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The importance of metrological traceability on the validity of creatinine measurement as an index of renal function[1)]

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[2)]

IFCC Scientific Division, Working Group on Standardization of Glomerular Filtration Rate Assessment (WG-GFRA)
Prepared for publication by

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Abstract

The glomerular filtration rate (GFR) is currently considered the best overall index of kidney function. The possibility that laboratories might routinely report an estimated GFR has become practically feasible with the development of a formula, the ''four-variable'' Modification of Diet in Renal Disease study (MDRD) equation that uses age, sex, race, and serum creatinine parameters. However, a limitation of this equation for general implementation in healthcare is related to the use of differently calibrated creatinine measurement procedures among laboratories. The only way to achieve universal implementation of the GFR prediction equation, with the associated clinical benefits for patients, is, therefore, to promote worldwide standardization of methods to determine creatinine, together with the introduction of a revised GFR-estimating equation appropriate for use with standardized creatinine methods.
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Keywords: calibration; creatinine; glomerular filtration rate; kidney function tests; reference standards; traceability.

Introduction

Worldwide, chronic kidney disease (CKD) is a major public health problem (1). In the United States (US), the incidence and prevalence of end-stage renal disease, kidney failure treated by dialysis, and transplantation have more than quadrupled over the last two decades (2). In 2003, Coresh et al. (3) estimated that the number of people in the US with earlier stages of CKD was approximately 19 million, including approximately eight million people with a reduced glomerular filtration rate (GFR). In Europe, the annual incidence of end-stage renal disease has doubled over the past decade to reach approximately 135 new patients per million of population (1).

The US National Kidney Foundation has recently defined CKD as either structural or functional kidney damage or a GFR <60 mL/min 1.73 m^2 for 3 months or more, irrespective of cause (4). The threshold of GFR <60 mL/min 1.73 m^2 was selected as the definition of CKD because at this value approximately half of an adult's normal kidney function is lost, leading to several possible complications (5). The National Kidney Foundation also classified stages of CKD severity based predominantly on GFR estimation (4). GFR is, therefore, currently considered the best overall index of kidney function.

GFR estimates

GFR can be assessed by measuring the urinary clearance of exogenous filtration markers such as inulin, iohexol, ^{125}I-labeled iothalamate, ^{51}Cr-labeled EDTA, or ^{99}Tc-labeled diethylenetriaminepentaacetic acid (6, 7). However, because of difficulty in use, special spec-

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imen handling, cost, radiation exposure, and radionuclide regulatory requirements, these methods have limited use in clinical practice and are typically confined to specialized settings (8). Creatinine clearance may be a useful alternative when exogenous filtration markers are not available. However, it requires a timed (usually 24 h) urine collection, which is often problematic and inaccurate, making the test unsuitable for widespread clinical application (9). Thus, GFR is often estimated clinically from serum concentrations of endogenous creatinine or cystatin C (10). However, serum cystatin C has not yet been adequately evaluated as an index of GFR (11). Serum creatinine is frequently ordered to assess kidney function, but the sensitivity of serum creatinine alone for the detection of CKD is poor because it is affected by the GFR and by factors independent of GFR, including age, sex, race, muscle mass, diet, and certain drugs (9). The serum creatinine alone fails to identify half of patients with stage 3 CKD, having GFR between 30 and 59 mL/min 1.73 m^2, and performance is even worse in certain patient groups, e.g., older subjects (12).

More accurate and precise estimations of GFR can be obtained with prediction equations that empirically combine all of the average effects from confounding variables that affect serum creatinine other than GFR (13). Theoretically, estimating equations for GFR should be: (a) developed in a large cohort, including a variety of racial and ethnic groups for international comparisons; (b) evaluated in an independent cohort; (c) validated to have acceptable bias against a ''gold standard'' measure of GFR; and (d) practical to implement, taking into consideration cost, required data elements, generalizability, and reliability of the creatinine measurement procedure (5).

There are now at least 25 different equations for estimating GFR, but most (including the Cockcroft-Gault equation) require additional information, such as a measure of body surface (based on height and/or weight measurements), that is not readily available, thus limiting the wider use of this approach. The possibility that clinical laboratories might routinely report an estimated GFR derived from the serum creatinine concentration has become practical with the development of a formula with only the variables age, sex, race, and serum creatinine (14). This formula, the ''four-variable'' MDRD equation [developed from the US Modification of Diet in Renal Disease study (MDRD)], is based on GFR values measured by ^{125}I-iothalamate clearance in 1628 adults and subsequently validated in another 1775 adults in the African American Study of Kidney Disease, with 91% of subjects having a GFR estimate within 30% of the measured value (15, 16). The MDRD equation does not require a body weight variable because it normalizes GFR for a standard body surface area of 1.73 m^2.

