the causative agent of ocular adnexal MALT lymphoma. To explore further the relationship between *C psittaci* and nongastrointestinal-associated MALT lymphoma, Aigelsreiter and colleagues^[11] studied 47 cases of nongastrointestinal MALT lymphomas and 27 autoimmune precursor lesions by polymerase chain reaction and direct sequencing.

Of note, 100% (5/5) of lung MALT lymphomas in this study tested positive for *C psittaci*, whereas all control normal lung specimens were negative. MALT lymphomas in other nongastrointestinal sites showed some but not as strong an association with *C psittaci*. However, this study also found that there was a high prevalence of *C psittaci* infection in patients with Sjogren syndrome and Hashimoto thyroiditis, 2 conditions that are frequently found to be precursors to MALT lymphoma in the salivary gland and thyroid, respectively. This study has important implications for the use of tetracycline antibiotic drugs for treatment of nongastrointestinal-associated MALT lymphoma because these medications have proven effective in cases that were refractory to chemotherapy.

Read the [abstract](#) for more details.

The Top 2011 Game Changer in Pathology

Important New Marker for Bloodstream Infections

Rapid diagnosis of bloodstream infections in the emergency department is challenging. In a landmark study, Riedel and colleagues^[12] examined procalcitonin to determine whether it could be used as a marker to rule out a blood stream infection, a disorder that affects 500,000 patients annually. The authors studied 367 patients admitted to the emergency department with signs and symptoms of systemic infection. Serum samples were obtained at the same time the blood cultures were drawn. Procalcitonin levels of 0.1 ng/mL were considered the cutoff for a negative result. The authors found that the negative predictive value of a negative test was 98% compared with blood culture results, and therefore, blood cultures may not be necessary in this patient subset. More importantly, systemic antibiotic treatment, with its expense and potential toxicity, could be avoided. Serum procalcitonin level is likely to become as important a test to rule out bloodstream infection as D-dimer is to exclude thrombosis.

Read the [abstract](#) for more details.

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