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On the cover this month: David Bruns. Regarded as one of the most innovative and visionary clinical chemists of the day, Bruns was the editor of *Clinical Chemistry* from 1990 to 2007, during which he turned *Clinical Chemistry* from a small societal journal to a cutting-edge international publication. But, as with many highly regarded scientists, Bruns has a personal side that might surprise many. For example, he almost left science for a musical career. And then there are the pranks he tries to pull off. Learn more about this unique individual in this month's Inspiring Minds article.

MicroRNA In Vitro Diagnostics by Use of Immunoassay Analyzers
By Andreas Kappel, et al.

This study describes the development of an immunoassay to facilitate the translation of molecular microRNA markers from basic research to clinical care. Immunoassay analyzers are already established in thousands of laboratories worldwide. The assay described is very specific and sensitive from a technical perspective. Three microRNA markers for Alzheimer Disease were the first chosen for implementation by this approach; however, the method is amenable to other published sets of microRNAs for other human pathologies. Immunoassays for microRNA appear promising for the clinical implementation of microRNA signatures for many diseases.

Detection of Fetal Subchromosomal Abnormalities by Sequencing Circulating Cell-Free DNA from Maternal Plasma
By Chen Zhao, et al.

Sequencing-based noninvasive prenatal testing has been largely focused on whole chromosome aneuploidies. These account for 30% of live births with a chromosome abnormality. Microdeletion or microduplication syndromes are more common but more challenging to detect. The authors of this article present a novel approach to noninvasively detect microdeletions genome wide. They developed a normalization method to reduce sequencing noise, followed by an algorithm to search for elevated or depleted regions. A decision tree was used to differentiate whole-chromosome events from microdeletions. They tested their algorithm in a blinded study with microdeletions ranging from 3 to 40 megabases, achieving a sensitivity of 94.4% and a specificity of 99.4%.

Embryo Genome Profiling by Single-Cell Sequencing for Preimplantation Genetic Diagnosis in a β-Thalassemia Family
By Yanwen Xu, et al.

The embryonic genome contains all the information needed for preimplantation genetic diagnosis. Availability of such information greatly improves the chances for carriers of Mendelian disorders to conceive healthy babies. The authors of this study developed a straightforward strategy to obtain full embryonic genome information for a β-thalassemia carrier couple. Sequencing was conducted on single blastomere cells and on the family trio to further phase the embryonic genome. Mendelian disorder diagnosis and HLA matching tests were performed

on the whole genome. These approaches enabled accurate detection of aneuploidies in embryos. This retrospective study demonstrates the feasibility of genetic diagnosis in the preimplantation embryo through whole genome, high-resolution variation detection and forecasts the development of clinical models for next-generation sequencing applications in establishing preimplantation genetic diagnoses.

Noncompetitive Immunoassay Detection System for Haptens on the Basis of Antimetatype Antibodies
By Kazuya Omi, et al.

This study was conducted to establish a novel methodology to develop sandwich immunoassays for measuring haptens based on antimetatype antibodies. To construct a sensitive and specific sandwich immunoassay for haptens, the authors generated antimetatype monoclonal antibodies against a hapten-antibody immunocomplex using an ex vivo antibody development system, called the Autonomously Diversifying Library system. This methodology to develop antimetatype antibody against haptens enabled the systematic establishment of high-throughput sandwich immunoassays for haptens such as estradiol and 25-hydroxyvitamin D with high sensitivity and specificity. This new method represents a simple and practical approach for routine assays of haptens.

Significance of Serum 24,25-Dihydroxyvitamin D in the Assessment of Vitamin D Status: A Double-Edged Sword?
By Kevin D. Cashman, et al.

24,25-dihydroxyvitamin D in serum may carry both nuisance, but also nutritional, status-relevant value. In this article the authors investigated the impact of 24,25-dihydroxyvitamin D on the performance of immunoassays and also the utility of the ratio of serum 24,25-dihydroxyvitamin D to 25-dihydroxyvitamin D as an index of inactivation and response to vitamin D supplementation. 24,25-dihydroxyvitamin D contributed to the positive bias observed in some immunoassays relative to LC-MS/MS-derived 25-dihydroxyvitamin D estimates. Adjustment for 24,25-dihydroxyvitamin D brought estimates closer to true values. In addition, the ratio of serum 24,25-dihydroxyvitamin D to 25-dihydroxyvitamin D was associated with 25-dihydroxyvitamin D3 and with response of serum 25-dihydroxyvitamin D to vitamin D supplementation.

Impact of Sex on the Prognostic Value of High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study
By Torbjørn Omland, et al.

Recent improvements in assay methodology permit measurement of very low levels of circulating troponins. The authors of this study measured cardiac troponin I with a new, high-sensitivity assay in nearly 10 000 individuals and found that the association between cardiac troponin I and cardiovascular death was significantly modified by gender. This interaction was mediated both by lower risk of women in the low concentrations range and by higher risk in women in the high concentration range. These insights should stimulate further investigations of how this marker can be used to improve cardiovascular health in women.

Diagnosis of Type 1 and Type 2 Myocardial Infarction Using a High-Sensitivity Cardiac Troponin I Assay with Sex-Specific 99th Percentiles Based on the Third Universal Definition of Myocardial Infarction Classification System

By Yader Sandoval, et al.

This study set out to determine the frequency, characteristics, and mortality of type 1 and type 2 myocardial infarctions, or MIs, versus non-MIs when using a high-sensitivity cardiac troponin I assay with gender-specific 99th percentile cutoffs. Three hundred ten patients with serial high-sensitivity troponin measurements were enrolled. Forty-one percent of these patients had at least one troponin measurement above the gender-specific 99th percentile cutoffs. Thirty-two acute MIs occurred in the follow-up period. Type 2 MIs represented 69% of all acute MIs, whereas type 1 MIs represented 31%. The authors found that there were fewer MI diagnoses when using high-sensitivity cardiac troponin I measurements than when using contemporary cardiac troponin I measurements. This finding was contrary to the commonly accepted idea that high-sensitivity troponin measurements will lead to excessive false-positive MI diagnoses.