Suggestions for Laboratories

NKDEP
National Kidney Disease Education Program

This document has been developed by the National Kidney Disease Education Program (NKDEP) to provide clinical laboratories with information that can help them::

- accurately report estimated glomerular filtration rate (eGFR) based on serum creatinine;
- understand the NKDEP initiative to standardize the measurement of serum creatinine; and
- communicate with healthcare providers about the implications of changes in serum creatinine values that will result from the creatinine standardization initiative.

Estimating GFR

The NKDEP strongly encourages clinical laboratories to automatically report eGFR when serum creatinine is reported. An eGFR calculated from serum creatinine is a practical way to detect, evaluate, and manage people with chronic kidney disease (CKD), especially people with risk factors for CKD—diabetes, hypertension, cardiovascular disease, or family history of kidney disease—in whom CKD might otherwise go undetected and untreated.

In adults ages 18 years and older the Modification of Diet in Renal Disease (MDRD) Study equation has been shown to be reliable in estimating GFR from serum creatinine, when the patient's age, gender, and race are also known.[1,2] Use of the MDRD Study equation to estimate GFR is the best means currently available to more appropriately utilize serum creatinine values as a measure of kidney function. The MDRD Study equation has been validated extensively in Caucasian and African American populations with impaired kidney function (eGFR <60 mL/min/1.73m^2), and ages between 18 and 70 years. The MDRD Study equation has shown good performance for patients with all common causes of kidney disease, including kidney transplant recipients.[3]

The NKDEP Laboratory Working Group report[4] states that the MDRD Study equation should only be used in individuals age 18 and older. The report also notes that the MDRD Study equation has not been validated for use with the elderly (over 70 years of age), pregnant women, patients with serious comorbid conditions, or persons with extremes of body size, muscle mass, or nutritional status. Application of the equation to these patient groups may lead to errors in GFR estimation.[4] GFR estimating equations have poorer agreement with measured GFR for ill hospitalized patients[5] and for people with near normal kidney function[3] than for the subjects in the MDRD Study. Validation studies are in progress to evaluate the MDRD Study equation for additional ethnic groups, the elderly, various disease conditions, and people with normal kidney function.

A laboratory may want to limit the patients for whom eGFR is reported because of the limitations described above. However, if a computer reporting system cannot identify patients for whom reporting eGFR is most appropriate, it is suggested that laboratories report eGFR for all patients and allow the clinician to determine the suitability of a result for a patient's condition.

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Contact Information

For assistance, please contact the National Kidney Disease Education Program.
Email: csp@info.niddk.nih.gov

U.S. Department of Health and Human Services
National Institutes of Health

Which GFR Estimating Equation Should Be Used

The NKDEP recommends using one of two versions of the four-variable MDRD Study equation, depending on whether or not serum creatinine methods have been calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference method. The two MDRD Study equations include the ***original MDRD Study equation***, and the recently developed ***IDMS-traceable MDRD Study equation***. Note that neither equation requires weight or height because the result is reported normalized to 1.73 m^2 body surface area, which is an accepted average adult body surface area.

- Clinical laboratories using creatinine methods that ***have not been calibrated*** to be traceable to IDMS should continue using the original MDRD Study equation.
- Clinical laboratories using creatinine methods that ***have been calibrated*** to be traceable to IDMS should use the recently developed IDMS-traceable MDRD Study equation. Use of the IDMS-traceable equation must be coordinated with introduction of such a creatinine method. During the transition to IDMS-traceable calibration, methods that produce results that have acceptable bias (as defined in reference 4) when compared to an IDMS-traceable method should use the IDMS-traceable MDRD Study equation.

Original MDRD Study Equation

This equation should be used with creatinine methods that ***have not been calibrated*** to be traceable to IDMS. It is appropriate to use this equation because most methods in this category will produce creatinine results that have bias similar to that of the method used in developing the original MDRD Study equation. If you have any questions 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.

The equation requires four variables:

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

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

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

When S_{cr} is in µmol/L (SI units):

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

IDMS-Traceable MDRD Study Equation[7]

This equation should be used only with those creatinine methods that ***have been calibrated*** to be traceable to IDMS. During the transition to IDMS-traceable calibration, methods that produce results that have acceptable bias (as defined in reference 4) when compared to an IDMS-traceable method should use the IDMS-traceable MDRD Study equation. 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.

