NKDEP
National Kidney Disease
Education Program

Lab Working Group Meeting
Washington, DC
March 11, 2005

Members in Attendance
John Eckfeldt, Chair, University of Minnesota
Joris Delanghe, University Hospital Ghent
James Fleming, Laboratory Corporation of America
Elisa Gladstone, NIDDK
Neil Greenberg, Ortho Clinical Diagnostics
Ethan Hausman, FDA
Glen Hortin, NIH Clinical Center
Thomas Hostetter, NIDDK
Harvey Kaufman, Quest Diagnostics
Anthony Killeen, University of Minnesota
David Lacher, CDC
Timothy Larson, Mayo Clinic Renal Laboratory
Andrew Levey, Tufts New England Medical Center
Frederick Van Lente, Cleveland Clinic Foundation
Greg Miller, Virginia Commonwealth University
Gary Myers, CDC
David Seccombe, Canadian External Quality Assessment Laboratory
Michael Welch, National Institute of Standards and Technology

Guests
Andrea Defrance, Abbott Laboratories (via WebEx)
Bill Donohue, Accutest
Dennis Bozimowski, Abbott Laboratories
Chandra Jain, Beckman (via WebEx)
Holly Korba, Ortho Clinical Diagnostics (via WebEx)
Nancy Ring, ITC (via WebEx)
Joann Walter, Dade-Behring

Meeting Objectives
- John Eckfeldt opened the meeting, walked through the day's agenda and outlined objectives for the Laboratory Working Group (LWG) meeting and the Manufacturers' Forum.
- Tom Hostetter, director of the NKDEP, welcomed new members of the LWG: David Lacher, David Seccombe, Glen Hortin and Joris Delanghe.
- Tom proposed adding to the agenda a discussion about seeking NIH 1% set-aside evaluation funds for LWG activities. Research targets might include number of labs currently reporting GFR, barriers to doing so (from both labs and clinician), etc. John agreed with value of such an effort and proposed further discussion at end of meeting.

- John Eckfeldt outlined agenda for the Manufacturers' Forum: Tom Hostetter will review problem of CKD, Greg Miller will recap 2004 Manufacturers' Forum, Gary Myers will review recommendations for standardization, Fred Van Lente will talk about the CKD-Epi Project. The goal is to get feedback from participating manufacturers regarding barriers or other issues that will delay implementation of recommendations for standardization.
- In response to a question about the number of manufacturers such recommendations might affect, John Eckfeldt noted that, in North America, there are five manufacturers who have approximately 95% of the market (noting that each might have a number of different methods) but that there are probably another 10-20 who share the remainder of the market.

LWG Updates

- John Eckfeldt updated the group on the College of American Pathology's (CAP) Creatinine Accuracy Calibration Verification/Linearity Survey:
  - The problem with classic proficiency testing of the creatinine assay is the non-commutability introduced by use of processed human plasma products. So CAP used pooled fresh frozen serum to conduct two surveys — one in 1994 and another in fall of 2003.
  - Data was similar in both studies: there is a fair disparity of calibration and therefore bias across various methods. The challenge is if such surveys are only conducted every few years, it can be difficult to know what is happening in the interim.
  - CAP has developed a new accuracy-based survey, which is different in two ways: uses fresh frozen serum and has high-level reference method assigned target values (LC-IDMS values assigned by NIST).
    - Michael Welch was asked how many times LC-IDMS was done when NIST levels were assigned. He estimated that it was about four times, and noted that the LC-IDMS has been validated against GC-IDMS (to within 1%).
  - The LN24 survey will be conducted twice a year; there should be enough reference material to last about three years. Participating labs get reports on the accuracy of their calibration (i.e., degree of bias in their results). John estimated that approximately 25 percent of North American labs would meet the goals outlined in the LWG's draft manuscript.
  - There are 130 labs signed up for this survey this year, which will provide much more data on different methods and real-time data on North American labs.
- John also updated the group on CAP-NIST joint effort to develop a commutable reference material. The goal was to make one big pool and split it — with NIST using for calibration and CAP using for linearity — but it became too difficult logistically and financially to accomplish. It was decided that the advantage of combined pool would not be that great, so two separate sets of materials were made for CAP's LN24 and NIST SRM 967.
  - Glen Hortin asked whether female protein concentration was the same as male. The group consensus was that there is not much of a difference.
  - It was also noted that it is difficult to get fresh serum pools with concentrations of serum creatinine lower than 0.7 mg/dL — would have to be from children or elderly women.
- It was reported that NIST commutable reference material should be available by the end of the summer. John Eckfeldt expressed interest in doing a study to compare the NIST and CAP

reference materials to make sure that they truly are commutable. Mike Welch has agreed to do the required LC-IDMS analyses.

