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Opinion Paper

Focusing on the clinical impact of standardization of creatinine measurements: a report by the EFCC Working Group on Creatinine Standardization

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Abstract

The recent campaign for standardization of creatinine measurements has been promoted to allow the widespread use of formulas for estimating the glomerular filtration rate (GFR). However, studies on trueness verification and measurement interferences still show disappointing interassay variation of serum creatinine results. Creatinine recalibration has major clinical consequences. In particular, in pediatrics where reference ranges for serum and plasma creatinine are low, calculation of the GFR is problematic when based on alkaline picrate methods because of method non-specificity and the lack of appropriate GFR estimating formulas. Therefore, enzymatic creatinine assays are preferred. In the near future, cystatin C might offer an interesting alternative for GFR estimation. For the calculation of drug doses, the Modification of Diet in Renal Disease study formula generally offers reliable data. However, attention has to be paid to the elderly. Also, the calculation of the Model for End-Stage Liver Disease score, which is used to prioritize patients for liver transplantation, may significantly be influenced by recalibration of creatinine assays. Creatinine restandardization may also affect the current guidelines for referral of chronic kidney disease patients to nephrologists.

Keywords: analytical error; creatinine; cystatin C; drug dose calculation; glomerular filtration rate.

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Introduction

Efforts to improve the identification and management of patients with chronic kidney disease (CKD) are based on the implementation of more accurate means for assessing kidney function and kidney damage at an early clinical stage (1). In this respect, standardization of serum creatinine measurements is very important because of the central role of this biomarker in the assessment of renal function [e.g., for the calculation of creatinine clearance, a parameter largely determined by glomerular filtration rate (GFR), and the use of creatinine values for estimation of GFR (2)]. Accurate and precise estimations of GFR can be obtained using equations that empirically combine all of the average effects from biological factors that affect serum creatinine concentrations in serum, apart from GFR (3). The currently recommended estimation equation for identifying and monitoring patients with CKD has been developed from the Modification of Diet in Renal Disease (MDRD) Study (4, 5). Assays not calibrated to be in agreement with the kinetic alkaline picrate method, used in this study, introduce a source of error into GFR estimates. More recently, a new formula, named the CKD Epidemiology Collaboration (CKD-EPI) has also been introduced (6) which provides a more accurate GFR estimation for patients with GFR values between 60 and 90 mL/min.

Analytical issues

The European In Vitro Diagnostics directive (7) requires traceability for about 80 analytes, including creatinine. Industry should make their methods traceable to the reference methods and materials. The National Kidney Disease Education Program (NKDEP), the College of American Pathologists (CAP), and the National Institute for Standard and Technology (NIST) have collaborated to prepare a serum-creatinine reference material (NIST 967) with demonstrated commutability with native clinical specimens in routine methods. These materials are value-assigned with the gas chromatography-isotope dilution mass spectrometry (GC-IDMS) and liquid chromatography (LC)-IDMS reference measurement procedures (8). Nearly all clinical laboratory methods are now expected to have calibration traceable to an IDMS reference measurement procedure. The MDRD Study equation used for estimating GFR in adults has been updated to use coefficients appropriate for such methods (9). Routine reporting of estimated GFR (eGFR) for adults based on an IDMS-traceable creatinine is becoming

the clinical standard for patient care (10). However, variability in creatinine results may still contribute to substantial uncertainty in estimating GFR (11).

Since Jaffe (12) only observed complex formation between picric acid and creatinine in an alkaline environment, and never described an analytical method, variation amongst Jaffe methods is broad (13). In particular for lower creatinine concentrations, values may differ significantly from the target value for the Jaffe and the dry chemistry methods (11). The total error budget was mainly consumed by the bias, and to a much lesser extent by within-laboratory variation. Disappointing results were obtained for the analytical bias of current creatinine methods. This bias is due to the analytical interference by pseudo-chromogens for the Jaffe group (14) and the calibration used in the dry chemistry method (11).

