Clinical Chemistry

March 2016 Audio Summary

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ON THE COVER Newborn. This image invokes a sense of calmness and wellbeing, which is the wish for the family of every infant. Although the vast majority of babies are born healthy, a small number will have genetic or biochemical disorders that may not become evident until irreversible damage has already occurred. In the United States all states have newborn screening programs in which dried blood spots are tested for a variety of diseases. However, as with any process, the quality of output (test results) depends on the quality of input (specimen collection). Dried blood spots are no exception. This month's issue of Clinical Chemistry includes an article describing the effect of dried bloodspot quality on newborn screening analyte concentrations, along with recommendations for minimum acceptance criteria for sample analysis. An accompanying editorial further highlights this topic.

Paper-Based Quantification of Male Fertility Potential
Reza Nosrati, et al.

Infertility is a growing global health concern, affecting ~70 million couples. Male infertility accounts for ~50% of the cases. Semen analysis is critical for determining male fertility potential. However, conventional testing is costly and complex. Here, the authors present a paper-based approach using a colorimetric enzymatic assay to simultaneously quantify live and motile sperm concentration, and motility within 10 minutes. Detection limits of 8.5 million/mL and 15.2 million/mL were achieved for live and motile sperm concentration, respectively. Clinical testing with the device yielded identical outcomes compared with standard approaches. The authors conclude that this technology provides reliable clinical testing, with additional potential for self-screening.

Effect of Dried Blood Spot Quality on Newborn Screening Analyte Concentrations and Recommendations for Minimum Acceptance Criteria for Sample Analysis.
Roanna S George and Stuart J Moat

United Kingdom newborn screening laboratories reject samples deemed unsuitable for analysis. However, there is a lack of scientific evidence to determine minimum bloodspot quality acceptance criteria for sample analysis. In this study whole blood pools were spiked with analytes measured in the United Kingdom newborn screening program and the effect of sample volume and sample quality were evaluated. The authors found that smaller volume and compressed bloodspots produced significantly lower results; therefore there was a significant risk of missing a baby with a treatable disorder. This work is essential for setting minimum acceptance criteria for bloodspot quality, and to improve the performance of newborn screening programs.

Soluble CRTC3: A Newly Identified Protein Released by Adipose Tissue That Is Associated with Childhood Obesity
Anna Prats-Puig, et al.

CREB-regulated transcription coactivator 3 or CRTC3 is found in adipocytes where it may promote obesity through disruption of catecholamine signaling. Whether CRTC3 is secreted by adipose tissue, is detectable and quantifiable in the circulation, and has serum concentrations related to other metabolic markers in

children is unknown. To investigate these questions, the authors cultured explants of adipose tissue and studied associations between serum CRTC3 concentrations and metabolic markers. Serum concentrations of CRTC3 at around age 7y were found to be associated with changes in waist and high molecular weight adiponectin at around age 10y. CRTC3 represents a newly identified protein that is present in the circulation and appears to be related to childhood obesity.

Evaluation of Temporal Changes in Cardiovascular Biomarker Concentrations Improves Risk Prediction in an Elderly Population from the Community
Kai M Eggers, et al.

The authors of this study investigated 1016 elderly community-dwelling subjects and found that several cardiovascular biomarkers and their temporal changes predicted adverse events during 10 years of follow-up. Concentrations of growth-differentiation factor-15 were particularly predictive for all-cause mortality whereas N-terminal pro-B-type natriuretic peptide concentrations also predicted cardiovascular events. The other investigated biomarkers (which included mid-regional pro-adrenomedullin, high-sensitivity cardiac troponin I, soluble ST2, galectin-3) exhibited less distinct associations with adverse events. The findings of this study are of considerable interest given the emphasis on circulating biomarkers as tools to detect and monitor at-risk subjects from the community with preclinical and potentially modifiable stages of cardiovascular disease.

Two-Hour Algorithm for Triage Towards Rule-Out and Rule-In of Acute Myocardial Infarction by Use of High-Sensitivity Cardiac Troponin I
Jasper Boeddinghaus, et al.

In this study the authors derived and validated a 2-hour algorithm for rapid "rule-out" and "rule-in" of acute myocardial infarction using high-sensitivity cardiac troponin I. The authors prospectively enrolled 1435 (derivation cohort) and 1194 (external validation cohort) unselected patients presenting with suspected acute myocardial infarction to the emergency department. Applying the developed 2-hour algorithm in the external validation cohort, 60% of patients could be classified as "rule-out", 13% as "rule-in" and 27% to "observe". The cumulative 30-day survival rates for patients classified as "rule-out" were 100% in both cohorts. The findings highlight the suitability and attractiveness of assay-specific high-sensitivity cardiac troponin 2-hour algorithms for routine clinical care.

Clinical Significance of Circulating Tumor Microemboli as a Prognostic Marker in Patients with Pancreatic Ductal Adenocarcinoma
Ming-Chu Chang, et al.

Circulating tumor microemboli have potential as prognostic biomarkers in cancer. The role of circulating tumor microemboli in pancreatic cancer has not been reported before. In this prospective study, circulating tumor cells and circulating tumor microemboli were enumerated in the peripheral blood of patients with pancreatic cancer before treatment. Associations of circulating tumor cells and circulating tumor microemboli with patients' clinical factors and prognosis were determined. Circulating tumor microemboli were found to be an independent prognostic factor of overall survival and progression free survival in patients with early as well as advanced disease and, overall, in all patients. Circulating tumor

micro emboli could represent a potential biomarker with prognositic value in pancreatic cancer.

Mass Spectrometry–Based Adrenal and Peripheral Venous Steroid Profiling for Subtyping Primary Aldosteronism
Graeme Eisenhofer, et al.

The choice of appropriate therapeutic intervention for primary aldosteronism requires adrenal venous sampling studies to subtype patients according to presence or absence of a unilateral aldosterone-producing adenoma. These are complex and difficult procedures with attendant inaccuracies in assessing lateralized aldosterone production. The current study establishes that LC-MS/MS-based steroid profiling achieves enhanced magnitudes of measured aldosterone lateralization ratios in patients with unilateral disease and provides for multiple measures for subtype discrimination based not only on steroid profiles in adrenal venous plasma, but also peripheral plasma. Subtyping patients with primary aldosteronism based on peripheral measurements offers advantages over adrenal venous sampling for this purpose.

Complement C3 and High Risk of Venous Thromboembolism: 80 517 Individuals from the Copenhagen General Population Study
Ina Nørgaard, et al.

Whether complement activation may contribute to venous thromboembolism, including deep venous thrombosis and pulmonary embolism is presently unknown. To address this question 80 517 individuals without venous thromboembolism from the Copenhagen General Population Study were studied. Study participants were recruited in 2003-2012, had complement C3 concentrations measured at baseline, and were followed until April 2013. 1176 participants developed venous thromboembolism. The hazard ratio for development of venous thromboembolism was found to be 2.43 times greater per 1g/L increment in complement C3 concentration. These findings suggest that a high concentration of complement C3 is associated with high risk of venous thromboembolism in the general population.