- There was discussion about the age of data (i.e., 1994 data) and impact on measurements of bias. It was noted that a comparison of 1994 and 2003 studies found that manufacturer biases have not really changed much.

- There was group consensus that one of the issues likely to be raised by manufacturers is the availability of reference services to support them. They may want to recalibrate, but could need some reference services to get their samples tested.
    - Neil Greenberg said one of the challenges is finding candidate organizations to do LC-IDMS to support manufacturers. (The group agreed that it is much more feasible for labs to use LC-IDMS instead of GC-IDMS.)
    - John agreed that it would be nice to have a few labs set up to do this, if a business model could be found that would cover their costs. Key issues are shipping and capacity of labs to provide quick turnaround of results.

- John asked Mike Welch to summarize the status of the Joint Committee on Traceability in Laboratory Medicine (JCTLM). Mike reported that three GC-IDMS reference measurement procedures have been approved and that two LC-IDMS procedures are under review.

- Neil Greenberg noted the importance of developing a master plan, so that new estimating equation (one not reliant on existing bias) is available for use once clinical labs introduce IDMS-traceable methods — so as not to introduce a method bias.
    - Greg Miller noted that one of the objectives of this LWG meeting was to begin to develop an operational timeline for implementing this.

- The group also discussed the issue of international coordination, in particular the efforts of the KDIGO (Kidney Disease: Improving Global Outcomes) group, which met in Amsterdam in November 2004, to globalize KDOQI guidelines. It was agreed that international efforts must be coordinated so that different methods do not emerge on different continents.
    - Joris Delanghe offered an overview of the European situation, which he reports have changed radically as of December 7, 2003 due to EC standardization regulations (CE marking). Joris noted that Roche, the market leader, recalibrated to remove bias but did not fully consider all of the clinical consequences of this recalibration. He cautioned that as individual manufacturers recalibrate, it could confuse clinicians.
    - Joris said that despite technological progress, there are still significant inter-lab biases in the measurement of serum creatinine and that these need to be reduced. The EC4 (European Communities Confederation of Clinical Chemistry and Laboratory Medicine) has decided to establish a working group to address this. At a November 2004 meeting, the EC4 decided that one of goals is to better understand where problems are located within the European IVD landscape. EC4 members are very concerned about impact on prediction formulas — due to changes, concern is that clinicians who are unaware of changes in measurement bias may be getting inaccurate results for their patients.
    - It was decided that there were several ways to coordinate activities with the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) and EC4:

        - Participate in the EC4 creatinine subgroup meeting to be held at the European clinical chemistry meeting in Glasgow scheduled for May 9-12 (Greg Miller plans to attend).
        - Engage in dialogue with the IFCC and EC4 reps at AACC meeting in Orlando this July.
    - Neil Greenberg emphasized need for a coordinated global timetable, noting that global manufacturers need one approach and one solution. Separate national initiatives or timetables will add a barrier for manufacturers and introduce an element of clinical confusion, which must be reduced as much as possible.

- There was discussion about role of physician-operated labs (POLs), which represent a large number of lab sites, but a low volume of patients. Many POLS in U.S. use stabilized liquid product, which raises accuracy concerns.
    - After considering a round-robin with smaller labs, it was agreed that it would be more efficient to do this with vendors than with labs themselves. Suggestion was to get a list of FDA-approved methods from FDA website (http://www.fda.gov/cdrh/oivd/index.html).
        - **ACTION:** Ethan Hausman agreed to conduct this research for group, but noted that since product codes are not segregated by physician office and do not expire, this will be a very large list. Ethan will do his best to get list of several hundred names.