In the earliest methods, serum creatinine was assayed by reactions based on alkaline picrate after deproteinization or dialysis, which eliminated the pseudo-chromogen effect of proteins (2). Today, however, analyzers use untreated serum or plasma, making creatinine assays using alkaline picrate reaction prone to the so-called ''protein error'' (14). On average, this effect produces a positive difference of 27 μmol/L creatinine compared with enzymatic methods (14). Because urine contains relatively little or no protein, the protein error affects only creatinine determinations in serum or plasma. Therefore, creatinine clearance is underestimated when creatinine methods affected by protein error are used. The disappointing results of studies investigating interlaboratory variation for serum creatinine using commutable serum samples (15, 16) prove that, notwithstanding the stricter regulations, between-laboratory variation of Jaffe based methods has not decreased over the last decade, despite technical progress in laboratory automation. Despite the known limitations, methods based on the Jaffe reaction are still extensively used for measuring serum creatinine.

Clinical implications of creatinine standardization

Implementing traceability of serum creatinine assays to GC- or LC-IDMS leads to changes in clinical decision-making criteria currently used for serum creatinine concentrations and creatinine clearance, since calibration to an IDMS reference produces a decrease in serum creatinine values by 10%–30% for most methods. Particularly, the calibration changes may have a broad spectrum of clinical consequences because of the key role of creatinine values in many derived calculations and nomograms applied in routine clinical practice. In the present review, the clinical critical issues and the remaining problems due to creatinine restandardization are discussed.

Drug dose calculation

Estimation of creatinine clearance is a key element in the calculation of the correct dose of many drugs that are characterized by a narrow therapeutic index and renal elimination (17). The implementation of eGFR reporting and standardization of creatinine measurements has created some uncertainty and confusion concerning the assessment of kidney function for drug dosing adjustment (10). For many years pharmaceutical manufacturers have used the Cockcroft–Gault (CG) equation to estimate creatinine clearance as the basis for drug dose adjustment recommendations. There is no modified CG equation available for use with the IDMS-traceable creatinine results. Consequently, creatinine clearance estimated from the CG equation will be increased upon restandardization. Although CG estimation has been the traditional means of assessing kidney function, it has been subject to the variation in creatinine values that occurred before standardization. However, some experimental studies have demonstrated that creatinine clearance values obtained using restandardised values are closer to the gold standard for GFR determination (e.g., insulin, Cr^{51}-EDTA clearance) compared with previous values obtained by uncompensated Jaffe methods (14). Moreover, the original publication by Cockroft and Gault does not contain detailed information regarding standardization of the creatinine assay used. One should not ignore that the CG formula estimates creatinine clearance, which is not synonymous for GFR, since creatinine clearance is partly influenced by tubular secretion of the compound. In contrast, the MDRD and CKD-EPI formulas provide an estimate for GFR. Because the MDRD Study equation is relatively new, eGFR data is not part of drug safety information or package inserts approved by notified bodies. There is concern about dosing toxic drugs with narrow therapeutic indices, particularly the antineoplastic agent carboplatin. Some clinicians request back-calculation to a non-standardized creatinine which can then be used in the CG equation. However, the MDRD Study equation is superior to the CG equation in predicting kidney function in most people (18). CG equation estimates vary depending on the creatinine method used, which does not allow use of a single correction factor to back-calculate to the non-standardized value. Consequently, back-calculation appears to be unnecessary (19). Concordance for drug dosing recommendations based on measured GFR for renally cleared drugs was best for MDRD (88%) compared to the CG equation adjusted for ideal body weight (CGIBW) (82%) and CG (85%). Of the three estimating methods, the CG equation was the most likely to generate higher recommended drug dosages, and CGIBW was most the likely to generate lower recommended drug dosages. Overall concordance of recommended drug dosing was high (10). The MDRD produced recommendations that were lower than CG in 9% of the study population and higher in 10% when the CGIBW was used. Reliance on the CG as the sole method of estimating kidney function for drug dosing purposes does not appear to be supported by these data (19). Narva encourages the use of the MDRD equation for drug dosing adjustment in adults (10). However, some authors have argued that the use of factors and exponents for the mathematical transformation of serum creatinine results increases uncertainty, and therefore the MDRD-derived GFR values cannot be recommended as the basis for administration of drugs excreted by the kidneys (20). In contrast, implementation of the CKD-EPI formula (6) in place

of the MDRD formula will not have much clinical impact on this specific application since drug dose adjustment is rarely needed in patients with GFR > 60 mL/min.