This equation has been demonstrated to be useful for CKD patients and performs similarly in type 2 diabetics and kidney transplant recipients, but its use is still unclear for people with low values for serum creatinine and high values for GFR, including healthy individuals, children and pregnant women (5). Validation studies are in progress to evaluate the MDRD equation for other ethnic groups (in addition to Caucasians and African-Americans) and various disease conditions.

A major barrier to the general implementation in healthcare of equations for estimating GFR is the use of different creatinine measurement procedures among laboratories (17–19). Lacking standardization for creatinine measurement, assays not calibrated in agreement with the method used in the core laboratory to develop and validate a specific equation (e.g., laboratory at the Cleveland Clinic for development of the MDRD equation) introduce an additional source of error into GFR estimates. Care should be taken concerning clinical consequences of differences in calibration compared to the core laboratory, especially considering that the relationship of an individual laboratory's assay to that provided by the core laboratory is generally unknown (20, 21). Although the US National Kidney Foundation clearly advised in its 2002 guidelines the use of only corrected creatinine values in GFR estimation with the MDRD formula, many laboratorians, practitioners, and nephrologists do not seem to be aware of this important source of error in routine clinical practice (22). Calibration bias contributes to larger uncertainty in GFR estimates at lower creatinine values within the concentration range associated with normal kidney function. Myers et al. (2) recently showed the effect on estimated GFR by the MDRD equation of different calibration biases of creatinine methods. In their example, for a 60-year-old Caucasian female, for whom the estimated GFR was 60 mL/min 1.73 m^2 at a creatinine of 1.00 mg/dL (88 μmol/L), a calibration difference of 0.12 mg/dL (11 μmol/L) was associated with an error in GFR estimate of −12%. The error in GFR estimates over the range of biases examined [−0.06 to +0.31 mg/dL (−5 to +27 μmol/L)] was from +7.5% to −27% and, of relevance here, data from External Quality Assessment Schemes (EQAS) suggest that this amount of systematic variation across laboratories is common (23, 24).

Steps to improve GFR estimates by the MDRD equation

From the previous considerations, it is clear that the only way to achieve universal implementation of the serum creatinine-based GFR prediction equation, with the associated clinical benefits for patients, is to promote worldwide standardization of creatinine measurement procedures, together with revalidation of the MDRD equation using standardized creatinine results.

There is now international agreement that the implementation of calibration traceability to high-order reference methods and materials is the best approach to achieve the needed comparability in biochemical measurement results, regardless of the measurement procedures used and/or the laboratories where the analyses are performed (25). This effort

must involve international cooperation among the in vitro diagnostic (IVD) manufacturers, clinical laboratories, professional organizations, government agencies, and EQAS providers. Achievement of improved accuracy for creatinine measurements requires that the values assigned by manufacturers to calibrators and control materials supporting all routine measurement procedures are traceable to higher-order reference measurement procedures and reference materials (2).

The National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 914, crystalline creatinine, is the available primary reference material. Solutions of SRM 914, prepared gravimetrically by dissolving SRM 914 in aqueous buffer, are intended for use in calibration of the high-order reference measurement procedures [i.e., gas chromatography-isotope dilution mass spectrometry (GC-IDMS) and liquid chromatography (LC)-IDMS] performed in reference laboratories. The GC-IDMS method requires a separation step to remove creatine, which gives the same derivatization product as creatinine, before derivatization of the creatinine or the GC step, and is therefore a very time-consuming procedure with limited sample throughput (26–28). Conversely, the LC-IDMS method has much simpler and faster sample preparation and would be more amenable to assist IVD manufacturers in validating traceability of their systems and to promote a standardization program on a larger scale (29).

The NIST SRM 909b (two levels) and the Institute for Reference Materials and Measurements (IRMM) BCR 573/4/5 (three levels) are lyophilized secondary reference materials with values assigned by the reference method that could theoretically be used to calibrate routine methods. However, the matrix of these human serum-based materials has been modified by converting plasma to serum and by lyophilization, thus altering the recovery of creatinine in these fluids by routine methods (30). Because the commutability of these materials with native human sera has not been established for routine methods, they are in practice unsuitable for direct calibration. Reference material that is non-commutable with native human serum samples can cause significant errors in method calibration (31). In this situation, an alternative approach to standardizing results and establishing traceability to a reference measurement procedure is for IVD manufacturers to split fresh human samples with a laboratory performing a reference measurement procedure and use the results obtained from this comparison to align the calibration of commercial systems (32).