Manufacturers' Forum: Presentations

- John Eckfeldt welcomed manufacturers (some in person, some participating via WebEx) to Forum and reviewed agenda.
    - *NB: The first part of the Manufacturers' Forum was devoted to presentations from LWG members. These presentations have been posted to the NKDEP website, as PDFs, at http://www.nkdep.nih.gov/about/workinggroups/laboratory.htm.*

- Tom Hostetter provided an overview of CKD in the United States, including the rising incidence of ESRD, the inadequate screening of high-risk patients, the role of GFR as a predictor of cardiovascular disease in CKD patients, and the results of an NKDEP-sponsored survey (using a hypothetical patient scenario) which found that most physicians wait too long to diagnose CKD. Tom emphasized that because early CKD is asymptomatic, physicians are almost completely dependent on laboratory diagnosis, which is why NKDEP convened the Laboratory Working Group.

- Greg Miller provided an overview of US and European studies regarding laboratory bias in measurement of creatinine measurement. Key points included:
    - A number of manufacturers have biases of >0.2 mg/dL. Roche has lowest calibration bias — near zero — because they have recalibrated their assays to be traceable using the IDMS method.
    - The MDRD prediction equation was developed using Beckman CX, so the bias inherent in this method is included in the equation. Roche's correction of bias has introduced a dilemma for clinical labs by reducing the bias on which the MDRD relies.
    - A longitudinal study found that inter-lab as well as intra-lab variations contribute to overall bias in the measurement of serum creatinine.
    - The impact of method variability, at a true GFR of 60, could be 17 mL/min/1.73 m^2, or ±14%.

- The higher the GFR, the greater the impact of this uncertainty, which is why NKDEP recommends not reporting precise numbers above 60.
    - Chandra Jain asked about use of correction factors (i.e., compensating coefficients). Greg said that while this is an acceptable approach, the problem is that it is difficult to manage across labs; a more efficient approach may be to help labs recalibrate. Chandra agreed, but said that using correction factors may be a fall-back plan. She also suggested the short-term solution of using only Beckman CX method because of its relation to MDRD equation.
    - Neil Greenberg reiterated that using MDRD with current field methods as currently calibrated will yield a relatively accurate GFR. He emphasized that if manufacturers improve traceability to IDMS creatinine values, the estimated GFR will become less accurate.

- Gary Myers gave a presentation on why, despite this, it is important to standardize creatinine measurement — so that estimated GFR is accurate and comparable regardless of where or when tests are performed. Some key points:
    - Standardization is achieved by establishing traceability to reference measures of a higher order. JCTLM has approved three reference measurement procedures: all of these are GC-IDMS, but two LC-IDMS methods (which are simpler) are under consideration.
    - JCTLM has approved a primary reference material (NIST: SRM 914a) as well as five secondary reference materials (from IRMM and NIST). However, these secondary materials have not been evaluated for commutability with field methods, and IRMM and NIST materials have not been cross compared so should not be interchanged.
    - Standardization does not correct for non-specificity problems, which must be addressed by IVD manufacturers.
        - Chandra Jain asked when LC-IDMS procedures might be approved by JCTLM. Mike Welch answered that these might be approved as early as this year.

- Fred Van Lente provided an overview of the CKD-Epi project, which has three aims: to improve equations for estimating GFR from serum creatinine, to develop and validate equations for estimating GFR from serum cystatin and to assess utility of proteinuria and albuminuria as risk factors for CKD progression.
    - Project participants: Tufts New England Medical Center, Johns Hopkins, Cleveland Clinic Foundation and University of Pennsylvania
    - Study elements include: pooling databases to maximize number of subjects with reliable measurement of GFR, improving representation diabetics and normal subjects, standardizing creatinine measurements to IDMS, and re-evaluating statistical tools used to develop equations.
        - Chandra asked which IDMS method is being used (answer: Ghent) and if there is any other lab in the U.S. besides NIST that does IDMS reference (answer: no).

Manufacturers' Forum: Discussion

- John Eckfeldt opened discussion by inviting manufacturers to provide input on timing and process for change in creatinine standardization and estimating equations. The goal is to do this in coordinated way so that as the calibration changes the equation coefficient also changes.

