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On the cover this month: Vitamin D is an increasingly important topic in modern health care. However, even after years of research, it is not clear what path should be taken regarding vitamin D values in the population. What is the true prevalence of vitamin D deficiency? What should be measured? What 25-hydroxyvitamin D cutoff values should be used to define vitamin D deficiency? Should vitamin D supplementation be promoted in the general population? Does vitamin D have an association with any chronic condition beyond the risk for fractures? In this month's Q&A feature 4 experts discuss what we still do not know and where we might be headed.

Untargeted Metabolic Profiling Identifies Altered Serum Metabolites of Type 2 Diabetes Mellitus in a Prospective, Nested Case Control Study
By Dagmar Drogan, et al.

Prospective studies applying broad untargeted metabolite profiling to comprehensively reveal metabolic alterations preceding the onset of type 2 diabetes mellitus are scarce. Therefore, the authors of this study selected 300 incident diabetics and 300 matched controls from the European Prospective Investigation into Cancer and Nutrition-Potsdam cohort for UPLC-MS-based serum metabolite profiling. Multivariate classification and subsequent multivariable-adjusted regression indicated several metabolic alterations early in the development of diabetes. Amongst others, the chance to develop diabetes increased with hexose sugars and isopentenyladenosine-5'-monophosphate, and it decreased with lysophosphatidylcholine, phosphatidylcholine, sugar alcohols, and deoxyhexose sugars. These findings could be used to generate new hypotheses about diabetes etiology.

Electronic Medical Record–Based Performance Improvement Project to Document and Reduce Excessive Cardiac Troponin Testing
By Sara A. Love, et al.

In this study the authors assessed test utilization and rationale behind provider ordering of cardiac troponin I for the diagnosis of myocardial infarction after implementation of a hospital-wide serial order protocol. During 2 months in 2013, any request for additional cardiac troponin I testing for a patient within a 30-day window of an initial serial cardiac troponin I order prompted an electronic health record best practice alert that included clinical decision support. The alert pop-up could be bypassed if the provider gave a clinical indication. The results showed that providers largely ignored pop-up electronic health record alerts that warned for potential overutilization of cardiac troponin I testing, independent of diagnosis, including acute coronary syndrome.

Multiple Reaction Monitoring with Multistage Fragmentation (MRM^3) Detection Enhances Selectivity for LC-MS/MS Analysis of Plasma Free Metanephrines
By Michael J. Wright, et al.

LC-MS, using multiple reaction monitoring, is a powerful tool for the quantification of target analytes in complex matrices. However, this technique lacks selectivity when plasma free metanephrines are measured. In this study the authors proposed the use of multistage fragmentation to improve the analytical selectivity of plasma free metanephrine measurement. The use of secondary fragments for quantification enabled clinical reporting of results by the removal of the effects of interfering compounds that the authors observed in 1% of their patient samples, as well as several compounds described in the literature. The proposed assay demonstrated sufficient levels of analytical sensitivity and precision for clinical usage.

Brain Tumor Mutations Detected in Cerebral Spinal Fluid
By Wenying Pan, et al.

In this paper, the authors characterized the landscape of cell-free DNA and showed that tumor-derived cell-free DNA was detectable in the cerebral spinal fluid of patients with different types of primary and metastatic brain tumors. They developed a hybrid capture-based method to globally characterize the somatic mutation profile from the cerebral spinal fluid DNA. By applying this method to the cerebral spinal fluid sample from a patient with suspected leptomeningeal disease, they identified somatic mutations that were concordant with genetic testing on the primary tumor biopsy. The authors believe their method could potentially be used as a minimally invasive "liquid biopsy" to analyze the brain tumor genome.

Clinical Sensitivity and Specificity of Meconium Fatty Acid Ethyl Ester, Ethyl Glucuronide, and Ethyl Sulfate for Detecting Maternal Drinking during Pregnancy
By Sarah K. Himes, et al.

The authors of this study quantified 9 fatty acid ethyl esters, ethyl glucuronide, and ethyl sulfate by LC-MS/MS in the same meconium sample. Moderate to substantial agreement was observed between maternal self-reported drinking of 19 weeks or greater duration and ethyl glucuronide in meconium of ≥30 ng/g, a cutoff that was found superior to all other individual and combination marker cutoffs. With meconium ethyl glucuronide ≥30 ng/g as the gold standard, an 82% sensitivity and 75% specificity were observed for maternal self-reported drinking of 19 weeks or greater duration. A significant dose-concentration relationship between self-reported drinks per drinking day and meconium ethyl glucuronide ≥30 ng/g was observed. These data will aid more accurate detection of prenatal alcohol exposure.

Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90 000 Individuals from the General Population
By Anette Varbo, et al.

Increased concentrations of nonfasting remnant cholesterol and low-density lipoprotein cholesterol concentrations are causally associated with increased risk of ischemic heart disease. The authors of this study compared stepwise increasing concentrations of nonfasting remnant and low-density lipoprotein cholesterol for their association with risk of ischemic heart disease, myocardial infarction, and all-cause mortality in approximately 90 000 individuals from the general population. They found that both lipoproteins were associated equally with risk of ischemic heart disease and myocardial infarction; however, only nonfasting remnant cholesterol concentrations were associated stepwise with increased risk of all-cause mortality. These findings suggest a need for future intervention studies focused on lowering nonfasting remnant cholesterol.

Clinical Actionability Enhanced through Deep Targeted Sequencing of Solid Tumors
By Ken Chen, et al.

This paper examines how to use DNA sequencing to improve diagnosis and treatment of cancer patients. The generation of comprehensive in-depth genomic profiles from clinical tumor samples has potential to substantially improve patient care. The authors of this study developed a targeted exome sequencing platform that achieved ultra-high sequencing depth in cancer-related genes. They found that their platform benefited significantly more patients than existing approaches and was more cost-effective. This study provides a guideline and a potential solution for implementing automated sequencing-based genomic testing in a cancer care clinic.