NKDEP Laboratory Working Group Meeting
AACC Conference – Chicago, IL
July 27, 2006

Meeting Notes

Greg Miller, Medical College of Virginia (Chair)
Ed Ashwood*, ARUP
Christa Cobbaert*, EC4 EWGCS
Joris Delanghe, EC4 EWGCS
Paul D'Orazio*, Instrumentation Laboratory
John Eckfeldt, University of Minnesota
Jim Fleming, Lab Corp
Elisa Gladstone, NIDDK/NKDEP
Neil Greenberg, Ortho Clinical Diagnostics
Harvey Kaufman, Quest Diagnostics
David Lacher, CDC/NCHS
Cynthia LaCivita*, ASHP
Heidi Leinberger*, Radiometer America
Leigh Ann Milburn, Saint Luke's Hospital
Andy Narva, IHS, NIDDK/NKDEP
Mauro Panteghini, IFCC
Don Parker*, Bayer Diabetes Care
Karen Phinney*, NIST
Dan Seymour*, Beckman Coulter
David Seccombe, CEQAL
Anne Skurup*, Radiometer ApS
Linda Thienpont*, University of Ghent
Mike Welch, NIST
Reba Wright*, Olympus
*Guest

Greg Miller opened the meeting with introductions and a review of the agenda. Below are notes on the discussion related to each agenda item.

MDRD use in Pharmacy Practice

- The NKDEP Laboratory Working Group (LWG) has begun discussion with health system pharmacists because serum creatinine standardization has implications for drug dosing. The NKDEP will continue communication with the pharmacy community.
- Goal: Provide a process whereby the Modification of Diet in Renal Disease (MDRD) equation replaces Cockcroft-Gault (C-G) in pharmacy practice (C-G is currently embedded in manufacturers' labeling for particular drugs).
    - Leigh Ann Millburn said the pharmacy community is beginning to understand the value of eGFR for staging kidney disease, but there has been some resistance in the profession because most data are based on C-G. As of yet, there are no data to make a correlation between C-G and MDRD for dosing purposes.
    - Andy Narva suggested that we inform labs and their clients that C-G is not normalized for body size, as is the MDRD equation.
- Andy Levey recently proposed that the NKDEP establish a sub-committee to examine this issue and have discussions with the FDA about making new recommendations to the pharmaceutical industry to use the MDRD instead of C-G for drug dosing recommendations.
    - NIDDK is currently reviewing the proposal to establish this sub-committee. NIDDK expects to formally respond to the proposal in late September or early

October. Potential members include Leigh Ann Milburn, Cynthia LaCivita, Harvey Kaufman, Jim Fleming, and a hospital-based laboratorian to be identified by the NKDEP.

- Cynthia LaCivita said the American Society of Health-System Pharmacists (ASHP) would do what it can to facilitate the education of pharmacists. (ASHP's 30,000 members have already received the Creatinine Standardization Program's pharmacy recommendations.)
- **ACTION ITEM**: When established, the sub-committee will propose how to work with the pharmacy industry. NKDEP will recruit a hospital-based laboratorian and someone from the FDA to serve on the committee. The LWG will respond to the sub-group's proposal during an October/November conference call.

Suggested Text for Lab Reports

- The group discussed whether it is necessary to provide labs with an example of text that can be used on lab reports to explain why eGFR is not being reported for a particular patient. The decision is not to recommend text; rather, labs will deal with non-report issues as they see fit. Some of the reasons for the decision include:
  - Too little space on reports, and some providers do not like interpretive comments on the actual report.
  - Text may be counter-productive if the NKDEP's goal is to educate providers about the value of eGFR.
  - As an example of a comparable situation, labs do not provide a cautionary comment with lipid measurements when a patient's numbers are extreme due to pancreatitis – we should not do it here.
- The group agreed that the following language could be promoted for use when essential patient data are missing (age and/or gender): "The NKDEP does not recommend reporting eGFR when age and/or gender are not available". [Note: This information can be posted in the FAQ section of the website.]