- Neil Greenberg noted that so far, key questions asked by manufacturers have been: when will reference materials be available, and what sort of reference services will be available? Also on manufacturers' minds: the errors that recalibration will cause in GFR estimates (due to the bias factored into the MDRD equation), the need for a full-scale coordinated program that involves clinician and patients as well as manufacturers and labs, and manufacturers' need to let their customers (i.e., labs) make changes on their own timeframe — which means that there will need to be two separate calibration systems in place for some time to come.
- Asked if there are precedents for what NKDEP is trying to accomplish, Neil pointed to the National Cholesterol Education Program (NCEP) effort from approximately 15 years ago. He noted that although this was not a fully orchestrated effort, the NCEP developed a timetable with expectations that transition would occur over 4-5 year period, and this seemed to work for manufacturers.
    - Greg Miller said that LWG does not want to follow the hemoglobin A1c model, which has been fragmented. Neil agreed, and noted that the laboratory community should not indefinitely support multiple systems and calibration processes.
- Chandra Jain emphasized the importance of coordination with Europe, so as to avoid the emergence of three different calibration systems.
    - Joris Delanghe agreed, noting that regulations enacted in December 2003 (related to requirement for CE markings) have forced a number of manufacturers to take measures.
    - John Eckfeldt reinforced Chandra's point, stating that otherwise it will be too confusing for manufacturers who make products for global marketplace.
- Greg Miller noted that it will also be important to coordinate calibration changes with pharmacy applications because it could have a significant impact on modification of doses.
    - John Eckfeldt noted that representatives from pharmacy community should be involved with the process; Ethan Hausman suggested also reaching out to commercial pharmacy systems. Tom Hostetter noted that the NKDEP is already talking with the American Society of Health-System Pharmacists.
    - Tony Killeen noted that some pharmacists have already switched from Cockcroft-Gault estimating equation to MDRD equation.
    - Chandra Jain emphasized the need for pharmacist as well as physician education.
        - David Seccombe noted that the primary purpose of introducing common reporting of GFR was to improve diagnosis earlier in disease process and optimize the opportunity for prevention. He asked if LWG focus therefore should be on improving GFR reporting at the laboratory level, or if primary focus at this point should be on helping PCPs understand the importance of using GFR — and only later look at implications for pharmacokinetics. His opinion: we can't take on all of this at once.
        - Tom Hostetter noted that NKDEP and NKF have recommended that PCPs use estimated GFR for early identification of CKD, but that pharmacists just stick with what they are doing now. So, in effect, there are two parallel systems at the moment — in the future these systems could be brought together and pharmacists can recast their kinetics in terms of estimated GFR (derived from recalibrated measurements and new estimating equation), but at the moment it seems like a dangerous thing to do.

        - A manufacturer noted that they can only provide one creatinine measurement system, so pharmacists will still only be using the numbers they get from the lab. If those numbers are shifting because of calibration change, pharmacists will have to invest in a new scale (i.e., MDRD or a new estimating equation) and will need to be educated.
        - Tom Hostetter noted that Cockcroft-Gault equation is less accurate than MDRD, so there will eventually be a need for pharmacists to migrate to a new estimating equation.
    - In response to a manufacturer's question about whether there is government commitment to such education, Tom stated that indeed there was but that it is important to keep in mind that, unlike pharma, the government does not have sales forces that can assist with this. However, he noted that several pharma companies are very interested in this and are attempting to increase use of GFR. Tom believes that government has been as effective as it could be without having a true marketing arm — but invited the group to share ideas about how to do an even better job of marketing GFR messages.

- Tony Killeen suggest the group focus efforts on influencing lab reports that go to physicians; John Eckfeldt suggested that we focus on family physicians in particular.
    - Tom Hostetter said that family practice groups can be difficult to reach because they have so much to do and hear from special interests all the time. However, he noted that the NKDEP has already reached out to nephrologists across the country (mailed info on GFR to 6,000 of them), which is who many PCPs reach out to for information and guidance.
    - David Seccombe said that the most effective way to communicate is through labs, and that he is working in British Columbia to standardize how GFR is reported to physicians themselves. David recommended establishing a common way that everyone should report GFR and making this a basis for accreditation.
        - Tom Hostetter noted that NKDEP will revise its "Suggestions for Laboratories" sheet and share with LWG members to offer feedback/revisions.
        - **ACTION**: NKDEP will e-mail a copy to LWG members.
- Dennis Bozimowski said that Abbot Laboratories is currently looking at reformulating and optimizing its serum creatinine measurement and talking about how to make transition. He asked how Roche has compensated for reduction in their bias, and how the compensation they have introduced into their calibration has impacted reported GFR.
    - Joris Delanghe said they did not fully realize the problems this would cause, and their recalibration has rendered estimating equations substantially less accurate. In effect, they solved one problem but introduced another.
    - Dennis sought confirmation that the NKDEP is not recommending that labs follow Roche's suit and introduce a compensatory coefficient as an interim solution.
        - Greg Miller said that LWG will consider making a stronger recommendation not to introduce a calibration at this time, instead waiting until a coordinated program is developed that will change calibration and coefficient for equations at the same time.
- Glen Hortin suggested that as manufacturers consider recalibrations, they should concentrate on seeking optimal performance at creatinine values near 1 mg/dL rather than having the widest possible measuring range. He noted that sometimes manufacturers think they are doing good thing by having method that can go much higher, but this could have a negative impact

