



**NKDEP Laboratory Working Group Meeting
July 17, 2007 – AACC Annual Meeting**

NKDEP Laboratory Working Group Meeting Minutes

Participants: Greg Miller (Chair), Edward Ashwood, Christa Cobbaert, John Eckfeldt, James Fleming, Elisa Gladstone, Neil Greenberg, Glen Hortin, Chandra Jain, Harvey Kaufman, John Lieske, Andrew Narva, Mauro Panteghini, George Schwartz, David Seccombe, Paul D’Orazio, Peter Hickman, Jill Tate, David Bunk, and Joseph Keifer.

By phone: David Lacher, Thomas Hostetter (phone connection was poor)

Summary of Action Items:

- The Whole Blood creatinine measurement subcommittee will work on developing a validation protocol for manufacturers to use to ensure the guidelines are met.
- Schedule a conference call to follow up on pediatric measurement and recommendations for method performance in the lower concentration range.
- Schedule a conference call to discuss the best way to address the issue of specificity and further discuss options of data gathering from EQA/CAP and proposed experiments.

Meeting Minutes:

1. Awards:

Andy Narva presented an award to John Eckfeldt in recognition for his role as the first chair of LWG for 3 years and serving as the driving force behind the group’s activities. He also presented and award to Greg Miller for his excellent leadership of the LWG as the current chair for the past 2 years.

2. Update on NKDEP/IFCC Urine Albumin Meeting, Objectives and Activities:

Greg Miller presented a summary of the March meeting of IFCC and NKDEP members to discuss urine albumin testing. The objective of the meeting was to frame the issues, develop a path forward for improving standardization, and impact successful implementation of clinical practice guidelines.

Meeting Summary:

- The group discussed the current status of albumin measurement, defining the measurand, sample handling issues reporting issues, measurement issues, and reference systems.
- The plan for moving 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 a 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 relationship between albumin creatinine ratio (ACR) and albumin excretion rate (AER).

3. **Whole Blood Creatinine Measurement, the Subcommittee's Calibration Recommendations:**

John Eckfeldt presented the report developed by the subcommittee. Highlights from the report are:

- 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.
- Recommendations on how to achieve this are provided in the report.
- Total error for WB creatinine should be the same as the error reported by Myers et al. (*Clin Chem* 2006; 52:5-18) for serum/plasma creatinine, especially if the results will be used for eGFR calculation.
- Finger stick versus venous WB comparison should be evaluated and reported to document that there is no difference.
- Methods to present WB creatinine device performance should use Westgard MEDx or Fraser plots with the caveats that uncertainty for bias and imprecision should also be reported, and acceptability criteria should be developed.
- These recommendations will be disseminated by either publishing them on the NKDEP website or as a peer-reviewed journal article.
- Comments:
 - Paul D'Orazio proposed that there be a mechanism to evaluate that manufacturers meet the guidelines. The group should develop a validation protocol including variables like hematocrit with standard elements for manufacturers to follow. This will be discussed further in the manufacturer's forum. The WB creatinine measurement subcommittee will work on this.
 - It would be desirable to use NIST SRM 967 to verify traceability with whole blood devices if it was compatible with the various technologies used.
 - Glen Horton suggested that hematocrit effect be examined to specify the range of hematocrit over which the device will work correctly.
- The LWG voted to accept these recommendations with the understanding that there will be additional follow up work to include a validation protocol.

4. Measurement of Creatinine for Non-adults, Status of the Subcommittee's Recommendations:

- Harvey Kaufman presented introductory comments regarding measurement of creatinine in non-adults. He stated that the recalibration of creatinine based on the IDMS method has caused some unintended consequences at the low concentrations frequently seen in non-adults. There are several equations for estimating GFR in children. The most common of these is the Schwartz equation.
- George Schwartz presented information about estimating GFR data from the CKiD Study.
 - Adult formulas for eGFR (Cockcroft-Gault, MDRD, and cystatin C) should not be used to assess kidney function of children.
 - The original Schwartz equation overestimates GFR based on comparison with iohexol GFR.
 - Using the CKiD data, four possible formulas were presented for eGFR in children.
 - The updated Schwartz equation is good for a quick bedside screen.
 - Multivariate gender-based equations incorporating BUN and Cystatin C are significantly better for predicting GFR in children.
 - There was discussion about methodology used in CKiD Study.

