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ON THE COVER *Mother and fetal nucleic acids*. In the past decade, cell-free nucleic acids have drawn attention for their potential in noninvasive diagnosis, especially cancer detection and prenatal testing. Cell-free DNA (cfDNA)-based noninvasive prenatal testing has been used widely for the screening of fetal aneuploidy. While cfDNA can reveal static genetic information about the fetus, cell-free RNA (cfRNA) can reflect the dynamic changes of different tissues during pregnancy in both the mother and the fetus. However, cfRNA can be highly degraded and present in low concentrations, making it challenging to prepare useful sequencing libraries from cfRNA. This issue of *Clinical Chemistry* contains an article describing the systematic assessment of different RNA-sequencing library preparation methods for cfRNA samples, plus a new approach for simultaneously monitoring of immune response and microbial infections during pregnancy through plasma cfRNA sequencing.

Simultaneously Monitoring Immune Response and Microbial Infections during Pregnancy through Plasma cfRNA Sequencing
By Wenying Pan, et al.

Since its invention in 2008, cell-free DNA shotgun sequencing has changed the landscape of prenatal testing. However, we still lack a noninvasive and unbiased method to monitor immune response and microbial infections during pregnancy. The authors of this study attempted to fill this gap by using plasma cell-free RNA sequencing. They assessed the relative merits of several recently developed RNA-sequencing methods on plasma cell-free RNA samples. They analyzed the dynamic changes of the human transcriptome and the microbiome of plasma during pregnancy of a sample group of 60 women. Their analysis demonstrated that cell-free RNA sequencing can be used to monitor viral infections.

Evaluation of Lipoprotein(a) Electrophoretic and Immunoassay Methods in Discriminating Risk of Calcific Aortic Valve Disease and Incident Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis
By Jing Cao, et al.

This paper evaluated the clinical efficacy of three lipoprotein(a) analytical techniques for detecting coronary heart disease and aortic valvular calcification in a multi-ethnic population of 4,679 individuals. Study results demonstrated that lipoprotein(a) particle number, cholesterol content, and mass concentration are associated with presence of aortic valve calcification and incident coronary heart disease over 12 years. The findings benefit laboratories in justifying their selection of the most appropriate lipoprotein(a) assay.

High Lipoprotein(a) and Low Risk of Major Bleeding in Brain and Airways in the General Population: a Mendelian Randomization Study
By Anne Langsted, et al.

The physiological role of lipoprotein(a) is unclear; however, lipoprotein(a) may play a role in hemostasis and wound healing. The authors of this study tested the hypothesis that high lipoprotein(a) concentrations are associated with lower risk of major bleeding in brain and airways in 109,169 individuals from the Copenhagen City Heart Study and the Copenhagen General Population study, two similar prospective studies conducted in the Danish general population. High lipoprotein(a) concentrations were found associated observationally and causally with lower risk of major bleeding in brain and airways. These study results may allow a better understanding of the physiological role of lipoprotein(a) in hemostasis and in wound healing.

High-Sensitivity Cardiac Troponin I as a Gatekeeper for Coronary Computed Tomography Angiography and Stress Testing in Patients with Acute Chest Pain
By Maros Ferencik, et al.

Most patients presenting to the emergency department with suspected acute coronary syndrome undergo non-invasive cardiac testing with a low diagnostic yield. The authors of this study determined whether use of a combination of high-sensitivity cardiac troponin I and cardiovascular risk factors might improve selection of patients for cardiac testing.In the ROMICAT I and II trials, they derived and validated a threshold for high-sensitivity cardiac troponin I (<4 ng/L) that when combined with fewer than 2 cardiovascular risk factors could identify a third of patients as not needing cardiac testing. Use of these thresholds also increased efficiency of care by increasing emergency department discharge rate, decreasing length of hospital stay, radiation dose, and costs of care.

Activity of the Calcineurin Pathway in Patients on the Liver Transplantation Waiting List: Factors of Variability and Response to Tacrolimus Inhibition
By Ofelia Noceti, et al.

This study examined activity at different levels of the calcineurin pathway ex-vivo in peripheral blood mononuclear cells from patients enlisted for liver transplantation to study factors affecting its variability and its response to tacrolimus inhibition. Flow cytometry was used to measure NFAT1 translocation to the nucleus, expression of intracytoplasmic IL-2 and membrane CD25 as activation markers, in basal, non-stimulated and stimulated conditions, and in response to increasing concentrations of tacrolimus. Also studied was the influence of polymorphisms in 3 key genes of the calcineurin pathway, coding cyclophiline, on the individual basal activity and pharmacodynamics response of the catalytic subunit of calcineurin and the IL-2 alpha receptor. These results point to strong tacrolimus pharmacogenetic sources of variability and to potential biomarkers for the monitoring of tacrolimus pharmacodynamics.

Rapid, Secure Drug Testing Using Fingerprint Development and Paper Spray Mass Spectrometry
By Catia Costa, et al.

This study reports on a novel application of paper spray mass spectrometry for the rapid detection of cocaine, benzolyecgonine and methylecgonine in fingerprint samples. A fingerprint provides a rapid, secure and non-invasive matrix for drug screening. A paper spray mass spectrometry method is described in which a fingerprint can be developed prior to analysis and photographed, providing traceable analysis. When this method was applied to 239 measured fingerprint samples collected from drug-dependent and drug-free individuals, it yielded a 99% true positive rate and a 2.5% false positive rate based on a single fingerprint per donor.

Human Hepatocyte Metabolism of Novel Synthetic Cannabinoids MN-18 and Its 5-Fluoro Analog 5F-MN-18
By Xingxing Diao, et al.

Novel psychoactive substance abuse including synthetic cannabinoids is a serious public health problem in the United States. Synthetic cannabinoids are highly metabolized in humans, and their major metabolites were used as markers to confirm their consumption. MN-18 and 5F-MN-18 are two novel synthetic cannabinoids, but no human metabolism data are currently available, making it challenging for a forensic laboratory to confirm their intake. This study characterized the human metabolism of MN-18 and 5F-MN-18 with human hepatocytes incubation and high-resolution mass spectrometry analysis. These metabolite data enable clinical and forensic laboratories to monitor MN-18 and 5F-MN-18 intake by identification of urinary metabolites.