on accuracy around the levels (i.e., 1 mg/dL) of greatest clinical significance for detection of early CKD.

  - Dennis agreed and said that Abbot was thinking of that. He noted, however, that it was possible to calibrate in the 0-2-4 range, and then do automatic dilutions to cover a wider serum creatinine concentration range.

- Glen Hortin also mentioned the importance of reporting serum creatinine to two decimal places so we achieve sufficient precision — especially at target range (i.e., 1 to 1.5 mg/dL).

  - Group consensus was to use two decimal places for all results, even though it will not mean as much at higher decimal points. Greg Miller noted that the second decimal place can have as much as a 5% impact on estimated GFR.

- John Eckfeldt returned the discussion to the issue of timing, asking if it was true that it could take labs several years to recalibrate. He noted that the NIST fresh frozen serum (SRM 967) should be available to manufacturers as early as late summer or early fall 2005 and that the new CAP survey mails twice a year (May and November). He asked what other things should be done to prepare for recalibration.

  - Rick Miller asked when commutability studies on SRM 967 will be completed. John Eckfeldt said that he plans to do these studies at University of Minnesota this summer and hopes to be done by the time NIST releases the material. John noted that if labs wanted to get a jump start, they could use reference materials LN24-02 and LN24-07, which have NIST values on them but that, ultimately, NIST SRM 967 will be best.

    - Neil Greenberg noted that using SRM 967 as the highest order reference material would be consistent with ISO 17511 calibration traceability standards. He said we should tell manufacturers to use this material as a primary calibrator, and then use that to calibrate a selected method. By doing that, they should be able to demonstrate through validation that patient sample results will compare very well with LC-IDMS. If they can do that, it might remove the need for laboratory services (high volume LC-IDMS) on a routine basis.

    - John Eckfeldt agreed, emphasizing that key is to do the validation of commutability.

- Neil Greenberg noted that an ongoing problem for manufacturers is that various competent authorities have declared that there is a problem because manufacturers do not have traceable calibration to higher order reference materials. This is a real dilemma for manufacturers, because all of the tools required to implement the traceable calibration will not exist until there are commutable materials, like the upcoming SRM 967, that can be used to implement an operational process. Neil stated that it would be helpful if professional groups could help manufacturers explain this to relevant authorities.

  - Greg Miller stated that NKDEP wanted to avoid the NCEP model, in which calibration based on patient samples proved to be so expensive, which is why it focused on higher order reference material. The forthcoming availability of SRM 967 as the highest order reference material will establish traceability in a much less expensive way.

  - Rick Miller noted that this will need to include more than a few methods, and that NKDEP should solicit the participation of other manufacturers in the study.

- The group agreed with this suggestion. John Eckfeldt suggested reaching out to a cross-section of manufacturers who wanted to do commutability studies.
    - **ACTION:** NKDEP will provide the LWG with recommendations for a process to reach out to manufacturers. Rick Miller volunteered to use AACC industry mailing list to spread the word, and there was discussion about working with Tony Killeen to get the word out through CAP.

- Bill Donohue expressed interest in talking with lab directors who aren't reporting GFR to learn why they are not doing so.
    - Tom Hostetter noted that NKDEP and CMS are working together on a pilot program in Georgia to reach out to lab directors, which is being extended to a dozen academic medical centers around the country, but that they do not have good data at moment about the fraction of labs that are reporting estimated GFRs along with serum creatinine.
    - Tony Killeen said that CAP is going to ask this question on one of its upcoming surveys.
    - Chandra Jain asked if we wanted to know simply who is reporting GFR, or if we wanted to know who is using MDRD equation to estimate GFR. John Eckfeldt said that we'd want to know both, but Tom said that because of difficulty of using Cockcroft-Gault (i.e., the need to factor in weight) he thinks that anyone reporting GFR is likely using MDRD.
    - David Lacher noted that MDRD equation requires knowing race of patient and asked what percentage of that time that data is available.
        - John Eckfeldt noted that equation requires only that patient be classified as African American or non-African American, and that physician determines this.
        - Tom Hostetter noted that there are some efforts underway to look at other discrete ethnic groups.

