Clinical Chemistry

April 2017 Audio Summary

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ON THE COVER: BIOHAZARD! Although people who work in laboratories are taught to respect this symbol and the warning it implies, the symbol did not exist until roughly 50 years ago. Noting the variety of warning symbols that were in use at that time, a confusing and dangerous situation, in 1966 Charles Baldwin of Dow Chemicals set out to create a bold universal symbol that had no up or down design and could be placed on a container in any direction and still be recognizable. After immediate acceptance by government agencies, this symbol became (and still is) the symbol for biohazard materials. Emerging infectious diseases represent one source of biohazard materials that laboratories must deal with. But are laboratories prepared? This month's issue of *Clinical Chemistry* contains a Q&A on the topic of laboratory preparedness, in which experts answer the question, "are we there yet?"

Association of Blood Eosinophil and Blood Neutrophil Counts with Asthma Exacerbations in the Copenhagen General Population Study
By Signe Vedel-Krogh, et al.

Inflammatory subtypes in asthma might have different exacerbation risks. The authors of this study found an association between high blood eosinophil counts and the risk of both moderate and severe exacerbations in individuals with asthma from the general population. High blood neutrophil counts were only associated with moderate exacerbations and demonstrated interactions with blood eosinophil count on moderate exacerbations. Asthma exacerbation risk depends on both eosinophil and neutrophil inflammatory patterns which display interactions.

Multicenter Evaluation of Cystatin C Measurement after Assay Standardization
By Anne-Sophie Bargnoux, et al.

The French Society of Clinical Biology conducted a multicenter evaluation of 8 standardized cystatin C assays in 2015 using four reference procedure-assigned values to commutable control materials. Although a secondary European reference material has been introduced to align assays, several commercially available measurement procedures remain clinically unsatisfactory with respect to the combined expanded uncertainty because of unacceptable substantial bias. Only Siemens reagents on the Siemens systems and, to a lesser extent, Diasys reagents on the Cobas system provided results that satisfied the minimum performance criterion calculated according to the intra-individual and inter-individual biological variations.

Liquid Chromatography-Tandem Mass Spectrometry Assay of Leukocyte Acid α-Glucosidase for Post-Newborn Screening Evaluation of Pompe Disease
By Na Lin, et al.

This paper presents a highly accurate liquid chromatography tandem mass spectrometry or LC-MS/MS method which is capable of determining low residual acid α-Glucosidase activity. The analytical range, defined as enzyme specific response signal divided by non-enzymatic response signal, was over 700-fold higher than the fluorometry assay. As low as 0.1% of normal activity can be accurately measured in these cell line studies. For the first time, infantile-onset, late-onset Pompe disease, and pseudodeficiency patients can be partially differentiated by measuring acid α-Glucosidase in a blood specimen. This differentiation could only be achieved in the past by testing cultured fibroblast samples with a fluorometry method.

Closed-Tube PCR with Nested Serial Invasion Probe Visualization Using Gold Nanoparticles
By Jianping Wang, et al.

In this study the authors constructed a colorimetric DNA detection method by combining three reactions (the template amplifier, sequence identifier, and signal generator) in a single tube. By controlling the temperature at each step, the three reactions could proceed in a given order, and could automatically switch from one to another. The combination of PCR-based template replication and invader-based signal amplification allowed the method to detect 30 copies of targeted DNA, and to selectively pick up 0.1% mutants from large amounts of background DNA, achieving a "liquid biopsy" by naked eye.

Noninvasive Prenatal Screening of Fetal Aneuploidy without Massively Parallel Sequencing
By Chenming Xu, et al.

The authors of this paper describe their development of a methodology for prenatal aneuploidy screening. As compared with current screening techniques that are based on next-generation sequencing platforms, their new method does not require sequencing to offer comparable performance in aneuploidy detection. It uses high-throughput ligation-dependent probe amplification to measure the copy number change of targeted chromosomal regions in cell-free DNA. The authors validated this method by conducting Down syndrome screening in 1182 pregnant women and achieved 100% sensitivity and 99.7% specificity. The low-cost, simplicity, and accuracy of this method potentially make it a good candidate to be offered as a standard prenatal test worldwide.

Discordance between Circulating Atherogenic Cholesterol Mass and Lipoprotein Particle Concentration in Relation to Future Coronary Events in Women
By Patrick R Lawler, et al.

