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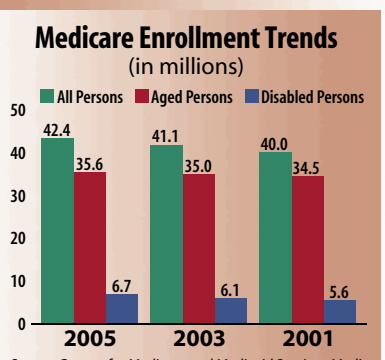
NEWS BRIEF

IOM Report Cites Need for QIO Reforms

Quality improvement organizations (QIOs) would be more effective if they focused solely on providing technical assistance on quality improvement to health care organizations and practitioners and transferred other activities—such as case reviews—to other organizations, says a new report from the Institute of Medicine (IOM). The report, requested by Congress, is the result of a year long review of QIOs' organizational structures, responsibilities, and role in improving the quality of health care.

The IOM review committee recommended that QIOs concentrate on helping providers improve their delivery of care and their organizational cultures and information systems, instead of handling beneficiary complaints, appeals, and other case reviews. QIOs are currently required to examine patient complaints and requests for coverage and to review claims to make certain that care meets national quality standards and guidelines and that Medicare has been billed appropriately for the services reimbursed.



Source: Centers for Medicare and Medicaid Services, Medicare Enrollment Reports, National Trends 1966-2005

The report suggests that the Centers for Medicare and Medicaid Services (CMS), which manages the QIO program, should contract with a few selected QIOs or other groups that have expertise in investigating medical complaints to handle Medicare beneficiary claims and appeals. This redistribution of responsibilities would address conflicts of interest that might arise when case reviews are conducted by the same QIO that must maintain good relationships with health care facilities that participate voluntarily in its quality improvement programs.

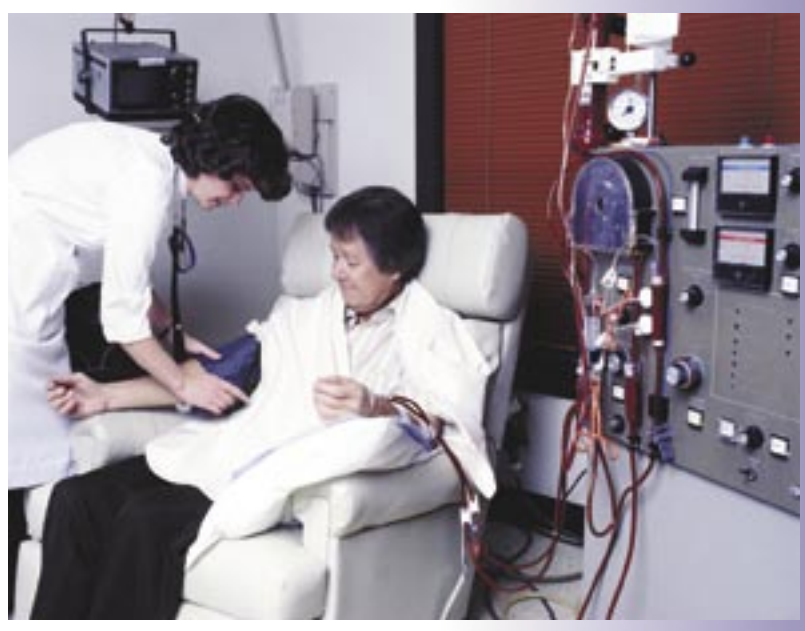
The IOM committee concluded that QIOs' governing board structures must be strengthened and that boards should maintain a greater balance between physicians and patient representatives, as well as the inclusion of more health care consumers, representatives of other health care fields, and members with expertise in health information technology.

