Clinical Chemistry

November 2013 Audio Summary

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On the cover this month: Francis Crick's original sketch of the structure of DNA. Drawn on a scrap of A4 paper, this image provided the first look at the double-helix structure of DNA. It is important to remember that 60 years ago there were no software programs for drawing structures, and neither Francis Crick nor James Watson had any artistic talent. Francis Crick asked his wife Odile, an accomplished artist, to abandon her painting and illustrate her husband's work. It was Odile's exquisite and iconic drawing of the double helix that was included in their 1953 research study that was submitted to Nature. Not only that, it was James Watson's sister Betty who typed the historic paper. It makes one wonder how Crick and Watson would have fared without the help of two women, Odile Crick and Betty Watson. Skipping ahead 60 years, this month's issue of *Clinical Chemistry* contains what we believe is an important research study and accompanying editorial describing maternal plasma DNA bisulfite sequencing for noninvasive prenatal testing.

Noninvasive Prenatal Methylomic Analysis by Genomewide Bisulfite Sequencing of Maternal Plasma DNA

By Fiona Lun, et al.

Epigenetic mechanisms play an important role in development. Human fetal tissues are not readily accessible. Cell-free fetal DNA molecules in maternal plasma can be sampled noninvasively. The authors of this study applied genomewide bisulfite sequencing to analyze maternal plasma DNA. From these data the placental methylation profile could be deduced in a genomewide and noninvasive manner. Using polymorphic differences between the mother and the fetus, the methylation status of the fetal-specific reads were determined. Owing to the noninvasive nature of this approach, serial assessments of the fetal and placental methylation profiles could be performed. This development offers a powerful method for biomarker discovery and clinical testing.

MicroRNA Signature Helps Distinguish Early from Late Biochemical Failure in Prostate Cancer

By Zsuzsanna Lichner, et al

Prostate cancer is common in men, but only a small percentage of patients develop aggressive disease. There is no biomarker to predict disease outcome at time of prostatectomy. The authors of this paper investigated the potential of microRNAs to estimate the risk for biochemical failure, an indicator of prostate cancer progression. microRNA expression was screened in prostatectomy samples and was used to build statistical models to predict biochemical failure. These investigators also showed that miR-152, featured in the models, impacts cell proliferation and is a possible regulator of Erbb signaling pathway. microRNA signatures may prove useful in the early detection of aggressive prostate cancer, thereby impacting therapeutic decisions.

Quantitative PCR Measurement of tRNA 2-Methylthio Modification for Assessing Type 2 Diabetes Risk
By Peiyu Xie, et al.

In this article the authors describe a novel method for the measurement of 2-methylthio modification in total RNA caused by the type 2 diabetes risk gene Cdkal1. The 2-methylthio modification attenuated reverse transcription due to steric hindrance. Applying this finding, the authors developed a simple yet sensitive quantitative PCR-based method to measure 2-methylthio modification in RNA isolated from human specimens. The method revealed that 2-methylthio modification was associated with the risk allele of Cdkal1 as well as insulin secretion. These results not only implicate the critical role of 2-methylthio modification in type 2 diabetes, but also demonstrate that the method can be used for assessing type 2 diabetes risk.

Biomarkers of Cardiovascular Stress and Incident Chronic Kidney Disease
By Jennifer E. Ho, et al.

In this study, the authors examined three biomarkers of cardiovascular stress and their associations with incident kidney disease. In the Framingham Heart Study, a longitudinal community-based cohort, growth differentiation factor-15 levels were associated with the development of chronic kidney disease and a rapid decline in renal function. All three biomarkers (growth differentiation factor-15, soluble ST2, and highly sensitive troponin I) had suggestive associations with the development of microalbuminuria. Adding growth differentiation factor -15 to traditional clinical variables improved risk prediction of incident kidney disease.

Soluble Urokinase Plasminogen Activator Receptor for Risk Prediction in Patients Admitted with Acute Chest Pain
By Stig Lyngbæk, et al.