Despite important implications for cardiovascular disease prevention, there remains uncertainty whether measurement of circulating total atherogenic lipoprotein particle cholesterol mass as nonHDLc or particle concentration as apoB and LDLp more accurately reflects risk of incident coronary heart disease. One way to determine which marker could provide the most accurate risk assessment is to examine risks when the markers are in disagreement or discordant with one another. Using such an approach in 27,533 initially-healthy women, the authors of this paper observed that direct measurement of lipoprotein particle concentration (mainly as apoB) appeared to more accurately track risk, and thus may better inform coronary heart disease risk assessment in clinical practice.

Prognostic Role of Molecular Forms of B-Type Natriuretic Peptide in Acute Heart Failure
By Toru Suzuki, et al.

This study explored the prognostic value offered by various molecular forms of B-type natriuretic peptide, abbreviated BNP, in cardiovascular disease. Several molecular forms of BNP are known to be present in circulation, but their associations with acute heart failure have been unknown. Nine hundred and four patient plasma samples were analyzed for BNP 5-32, 4-32 and 3-32 using immunocapture followed by MALDI-ToF mass spectrometry. BNP molecular forms were independently associated with poor prognosis at 6 months and 1 year in acute heart failure patients. The risk prediction qualities shown by BNP molecular forms were comparable to conventional measurements of BNP.

Estimated Glomerular Filtration Rate and Albuminuria Are Associated with Biomarkers of Cardiac Injury in a Population-Based Cohort Study: The Maastricht Study
By Remy J.H. Martens, et al.

It is unclear at what point over the course from normal kidney function to chronic kidney disease its association with cardiovascular disease appears. The authors of this study evaluated cross-sectional associations of estimated GFR and albuminuria with high-sensitivity cardiac troponin T and I, and amino-terminal-proBNP in 3103 individuals from a population-based cohort study. Estimated GFR and albuminuria were found associated with these biomarkers of clinical and subclinical cardiac injury at levels which do not fulfill the criteria for chronic kidney disease. Although reduced renal elimination may partly underlie the associations of estimated GFR with cardiovascular disease, these findings support the concept that estimated GFR and albuminuria are, over their entire range, associated with cardiac injury.

Estimates of Within-Subject Biological Variation of Protein C, Antithrombin, Protein S Free, Protein S Activity, and Activated Protein C Resistance in Pregnant Women
By Ann Helen Kristoffersen, et al.

Within-subject biological variation and reference change values are difficult to estimate when analyte concentrations change. A recently described model was used to examine whether different coagulation analytes with a time dependent change in concentration during pregnancy could be transformed into "steady state" by the use of multiples of the median and the natural logarithm of multiples of the median. Steady-state was achieved, and the within-subject variation calculated in pregnancy was found similar to the variation in non-pregnant women. Information about the within-subject variation of these coagulation analytes in pregnant women can be a supplemental tool in the monitoring of women with suspected pregnancy complications. However further validation is needed.

Characterization of a Blood Spot Creatine Kinase Skeletal Muscle Isoform Immunoassay for High-Throughput Newborn Screening of Duchenne Muscular Dystrophy
By Stuart J Moat, et al.

Duchenne muscular dystrophy is a lethal X-linked neuromuscular disorder. Widespread screening for Duchenne muscular dystrophy has not been adopted and currently no country nationally performs screening for Duchenne muscular dystrophy. There is renewed interest in implementing screening as new molecular therapies to treat this condition are on the horizon. Bloodspot creatine kinase enzyme assays previously used in newborn screening programs for Duchenne muscular dystrophy are non-specific as it is the CK-MM isoform that is found predominantly in skeletal muscle and is increased in boys with Duchenne muscular dystrophy. The authors of this study report development of a high-throughput immunoassay to detect the CK-MM isoform in bloodspots for the screening of Duchenne muscular dystrophy.

Diurnal and Long-term Variation in Plasma Concentrations and Renal Clearances of Circulating Markers of Kidney Proximal Tubular Secretion
By Matthew B. Rivara, et al.

There are no validated methods to measure proximal tubular solute clearance, an essential kidney function. This study evaluated diurnal, prandial, and week-to-week variation of four endogenous secretion markers—indoxyl sulfate, p-cresol sulfate, hippurate, and cinnamoylglycine—in 25 healthy adults over a 14-week period. Diurnal variation in plasma concentrations was found to be greatest for hippurate, followed by cinnamoylglycine, indoxyl sulfate, and p-cresol sulfate. Plasma concentrations of hippurate and indoxyl sulfate increased significantly following meals. Variation in renal clearances over 14 weeks was similar among the secreted solutes. These findings will inform methodology of future studies of kidney tubular secretion.