The complete IOM report can be accessed on the National Academies Web site at http://darwin.nap.edu/books/0309101085/html/

NKDEP Launches Creatinine Standardization Program

Why Labs Should Recalibrate Serum Creatinine Methods, Report Estimated GFRs

By Richard Pizzi



Clinicians can do very little to improve the prognosis of patients with end-stage renal disease (ESRD), a complete or near complete failure of the kidneys to excrete wastes, concentrate urine, and regulate electrolytes. But with the incidence of type 2 diabetes—the most common cause of ESRD—growing at an alarming rate in the U.S., public health officials and patient advocates want to raise awareness of the seriousness of kidney disease and push for early detection and intervention. In fact, most cases of chronic kidney disease (CKD) exist for many years before progressing to ESRD, and treatments are available that can prevent or slow disease progression. Now, with the recent release of a major report by the Laboratory Working Group (LWG) of the National Kidney Disease Education Program (NKDEP)—an initiative of the National Institutes of Health designed to reduce the morbidity and mortality caused by kidney disease and its complications—laboratory test results will play an even more vital role in the early detection of CKD. The report—a centerpiece of NKDEP's Creatinine Standardization Program—contains new recommendations for measuring serum creatinine and for reporting estimated glomerular filtration rate (GFR), two key indices of kidney function.

See **Creatinine**, *continued on page 6*

Debate Flares over OTC HIV Tests

Laboratorians, Others Raise Concerns About Rapid Self Testing

By Julie McDowell

Pressure on the Food and Drug Administration (FDA) to approve HIV test kits for over-the-counter (OTC) and home use continues to mount, with President George W. Bush proposing in his February State of the Union Address that at least $90 million in federal funding be committed to purchasing and distributing rapid HIV test kits to more than 3 million additional Americans in targeted regions of the U.S. where infection rates and undetected cases are a public health concern. One in vitro diagnostic manufacturer, OraSure Technologies, Inc. (Bethlehem, Pa.), is poised to benefit from this federal push, and company officials have been clear about their plans to seek FDA approval for OTC sale of OraQuick Advance, a test already being sold to labs that uses oral fluid, as well as fingerstick or venipuncture blood or plasma, to determine the presence of HIV-1 and -2 antibodies. However, critics in the clinical laboratory community are raising concerns about the potential for erroneous results and quality problems if rapid HIV testing moves out of the control of trained health care workers and into the hands of the general public. Adding to those concerns were reports last December of an excessive number of false positive Advance test results at clinics in San Francisco, New York City, and Los Angeles.

To gather input on the potential OTC sale of this HIV test, the FDA's Blood Products Advisory Committee (BPAC) met with public health officials, health care providers, consumers, and industry representatives in November 2005. BPAC officials heard pros and cons about home HIV testing, including associated psychological and social issues, and

See **HIV Test**, *continued on page 3*

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Labs Should Always Report GFR

Creatinine, *from page 1*

"We're very anxious to communicate—in as broad a way as possible—the importance of this program and the recommendations we've made," said Greg Miller, PhD, Professor of Pathology at Virginia Commonwealth University (Richmond, Va.) and the current chair of NKDEP's LWG. "It's essential that all interested parties—particularly labs—understand how to implement the recommendations." Miller emphasized that putting the recommendations proposed by the LWG into practice requires the active involvement and input not only of clinical labs, but of IVD manufacturers, pharmacists, proficiency testing providers, regulatory organizations, and software providers. The practical changes that follow from the recommendations will have global implications, not only for methods and materials in labs around the world, but for the clinical care of those patients at greatest risk of CKD.

The Initial Inspiration

The new recommendations on measuring serum creatinine actually have their origins in clinical advances achieved within the last decade in treating CKD. Elisa Gladstone, MPH, Associate Director of NKDEP, says that if detected early, CKD can be slowed, and in some cases halted, which makes the accurate estimation of kidney function critical to patients and clinicians. "We know now that with the timely use of ACE inhibitors and ARBs [angiotensin II receptor blockers] we can slow the progression of kidney disease," she said. "And it's been demonstrated that intense glycemic control and blood pressure management will also have a renoprotective effect for patients who are diagnosed early. It was this evidence that led us to establish a Laboratory Working Group to discuss the issues related to creatinine standardization and estimated GFR."