Plasma soluble urokinase plasminogen activator receptor concentrations have previously been shown to predict mortality and myocardial infarction in several clinical settings. Prognostic implications of increased concentrations of soluble urokinase plasminogen activator receptor in patients presenting with acute chest pain are unknown. The authors of this study measured soluble urokinase plasminogen activator receptor concentrations at baseline in 449 consecutive chest pain patients admitted on suspicion of non-ST segment elevation acute coronary syndrome and followed them for 5.7 years. Soluble urokinase plasminogen activator receptor was a strong and independent marker of all-cause mortality. Moreover, soluble urokinase plasminogen activator receptor improved the predictive ability of abnormal ECG findings and increased levels of troponin. Soluble urokinase plasminogen activator receptor measurement may provide improved clinical decision making for chest pain patients.

Standardization of LC-MS for Therapeutic Drug Monitoring of Tacrolimus
By Thomas Michael Annesley, et al.

In an international proficiency-testing scheme for tacrolimus measurement, mass spectrometry respondents represent the largest method group. However, these methods lack standardization, which may explain the relatively poor interlaboratory agreement for such methods. In this study the authors provide a possible path towards the standardization of tacrolimus quantification. Using a 40-member whole blood tacrolimus proficiency panel circulated to 7 laboratories, and a common LC-MS platform and LC-MS reagent kit intended for whole blood tacrolimus quantification, the authors found excellent agreement with a validated reference method procedure. Imprecision for pooled patient samples ranged from 2.0 to 5.4%, and the mean difference from the reference measurement procedure ranged from 0.4 to 4.4%. The authors conclude that tacrolimus assay standardization, which must include all facets of the analysis, is necessary to compare patient results between laboratories and to interpret consensus guidelines.

First Metabolic Profile of XLR-11, a Novel Synthetic Cannabinoid, Obtained by Using Human Hepatocytes and High-Resolution Mass Spectrometry
By Ariane Wohlfarth, et al.

Since the mid-2000s, synthetic cannabinoids have been abused as recreational drugs. XLR-11 is one of the most recent and widely abused drugs and its use is now linked with acute kidney injury. To investigate XLR-11 metabolism, the authors incubated XLR-11 with pooled human hepatocytes. Samples were analyzed by high-resolution mass spectrometry and the data thoroughly data-mined with different data processing algorithms. More than 25 metabolites were found that resulted from hydroxylation, carboxylation, hemiketal and hemiacetal formation, internal dehydration, oxidative defluorination, and further glucuronidation. These are the first data defining major urinary targets of XLR-11 metabolism that could document XLR-11 intake in forensic and clinical investigations.

Work Flow Analysis of Around-the-clock Processing of Blood Culture Samples and Integrated MALDI-TOF Mass Spectrometry Analysis for the Diagnosis of Bloodstream Infections
By Wilhelm Schneiderhan, et al.

Delayed effective antimicrobial treatment dramatically increases septic shock-related mortality. Thus, rapid microbiological testing is crucial for the management of sepsis. The authors evaluated the effect of a 24/7 processing of samples in combination with MALDI-TOF mass spectrometry on timeliness of bacterial identification. For 912 positive blood cultures, the turnaround time of bacterial identification was calculated for routine biochemical identification and for 24/7 MALDI-TOF mass spectrometry identification. Continuous microbiological

testing reduced the turnaround time for reporting the bacterial species by 52.2 hours. Future studies are required to demonstrate the improved treatment of severe infections resulting from rapid pathogen identification.

Reproducibility of Metabolomic Profiles among Men and Women in 2 Large Cohort Studies
By Mary K. Townsend, et al.

Reproducibility data are unavailable for many metabolites measured by metabolomics platforms. Using a liquid chromatography-tandem mass spectrometry platform, the authors quantified 257 metabolites from archived plasma to evaluate metabolite interassay reproducibility and reproducibility over a 24-48 hour processing delay and within individuals over 1 to 2 years. The majority of plasma metabolites had low interassay coefficients of variation, were not affected by a 24-hour processing delay, and were reproducible within individuals over 1 to 2 years. These data are useful for epidemiologic studies in which attenuation of metabolic profile-disease effect estimates due to measurement error is a key consideration.