However, special attention should be paid to the elderly. The MDRD formula has only been validated for patients between 18 and 70 years of age. The MDRD formula overestimates renal function as age increases. While the optimized CG equation underestimates renal function, this was of a smaller magnitude, consistent across age, and thus better suited for dose calculations in the elderly (21). Larger-scale studies using gold standard markers of renal function estimation are needed to determine the accuracy of MDRD in elderly patients. Patients with >50% discrepancies between MDRD and gentamicin clearance were, on average, 23 years older, 16 kg lighter, 5 cm shorter, and with serum creatinine 113 μmol/L lower than the population used to develop the MDRD equation (21). It is unreasonable to expect MDRD to accurately predict renal function in patients who possess markedly different characteristics compared with the population it was developed in. With the background of an ageing population in the developed healthcare systems, it is essential that the elderly are studied as a group within their own right (22). Therefore, it is important not to extend the use of MDRD to the age groups for which the formula has not been validated. The new CKD-EPI formula has been validated in a wider range of ages, and also seems to be more accurate in elderly patients (23, 24).

The NKDEP (25) has recently published an educational advisory on estimating kidney function for drug dosing purposes. The advisory encourages the use of MDRD or CG estimating equations and, when there is concern that estimated kidney function is not adequate for patient safety or there is a distinct difference in recommended dose between the two methods, suggests consideration of measured creatinine clearance or assessment of GFR by the clearance of exogenous compounds.

Recombinant erythropoietin is used as a supportive drug in the treatment of CKD. Reimbursement of erythropoietin for anemia in renal sufficiency depends on residual GFR (26), when anemia in patients with an eGFR <60 mL/min/1.73 m^2 is certified by a nephrologist as being of renal origin. It is clear that regulations should match with appropriate GFR calculating formulas in order to achieve proper decision-making processes.

GFR estimation in pediatrics

Creatinine restandardization should be a major concern in pediatrics due to the lower reference ranges for serum creatinine in infants and children (27, 28). For calculating GFR, this systematic positive bias has been greatly compensated by overestimation attributable to tubular secretion of creatinine, which is relatively more important in children (14). Although some Jaffe method manufacturers try to correct for the protein error through the use of a fixed compensation factor for the protein content in adults (14), this procedure overcorrects with pediatric samples because of the lower serum protein concentrations in children. This overcorrection produces inaccurate GFR estimates, especially in neonates and children. Compensating calibration in Jaffe assays to IDMS standards results in a underestimation of serum or plasma creatinine due to the lower reference values for total protein in younger children.

A recent specificity study has updated the non-specificity information for current creatinine assays (29). The interference by bilirubin and adult hemoglobin (Hb A) on serum creatinine measurements was <10% for most of the Jaffe and enzymatic methods. Children, particularly younger children, have lower albumin and IgG concentrations compared with adults. The small interference observed for the enzymatic methods supports the earlier statement from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Scientific Division recommending that more specific creatinine methods be adopted (30). Manufacturers have been successful in minimizing bilirubin and Hb A interference in most Jaffe and enzymatic methods (29). Updating the currently used estimation formulas for calculating creatinine clearance and GFR is far from easy.

For adults, an improved GFR-estimating equation based on serum creatinine values traceable to IDMS reference measurement procedures has been recently presented (9). In enzymatic creatinine methods, analytical non-specificity is largely eliminated (11). The lower enzymatic creatinine result (when the result has not been adjusted to Jaffe-like results) leads to a marked increase in creatinine clearance estimations because of the increased effect of tubular secretion on test results. The use of enzymatic assays emphasizes the relative proportion of tubular secretion of creatinine which makes serum or plasma creatinine lesser suited as a GFR marker in children. Thus, paradoxically, the analytical improvement makes creatinine less suited as a GFR marker in pediatric medicine (28). In individuals who have been administered cimetidine (a blocker of tubular secretion of creatinine), this effect on tubular secretion can be corrected. However, the cimetidine protocol (31) cannot be used on a wide scale.