Stimulated by the promise of more effective therapies for at-risk populations, NKDEP organized the LWG in early 2003. John Eckfeldt, MD, PhD, Professor of Laboratory Medicine and Pathology at the University of Minnesota (Minneapolis), served as the group's first chair and led discussions on the problem of calibration bias that created variability in estimated GFR values between laboratories. Under the early leadership of Eckfeldt, the LWG focused on the current state-of-the-art creatinine measurements and debated the importance of using the Modification of Diet and Renal Disease (MDRD) equation in estimating GFR.

After some of the initial discussions, the LWG focused on how improvement of creatinine measurement methods and the reporting of estimated GFRs would promote early detection of kidney disease. "We came to the conclusion that there was a need for a broad laboratory standardization effort that would engage IVD manufacturers, as well as the clinical labs," Eckfeldt said. "We had representation from the clinical lab professional organizations, IVD manufacturers, proficiency testing providers—international as well as U.S. representation—and we believed that there was compelling clinical evidence for the recommendations we settled on." These recommendations solidified under the direction of Gary Myers, PhD, Chief of the Clinical Chemistry Branch at the Centers for Disease Control and Prevention (CDC), who spearheaded development of the LWG report that was published in January in *Clinical Chemistry* (2006; 52:5–18), and Miller, who took over leadership of the LWG in June 2005.

Estimating GFR: A Reliable Renal Function Indicator

The new report recommends two distinct, but equally important, guidelines for improving creatinine measurements and estimating GFRs. The report also makes clear that the recommendations will affect IVD manufacturers, pharmacists, and clinicians, and indicates what actions the various constituencies should take to facilitate the changes. "It's worth emphasizing again that we're doing this because physicians have generally underappreciated the clinical interpretation of small changes in creatinine," Miller said. "The difficulty in interpretation is that very small changes in creatinine, even within the upper reference interval, are consistent with patients who have lost roughly half their renal function measured as GFR." He points out that the NKDEP algorithm takes into account the impact of those small changes in creatinine by presenting creatinine as an estimate of GFR, and it provides clinicians with information that can be interpreted directly relative to renal function.

The NKDEP recommendations strongly encourage clinical laboratories to automatically report estimated GFR whenever serum creatinine is ordered. In the paper, the authors contend that an estimated GFR from serum creatinine is a practical way to identify people with CKD who might otherwise go untreated. NKDEP's Gladstone acknowledges that while estimated GFR is not "perfect," it is a diagnostic tool that can flag for primary care providers the patients whom they may not have considered at risk for kidney disease. "Having ready access to estimated GFR will empower providers to recognize which patients have signs of CKD," she said. "It allows them to manage patients more effectively and work collaboratively with nephrologists once GFR levels drop below a certain point."

The LWG goes on to suggest in the report that labs use the standard MDRD equation to estimate GFR from serum creatinine because it has been proven to be reliable when the patient's age, sex, and race are also known. But as a patient's race may not always be available to many clinical labs, and a patient may be of mixed ethnicity, the NKDEP recommends that estimated GFR values for both African Americans and non-African Americans be reported, as a way to give clinicians more definitive information (see sidebar).

Recalibrating to IDMS

Miller cautions that laboratorians must remember that there are now two different "abbreviated" MDRD equations for estimating GFR using patient age, sex, race, and serum creatinine (see sidebar, p. 8). The "conventional calibration MDRD equation" should be used by labs currently using creatinine methods that have not been calibrated to be traceable to isotope dilution mass spectrometry (IDMS) reference measurement procedures. The recently developed IDMS-traceable MDRD equation should be employed only by labs using creatinine methods that have been recalibrated to be traceable to IDMS. NKDEP recommends that all labs eventually introduce serum creatinine methods that are calibrated to be IDMS-traceable, as the use of high level reference method traceability will provide a uniform calibration standard. But whichever MDRD equation labs use to estimate GFR, the MDRD equations remain more accurate as a means of estimating GFR—for most patients—than a creatinine clearance calculated from creatinine measurements in serum and a 24-hour urine.

