Clinical Chemistry

November 2018 Audio Summary

This is the November 2018 issue of *Clinical Chemistry*, Volume 64, Issue 11.

ON THE COVER Human Influenza Virus Type A. Influenza viruses infect millions of people each year in the US. Because patients with positive influenza diagnostic testing results are more likely to receive antiviral therapy and less likely to be prescribed unnecessary antibiotics, access to reliable influenza testing is critical. Recently, the first point-of-care molecular diagnostic test was cleared by the U.S. Food and Drug Administration for the detection of influenza. At the same time, concerns about the performance of current rapid antigen tests has led to modified regulatory requirements for these devices. Thus, clinical laboratorians will face questions regarding new testing modalities. To help readers navigate through the rapidly evolving landscape of influenza diagnostics, this month's issue of *Clinical Chemistry* contains a Q&A in which five experts from the clinical laboratory, industry, public health and regulatory agencies discuss recent advances and ongoing challenges in influenza diagnostics.

Using Machine Learning to Aid the Interpretation of Urine Steroid Profiles
By Edmund H Wilkes, et al.

Urine steroid profiles are used for the diagnosis and monitoring of disorders of steroidogenesis. This study aimed to determine the utility of machine learning algorithms for supporting the interpretation of urine steroid profiles in routine clinical practice. The study findings suggested that machine learning algorithms are highly capable of accurately interpreting urine steroid profiles in an automated fashion. Potentially, these tools could be used to support current clinical practices. This strategy is particularly pertinent given the increased need for evidence and traceability required for clinical service accreditation, and the increasing demand on laboratories to improve efficiency with limited resources.

Direct Comparison of Cardiac Troponin T and I Using a Uniform and a Sex-Specific Approach in the Detection of Functionally Relevant Coronary Artery Disease
By Deborah Mueller, et al.

In a large prospective study adjudicating the presence of functionally relevant coronary artery disease in 2,062 patients referred for work-up, this study directly compared the diagnostic accuracy of high sensitivity cardiac troponin I and T, first using a uniform approach in all patients, and second using a sex-specific approach analyzing women and men separately. The study findings indicated that high sensitivity cardiac troponin I and T had moderate and comparable diagnostic accuracy in both men and women. Similarly, these biomarkers also had comparable prognostic accuracy for predicting myocardial infarction and cardiovascular death during 2-year follow-up.

Comparison between High-Sensitivity Cardiac Troponin T and Cardiac Troponin I in a Large General Population Cohort
By Paul Welsh, et al.

This study directly compared high sensitivity cardiac troponin I and troponin T in the general population to ascertain features that might influence their comparative utility for cardiovascular disease risk screening. Cardiac troponin I was found to be more frequently detectable than troponin T, particularly in lower risk groups. Observed 99th centiles for these troponins varied considerably by age and sex, particularly for troponin T. Surprisingly, the troponins were only weakly correlated with each other, and had distinct associations with classical cardiovascular disease risk factors. These data are likely influence future decisions about the use of troponins in cardiovascular risk stratification.

Endothelin-1 Measurement in Patients Undergoing Diagnostic Coronary Angiography—Results from the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) Study
By Nasrien E. Ibrahim, et al.

Endothelin-1 is a vasoconstrictor produced by vascular endothelial cells. In a cohort of 1,084 patients referred for coronary angiography, the authors of this study investigated cross sectional associations between biologically active Endothelin-1 concentrations and prevalent coronary artery disease, as well as the value of Endothelin-1 for prognostication of future cardiovascular events. Among those without prevalent myocardial infarction at presentation, Endothelin-1 concentrations were not associated with presence or severity of coronary artery disease. Increased Endothelin-1 concentrations predicted incident heart failure, incident myocardial infarction, all-cause mortality, as well as the composite of incident heart failure, myocardial infarction, and cardiovascular disease mortality. Increased Endothelin-1 concentrations powerfully predict incident cardiovascular events and death.

Ultra-Sensitive Mutation Detection and Genome-Wide DNA Copy Number Reconstruction by Error-Corrected Circulating Tumor DNA Sequencing
By Sonia Mansukhani, et al.

Minimally invasive circulating free DNA analysis can portray cancer genome landscapes but highly sensitive and specific genetic approaches are necessary to accurately detect the often low frequency variants. Here the authors describe the development of a novel, customizable circulating free DNA sequencing technology that incorporates molecular barcodes for sequencing error correction, allowing ultra-low variant detection at 0.15%. The new duplexCaller software identifies duplex DNA fragments, which represent both strands of the input circulating free DNA molecules, reducing false positives by 97.5% compared to conventional mutation calling. Additional analysis of off-target reads allows simultaneous genome-wide copy number aberration profiling, maximizing information gain from a single assay.

Diagnostic Thresholds for Androgen-Producing Tumors or Pathologic Hyperandrogenism in Women by Use of Total Testosterone Concentrations Measured by Liquid Chromatography-Tandem Mass Spectrometry
By Anu Sharma, et al.

Previous studies defining diagnostic thresholds of total testosterone to identify pathologic hyperandrogenism used radio-immunoassays, which have been shown to be less accurate in measuring total testosterone in women compared to the gold standard liquid chromatography mass spectrometry abbreviated LC-MS/MS. Data on total testosterone thresholds measured by LC-MS/MS are lacking. Using a retrospective cohort design, the diagnostic threshold for total testosterone measured by LC-MS/MS for pathologic hyperandrogenism in women with biochemical severe hyperandrogenemia was greater than or equal to 5.1 nmol/L. In postmenopausal women, the diagnostic threshold was lower (greater than or equal to 2.2 nmol/L). Use of the revised postmenopausal threshold would lead to increased evaluation and a higher likelihood of cure with surgical intervention.

Biochemical Diagnosis of Chromaffin Cell Tumors in Patients at High and Low Risk of Disease: Plasma versus Urinary Free or Deconjugated O-Methylated Catecholamine Metabolites
By Graeme Eisenhofer, et al.

This paper presents the first international multicenter study to prospectively compare mass spectrometry-based measurements of plasma with urinary free or deconjugated metanephrines to diagnose pheochromocytoma. While the plasma test was found to offer higher diagnostic performance than urinary tests, this is of less importance for patients who are at low risk of disease due to hypertension, as compared to those tested because of an incidentaloma, genetic risk, or previous disease history. For the latter two high-risk groups the plasma test should include methoxytyramine. Routinely used urinary deconjugated metanephrines should be phased out in favor of the free metabolites at centers where plasma measurements are not possible.

Diagnostic Biomarkers: Are We Moving from Discovery to Clinical Application?
By Lucy A Parker, et al.

This study assessed the proportion of diagnostic biomarkers proposed in biomedical journals that advance to become clinically useful diagnostic tools. Studies were retrieved that were published before 31st December 2016 and cited 107 original-research articles published in 2006 which assessed the diagnostic value of a test. Of 107 tests proposed in 2006, only 28 (26.2%) made progress toward clinical application in the following 10-years. PCR-based tests were more likely to have made progress than those based in proteomics. Lack of regulatory standards for evaluation of diagnostic tools is a major challenge, and few biomarkers have made progress towards clinical application in the 10-years since their discovery.