- Ethan Hausman asked if there has been any modeling on how recalibration might affect GFR estimates for children.
    - Tom Hostetter said that if recalibration moves creatinine measurements down, it might raise estimates of GFR clearance in children.
    - Joris Delanghe said that cystatin C might be the only alternative for kids.

- Tony Killeen let the group know that CAP has an overrun of fresh frozen serum material (a single value of .90 mg/dL, established by GC-IDMS) from 2003 that it is selling.

- Greg Miller emphasized that one of the critical issues for moving forward is to establish a timeline for calibration and changing coefficient for equations.
    - Fred Van Lente said that the CKD-Epi project expected to have some revised estimating equations available by the end of the summer.
    - Mike Welch said that SRM 967 should be available by the end of the summer as well. (He also noted that NIST is using both GC-IDMS and LC-IDMS reference measurement procedures on this material.)
    - John Eckfeldt said that labs could therefore expect to begin introducing methods with IDMS-traceable calibration in early 2006, or possibly even late 2005.

- Greg Miller noted that LWG could begin work now on developing education plans, and drafting educational materials, for labs and clinicians.

- Harvey Kaufman said that if we are looking at next summer, and labs need two years to clear out their stocks, we might be looking at 2009 for all labs to complete the process.

    - John Eckfeldt said that goal is to support those who are ready to recalibrate sooner — so that they know what reference material and equation to use. Everyone does not have to switch at same time, but those who are ready need to know what to do.

- Bill Donohue asked if there was any buy-in among payors, stating that in his opinion the real value proposition to this whole initiative seems to be for HMOs, insurers, etc. He asked if they are enthusiastic about the effort.

    - Tom Hostetter said yes they are: CMS sits on the NKDEP Steering Committee and has an MOU with NKDEP, and is interested in finding ways to reduce progression to ESRD and lower their costs. Tom also shared updates about other Federal partners — the Indian Health Service and the Veterans' Administration are both estimating GFR — and said some of the larger HMOs have also begun to do so. He noted that Hawaii has legislated that GFR be reported by all state-accredited labs, and that similar legislation is being considered in New Jersey and elsewhere.

- David Seccombe said that in Canada they have been trying to launch an economic study to calculate the impact of calibration bias for creatinine measurement and GFR estimates on downstream healthcare costs. A recent study on measurement of calcium found that there was a significant cost ($199 million per year) due to calibration bias. Because estimates of GFR are tied to guidelines and drive clinical decisions, David thinks that creatinine calibration bias would have a similar impact.

    - Tom Hostetter agreed that such a study is a great idea.

- John Eckfeldt adjourned the Manufacturers' Forum, thanking all participants for their input.

LWG Business

- John Eckfeldt reconvened the LWG meeting by asking if the group should broaden its scope to look at urinary albumin as well as serum creatinine.

    - Tom Hostetter noted that the NKDEP and NKF have focused to date on GFR, even though microalbuminuria is more sensitive, because serum creatinine tests are ordered much more frequently. He also noted that if a clinician orders a microalbuminuria test, he or she probably already suspects CKD.

    - John said that there are issues related to urinary creatinine as well as urinary albumin, but that bias among various clinical methods can vary by as much as 20-25%.

    - Consensus was that there is not strong support for expanding the scope to microalbuminuria at this point, and that more information was needed. It was agreed that microalbuminuria serves as a validator for low estimated GFR, and that microalbuminuria is of secondary if not equal importance.

    - **ACTION:** It was agreed that the LWG would read papers on the topic and discuss the issue at its next meeting.