The recalibration of methods will need to come primarily from IVD manufacturers, not clinical labs, notes Eckfeldt. "In today's world, most laboratories don't adjust the calibration of their methods, but simply follow the manufacturer's instructions on calibration," he explained. "Labs don't try to adjust methods to values they think are more accurate because there is not the time or internal resources to do that, considering the large number of different analytes that a typical clinical lab measures."

Recognizing this situation, the LWG directed their recommendation to standardize creatinine methods to IDMS-traceability primarily at manufacturers. After recalibration, manufacturers should provide information to clinical labs on the relationship between the recalibrated method and the previous "conventional calibration" method. It will then be the responsibility of the lab to communicate the implications of the calibration change to clinicians and pharmacists.

The importance of recalibration to IDMS-traceability cannot be overstated, asserts Miller. "Most of the methods in current use are reporting creatinine values that are a little bit too high. The estimates range between ten and twenty percent higher than when the creatinine method is calibrated to be traceable to IDMS," he said. Miller adds that the reason for the bias can be explained in part by the relative non-specificity of the commonly used alkaline picrate (Jaffe) methods. What may appear to be a small difference of one- or two-tenths of a mg/dL can have a significant impact on the estimation of GFR. Eckfeldt also warns that the classical Jaffe methods may, in the long run, turn out to have inadequate analytical specificity. He suspects, however, that over time more labs may shift to the analytically more specific enzymatic methods for creatinine measurement, although such methods currently account for only ten percent of overall creatinine measurements.

Other Stakeholders: The IVD Industry and Pharmacists

As Eckfeldt suggests, the bulk of the recalibration efforts will fall to the IVD industry. Miller estimates that the process may take two years or more, although he points out that a few companies have already changed their creatinine methods to be IDMS-traceable, most notably Roche Diagnostics (Indi-

Estimating GFR— The Two MDRD Equations

The NKDEP strongly encourages clinical laboratories to automatically report estimated GFR whenever serum creatinine is ordered. The NKDEP recommends using one of two MDRD equations, depending on whether or not serum creatinine methods have been calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference method.

Four Variables

- Serum or plasma creatinine concentration (S_{cr})
- Age in years (18 years or older)
- Sex
- Race (African American or not)

Conventional Calibration MDRD Equation

This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to IDMS. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

When S_{cr} is in mg/dL (conventional units):

GFR (mL/min/1.73 m^2) =
$186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$

When S_{cr} is in µmol/L (SI units):

GFR (mL/min/1.73 m^2) =
$186 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$

IDMS-Traceable MDRD Equation

This equation should be used only with those creatinine methods that have been calibrated to be traceable to IDMS. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

When S_{cr} is in mg/dL (conventional units):

GFR (mL/min/1.73 m^2) =
$175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$

When S_{cr} is in µmol/L (SI units):

GFR (mL/min/1.73 m^2) =
$175 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$

Source: Adapted from NKDEP Suggestions for Laboratories (Revised December 2005). www.nkdep.nih.gov/resources/laboratory_reporting.htm

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Reporting Estimated GFR Values
What the NKDEP Guidelines Recommend

The specific guidelines for reporting estimated GFR can be found in the Laboratory Working Group's report in the January issue of *Clinical Chemistry* and on the NKDEP Web site (see below), but Greg Miller, PhD, chair of the group, indicates that the important dividing point is 60 GFR (mL/min/1.73 m^2). GFR values below 60 are reported as numbers, while values greater than 60 are reported as simply "greater than 60." The impact of the inter-laboratory variability of creatinine measurement becomes much more significant for individuals with relatively low creatinine values, Miller says. "Because variability becomes excessive at low values, we recommend not reporting a numeric value for GFR until we have better control over method variability."

Reference: Clinical Chemistry *2006; 52:5–18. Access the report on the Web at: http://www.clinchem.org/cgi/content/full/52/1/5*

NKDEP Web site: www.nkdep.nih.gov/labprofessionals

anapolis, Ind.). Still, there remain additional barriers to overcome before industry can fully embrace the NKDEP recommendations.

