Clinical Chemistry

June 2013 Audio Summary

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On the cover this month: Alzheimer's brain. Amyloid plaques accumulate in the brains of Alzheimer patients, as shown on the left side of the cover image, but not in unaffected brains, as shown on the right. Clinical studies have provided evidence that cerebrospinal fluid amyloid β_{1-42} and τ proteins are reliable biochemical markers of Alzheimer disease neuropathology. Newly revised criteria for the diagnosis of Alzheimer disease include cerebrospinal fluid biomarkers for use in research settings. The selection of Alzheimer disease patients at the predementia stage by use of cerebrospinal fluid biomarkers may also improve the statistical power of clinical trial design. In this issue of Clinical Chemistry, Shaw and colleagues provide a comprehensive review of the clinical utility and analytical challenges in the measurement of cerebrospinal fluid amyloid β_{1-42} and τ proteins as Alzheimer disease biomarkers. These authors discuss the sources of analytical variability and global efforts to overcome the challenges of advancing the use of immunoassays for measuring amyloid β_{1-42} and τ proteins, the association of cerebrospinal fluid biomarkers with imaging biomarkers and genetic factors, and the clinical utility of immunoassay-based amyloid β and τ protein measurements for early diagnosis and predicting disease progression.

Alternative Calibration Strategies for the Clinical Laboratory: Application to Nortriptyline Therapeutic Drug Monitoring
By Matthew T. Olson, et al.

The measurement of the calibration curve with every assay batch is a time-consuming and expensive component in the execution of clinical mass spectrometry assays. To obviate this expense, the authors propose more efficient calibration strategies. The authors tested these strategies by measuring serum nortriptyline concentrations while employing the alternative calibration strategies. The investigation did not reveal any significant differences between results obtained with the alternative calibration strategy and those made by interpolation against the calibration curve.

Probe-Based Quantitative PCR Assay for Detecting Constitutional and Somatic Deletions in the *NF1* Gene: Application to Genetic Testing and Tumor Analysis
By Ernest Terribas, et al.

In this article the authors present a probe-based qPCR assay designed for interrogating the copy number status of the NF1 gene to detect constitutional and somatic deletions. About 5% of Neurofibromatosis Type 1 patients bear constitutional microdeletions encompassing the *NF1* gene, some of them in the form of mosaicism. Multiplex ligation-dependent probe amplification is the current standard for detecting *NF1* deletions, but additional techniques are required to make genetic testing more robust, to cope with the presence of mosaicism, or to deal with differences in DNA quality. The qPCR assay described is an inexpensive and fast methodology and fulfills these necessities.

Establishment and Validation of Analytical Reference Panels for the Standardization of Quantitative BCR-ABL1 Measurements on the International Scale
By Helen E. White, et al.

The goal of this study was to develop reference reagents to improve the standardization of BCR-ABL1 quantitative measurements across testing laboratories. Synthetic reference panels were prepared using the Armored RNA Quant technology and analytically calibrated to the primary standards of the World Health Organization. The reagents were robust, stable, reproducibly detected over 3 logs of BCR-ABL1 expression levels, and compatible with PCR methods already standardized on the international scale. These secondary reference reagents represent a major advance to support the worldwide standardization of BCR-ABL1 monitoring and the optimization of current and new therapeutic approaches in chronic myeloid leukemia.

A Comparison of the Theoretical Relationship between HDL Size and the Ratio of HDL Cholesterol to Apolipoprotein A-I with Experimental Results from the Women's Health Study
By Norman A. Mazer, et al.

This study investigated the relationship between HDL particle size and the ratio of HDL-cholesterol to ApoA-I concentration from both the theoretical and experimental perspectives. Theoretical predictions were derived from Shen's classic model of lipoprotein structure and were compared with NMR measurements of HDL size from 26 772 subjects in the Women's Health Study. The predicted relationship was found to be consistent with the experimental data, thereby supporting the underlying assumptions of the model. The application of the model to estimating the concentration of HDL particles is also demonstrated. The findings offer new insights into HDL structure, composition, and remodeling and suggest that the HDL-C to ApoA-I ratio could be a readily available biomarker for estimating HDL size and HDL-particle concentration.

Inhibition of the Renin-Angiotensin System Reduces the Rise in Serum Aldosterone in Acute Coronary Syndrome Patients with Preserved Left Ventricular Function: Observations from the AVANT GARDE-TIMI 43 Trial
By Jacob A. Udell, et al.

Acute coronary syndromes activate neurohormonal pathways, including aldosterone, with deleterious cardiovascular effects. Within the randomized, placebo controlled AVANT GARDE-TIMI 43 trial, the authors tested whether more complete renin-angiotensin-aldosterone system inhibition reduces aldosterone levels in post-acute coronary syndrome patients with preserved ventricular function but neurohormonal activation. Placebo patients demonstrated a significant, nearly 20% increase in aldosterone over 8 weeks as compared with a 1% decrease when monotherapy was used to achieve renin-angiotensin-aldosterone system inhibition by either an angiotensin II receptor antagonist or a direct renin inhibitor, and a 1.4% decrease when both drugs were combined. The clinical implications and role of more complete renin-angiotensin-aldosterone system inhibition in this patient population warrant further investigation.

Evaluation of a Dried Blood Spot Assay to Measure Prenatal Screening Markers Pregnancy-Associated Plasma Protein A and Free β-Subunit of Human Chorionic Gonadotropin
By Nicholas J. Cowans, et al.

A dried blood spot dual assay that measures the prenatal screening biomarkers pregnancy-associated plasma protein-A and free β-subunit of human chorionic gonadotropin was compared with a serum assay for the same markers in order to determine in which ways the two assays differed. After hematocrit correction, pregnancy-associated plasma protein-A was found to perform similarly on the dried blood spot and serum assays, whereas free β-subunit of human chorionic gonadotropin measurements were consistently higher on the dried blood spot assay, which was attributed to extra β-subunits being released from intact human chorionic gonadotropin during the drying process. Users of the dried blood spot assay will need to take this into account when calculating screening risks.

Cardiac Troponin Assay Classification by Both Clinical and Analytical Performance Characteristics: A Study on Outcome Prediction
By Per Venge and Bertil Lindahl

Current assays of cardiac troponins are judged by their analytical performance for measuring the concentration of the 99th percentile of a healthy reference population with an imprecision of ≤10% CV or in the range between 10 and 20% CV. Assays with these criteria are deemed "guideline acceptable" or "clinically usable," respectively. This study performed a head-to-head comparison of the clinical performance of four widely used "clinically usable" cardiac troponin I assays, with an assay designated "not acceptable" and showed that the comparison of cardiac troponin assays should be based not only on analytical performance but also on clinical performance.

Measurement of Thyroglobulin by Liquid Chromatography/Tandem Mass Spectrometry in Serum and Plasma in the Presence of Antithyroglobulin Autoantibodies
By Mark M. Kushnir, et al.

Measurement of thyroglobulin is commonly used for the follow-up of patients treated for differentiated thyroid carcinoma. Difficulty in using thyroglobulin as a biomarker of the recurrence of thyroid cancer is related to presence in many patients of endogenous antithyroglobulin autoantibodies, which can interfere with the measurements and cause false negative results. In this article the authors present a highly sensitive, robust liquid chromatography-tandem mass spectrometry method for quantification of thyroglobulin in serum and plasma samples that overcomes interference of thyroglobulin autoantibodies. In addition to assay validation, the authors also compared the mass spectrometric method to a commercial immunoassay using thyroglobulin autoantibody-positive and autoantibody-negative samples.