- Harvey Kaufman asked that if microalbuminuria might fall within the scope of the LWG, what about cystatin C?
  - John Eckfeldt asked whether, if there is not an intercomparability issue with cystatin C and serum creatinine, the LWG should worry about it.
  - Greg Miller said it might be valuable to try to prevent such an issue from occurring.
  - Andy Levey noted that serum creatinine works well at the low end of GFR, and if cystatin C helps with estimation of GFR, it is going to be at the low serum creatinine range — which is also the low cystatin C range. So, if there is a standardization problem at the low end of the cystatin C range, as there is with serum creatinine, the same problem could arise.
  - John asked if there was anything LWG or laboratory community could do now to help prevent future problems.
  - Andy said that some labs are already measuring cystatin C and estimating GFR using their own equations. He believes it is going to become an issue unless it is determined that measurement of cystatin C really does not really improve accuracy of GFR estimates.
  - John asked if the estimating equation being developed by the CKD-Epi Project was going to include both cystatin C and serum creatinine measurements in a single equation.
  - Andy said that they are going to investigate whether the addition of cystatin C to a creatinine-based equation will yield better estimates of GFR. He hypothesized that, in the range where there begins to be imprecision with creatinine (i.e., a GFR of 60 mL/min/1.73 m^2), one might be able to use cystatin C and/or microalbuminuria to yield a better measure of early CKD.
  - Andy also noted that analysis conducted of the pooled database to date suggests that cystatin C is prone to the same level of calibration variation (i.e., 3-5%) as is creatinine.
- John Eckfeldt revisited the discussion about KDIGO and IFCC and the importance of international cooperation.
  - Andy Levey noted that the goal of improving care for CKD has been pretty well accepted among nephrologists, and that there is pretty strong support for the KDOQI guidelines in the U.S. Other countries have come together to form KDIGO, which is an independent effort of clinicians but is serviced by the NKF. The main issues for KDIGO are the standardization of serum creatinine and microalbuminuria measurement and the definition of CKD.
  - Andy asked the group if, in the interest of international coordination, there should be a follow-up meeting with the global lab community hosted by KDIGO. He asked if this was a high priority for NKDEP
    - Joris Delanghe said that NKDEP should be involved through IFCC and Mauro Panteghini, and that it should try to address cystatin C as well as serum creatinine. He emphasized that development of new and divergent equations on international scale could introduce even more error/variability than small calibration issues.
    - Andy noted that, even with their problems, the MDRD equation and serum creatinine measurements are already being used worldwide, so the group needs to look at the issue

from both sides (i.e., lab calibration and equations). The hope with cystatin C is that because it does not depend on muscle mass or diet it could be used across populations. The goal of investigating cystatin C is to "pull back another layer of onion" and take small steps that ultimately yield more accurate and consistent estimates of GFR.

- John Eckfeldt said that Mauro Panteghini has proposed joint meeting of the LWG and IFCC in Orlando, either as part of the LWG meeting or perhaps in a separate session, to discuss these issues.
- It was agreed that the next LWG meeting would be held on the morning of Thursday, July 28 at the AACC meeting in Orlando — and that the session would ideally include representatives from the IFCC and KDIGO.

- Tom Hostetter underscored the importance of clinicians knowing that NKDEP and the LWG are pretty close to having something that solves the issue.

Review of Draft Manuscript

- Gary Myers led the group in reviewing the revised draft manuscript being prepared for submission to *Clinical Chemistry*. The group discussed each of the suggested edits and reached consensus on proposed changes.
  - **ACTION:** LWG members agreed to get additional edits to Gary within a week, who will send out a revised version within a few weeks. The goal is to submit it to the journal by the end of summer, with the hope that the paper will be published within the year.

Closing Business

- John Eckfeldt reiterated the target timeline for next steps: new reference material (SRM 967) and a new estimating equation available by the end of summer 2005, which will allow labs to begin recalibration efforts in early 2006, with gradual implementation throughout 2007 – 2008.
- Harvey Kaufman repeated request to learn more about why some labs are using GFR and some are not.
  - **ACTION:** NKDEP will share with the group ideas for an evaluation proposal to NIH, seeking 1% evaluation set-aside funds to learn more about this and related issues.
- Greg Miller noted that misinformation is being circulated about what laboratories should be doing at the moment regarding recalibration and that correct information should be posted on the NKDEP and AACC websites.
  - **ACTION:** Greg offered to write up a draft of recommendations for laboratories that are appropriate right now and will circulate it to the group for comment.
- It was agreed that Greg Miller would replace John Eckfeldt as the chairman of the LWG, beginning with the next meeting in July.
- John Eckfeldt adjourned the meeting, thanking all of the participants for their contribution to the discussion and the broader initiative.