Neil Greenberg, PhD, Manager of Regulatory Affairs at Ortho-Clinical Diagnostics (Rochester, N.Y.), cautions that the ability of IVD manufacturers to support the use of the IDMS-traceable equation for calculating GFR may be limited. He says that the devices that IVD manufacturers sell are not necessarily capable of providing the estimated GFR value from the MDRD equation. "The calculation prescribed by that equation requires additional information beyond what is generated on the laboratory analyzer," Greenberg noted. "Our devices, the analyzers and reagents for measuring creatinine, simply generate measurements for the analyte in the samples presented. The laboratory information systems [LIS] vendors may be the more appropriate group to introduce the changes needed to support the use of the GFR estimating equations. It's their technology that captures the additional demographic parameters from other databases in the laboratory—or other medical information systems—that's needed to perform the calculations required in the new equations."

Nevertheless, Greenberg—also a member of the NKDEP Working Group—believes that IVD manufacturers can support the recommendations by improving calibration and performance of the creatinine measuring devices that they sell. He adds that in the coming years, with the availability of a more robust reference system for creatinine, in vitro diagnostics companies will undoubtedly enhance calibration traceability and improve the laboratory's ability to provide truer creatinine values.

The NKDEP has attempted to address Greenberg's point about the significant role of LIS vendors. The LWG recommends that LIS vendors provide their customers with the option to use either the conventional or the IDMS-traceable MDRD equation. But it also suggests that vendors offer the option to adjust the creatinine values reported for use with the Cockcroft-Gault (C-G) equation for estimating creatinine clearance, to account for differences between IDMS-traceable creatinine results and results reported with an older creatinine method calibration. The C-G equation remains the most commonly used method by pharmacists—another key group involved in the management of patients with CKD—to estimate creatinine clearance, particularly when calculating appropriate drug doses based on a patient's kidney function.

"Pharmacists cannot generally deviate from the Cockcroft-Gault equation because they are locked into whatever the pharmaceutical manufacturers recommend as a procedure for estimating doses of various medications," Miller revealed. "Pharmacists need software flexibility in order to adjust creatinine values to be compatible with the current algorithms that they use, which were all developed with the older conventional creatinine methodology. This is all very critical because many drugs that are cleared by the kidney have a potentially toxic impact if dosed incorrectly."

Greenberg adds that the pharmacists will likely have to request support from the pharmaceutical manufacturers, who may provide new dosing guidelines based on estimated GFR using the MDRD equation. Still, this aspect of the NKDEP recommendations may be among the most difficult to implement quickly, given the numerous constituencies involved and the significant technological and labeling changes required.

Global Changes: Another Hurdle

While the NKDEP is an NIH initiative, funded by U.S. taxpayer dollars, LWG members expect that the recommendations will have global impact. "There is a real need for international cooperation on this subject," Eckfeldt said. "You ultimately can't have different geographic regions using completely different methods and estimating equations. Not to mention the difficulty that such a situation creates for multinational IVD manufacturers who would have to implement different calibrations for different regions of the world."

While Eckfeldt's endorsement of international cooperation makes sense, Greenberg—who recently assumed the chair of the International Federation of Clinical Chemistry and Laboratory Medicine's working group on calculating GFR—says that resistance to the NKDEP recommendations is stronger internationally than here in the U.S. because some international clinical chemistry societies are not yet convinced of the clinical validity of the MDRD equation. "There are certain constituencies around the world that may not necessarily accept the approach that NIH is promoting and would prefer to continue using more traditional means to identify at-risk patients," Greenberg noted. "This would mean continuing to use full creatinine clearance measurement to identify those patients." Greenberg suggests that such resistance may ultimately be counterproductive because the NKDEP data indicates that the conventional, operationally challenging, and far more costly creatinine clearance method is simply not as good at identifying individuals at-risk for CKD.