The availability of a secondary commutable reference material, intended for direct calibration of routine methods, is critical for effective implementation of creatinine standardization (Figure 1). With this aim in mind, NIST has quite recently prepared a new serum-matrixed creatinine reference material, designated SRM 967 (2). This material is a fresh-frozen pooled human serum prepared according to Clinical and Laboratory Standards Institute (CLSI) guideline

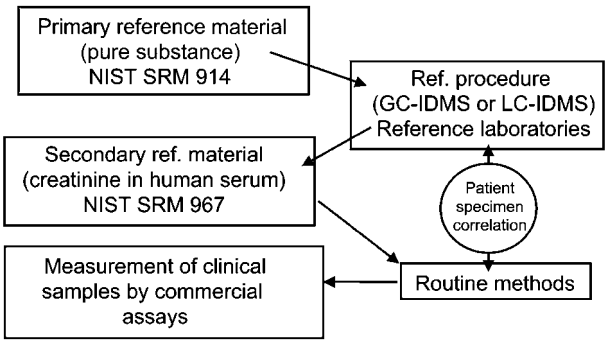

Figure 1 The reference measurement system for creatinine.

C37-A (33). Two concentration levels have been prepared and the creatinine values [0.75 and 3.92 mg/dL (67 and 346 μmol/L)] were assigned by NIST with the GC-IDMS and LC-IDMS reference methods. Considering its characteristics, the new material is expected to be commutable with native human sera. Commutability of SRM 967 with native human serum samples using a variety of routine creatinine measurement procedures and reference methods will soon be experimentally validated.

Recently a re-stated MDRD equation based on creatinine values traceable to an IDMS reference method was developed (Table 1) (34). The new IDMS-traceable MDRD equation is to be used only with standardized creatinine results.

Given the resources now available, it is time for all IVD manufacturers to establish calibrations that are traceable to the reference system, and for clinical laboratories to implement these standardized assays together with the revised GFR-estimating equation appropriate for use with zero-biased routine methods.

The current situation

Although standardization may seem easy in principle, implementation of a plan to introduce standardized creatinine measurement procedures and the IDMS-traceable MDRD GFR-estimating equation can be complicated because the suggested steps must be recognized as sound by all those involved in measuring creatinine and estimating GFR.

In the European Union the implementation of calibration traceability in Laboratory Medicine to available higher-order reference measurement procedures and reference materials is already mandatory by law

Table 1 Isotope dilution mass spectrometry-traceable MDRD study four-variable equation for estimating the glomerular filtration rate (GFR).

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

Serum creatinine values are expressed in mg/dL. If creatinine values are expressed in μmol/L, divide the values by 88.4 before introducing them into the equation. This equation is only for use with creatinine results from methods that have been calibrated to the reference system for creatinine.

(35). Internationally, we are in a transition period in which some manufacturers have already recalibrated their creatinine assays to IDMS worldwide. However, some manufacturers sell kits with different calibrations in Europe compared to other parts of the world, and some manufacturers still maintain old calibrations and will recalibrate with the introduction of new reagent lots. This confounding situation clearly emerges upon examination of data from recently performed external quality assessment surveys.

In 2002, the International Measurement Evaluation Program-17 survey of more than 800 laboratories in 35 countries demonstrated almost universal overestimation of serum creatinine in a serum pool with an IDMS certified concentration of 0.84 mg/dL (74 μmol/L) (36). Of the 14 method groups, 11 demonstrated significant positive bias compared with the reference value, typically varying between +10% and +15%. In 2003, the College of American Pathologists survey of 5624 predominantly North American laboratories found similar overestimation of serum creatinine by all but one IVD manufacturer's routine methods in an off-the-clot serum pool with a GC-IDMS measured concentration of 0.90 mg/dL (80 μmol/L) (24). A more recent (December 2005) national proficiency study involving predominantly North American clinical laboratories demonstrated that, of the five major manufacturers in the US market, one had values aligned to IDMS and four were biased high at various concentration levels (WG Miller, personal communication). In spite of European Directive 98/79/EC on IVD medical devices, the situation appears to be no different in Europe. In a recent, still unpublished study involving 172 laboratories from six European countries under the auspices of the European Community Confederation of Clinical Chemistry and Laboratory Medicine (EC4), creatinine assays from four major manufacturers did not fulfill the traceability goal for results obtained in a human sample with creatinine concentration by GC-IDMS of 0.85 mg/dL (75 μmol/L). Collectively, these observations suggest that a large number of routine analytical systems for serum creatinine are still biased high and that further work is needed to achieve substantially improved accuracy in creatinine results with routine methods. The pending release by NIST of SRM 967 is expected to provide IVD manufacturers with an important tool to enable closure of this gap.