Pediatric Issues

- Joris Delange explained that creatinine standardization would present difficulties with estimating GFR and medication dosing for children, especially toddlers, as their creatinine values are so low relative to the values for adults that the percent change in value due to standardization would be very large.
  - The standardization will reduce values significantly, making it difficult to obtain accurate eGFR values in toddlers; the Schwartz formula will no longer be valid when the IDMS-based standardization is in full effect.
  - The group may want to begin thinking about using cystatin-C as an alternative for determination of eGFR in younger age groups.
  - The positive error caused by non-specificity more or less counteracts the tubular secretion effect. By obtaining a higher analytical quality from more specific methods we are creating a kind of disequilibrium between these two errors. We have to see if the creatinine will still be a valid estimator of eGFR in pediatric practice.

- David Seccombe pointed out that assays typically do not perform well at low creatinine concentrations anyway.
- Key issue: Recalibration of assays may lead to (the need for) drastic changes in drug dosing (e.g., nephrotoxic drugs). Creatinines, at .1 to .2 mg/dL lower, can translate to a 50% change in measurements for children, which will highly impact results of the Schwartz equation. NKDEP must make sure that pediatricians (or pediatric nephrologists) are informed when these changes take place and about the implications for dosing practices.
- **ACTION ITEM**: A small writing group will develop text to add to what is currently posted on the NKDEP website as this issue needs to be more thoroughly addressed. NKDEP will consider developing a pediatrics page and needs to provide information to labs on the impact of standardization on assessment and drug dosing for children.
    - The group, which will include Leigh Ann Milburn, Cynthia LaCivita, Harvey Kaufman (Chair), John Eckfeldt, Joris Delanghe, and one or more pediatric nephrologists, will begin with a conference call (at the end of August). After completion of the draft (end of September), the larger LWG will review language and discuss it during the October/November call.
        - Questions: How accurate is the Schwartz equation in measuring true GFR? What was used to dose drugs before the Schwartz equation?
    - Information will be disseminated through pediatric nephrology channels.
    - Elisa Gladstone will send an email confirming what research/trials are currently being carried out related to testing the validity of the Schwartz and MDRD formulae, including information about the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD).

Creatinine Measurement Using Whole Blood Devices

- Whole blood device manufacturers cannot use serum-based reference materials, so they are beginning to ask what they can use and how they should be reporting creatinine values.
- The LWG needs to be aware of issues associated with measurement using whole blood analytes, so Greg introduced Don Parker (Bayer Diabetes Care), whom he invited to share about his experience with whole blood glucose measurement. (See Don's slides on the NKDEP website at www.nkdep.nih.gov/labprofessionals.)
    - Regarding blood samples from different body sites—there are differences in concentration of an analyte between capillary and venous blood. Don noted that doctors tend to think, "blood is blood" (and it is not). The LWG needs to ask: What are the possible differences when measuring an analyte in capillary, venous, or arterial blood? Anne Skurup commented that she performed a thorough literature search and did not find information on whether or not differences in concentration occur between serum, whole blood, or capillary blood.
    - See slides for blood glucose monitoring testing issues and test system issues.
    - Current question: What recommendations can be provided regarding calibration for whole blood devices?
        - Anne Skurup reported that Radiometer measures whole blood creatinine and developed an algorithm for the relationship between

whole blood and plasma or serum. They based calibration traceability on a serum creatinine reference system—building in a correction that takes into account the difference between plasma serum and whole blood. Whole blood results are reported as equivalent to venous serum or plasma concentrations.

- Don Parker recommended an early recommendation to report creatinine measured in any matrix in concentration equivalent to venous serum or plasma. This recommendation will avoid a confusing situation that developed in whole blood glucose testing that had up to four different reporting schemes for different matrices

- The LWG agreed that a recommendation be made that whatever measurement system and sample matrix is being used, the calibration be such that the reported value be the equivalent of a venous serum creatinine.
- Neil Greenberg suggested, and the group agreed, that the LWG should poll Radiometer's competitors to learn whether anyone has done comparisons of results with different matrices. (Anne Skurup will help identify the other manufacturers.)
- Don Parker suggested using as a model a process that was described in a *Clin Chem* article (Paul D'Orazio et al, 2004) about blood glucose. The article describes how blood glucose should be reported as glucose plasma, regardless of the sampling site.
- Don Parker agreed to provide references on whole blood measurements for review by the LWG.

- **ACTION ITEM**: Send a letter to manufacturers of whole blood devices, asking them to name a representative to a sub-committee to develop recommendations for reporting creatinine results based on whole blood measurement and to recommend strategies for calibration of whole blood systems. John Eckfeldt, Don Parker and Paul D'Orazio agreed to form an initial group to review the current whole blood measurement situation and recommended a path forward that can be reviewed and discussed on the October call.

