Clinical Chemistry

February 2017 Audio Summary

This is the February 2017 issue of *Clinical Chemistry*, Volume 63, Issue 2.

ON THE COVER Faces of the many SYCL members who have participated in the building of the Clinical Chemistry Trainee Council. With the help of these scientists the Journal created a program that now has approximately 10,000 subscribers worldwide. This month the Journal launches its most ambitious program yet, based on the concept of adaptive learning, entitled the AACC Learning Lab for Laboratory Medicine on NEJM Knowledge+. In an Editorial in this month's issue, Editor-in-Chief Nader Rifai introduces readers to this educational program, which focuses on all sections of laboratory medicine and will be useful for preparing for certification exams as well as continuing education.

High Glycated Albumin and Mortality in Persons with Diabetes Mellitus on Hemodialysis
By Christina W. Chen, et al.

Glycated albumin is a test of glycemic control that may be useful in patients with kidney disease because of problems with hemoglobin A1c testing. This study tested whether glycated albumin values were associated with mortality in patients with diabetes mellitus on hemodialysis. The authors observed that single or repeatedly high glycated albumin values were associated with significantly increased 4-year mortality, even after adjustment for other risk factors. In contrast, similar analyses of hemoglobin A1c values gave less consistent associations with mortality risk. These findings provide evidence in support of glycated albumin as a useful test for monitoring glycemic control in diabetic patients on hemodialysis.

Decrease of Serum IGF-I following Transsphenoidal Pituitary Surgery for Acromegaly
By Min Yu, et al.

In the first months after surgical removal of growth hormone–secreting pituitary tumors, it is unclear whether the patients' acromegaly is in remission. Here the authors used a mass-spectrometric method to measure the growth-hormone mediator insulin-like growth factor-I, abbreviated IGF-I, during hospitalizations of 2-3 days after surgery. In the patients who achieved remission mean IGF-I decreased to approximately half of the preoperative values, but in nonremission patients IGF-I exhibited smaller changes, decreasing on average by only 19% from the preoperative values. The authors conclude that mass-spectrometric IGF-I measurements in the immediate postoperative period have the potential to be useful in identifying patients whose acromegaly is or is not in remission thereby facilitating patient management.

Combined Count- and Size-Based Analysis of Maternal Plasma DNA for Noninvasive Prenatal Detection of Fetal Subchromosomal Aberrations Facilitates Elucidation of the Fetal and/or Maternal Origin of the Aberrations
By Stephanie C. Y. Yu, et al.

Maternal plasma DNA-based noninvasive prenatal testing has been expanded to include the detection of certain subchromosomal copy number aberrations. However, false-positive results are expected to become more prevalent when more subchromosomal regions are analyzed. In this study the authors demonstrate that size-based analysis can be used as an independent method to validate the copy number aberrations detected by count-based analysis. In addition, a combination of size-based and count-based analyses can elucidate whether a fetus has inherited a copy number aberration from its mother who herself is a carrier of the copy number aberration. The authors conclude that this strategy has the potential to improve the diagnostic specificity of current tests.

BRCA Testing by Single-Molecule Molecular Inversion Probes
By Kornelia Neveling, et al.

In this article the authors describe a fully automated clinical sequencing workflow based on single molecule molecular inversion probe enrichment, in combination with 2-color massively parallel sequencing-by-synthesis. Molecular inversion probes are DNA oligonucleotides used as baits for the enrichment of specific regions of interest. As proof of principle, the authors chose the analysis of the breast and ovarian cancer associated genes BRCA1 and BRCA2. Extensive automation of wet laboratory work, file handling, data transfer, and analysis was established to achieve fast and reliable processing times. The newly implemented workflow was extensively tested for more than 500 samples from 2 different laboratories, yielding in an analytical sensitivity and specificity of 100%.

Universal Haplotype-Based Noninvasive Prenatal Testing for Single Gene Diseases
By Winnie W.I. Hui, et al.

Relative haplotype dosage analysis has been developed for the noninvasive prenatal assessment of single gene diseases. This approach requires the input of parental haplotype information previously determined using complex methodologies or by inference. Here the authors used linked-read sequencing technology for direct haplotyping of parental DNA followed by relative haplotype dosage analysis of maternal plasma DNA for a range of single gene diseases. The approach bypasses the need for mutation-specific assays and DNA from other affected family members. Thus, the approach is universally applicable to pregnancies at risk for the inheritance of a single gene disease.

RT-qPCR and RT-Digital PCR: A Comparison of Different Platforms for the Evaluation of Residual Disease in Chronic Myeloid Leukemia
By Mary Alikian, et al.
In chronic myelogenous leukemia, quantitative monitoring of BCR-ABL1 transcript levels by reverse transcription-qPCR is the gold standard strategy for evaluating patient response to life-long administered tyrosine kinase inhibitor (TKI) therapies. Patients with sustained deep molecular responses can consider therapy discontinuation where both sensitive and accurate quantification of disease levels are important to predict eligibility for discontinuation and allow timely therapeutic re-intervention before overt relapse. In this sense, digital PCR provides a suitable alternative to the gold-standard. In the current study, the authors compared three different digital PCR platforms and investigated whether they could be applied in a clinical setting to quantify BCR-ABL1 transcripts in chronic myelogenous leukemia patients. Digital PCR was able to quantify low-level BCR-ABL1 transcript copies but was unable to improve sensitivity below the level of detection achieved by reverse transcription-qPCR; however, digital PCR was able to perform these sensitive measurements without use of a calibration curve.

Next Generation Sequencing of Circulating Cell-Free DNA for Evaluating Mutations and Gene Amplification in Metastatic Breast Cancer
By Karen Page, et al.