International initiatives

The National Kidney Disease Education Program (NKDEP) (http://www.nkdep.nih.gov/index.htm) is an initiative of the US National Institutes of Health designed to reduce the morbidity and mortality caused by kidney disease and its complications. The NKDEP Laboratory Working Group recently published recommendations for improving serum creatinine measurement (2). Briefly, IVD manufacturers should ensure optimal performance at 1.00 mg/dL (88 μmol/L) for existing and new methods, and ensure that comparable trueness and imprecision extend throughout the analytical measurement range. A desirable total error goal for creatinine measurement is to contribute a maximum 10% increase in the relative error of the estimated GFR. A figure relating bias and imprecision combinations that are consistent with this total error was included in the report (2). For example, a routine creatinine method with imprecision (including between-laboratory calibration variability) of $<8\%$ CV and bias (compared to an IDMS reference method) of $<5\%$ at creatinine concentrations ≥ 1.00 mg/dL (88 μmol/L) would achieve this total error goal.

Finally, IVD manufacturers must address analytical non-specificity of routine serum creatinine methods. Standardization of calibration does not correct for analytical interferences related to an assay's non-specificity. Establishing calibration traceability to the creatinine reference system will align the average performance of methods to each other, but will not substitute for improvement of suboptimal routine methods. To account for the sensitivity of Jaffe-based methods to non-creatinine chromogens, some manufacturers have adjusted the calibration to minimize the pseudo-creatinine contribution of plasma proteins, producing results more closely aligned to IDMS, but this strategy makes an assumption that the non-creatinine chromogen interference is a constant among samples, which is an oversimplification (37). Analytical non-specificity for substances found in individual patient samples can affect the accuracy of GFR estimates computed from serum creatinine values for any method, including the so-called ''compensated'' Jaffe methods (38).

The use of assays that are more specific for serum creatinine, such as those based on some enzymatic procedures, may provide more reliable estimated GFR values (13). Supporting the choice of more specific assays by clinical laboratories is one of the main tasks of the newly created IFCC Working Group on Standardization of GFR Assessment (WG-GFRA). Other major tasks are summarized in Table 2. All of these actions will coordinate to achieve the ultimate goal, which is to routinely report an accurate estimate of GFR in all pertinent clinical situations.

Table 2 Main tasks of the IFCC Working Group on Standardization of Glomerular Filtration Rate (GFR) Assessment (WG-GFRA).

- Educate laboratory professionals regarding the importance of assessing risk of chronic kidney disease through the appropriate use of the GFR-estimating equation, with the international dissemination of relevant documents and educational materials
- In cooperation with the U.S. National Kidney Disease Education Program, develop guidelines to coordinate global introduction of standardized creatinine measurements in conjunction with the appropriate GFR-estimating equation
- Prepare a recommendation for use of specific assays for routine creatinine measurements
- Establish a reference laboratory network for creatinine to assist manufacturers in validating traceability of their methods and External Quality Assessment Scheme organizers in targeting commutable control materials