The equation requires four variables:

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

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

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

When S_{cr} is in µmol/L (SI units):

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

How to Report eGFR Values

Since a patient's race is often not available to clinical laboratories, and because mixed ethnicity can make it difficult to classify a patient's race, a general recommendation is to report the eGFR values for both African Americans and non-African Americans (see Sample Reports following). This practice allows the clinical provider to estimate the appropriate value for the patient's ethnicity. When ethnicity is known, it is acceptable to report a single eGFR appropriate for the race. The laboratory should exercise discretion regarding reporting multiple eGFR values when data for age or gender are not available.

The NKDEP recommends using serum creatinine values in mg/dL to two decimal places (e.g., 0.95 mg/dL), and values in µmol/L to the nearest whole number (e.g., 84 µmol/L), when calculating eGFR using the MDRD Study equation. This recommendation will reduce rounding errors that may contribute to imprecision in the eGFR value.

The NKDEP recommends reporting eGFR values ***greater than or equal to 60 mL/min/1.73 m²*** simply as "≥60 mL/min/1.73 m²," not as an exact number. For values ***below 60 mL/min/1.73 m²***, the report should give the numerical estimate rounded to a whole number (e.g., "32 mL/min/1.73 m²"). There are three reasons for this recommendation:

1. The equation has been most extensively evaluated in people with chronic kidney disease and reduced GFR and is less accurate for persons with normal or mildly impaired kidney function.
2. Inter-laboratory differences in calibration of creatinine assays, and the imprecision of the assays, have their greatest impact in the near-normal range and therefore lead to greater inaccuracies for values >60 mL/min/1.73 m².[4,8]
3. Quantification of eGFR values of 60 mL/min/1.73 m² and below have more clinical implications for classification of kidney function than values above this level.

Sample Reports

Note: If your printing system does not allow for superscripts, it is recommended to report mL/min/1.73 "square meters" or "m^2." The decision limits for eGFR can be indicated as >60 mL/min/1.73 m² because numeric values are not provided at higher values.

The following sample reports for eGFR have been developed using the original MDRD Study equation:

Sample report for a 63-year-old woman
Creatinine = 1.82 mg/dL
eGFR if African American = 36 mL/min/1.73 m²
eGFR if non-African American = 30 mL/min/1.73 m²

Sample report for a 63-year-old woman identified as African-American
Creatinine = 1.82 mg/dL
eGFR = 36 mL/min/1.73 m²

Sample report for a 62-year-old man
Creatinine = 1.35 mg/dL
eGFR if African American = >60 mL/min/1.73 m²
eGFR if non-African American = 57 mL/min/1.73 m²

Sample report for a 55-year-old man
Creatinine = 1.07 mg/dL
eGFR if African American = >60 mL/min/1.73 m²
eGFR if non-African American = >60 mL/min/1.73 m²

Communicating with Healthcare Providers when Reporting Creatinine Results that are Traceable to an IDMS Reference Method

The NKDEP encourages clinical laboratories to communicate with healthcare providers—including pharmacists—about the clinical issues associated with serum creatinine results using methods that have calibration traceable to IDMS.*

Healthcare providers should be informed that:

- The serum creatinine reference interval will change, in most cases, to lower values.
- Creatinine clearance values based on measured serum and urine creatinine results may change, and a new reference interval and interpretive criteria may need to be established. The effect on measured creatinine clearance will vary depending on the procedure used to calibrate serum and urine measurements.
- For most patients, an eGFR using the MDRD Study equation is more accurate than a creatinine clearance calculated from serum and urine measurements.[6] Therefore, NKDEP recommends not performing a measured creatinine clearance procedure for adults except when the patient's basal creatinine production is expected to be very abnormal, as may be the case with patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases) or with unusual dietary intake (e.g., vegetarian, creatine supplements).
- The MDRD Study equation should only be used in individuals age 18 and older. In addition, the MDRD Study equation has not been validated for use with the elderly (over 70 years of age), pregnant women, patients with serious comorbid conditions, or persons with extremes of body size, muscle mass, or nutritional status. Application of the equation to these patient groups may lead to errors in GFR estimation.[4] GFR estimating equations have poorer agreement with measured GFR for ill hospitalized patients[5] and for people with near normal kidney function[3] than for the subjects in the MDRD Study. Validation studies are in progress to evaluate the MDRD Study equation for additional ethnic groups, the elderly, various disease conditions, and people with normal kidney function.
- The clinical laboratory should notify the pharmacy and drug prescribers to inform them of the expected magnitude of change in serum creatinine values, compared to the previous method, and whether the creatinine clearance measured from serum and urine will be affected by the change. *Recommendations for Pharmacists and Authorized Drug Prescribers* will be available soon at www.nkdep.nih.gov/labprofessionals.
- Following implementation of serum creatinine methods with calibration traceable to IDMS, other equations used to estimate kidney function, such as Cockcroft-Gault, Schwartz, or Counahan-Barratt, will give values that, in most cases, are higher than the values obtained using traditionally calibrated creatinine methods. This change will affect interpretive criteria based on these estimates of kidney function.
- Creatinine measurements at low values usually observed in pediatric patients have a greater measurement variability than seen in adults, and estimates of kidney function based on these values will have greater variability than for adults.

* *The NKDEP is encouraging IVD manufacturers to provide information to clinical laboratories describing the relationship between creatinine results when measured with methods that have IDMS-traceable calibration compared to the results obtained using traditionally calibrated methods.*

PT/EQA Implications of Changing to a Creatinine Method with IDMS-Traceable Calibration

As laboratories make the transition from traditionally calibrated creatinine methods to IDMS-traceable methods, PT/EQA providers will need to make changes in participant grading to account for bimodal distributions of results.

The NKDEP is communicating with PT/EQA providers and IVD manufacturers to ensure appropriate grading during this transition (which is expected to occur during 2006-2008) so that laboratories do not fail a PT/EQA challenge as a result of recalibration of their creatinine method by a reagent/calibrator manufacturer. PT/EQA providers will be asked to create new instrument/method peer groups that reflect the calibration status (traditional or IDMS-traceable) of the various serum and urine creatinine methods used by participant laboratories. Participating laboratories will need to choose the correct instrument/method peer group for the respective creatinine method and calibration currently in use by their laboratory. For purposes of method classification and peer grouping for proficiency testing, if you have any doubts about the appropriate classification of the creatinine method and its associated calibration used in your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

Next Steps: The Creatinine Standardization Program

The NKDEP Laboratory Working Group has launched the Creatinine Standardization Program to assist IVD manufacturers and clinical laboratories in addressing inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of GFR. At the present time, traceability to IDMS reference methods can be established by collaborating with a reference measurement laboratory offering GC-IDMS or LC-IDMS reference method testing services. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) website provides information on approved reference measurement procedures and lists the submitting laboratories.

The National Institute for Standards and Technology (NIST) is in the process of releasing a new reference material (SRM 967) made from off-the-clot frozen serum pools [two levels, approximately 71 µmol/L (0.80 mg/dL) and 354 µmol/L (4.00 mg/dL)]. Value assignment by GC-IDMS and LC-IDMS and validation of commutability with a panel of native serum samples for a group of routine clinical methods for serum creatinine were completed in mid-2006. Commutability study results will be posted on the NKDEP website at www.nkdep.nih.gov/labprofessionals. Availability of this SRM will provide a practical reference material for use in establishing traceability to IDMS creatinine methods. NKDEP collaborated with NIST and the College of American Pathologists (CAP) to develop SRM 967 and the CAP LN24 Creatinine Accuracy Calibration Verification/ Linearity Survey. The materials for these two products were prepared by the same process, and CAP LN24 will be validated for commutability along with the NIST SRM. In addition to addressing inter-laboratory variation in creatinine assay calibration, the NKDEP Laboratory Working Group is also encouraging IVD manufacturers to improve the precision of serum creatinine measurements to meet the total error requirements published in the full report.[4]

The most current information about the NKDEP Creatinine Standardization Program, other resources for laboratory professionals, and a link to subscribe to free email updates about relevant topics are available at www.nkdep.nih.gov/labprofessionals. Updates will be made regularly as the standardization program develops.

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