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ON THE COVER *The hepatitis C virus (HCV).* As many as 5 million people in the US have been infected with this virus, yet it is greatly underdiagnosed because the majority of patients having HCV develop a chronic infection that can remain asymptomatic for years. Although antiviral drugs are available for effectively treating HCV, a current challenge is identifying individuals who have the infection. The CDC has issued guidelines for HCV screening, but there remain opportunities for improving the identification, treatment, and monitoring of those with infections. To provide an update on what experts see as the changing landscape of HCV testing and treatment, this issue of *Clinical Chemistry* contains a Q&A covering new therapies for treating HCV and their impact on laboratory testing and clinical management of patients.

High-Resolution, Accurate-Mass (HRAM) Mass Spectrometry Urine Steroid Profiling in the Diagnosis of Adrenal Disorders
By Jolaine M Hines, et al.

Multiple steroid profiling is a promising diagnostic tool in adrenal tumors, Cushing syndrome and disorders of steroidogenesis. However, widespread clinical use has been limited by technical complexity, slow turnaround, and associated high cost. The authors of this study developed a urinary, 26-steroid profiling assay and established reference intervals. Profiling with this liquid-chromatography high-resolution accurate-mass mass spectrometry method in a small cohort of patients with adrenal diseases demonstrated significant differences in steroid production of adrenocortical carcinoma versus other adrenal masses, adrenal versus pituitary Cushing syndrome, and congenital adrenal hyperplasia. This method has potential to become a standard clinical test for certain adrenal diseases.

A 13-Steroid Serum Panel Based on LC-MS/MS: Use in Detection of Adrenocortical Carcinoma
By David R Taylor, et al.

Adrenal gland tumors include adrenocortical carcinoma, a malignant tumor of the steroid hormone-producing adrenal cortex. Unfortunately, biochemical diagnosis of adrenocortical carcinoma can be challenging; measurement of increased amounts of steroid hormone precursor metabolites in urine by gas chromatography-mass spectrometry is the most useful test. No corresponding test exists in blood. In this study, a liquid-chromatography tandem mass spectrometry method to quantify 13 steroids in serum was developed and validated. Using this method, it was shown that direct serum measurement of steroid hormone precursors including 11-deoxycortisol and 17-hydroxypregenenolone is useful in discriminating adrenocortical carcinoma from cortisol-secreting adrenocortical adenoma, catecholamine-producing pheochromocytoma/paraganglioma and clinically non-hypersecreting, benign adrenocortical adenomas.

Very Deep Convolutional Neural Networks for Morphologic Classification of Erythrocytes
By Thomas JS Durant, et al.

The purpose of this study was to adapt recent developments in machine learning and convolutional neural networks to the morphologic classification of individual erythrocytes. The authors' approach involved training a very-deep convolutional neural network, known as DenseNet, with almost 4,000 individually labeled erythrocytes across ten possible morphologic classes. Using the highest performing training models, test results demonstrated a high degree of accuracy, precision, and recall. These findings indicate that erythrocyte morphology profiles may be measured with a high level of performance with automated image analysis and support the use of modern machine learning methods and neural network architectures for erythrocyte classification based on morphology.

Cerebrospinal Fluid Total Protein Reference Intervals Derived from 20 Years of Patient Data
By Christopher R McCudden, et al.

The authors of this manuscript present continuous, age and sex partitioned reference intervals for cerebrospinal fluid based on more than twenty years of patient results.   They derived laboratory data from a large clinical database and performed chart reviews to generate these reference intervals. Strengths of their study include its large sample size, the provision of multiple population partitions, and inclusion of multiple different analytical methods. This information likely will be broadly applicable to other laboratories.

Kringle IV Type 2, Not Low Lipoprotein(a), as a Cause of Diabetes: A Novel Genetic Approach Using SNPs Associated Selectively with Lipoprotein(a) Concentrations or with Kringle IV Type 2 Repeats
By Andra Tolbus, et al.

Low plasma concentrations of lipoprotein(a) are observationally associated with risk of type 2 diabetes, but whether this is due to low lipoprotein(a) concentrations per se, or to large number of kringle IV type 2 repeats remains unclear. The authors of this study identified genetic variants associated selectively with lipoprotein(a) concentrations or with kringle IV type 2 number of repeats, and investigated which of these traits confer risk of type 2 diabetes. Kringle IV type 2 number of repeats, but not lipoprotein(a) concentrations, were found causally associated with type 2 diabetes. For cardiovascular disease prevention, this is a reassuring finding for the future use of lipoprotein(a) lowering therapies that do not increase kringle IV type 2 number of repeats.

Cardiovascular Biomarkers in Hypertensive Patients with Medical Treatment—Results from the Randomized TEAMSTA Protect I Trial
By Annika Jagodzinski, et al.

This study investigated the effect of antihypertensive treatment on cardiovascular biomarkers in a randomized, double-blind, controlled trial. 481 hypertensive patients were randomized to either telmisartan and amlodipin or olmesartan and hydrochlorothiazide. Blood pressure, high sensitivity tropinin I and T, BNP and NT-proBNP were measured before randomization and after six months. Significant reductions of blood pressure, high sensitivity tropinin I, BNP and NT-proBNP concentrations were observed six months after treatment in both groups. High sensitivity troponin T was measureable in only 26% of the population and did not change after treatment. In summary the findings of this study suggest that a blood pressure reduction was associated with a decrease of cardiac biomarkers, which in turn might reflect a cardiovascular risk reduction.

High-Density Lipoprotein Subclasses, Coronary Artery Disease, and Cardiovascular Mortality
By Guenther Silbernagel, et al.

HDL cholesterol is a suboptimal biomarker for cardiovascular risk stratification in secondary prevention. The authors of this study therefore investigated the associations of HDL particle concentrations measured using nuclear magnetic resonance spectroscopy with endpoints in the LURIC study. High concentrations of HDL particles, especially small HDL particles, were found consistently associated with reduced cardiovascular mortality independently of coronary artery disease. HDL particle concentration appeared superior to HDL cholesterol for assessing the risk of cardiovascular death. It remains open, whether the consistent relationship between high HDL particle concentrations and reduced cardiovascular mortality may be translated into novel therapies.