The field of liquid biopsies, and cell free DNA in particular, is evolving rapidly. Here the authors show the potential clinical utility of concurrent tracking of driver mutations and gene amplification by next-generation sequencing of cell free DNA. The authors used a 158 amplicon next generation sequencing panel covering hot-spot mutations and copy number variation in 16 genes, with subsequent validation by droplet digital PCR. Half of 42 patients with metastatic breast cancer showed mutations and/or gene amplification in cell free DNA, and 9 patients had alterations in either the estrogen receptor or the HER2 gene that could herald a change in treatment. Additionally, in longitudinal samples mutations and amplifications in cell free DNA evolved over time and correlated with response by the Response Evaluation Criteria in Solid Tumors criteria, suggesting that these could be used to guide clinical practice in real time.

Serial Sampling of High-Sensitivity Cardiac Troponin T May Not Be Required for Prediction of Acute Myocardial Infarction Diagnosis in Chest Pain Patients with Highly Abnormal Concentrations at Presentation
By Matthias Mueller-Hennessen, et al.

This study assessed the positive predictive value of initial high-sensitivity cardiac troponin T alone and in combination with kinetic changes for prediction of acute myocardial infarction. 1,282 patients presenting to the emergency department with suspected acute myocardial infarction were enrolled. The authors found that a reliable acute myocardial infarction prediction as early as admission seemed feasible for chest pain patients with high baseline high-sensitivity cardiac troponin T concentrations. Moreover, addition of relative and absolute kinetic changes did not add incremental diagnostic value. The authors suggest that serial sampling may not be required in chest pain patients presenting with highly abnormal high-sensitivity cardiac troponin T concentrations at admission.

High-Sensitivity Troponin T vs I in Acute Coronary Syndrome: Prediction of Significant Coronary Lesions and Long-term Prognosis
By Brede Alexander Kvisvik, et al.

This study explored the potential differences between the high-sensitivity troponin T and I assays in the prediction of significant coronary lesions and long-term prognosis in patients with acute coronary syndrome. The value of NT-proBNP concentrations was also assessed. 390 patients admitted for coronary angiography were included. The authors found similar accuracy between the troponin assays for prediction of significant coronary lesions. During a follow-up of more than 8 years, NT-proBNP was found to be superior to both troponin assays as a prognostic marker for cardiovascular and all-cause mortality, as well as for the composite end point of cardiovascular mortality and hospitalization for myocardial infarction or heart failure.

Identification and Characterization of Cardiac Troponin T Fragments in Serum of Patients Suffering from Acute Myocardial Infarction
By Alexander S Streng, et al.

Cardiac troponin T is a preferred biomarker for the diagnosis of acute myocardial infarction. It is believed that cardiac troponin T is present as a heterogeneous mixture in human serum, containing intact and fragmented forms. In this study, the authors used a targeted mass spectrometry assay to identify selected peptides specific for cardiac troponin T and to determine their relative abundance in those fragments. Western blotting was also performed. The results of this study demonstrated that these fragments indeed were cardiac troponin T -derived products. Sites of proteolytic cleavage were identified in the two most abundant fragments. With this information, future troponin assays can be targeted to specific regions of cardiac troponin T.

Biomarkers and Coronary Lesions Predict Outcomes after Revascularization in Non–STElevation Acute Coronary Syndrome
By Daniel Lindholm, et al.

The risk of subsequent events in patients with non-ST-elevation acute coronary syndromes is often assessed by appraisal only of clinical characteristics. This study demonstrated that the combination of angiographic extent of coronary artery disease and the cardiac biomarkers NT-proBNP and GDF-15 provide additional prognostic information in revascularized non-ST-elevation acute coronary syndrome patients. The authors found that by combining the prognostic information from clinical variables, extent of coronary artery disease, and cardiac biomarkers, preferably in a decision-support algorithm, more precise prediction of subsequent ischemic events could be obtained, which might be useful to guide treatment decisions, such as those regarding antithrombotic therapy or other secondary prevention measures.

Simulation Models of Misclassification Error for Single Thresholds of High-Sensitivity Cardiac Troponin I Due to Assay Bias and Imprecision
By Andrew W. Lyon, et al.

This study used simulation modeling to examine the use of high sensitivity troponin I as a biomarker of myocardial infarction. Guidelines published in 2015 have suggested how to interpret high sensitivity troponin I concentrations. The authors evaluated how often troponin results would be misclassified owing to assay bias or imprecision if those guidelines were followed. They found the guidelines worked well for increased high sensitivity troponin I concentrations at or above the 99th percentile. However, they found that low concentrations of high sensitivity troponin I were quite susceptible to bias and that 5-10% of results could be misclassified. These findings carry clinical implications for the interpretation of high sensitivity troponin I results, with low values particularly prone to interpretation error.

Economic Considerations of Early Rule-In/Rule-Out Algorithms for The Diagnosis of Myocardial Infarction in The Emergency Department Using Cardiac Troponin and Glycemic Biomarkers
By Colleen M Shortt, et al.

This study performed a cost analysis evaluating the healthcare costs associated with the authors' recently reported rule-in/out myocardial infarction algorithms that utilize both conventional and high sensitivity cardiac troponins as well as the glycemic markers, glucose and hemoglobin A1c. The authors examined the costs associated with major components of a patient's hospital visit and how these vary depending on the algorithm. They found that combining cardiac troponin with glucose was the most cost-effective and a safe method for early rule-in/rule-out of myocardial infarction, whereas adding hemoglobin A1c to this strategy added costs. These findings demonstrate the cost saving opportunity for using an early rule-in/out algorithm incorporating troponin and glycemic markers.