National Kidney Disease Education Program

NKDEP Manufacturers' Forum
July 17, 2007 – AACC Annual Meeting

NKDEP Manufacturers' Forum Minutes

Participants: Greg Miller (Chair), Stella Argyriou, Harald Althaus, Dave Armbruster, Edward Ashwood, David Bunk, Dennis Bozimowski, Jose Cervera, Christa Cobbaert, Paul D'Orazio, Jeff DuBois, John Eckfeldt, Heidi Egensberger, James Fleming, Elisa Gladstone, Matt Gnezda, Neil Greenberg, Peter Hickman, Glen Hortin, Chandra Jain, Bob Janetschek, Harvey Kaufman, Steve Kazmierczak, Joseph Keffer, Yemi Lemma, John Lieske, Andreas Ludwig, Andrew Narva, Bola Nicholson, Rick Peluso, Mauro Panteghini, Andy Qiu, George Schwartz, David Seccombe, Jennifer Snyder, Kimberly Stowe, Jill Tate, Susanne Thostrup, Sari Tikanoja, Patrick Volkir, Bill Walters, Toto Wieth, Reba Wright, Jack Zakowski

Meeting Minutes:

1. **Measurement of Creatinine for Non-adults: Status of the Subcommittee's Recommendations:**

   - Harvey Kaufman provided introductory comments. The key difference in pediatric creatinine measurement is that the levels are lower than adults. Factors that need to be addressed are specificity and imprecision in this lower range. Manufacturers need to communicate with labs as they make changes in calibration traceability so they can communicate with their physicians and pharmacists.
   - George Schwartz, practicing pediatric nephrologist and developer of the Schwartz equation, spoke to the group. Estimating GFR requires precise and reproducible measurement. We are hoping to eliminate bias with use of reference standardization. In the CKiD Study, creatinine methods are validated using HPLC, and there is much variability among routine methods. Having a 0.2 mg/dL bias can be 50% of the typical result in children. Formulas for eGFR have been developed from the CKiD Study whose participants have kidney disease, and the revised equations need to be evaluated in children with normal kidney function.

2. **Creatinine Standardization: Overview of Recommendations for Method Specificity,** Neil Greenberg

   - A summary of the problem was presented. Even the modified Jaffe methods continue to have issues and while the enzymatic methods are an improvement, there are still specificity issues in these methods. HPLC methods with de-proteinization have been shown to agree well with IDMS and have good specificity. GC-IDMS remains the reference measurement procedure due to excellent specificity and relative SD.

- Performance goals published in 2006 by Myers et al. (*Clin Chem* 52:1, 5-18) were based on biological variability, but no criteria have been defined for sample-dependent random bias (specificity) performance. The August or September issue of *Clin Chem* will include a letter to the editor from Jan Krouer that points out this issue. Greg Miller, John Eckfeldt, and Gary Myers prepared a response to the letter that will also be published, and points out that the total error specification curve from the 2006 LWG paper could also be applied to specificity requirements since the area under the curve is the combination of bias versus imprecision for any given method that produces results that will not influence eGFR by more than 10%.
- Dr. Greenberg described an internal study performed at Ortho Clinical Diagnostics in which 410 samples were assayed by Jaffe, enzymatic, and HPLC methods. There was a positive bias for both Jaffe and enzymatic methods as compared to HPLC, but Jaffe had greater variability. This experiment helps to illustrate the random bias seen with individual samples. There was no clinical history available for these samples to investigate possible sources of sample related random bias. A more systematic study with knowledge about the clinical history for the samples is needed.
- Additional information is needed to understand non-specificity of current implementations of both Jaffe and enzymatic methods. Experimental designs were reviewed by the LWG and will be further developed.

3. Whole Blood Creatinine Measurement: The Subcommittee's Calibration Recommendations, John Eckfeldt

- The key issue in this report is that creatinine concentration values in whole blood (WB) should be adjusted and reported to be equivalent to venous serum/plasma concentrations that are traceable to IDMS reference measurement values. The full recommendations, including approaches to achieve equivalent results, were accepted by the LWG at this meeting and will be posted on NKDEP website soon.
- Finger stick capillary versus venous WB comparisons need to be performed and reported in the literature. It is unlikely there is a difference, but this fact should be documented.
- There needs to be an effort to assess and improve field method's analytical non-specificity for all patient samples expected to be encountered clinically, e.g. patients with diabetes, hypertension, or renal disease.
- There was a discussion about the need to provide a standard evaluation protocol and format to present data for WB creatinine. It was felt that manufacturers need to prove to the end-user that the recommendations are being met and a standardized protocol would be useful. Paul D'Orazio proposed that the subcommittee develop a protocol and consider use of NIST SRM967 in the protocol. Paul D'Orazio and Glen Horton suggested that the protocol include evaluation of the range of hematocrit over which a device is expected to operate. The subcommittee on WB will follow up.

4. Overview of NKDEP/IFCC Urine Albumin Meeting, Greg Miller

- Objectives of the conference were to frame the issues, develop a path forward for improving standardization, and impact a successful implementation of clinical practice guidelines.
- The current status of albumin measurement, defining the measurand, sample handling issues, reporting issues, measurement issues, and reference systems were discussed.

- The plan forward:
    1) Publish a report describing the current status and recommendations for addressing issues. Included in the report will be establishment of clinical requirements for measurement performance and recommendations for nomenclature and reporting. Submission is targeted for the end of this year.
    2) Define specifications for method robustness.
    3) Conduct round robin evaluation of routine and higher order methods to enable understanding of current method performance.
    4) Develop a reference system for urine albumin which includes defining the measurand, a reference material such as the Japanese material, and a reference measurement procedure such as the LC-IDMS method under development at Mayo.
    5) Develop a reference system for urine creatinine.
    6) Investigate the relationship between albumin creatinine ratio (ACR) and albumin excretion rate (AER).
- Minutes from this meeting will be posted on the NKDEP website, along with slides.

6. Meeting Adjourned at 12:00