For estimating GFR in children and infants, the Schwartz (32–34) and the Counahan–Barratt equations (35) are used. Both provide GFR estimates based on a constant multiplied by the child's height divided by the measured serum creatinine concentration. The values (SI units) for the constant used in both equations differ considerably: k = 38 (Counahan) and k = 48.7 (Schwartz) (28). Since these formulas were validated 30 years ago, reassessment of classical formulas for estimating creatinine clearance and GFR using modern creatinine assays is necessary. This will be difficult; compensated Jaffe results will be less suited than enzymatic methods as a basis of these calculations. The expression kL/[creatinine] (in which k is a constant and L the child's length) could theoretically be replaced by kL/[(creatinine; IDMS calibrated) + non-specificity correction] when using the new IDMS calibrated assays. However, this non-specificity correction shows variation (14) which increases the uncertainty of the estimation. As a result of restandardization, the formerly published Schwartz formula overestimates GFR. Like the original equation, the revised equation is based on height and creatinine measurements: with height measured in cm, a

calculation of 0.413 × (height/serum creatinine) (conventional units) or 46.67 × (height/serum creatinine) when creatinine is given in μmol/L, provides a good approximation to the eGFR formula. A newly developed chronic kidney disease in children (CKiD) study equation uses serum creatinine (Scr), blood urea expressed as nitrogen (BUN), and cystatin C (Cys C), plus height and gender, to eGFR, yielding the equation (36): GFR(mL/min/1.73 m^2) = 39.1 [height (m)/Scr (mg/dL)]$^{0.516}$ × [1.8/Cys C (mg/L)]$^{0.294}$[30/BUN mg/dL)]$^{0.169}$ [1.099](^{male})[height (m)/1.4]$^{0.188}$. The new equation gave better agreement with measured GFR than the updated Schwartz equation. Alternatively, the Lund-Malmö equation has been proposed, which was validated for both adults and children (37). It should, however, be taken into account that these formulas are only valid in combination with enzymatic methods with calibration traceable to an IDMS reference procedure. This updated Schwartz equation is theoretically suitable for use with methods for measuring creatinine that have similar performance and calibration traceability. However, as the majority of in vitro diagnostics manufacturers will choose for general solution based on a recalibration setup at the upper reference limit of an adult population, there is a risk for overcompensation in view of the differences in serum matrix. The updated Schwartz formula is the first pediatric GFR-estimating equation with coefficients suitable for use with IDMS-traceable creatinine methods. The Counahan equation was found to have nearly the same performance as the updated Schwartz equation (38).

Cys C has been proposed as a marker of renal function (27). However, advantages of Cys C over creatinine are not universally accepted (39). Cys C offers a promising alternative for calculating GFR in children, as only measurement in serum or plasma is required and better performance is observed in the blind range of creatinine (28). Formulas have been developed that allow reliable estimation of GFR based on Cys C (40). Unlike creatinine, serum Cys C reflects renal function in children independent of age, gender, height, and body composition (28). However, extra-renal conditions (e.g., upregulation in certain tumors, thyroid dysfunction) and pharmacological factors (e.g., glucocorticoid treatment) may influence the concentrations of serum Cys C (28). Moreover, international standardization for Cys C is still lacking. An IFCC working group is addressing Cys C standardization (41). GFR-estimating equations based on Cys C are currently limited to the laboratory method that was used to derive the equation. Current estimating equations will need to be revised to conform to standardized method calibration and to be validated in multicenter investigations.

Transplantation medicine

In transplantation medicine, the Model for End-Stage Liver Disease (MELD) Score has been shown to be the best predictor of short-term mortality for patients on the liver transplant waiting list (42). Consequently, the MELD Score (in which serum creatinine is one of the contributing parameters) is nowadays widely used to prioritize patients for liver transplantation: MELD Score = [0.957 × ln(serum creatinine; mg/dL) + 0.378 × ln(serum bilirubin; mg/dL) + 1.120 × ln(International Normalized Ratio) + 0.643) × 10 (if hemodialysis, value for creatinine is automatically set to 4.0 mg/dL).

