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On the cover this month: *Rat.* Imagine the next time you visit a clinic and your physician enters the room accompanied by a rat, dog, or a box containing honeybees and fruit flies. Is this really that far-fetched? Perhaps not. The olfactory senses of animals are proving to be as accurate in diagnosing diseases as are current screening tests performed in clinical laboratories. This issue of *Clinical Chemistry* contains a Q&A article in which experts from the field of olfactory detection of disease discuss the successes of this research field, pitfalls to avoid in the future, and future applications such as the "electronic nose."

Glucose Control in the Intensive Care Unit by Use of Continuous Glucose Monitoring: What Level of Measurement Error Is Acceptable?
By Malgorzata E. Wilinska and Roman Hovorka

Benefits of using emerging continuous glucose monitors in the ICU may be significant but should be documented. In this study the authors utilized a validated virtual population of the critically ill to contrast the outcomes from 3 established glycemic control protocols informed by either continuous or intermittent glucose measurements. Results showed similar efficacy of continuous-glucose-monitor-informed and intermittent blood-glucose-informed protocols but lower risk of hypoglycemia using continuous glucose monitoring with mean absolute relative differences up to 10%. This study is the first to perform a direct comparison of outcomes among the protocols and measurement methods.

Modeling of Effect of Glucose Sensor Errors on Insulin Dosage and Glucose Bolus Computed by LOGIC-Insulin
By Tom Van Herpe, et al.

Effective and safe glycemic control in critically ill patients requires accurate glucose sensors and adequate insulin dosage calculators. In this study accuracy thresholds for intermittent or continuous glucose sensors were determined. Real-life blood glucose trajectories, originating from the trial that clinically validated the LOGIC-Insulin calculator, were simulated by adding varying bias and imprecision. The developed clinical error grid system clinically interpreted the new LOGIC-Insulin calculations by comparing them to the original ones. Continuous sensors were found to have a lower probability for clinical errors than intermittent sensors at the same accuracy level. Proposed accuracy levels for glucose sensors are presented.

Validation of a Proposed Novel Equation for Estimating LDL Cholesterol
By Jeffrey W. Meeusen, et al.

LDL cholesterol remains a crucial analyte in managing cardiovascular disease. The authors of this study sought to verify a recently published LDL cholesterol calculation method which claims to improve on the Friedewald equation. They compared novel and Friedewald estimated LDL cholesterol to the LDL cholesterol

reference method, beta quantification, which was performed only on a subset of samples in the earlier study. The novel calculation appears to be incrementally more accurate. While changing a calculation is a simple matter in the modern laboratory, the Friedewald calculation is almost universally accepted and well standardized in laboratory medicine. Whether the benefits of the novel method justify its widespread adoption remains to be seen.

Precision and Reliability of 5 Platelet Function Tests in Healthy Volunteers and Donors on Daily Antiplatelet Agent Therapy
By Brad S. Karon, et al.

Mechanical circulatory support anticoagulation protocols call for titration and monitoring of antiplatelet agents in the perioperative period. The authors of this report studied the precision and reliability of five platelet function tests for differentiating normal from inhibited platelet function in healthy volunteers and donors on daily antiplatelet agent therapy. Multiplate impedance aggregometry was the only method found to demonstrate an acceptable reliability coefficient among healthy volunteers and donors on both aspirin and clopidogrel therapy.

Pediatric Population Reference Value Distributions for Cancer Biomarkers and Covariate-Stratified Reference Intervals in the CALIPER Cohort
By Victoria Bevilacqua, et al.

Cancer biomarkers have become an important tool in the fight against childhood and adult cancers. However, to harness the full potential of tumor biomarkers, it is important to have covariate stratified reference intervals for comparison. The Canadian Laboratory Initiative in Pediatric Reference Intervals program, also known as CALIPER, established age- and sex-specific pediatric reference values for 11 key cancer biomarkers using healthy community samples. All but one of the analytes examined required some partitioning by age, sex, or both. These reference intervals will not only be useful clinically but also in research efforts aimed at assessing the utility of these markers.

G-Protein Receptor Kinase 4 Polymorphism and Response to Antihypertensive Therapy
By Anne M. Muskalla, et al.

G-protein receptor kinase 4 polymorphism influences blood pressure regulation. The authors of this study investigated its role in the response to hypertensive therapy in patients with essential hypertension. In a prospective study, they assessed G-protein receptor kinase 4 polymorphisms R65L, A142V and A486V in 100 hypertensive individuals and correlated these to the individual response to antihypertensive therapy. Patients with homozygous double variant of 65L and 142V needed significantly more antihypertensive and especially diuretic therapy to reach the same mean arterial blood pressure as compared with other patients. Thus, G-protein receptor kinase 4 polymorphism is associated with antihypertensive treatment response in patients with essential hypertension.

Feasibility of Low-Throughput Next Generation Sequencing for Germline DNA Screening
By Nur Sabrina Sapari, et al.

New next generation sequencing formats have recently been introduced to enable the efficient analyses of low sample volumes in the range of 1-12 samples per run that are commonly processed in routine clinical practice. The authors of this study present early evidence that low-throughput next generation sequencing can be cheaper and faster than current approaches for screening germline DNA variants, and can provide highly reproducible, sensitive, and specific detection. They also identify potential quality metrics and describe the testing of 9 analytical processes for the identification of 12 Lynch Syndrome cases and 3 controls. This analysis highlights the clinical potential of low-throughput next generation sequencing and the challenges ahead.

Detection of Clonal Evolution in Hematopoietic Malignancies by Combining Comparative Genomic Hybridization and Single Nucleotide Polymorphism Arrays
By Luise Hartmann, et al.

Using a novel combination of both array comparative genomic hybridization and single nucleotide polymorphism data, the authors of this study established indicators for identifying multiple related clonal populations. They applied an analytical approach called “manual peak re-assignment” to individually adjust single nucleotide polymorphism data, allowing the characterization and, importantly, the confirmation of genomic aberrations present in clonal sub-fractions. The proficiency of this algorithmic approach was evaluated using 16 neoplastic hematopoietic specimens; results were compared with conventional fluorescence in situ hybridization and/or cytogenetic analysis. Improved monitoring of clonal progression by combined single nucleotide polymorphism/array comparative genomic hybridization analysis was also demonstrated using 3 selected case studies.