Clinical Chemistry

July 2018 Audio Summary

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ON THE COVER "L" Train on Lake Street. You know you are in Chicago by the creak and rattle of the "L" trains traveling overhead, blending into the sound of cars, buses, and people below. The "L" (not "El" for its elevated set of tracks), created in 1892 with the first elevated train called the "Alley L," was designed to solve the city's traffic problems, a goal still sought in 2018. But traffic aside, this historic city remains a gathering place because of its stunning architecture, art galleries, Millennium Park, and the Magnificent Mile. In July 2018, Chicago will also be the gathering place for thousands of laboratory professionals seeking the latest cutting-edge science in areas such as targeted cancer therapies, translational medicine, the HPV vaccine, nucleic acid detection using CRISPR-Dx, and meeting the diagnostic needs of a global population. Plus, there is the world's largest Clinical Lab Expo. So, enjoy the Windy City!

Detectable High-Sensitivity Cardiac Troponin within the Population Reference Interval Conveys High 5-Year Cardiovascular Risk: An Observational Study

By Martin P. Than, et al.

To understand the predictive value of high-sensitivity troponin assays this study followed patients for 5 years who presented to the emergency department with possible acute coronary syndrome but without a major adverse cardiac event diagnosis. Concentrations measured with both the Abbott high-sensitivity troponin I and the Roche high-sensitivity troponin T assays within the so-called "normal" concentration range were associated with increasing rates of future major adverse cardiac events. Concentrations measured with either assay showed a similar association with future major adverse cardiac events, but concentrations measured with the troponin T assay were much more strongly associated with all-cause mortality than those measured with the troponin I assay.

RNA Profiles of Circulating Tumor Cells and Extracellular Vesicles for Therapy Stratification of Metastatic Breast Cancer Patients

By Corinna Keup, et al.

Liquid biopsies may enhance therapy management. Here the authors compared messenger RNA profiles of circulating tumor cells and extracellular vesicles in 35 hormone-receptor-positive/HER2-negative metastatic breast cancer patients. Circulating tumor cells were isolated by immunomagnetic selection, extracellular vesicles by a membrane-affinity-based procedure from blood collected at three staging time points. Eighteen genes were analyzed by reverse transcription-quantitative PCR. The messenger RNA profiles of extracellular vesicles and circulating tumor cells showed substantial differences. Mechanistic target of rapamycin overexpression was frequently found in messenger RNA and Aurora kinase A signals appeared often in extracellular vesicles. Whereas mechanistic target of rapamycin signals in circulating tumor cells significantly correlated with response, signals in extracellular vesicles indicated non-response. These results emphasize the potential and challenges of liquid biopsies.

Validation of an Expanded Carrier Screen that Optimizes Sensitivity via Full-Exon Sequencing and Panel-wide Copy Number Variant Identification
By Gregory J. Hogan, et al.

Expanded carrier screening informs prospective parents about the risk of having a child with a severe Mendelian disease. Here, the authors validated and clinically characterized a 235-gene sequencing-based expanded carrier screening that found technically challenging mutations in highly homologous regions and supported panel-wide identification of copy-number variants. They demonstrated copy-number variant-finding proficiency not only in more than 50 positive reference samples, but also in more than 250,000 simulated samples with deletions across the panel. When exploring the screen's clinical impact in 36,859 patients, copy-number variants and challenging variants accounted for greater than 29% of the total disease risk assessed by the panel.

Small ncRNA-Seq Results of Human Tissues: Variations Depending on Sample Integrity
By Nicole Ludwig, et al.

The results of small non-coding RNA profiles (including microRNAs, piwi-interacting RNAs, transfer RNAs, small nucleolar RNAs, and ribosomal RNAs) vary substantially based on the experimental set-up and the sample integrity. The authors of this study sequenced all 64 possible combinations of 8 different experimental conditions in 8 tissue samples to investigate the variability in small non-coding RNA data. Their data emphasize the importance of sample integrity especially for next-generation-sequencing-based, high-throughput small non-coding RNA profiles. In particular for the prediction of novel microRNAs only samples with highest RNA integrity should be used to avoid identification of false “microRNAs.”

Characterization of Human Salivary Extracellular RNA by Next-generation Sequencing
By Feng Li, et al.

This manuscript presents the characterization of human salivary extracellular RNA by next-generation sequencing. Processing of human saliva for RNA-Sequencing is challenging as it requires isolation of a sufficient amount of RNA, adequate library construction, and computational processing. Lack of standardization of the laboratory procedures undermines saliva’s diagnostic potential. The authors of this study performed a comparison of different RNA isolation and library construction methods for RNA-sequencing to examine which kits showed the highest total RNA yield and recovery. Their results may give guidance in selection of the best adapted methods for salivary RNA processing.

Genetic Screening Test to Detect Translocations in Acute Leukemias by Use of Targeted Locus Amplification
By Mohamed Z. Alimohamed, et al.

Over 500 translocations are identified in acute leukemias. Translocation detection is important for prognosis and treatment. Currently, multiple techniques are needed for detection. The authors of this study developed a single test based on Targeted Locus Amplification, targeting the 17 genes most commonly involved in acute leukemia. This assay is capable of detecting cryptic and other translocations involving targeted genes, without prior knowledge of the chromosomal partner. It offers similar sensitivity to current diagnostic methods in detecting translocations, while maintaining 100% specificity even with only 10% aberrant cells present. Further optimization may make the Targeted Locus Amplification multiplex assay suitable for diagnostic use.

Full-Size Cardiac Troponin I and Its Proteolytic Fragments in Blood of Patients with Acute Myocardial Infarction: Antibody Selection for Assay Development
By Ivan A. Katrukha, et al.

Cardiac troponin I presents in the blood of patients with acute myocardial infarction as the intact molecule with a repertoire of proteolytic fragments. The degradation of cardiac troponin I could negatively influence its precise immunodetection. The authors of this study demonstrate that the ratio of cardiac troponin I fragments in serial samples did not show large changes for up to 36 hours following acute myocardial infarction. Monoclonal antibodies specific for epitopes within the region of amino acid residues 23-196 recognized more than 80% of cardiac troponin I by abundance. They suggest that antibodies specific to the cardiac troponin I epitopes encompassed by amino acid residues 23-36 and 126-196 may be the best compromise candidates for use in immunoassays.

Complement C3 and Risk of Diabetic Microvascular Disease: A Cohort Study of 95,202 Individuals from the General Population
By Katrine L. Rasmussen, et al.

This study tested the hypothesis that high concentrations of complement C3 are associated with increased risk of diabetic microvascular complications. The authors studied 95,202 individuals from the general population in prospective epidemiological analyses and employed Mendelian randomization. They found a positive association between plasma complement C3 and microvascular disease, and genetic analyses confirmed the epidemiological findings, potentially indicating causality. Plasma complement C3 measurements have the potential to play a central role in future risk stratification.