Moving Toward Standardization

The NKDEP's Creatinine Standardization Program will begin in earnest, says Miller, once the National Institute of Standards and Technology (NIST) completes a commutability study for a new serum creatinine reference material (SRM 967). Expected to be available soon, SRM 967 will simplify the process of establishing method calibration traceable to IDMS and maintaining calibration over time. Greenberg affirms that IVD manufacturers are anxiously anticipating the new material and says that its release will inaugurate the recalibration process and lead to a more uniform reporting of values across the various methods now available. "The NIST program will be a milestone," Greenberg proclaimed. "In the absence of a standard reference material prepared in a commutable serum matrix, IVD manufacturers often have to undertake fairly expensive studies using panels of residual patient samples to establish traceability to the best analytical methods. We can proceed in the absence of high quality reference materials, but that's not something that we want to live with in the long run."

Greenberg notes that as industry begins to address the NKDEP recommendations, laboratorians have already begun requesting more information from manufacturers. "Sometimes they want to know if we're going to provide for the GFR calculation on our instruments," he said. "Customers also ask about our timeline for providing alternative calibrations to support GFR estimates using the MDRD equation. The interest within the laboratory community is clearly growing."

The NKDEP LWG plans to take advantage of laboratorians' increased interest in the new recommendations for serum creatinine measurements and GFRs by initiating a major publicity push via its Web site and through manufacturers' forums, one of which will be held at this summer's AACC Annual Meeting in Chicago (July 23–27, 2006). There will also be a symposium session, "Estimating GFR: Improving Early Detection of Kidney Disease," at the AACC Annual Meeting during which an update on the status of the Creatinine Standardization Program will be presented (Monday, July 24, 2006, 10:30 a.m.–12 noon). Miller encourages laboratorians to attend this session and to visit the NKDEP Web site for additional information and to provide feedback. The Web site also offers an email listserv that will provide notice of updates to the program as they are posted.

No doubt, laboratorians and other stakeholders will need time to assess the new recommendations and incorporate them into clinical practice. "We view this as a collaborative process," noted Gladstone. "We're always open to suggestions as to how to make this easier for laboratory professionals, so we really encourage feedback from laboratorians."

Lines of communication must remain open between the various constituencies affected by the recalibration of serum creatinine methods and the standard reporting of estimated GFR, says Miller, as any misunderstandings or failure to communicate could have significant effects on patient care. "Because labs will have the responsibility to communicate the clinical impact of the changes, they need to understand exactly what is happening, why it's happening, and how it will impact them," he asserted. "That cannot be overemphasized." CLN

Some States Mandate Laboratory Reporting of Estimated GFR

While the NKDEP Laboratory Working Group (LWG) recommends that all labs report estimated GFR whenever serum creatinine is ordered, some state legislatures have gone even farther. Four states, led by New Jersey, have passed laws requiring labs to report estimated GFR with each serum creatinine test. Last year, Governor Richard Codey of New Jersey signed Bill S2232 mandating all clinical laboratories to do just that for each serum creatinine test ordered by a health care professional. Such laws are controversial. Many laboratorians think that increased reporting of estimated GFR is important to identify early kidney disease, but that state legislatures should not be micromanaging the practice of medicine.

For its part, the NKDEP has not initiated or actively supported any of the legislation in the various states. Individual legislators in different states have contacted the NKDEP for information on kidney disease and estimating GFR, which the organization has provided, but the NKDEP has not taken a position on the state-mandated reporting of estimated GFR.

Even members of the NKDEP LWG suggest that state mandates may not be the best way to proceed. Greg Miller, PhD, chair of the LWG, says that there can be technological barriers for some labs in calculating GFR that would make meeting any new state requirements difficult. "Many labs have an old LIS which can't support the MDRD equations. Furthermore, manufacturers' instruments cannot do the calculation because they don't have the necessary demographic information about the patient," Miller noted.

Although AACC opposes such legislation, it does not oppose the NKDEP initiative to promote the use of the estimated GFR.

The states that have mandated the reporting of estimated GFR are:

- New Jersey
- Tennessee
- Michigan
- Louisiana—requires estimated GFRs for all Medicaid patients

States that are considering legislation mandating the reporting of estimated GFR are:

- Alabama
- Florida
- Massachusetts
- Mississippi
- Oklahoma
- South Carolina
- Virginia