Communicating with LIS Vendors

- Greg Miller attended the meeting of AACC's Lab Information Systems and Medical Informatics Division. He was able to give a brief overview of the program and the implications for LIS vendors.
- The leaders of the Division have agreed to help the LWG communicate recommendations for software providers to their membership and other vendors. Greg will continue contact with the LIS section, as needed.

***Suggestions for Labs* and other Downloadable Documents**

- *Suggestions* and the Recommendations documents have recently been reviewed and discussed via conference call.
  - Greg Miller asked that LWG members review the Recommendations, especially the pharmacy document, and share them with colleagues.
  - Members should let Elisa know if any text needs to be revised so the group can discuss on the next call (October/November).

- All documents are now on the NKDEP website.

- FYI from Mauro Panteghini, in regards to the Recommendations related to reference intervals: Before the end of this year, the IFCC Committee on Reference Intervals and Decision Limits will be able to produce the reference interval for age (including children) and sex, applicable to standardized methods traceable to IDMS. It is expected that the creatinine reference intervals will be validated in populations worldwide.

Other Business

- Harvey Kaufman suggests we expand the *Suggestions* language around reference intervals (top of first page).
  - One of the issues with physicians is related the ICD-9 codes—when lab reports do not report actual values above 60, the physician does not know how to code for what would be CKD stages 1 and 2.
  - Providers want eGFR calculated higher than 59, so they can use the correct ICD-9 code.
- David Seccombe stated that some jurisdictions around the world are reporting actual values to 90, and anything greater than 90 as ">90." He noted there is some disagreement with the NKDEP's recommendation and asked the LWG whether we are losing a significant aspect of the value proposition clinically? David stated that the actual value (although it may not be that accurate) gives providers some metric of trending that they can apply to their decision-making process if labs report the actual above-60 value. Providers can monitor patients whose eGFRs may be trending down toward 60.
  - Greg Miller stated that this issue can be discussed on a future call but that the current decision has been made due to a) the effects of imprecision, and b) the effects of the lack of standardization in calibration have precluded considering reporting higher values. Higher values are sufficiently less reliable and more variable because of those problems. However, within a particular lab, you can make an argument about trending that may partially mitigate some of those considerations.
  - This will go on the agenda for a future meeting so the group can discuss whether the labs that have begun using IDMS-traceable methods can begin reporting actual values above 60.
  - Harvey Kaufman recommended that those responsible for developing codes should consider collapsing levels 1 and 2 or creating a 1/2 code.
  - Andy Narva expressed concern that identifying a lot of people with eGFRs over 60—that may or may not be accurate—is going to diminish the utility of this (diagnostic test) to clinicians. He agrees that collapsing codes for 1 and 2 into "normal GFR" would be worthwhile and enables diagnosing patients with proteinuria or something else. Trending at higher values, however, could be of value with patients with diabetes as their GFR is usually high early in the condition.
  - Anne Skurup said that Radiometer, which must meet the needs of clients in England and the U.S, is going to offer options for how eGFR will be reported.

Clients can indicate that they want Radiometer to report values above 60 as "above 60" or with a higher cut-off, for example, of 90.

- Andy Narva proposed that the group discuss standardization of nomenclature for reporting urine albumin to urine creatinine ratios. There is a high level of confusion among clinicians because of the various ways that the value is reported.

Next Steps

- Modify *Suggestions* sentence to restate that we do not recommend reporting eGFR when age or sex or not available, and expand the document's language around reference intervals.
- Develop a sub-group, chaired by Harvey Kaufman, which will develop recommendations aimed at pediatric issues and reporting, with a draft document to be delivered at the end of September. The document will be reviewed during the October/November conference call.
- Contact manufacturers of whole blood devices, organize a call, and review the issues with John Eckfeldt's, Don Parker's, and Paul D'Orazio's participation. The group will deal with issues and come up with recommendations for consideration by the working group as far as the best way to proceed with an appropriate recommendation around whole blood measurement.
- Discuss issues around reporting values from 60-90. (It is likely that the LWG will delay this discussion until next year's July meeting, as the LWG will need to review and report on the literature.)
- Discuss standardization of nomenclature for reporting urine albumin to urine creatinine ratios.
- See above for other Action Item details.