Substantial and clinically relevant interlaboratory variation in the MELD Score has been reported (43). The mean difference in the MELD Score between the highest- and the lowest-scoring laboratory was 4.8. This variation was primarily caused by the INR. Also, the variation in creatinine measurements resulted in differences of up to three MELD points in a single patient (43). Thus, standardization of creatinine measurements with changes in the parameter results may affect the MELD Score calculation. Moreover, since albumin concentrations are usually low in these patients and bilirubin concentrations are very high, a considerable bias in the creatinine results may occur due to bilirubin and albumin interference (29, 44), depending on the compensation methods used for adjusting results to the IDMS reference standard method.

Epidemiological studies

As a result of creatinine restandardization, measured and calculated creatinine clearance values will increase, and the corresponding reference interval will be different. In an attempt to reduce late referral and to improve the care of patients with CKD, different organizations have issued guidelines on when to refer patients to the nephrologist (45). Most suggest referral of patients with a GFR below 60 mL/min/1.73 m^2, and demand referral if the GFR is below 30 mL/min/1.73 m^2. Important differences in classifications were obtained when different correction formulas for creatinine (the basis for GFR calculation) were used. Implementation of the current guidelines for referral of CKD patients to nephrologists may lead to overload of nephrology care capacities. Standardization of serum creatinine assays is an important issue before guidelines can be implemented in clinical practice (46).

Conclusions

Creatinine recalibration has major clinical consequences. In particular, in pediatrics where reference ranges for serum and plasma creatinine are low, calculation of GFR is problematic when based on alkaline picrate methods because of method non-specificity and the lack of appropriate GFR estimating formulas. Therefore, enzymatic creatinine assays are preferred. Implementing traceability of serum creatinine results to IDMS may need to change clinical decision-making criteria currently used for evaluation of serum creatinine and creatinine clearance values. When introducing serum creatinine calibration traceable to IDMS, laboratories need to communicate the following to healthcare providers:

1. the serum creatinine reference interval will change to lower values, calculations of eGFR to adjust drug dosages will be affected by decreased creatinine values;
2. limitations of the formulas for calculating GFR have to be taken into account. This effort must involve cooperation among laboratorians, clinicians, pharmaceutical companies, and professional organizations.

3. calculations of eGFR or creatinine clearance to adjust drug dosages may be affected by standardization of creatinine values.