5. Creatinine Standardization, Recommendations for Method Specificity:

Neil Greenberg led the discussion about method specificity and how to set performance goals.

- 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 that points out this issue. The overall total error element in the 2006 paper did incorporate this component but it was not identified as a specific element in the total error criteria.
- A total error model that includes random bias due to specimen specific effects was developed by Lawton and Sylvestre.
- 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.
- Possible approaches for systematic specificity evaluation:

- Plan A: Using creatinine-free material, prepare test pools to study interfering substances (HSA, bilirubin, IgG, hemoglobin); labs and manufacturers would receive pool sets of 12-36 unique vials at 4 concentrations of creatinine. One question is whether to combine the interferents (12 vials/set) or keep them separate (36 vials/set).
- Plan B: Collect samples from patients in selected populations, e.g. diabetes, chronic liver disease, chronic kidney disease, oncology/myeloma patients, geriatric/nursing home populations and pediatric patients and assay them by commercial methods and LCMS or HPLC. This study is a more logistically difficult approach to manage all the clinical samples; and it would require IRB approval.
- Discussion:
 - Greg Miller, John Eckfeldt, and Gary Myers prepared a response to Jan Krouer's letter that will be published in the next month or two in *Clin Chem*. 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%.
 - Mauro Panteghini commented that commutability of materials to be used in an evaluation of analytical specificity is required; if some methods are not specific, this non-specificity must be included as part of the total error; the term "random bias" is confusing because "bias" is systematic error and "random" refers to variability.
 - Comments on the two proposed experiments:
 - Pools of about 2 L will be needed for the experiment in proposal A; using residual samples will require hundreds of samples versus using a unit of blood, which requires IRB approval.
 - Christa Cobbaert suggested that perhaps the specificity information can be found by looking at EQA and CAP survey sample results. However, non-commutability of these samples is a limiting factor.
 - John Eckfeldt commented that plan B would provide more information on what is happening with clinical samples; he is concerned that the simulated pools in Plan A would not behave like real samples.
 - Greg Miller suggested the possibility of recruiting centers to set up well-defined standardized enzymatic, rate Jaffe, and end point Jaffe methods. Run hundreds of samples by all 3 methods. Then, look at the distribution and follow-up the tails of distribution for explanations/interferents. John Eckfeldt commented that adding a reference method to this plan would be very beneficial. Perhaps the samples could be frozen and only assayed in the subset of samples that indicate a problem.
 - David Seccombe questioned what is our goal? Random bias is a function of samples and this component cannot be completely described; these plans are a lot of work and the practical application is not well defined. He also commented that the current routine methods do not work well in both the adult and pediatric populations. Perhaps we need to look at separate assay systems for each of these populations.
 - George Schwartz confirmed that hemoglobin causes lower results in enzymatic methods and this is a big problem in pediatric populations.
 - Glen Horton commented that the random bias component is population specific.

6. Estimated GFR Reporting:

- Greg Miller: Response to a question on the May CAP Survey indicates that 50% of labs are reporting eGFR, and that 78% followed the NKDEP guidelines to report numeric values only up to 60 mL/min/1.73m².
- Elisa Gladstone reported preliminary results of NKDEP's Clinical Lab Study: This was a nationwide survey sent to 6,350 labs from which there was a 48% response rate. For those labs reporting serum creatinine, 9.5% report using two decimal places and 38.4% report eGFR – this is lowest among physician office labs; if eGFR is reported, 66.7% report with every serum creatinine result, 71.6% use the MDRD equation, and 46.3% report “>60” when the calculated result is above 60.

7. Redesign of NKDEP's Website: Lab Professionals Section:

- Due to time constraints, this item was skipped. However, Nancy Accetta welcomes member feed back about the revised content of the lab professional section and the creatinine standardization recommendations pages. Please let Elisa or Nancy know if you want to review the proposed website text and they will send it to you.

8. Next Steps:

- Schedule a call to follow up on non-adult measurement and recommendations. We may need to set specifications even if they cannot be met, but would drive development of new methods specific to the non-adult population.
- Schedule a call to discuss the best way to address the issue of specificity and further discuss options of data gathering from EQA/CAP and proposed experiments.

9. Meeting Adjourned at 10:31 am