References

1. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005;365:331–40.
2. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5–18.
3. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.
4. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39:S1–246.
5. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresch J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–100.
6. Flynn FV. Assessment of renal function: selected developments. Clin Biochem 1990;23:49–54.
7. Cohen EP, Lemann J. The role of the laboratory in evaluation of kidney function. Clin Chem 1991;37:785–96.
8. Swan SK. The search continues – an ideal marker of GFR. Clin Chem 1997;43:913–4.
9. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933–53.
10. Price CP, Finney H. Developments in the assessment of glomerular filtration rate. Clin Chim Acta 2000;297: 55–66.
11. Larsson A. Cystatin C: an emerging glomerular filtration rate marker. Scand J Clin Lab Invest 2005;65:89–91.
12. Stevens LA, Levey AS. Chronic kidney disease in the elderly – how to assess risk? N Engl J Med 2005;352: 2122–4.
13. Lamb EJ, Tomson CR, Roderick PJ. Estimating kidney function in adults using formulae. Ann Clin Biochem 2005;42:321–45.
14. Levey AS, Greene T, Kusek JW, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000;11: A0828.
15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–70.
16. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, et al. African-American Study of Hypertension and Kidney Disease. Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. Am J Kidney Dis 2001;38:744–53.
17. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002;39:920–9.
18. Wuyts B, Bernard D, Van Den Noortgate N, Van De Valle J, Van Vlem B, De Smet R, et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. Clin Chem 2003;49:1011–4.
19. Lamb EJ, Wood J, Stowe HJ, O'Riordan SE, Webb MC, Dalton RN. Susceptibility of glomerular filtration rate estimations to variations in creatinine methodology: a study in older patients. Ann Clin Biochem 2005;42:11–8.
20. Hallan S, Asberg A, Lindberg M, Johnsen H. Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. Am J Kidney Dis 2004;44: 84–93.
21. McKillop DJ, Cairns B, Duly E, Van Drimmelen M, Ryan M. The effect of serum creatinine method choice on estimated glomerular filtration rate determined by the abbreviated MDRD formula. Ann Clin Biochem 2006;43: 220–2.
22. Van Biesen W, Vanholder R, Veys N, Verbeke F, Delanghe J, De Bacquer D, et al. The importance of standardization of creatinine in the implementation of guidelines and recommendations for CKD: implications for CKD management programmes. Nephrol Dial Transplant 2006;21:77–83.
23. Seccombe DW, Tholen D, Jacobson BE. Standardization of creatinine: a pre-requisite for implementing the MDRD formula for the estimation of glomerular filtration rate (eGFR). Clin Chem 2005;51(Suppl):A44.
24. Miller WG, Myers GL, Ashwood ER, Killeen AA, Wang E, Thienpont LM, et al. Creatinine measurement: state of the art in accuracy and inter-laboratory harmonization. Arch Pathol Lab Med 2005;129:297–304.
25. Panteghini M, Forest JC. Standardization in laboratory medicine: new challenges. Clin Chim Acta 2005;355: 1–12.
26. Siekmann L. Measurement of creatinine in human serum by isotope dilution mass spectrometry. J Clin Chem Clin Biochem 1985;23:137–44.
27. Welch MJ, Cohen A, Hertz HS, Ng KJ, Schaffer R, Van Der Lijn P, et al. Determination of serum creatinine by isotope dilution mass spectrometry as a candidate definitive method. Anal Chem 1986;58:1681–5.
28. Stöckl D, Reinauer H. Candidate reference methods for the determination of target values for cholesterol, creatinine, uric acid and glucose in external quality assessment and internal accuracy control. I. Method setup. Clin Chem 1993;39:993–1000.
29. Stokes P, O'Connor G. Development of a liquid chromatography-mass spectrometry method for the high-accuracy determination of creatinine in serum. J Chromatogr B 2003;794:125–36.
30. Séronie-Vivien S, Galteau MM, Carlier MC, Hadj-Aissa A, Hanser AM, Hym B, et al. Impact of standardized calibration on the inter-assay variation of 14 automated assays for the measurement of creatinine in human serum. Clin Chem Lab Med 2005;43:1227–33.
31. Miller WG, Myers GL, Rej R. Why commutability matters. Clin Chem 2006;52:553–4.
32. Clinical and Laboratory Standards Institute. Metrological traceability and its implementation; A report. CLSI document X5-R. Wayne, PA: CLSI, 2006.
33. Clinical and Laboratory Standards Institute. Preparation and validation of commutable frozen human serum pools as secondary reference materials for cholesterol measurement procedures; Approved guideline. CLSI document C37-A. Wayne, PA: CLSI, 1999.
34. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek J, et al. Expressing the MDRD study equation for estimating GFR with IDMS traceable (gold standard) serum creatinine values. J Am Soc Nephrol 2005;16:69a.
35. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Off J Eur Communities L 1998;L331:1–37.
36. Örnemark U, Van Nevel L, Smeyers P, Harper C, Taylor PD. The international Measurement Evaluation Program IMEP-17. Trace and minor constituents in human serum. EUR 20694 EN. Report to participants. Part 2: Method-

ology and quantity specifications. www.imep.ws. Accessed June 12, 2006.
37. Junge W, Wilke B, Halabi A, Klein G. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffé method. Clin Chim Acta 2004;344: 137–48.
38. Khatami Z, Dey D, Handley G, Klein G, Nagel R, Becher D. In the name of traceability. Author's reply. Ann Clin Biochem 2005;42:162–3.