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References

1. Panteghini M, Forest JC. Standardization in laboratory medicine: new challenges. Clin Chim Acta 2005;355:1–12.
2. Levey AS. Measurement of renal function in chronic renal disease. Kidney Int 1990;38:167–84.
3. Stevens LA, Levey AS. Clinical implications for estimating equations for GFR. Ann Intern Med 2004;141:959–61.
4. 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.
5. Levey AS, Greene T, Kusek JW, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. J Am Soc Nephrol 2000;11:A0828.
6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). Ann Intern Med 2009;150:604–12.
7. Dati F. The new European Directive on in vitro diagnostics. Clin Chem Lab Med 2003;41:1289–98.
8. Dodder NG, Tai SS, Sniegoski LT, Zhang NF, Welch MJ. Certification of creatinine in a human serum reference material by GC-MS and LC-MS. Clin Chem 2007;53:1694–9.
9. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Chronic Kidney Disease Epidemiology Collaboration. Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72.
10. Narva AS. Assessment of kidney function for drug dosing. Clin Chem 2009;55:1609–11.
11. Delanghe JR, Cobbaert CM, Galteau MM, Harmoinen A, Jansen R, Kruse R, et al. Trueness verification of actual creatinine assays in the European market demonstrates a disappointing variability that needs substantial improvement. An international study in the framework of the EC4 creatinine standardization working group. Clin Chem Lab Med 2008;46:1319–25.
12. Jaffe M. Ueber den Niederschlag welchen Pikrinsäure in normalen Harn erzeugt und ueber eine neue Reaction des Kreatinins. Z Physiol Chem 1886;10:391–400.
13. Hanser A-M, Hym B, Michotey O, Gascht D, Marchal A, Minery M, et al. Comparaison des méthodes de dosage de la créatinine sérique. Ann Biol Clin 2001;59:737–42.
14. Wuyts B, Bernard D, Van den Noortgate N, Van de Walle 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.
15. 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.
16. European Commission – Joint Research Centre, Institute for Reference Materials and Measurements (IRMM). Geel, Belgium: Institute for Reference Materials and Measurements, 2003.
17. Nagao S, Fujiwara K, Imafuku N, Kagawa R, Kozuka Y, Oda T, et al. Difference of carboplatin clearance estimated by the Cockroft-Gault, Jelliffe, Modified-Jelliffe, Wright or Chatelut formula. Gynecol Oncol 2005;99:327–33.
18. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459–66.
19. Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, Rodby R, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;54:33–42.
20. Kallner A, Khatami Z. How does the MDRD study equation compare with serum creatinine in routine healthcare? Anatomy of MDRD-eGFR. Scand J Clin Lab Invest 2008;68(Suppl 241):39–45.
21. Roberts GW, Ibsen PM, Schiøler CT. Modified diet in renal disease method overestimates renal function in selected elderly patients. Age Ageing 2009;38:698–703.
22. McMurdo M, Witham M, Gillespie N. Including older people in clinical research (editorial). Br Med J 2005;331:1036–7.
23. Aucella F, Guida CC, Lauriola V, Vergura M. How to assess renal function in the geriatric population. J Nephrol 2010;23 (Suppl 15):S46–54.
24. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol 2010;5:1003–9.
25. National Kidney Disease Education Program. http://nkdep.nih.gov (Accessed Dec. 2010).
26. Ferrari P, Xiao J, Ukich A, Irish A. Estimation of glomerular filtration rate: does haemoglobin discriminate between ageing and true CKD? Nephrol Dial Transplant 2009;24:1828–33.
27. Ceriotti F, Boyd JC, Klein G, Henny J, Queraltó J, Kairisto V, et al. IFCC Committee on Reference Intervals and Decision Limits (C-RIDL). Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem 2008;54:559–66.
28. Delanghe J. How to establish glomerular filtration rate in children. Scand J Clin Lab Invest 2008;68(S241):46–51.
29. Cobbaert C, Baadenhuijsen H, Weykamp CW. Prime time for enzymatic creatinine methods in pediatrics. Clin Chem 2009; 55:549–58.
30. Panteghini M, on behalf of the IFCC Scientific Division. Enzymatic assays for creatinine: time for action. Clin Chem Lab Med 2008;46:567–72.
31. Hellerstein S, Berenbom M, Alon US, Warady BA. Creatinine clearance following cimetidine for estimation of glomerular filtration rate. Pediatr Nephrol 1998;12:49–54.
32. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58: 259–63.
33. Schwartz GF, Gauthier B. A simple estimate of glomerular filtration in adolescent boys. J Pediatr 1985;106:522–6.

34. Schwartz GF, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 1984;104:849–54.
35. Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimates of glomerular filtration rate from plasma creatinine concentration in children. Arch Dis Child 1976; 51:875–8.
36. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–37.
37. Nyman U, Björk J, Lindström V, Grubb A. The Lund-Malmö creatinine-based glomerular filtration rate prediction equation for adults also performs well in children. Scand J Clin Lab Invest 2008;68:568–76.
38. Miller WG. Estimating equations for glomerular filtration rate in children: laboratory considerations. Clin Chem 2009;55: 402–3.
39. Dalton RN. Serum creatinine ad glomerular filtration rate: perception and reality. Clin Chem 2010;56:687–9.
40. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C – a new marker of glomerular filtration rate in children independent of age and height. Pediatrics 1998;101:875–81.
41. Blirup-Jensen S, Grubb A, Lindstrom V, Schmidt C, Althaus H. Standardization of cystatin C: development of primary and secondary reference preparations. Scand J Clin Lab Invest Suppl 2008;241:67–70.
42. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
43. Lisman T, van Leeuwen Y, Adelmeijer J, Pereboom IT, Haagsma EB, van den Berg AP, et al. Interlaboratory variability in assessment of the model of end-stage liver disease score. Liver Int 2008;28:1344–51 Comment in: Liver Int 2008;28:1325–7.
44. Parry DM. Use of single-value protein compensation of the Jaffe creatinine assay contributes to clinically significant inaccuracy in results. Clin Chem 2008;54:215–6.
45. National Kidney Foundation K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. Part 1. Executive summary. Am J Kidney Dis 2005;39(Suppl 1):S17–30.
46. 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.