A recent report by Schwartz and coworkers has described improved equations for estimating glomerular filtration rate (GFR) in children (1). The equations were developed with data collected from 349 children 1–16 years of age with GFRs of approximately 20–90 mL/min/1.73 m$^2$. The new equations were developed to meet the specific need for estimating GFR in this study group, but they have broader applicability for clinical practice. Estimated GFR (eGFR) is useful to classify chronic kidney disease and to make adjustments in drug dosage.

Changes in creatinine measurement procedures and calibration since the 1970s, when the original Schwartz equation to estimate GFR in children was published, have caused this equation to overestimate GFR compared with the measured GFR. The report by Schwartz and coworkers (1) presents a revision of the original Schwartz equation. Like the original equation, the revised equation is based on height and creatinine measurements, but the new equation uses creatinine as measured by an enzymatic method with calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure. This updated Schwartz equation should be suitable for use with clinical laboratory methods for measuring creatinine that have similar performance and calibration traceability. The updated equation now appears on the National Kidney Disease Education Program (NKDEP) Web page for calculating eGFR (http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_schwartz.htm).

A newly developed CKiD study equation uses serum creatinine, urea, and cystatin C, plus height and sex, to estimate GFR. The new equation gave better agreement with measured GFR than the updated Schwartz equation. Schwartz and coworkers compared the performance of the new CKiD equation with several other published equations that used creatinine, cystatin C, or both (1). Important observations were that large differences in eGFR were obtained with the various equations and that the use of coefficients derived from the CKiD participants improved the performance of previously published equations when they were applied to the CKiD group. These observations emphasize that estimating equations derived from a particular study group work best when applied in the context of the study participants’ demographics, their disease conditions, and the laboratory methods used to derive the formulas.

Laboratory concerns that can limit the suitability of an estimating equation for general clinical use include the standardization of the calibration and the specificity of routine measurement procedures. In addition, the more laboratory results that an equation uses, the more the cumulative uncertainty from each result can influence the eGFR value.

Creatinine measurement has been addressed by the Laboratory Working Group of the NKDEP, and nearly all clinical laboratory methods are expected to have calibration traceable to an IDMS reference measurement procedure during 2009. The Modification of Diet in Renal Disease Study equation used for estimating GFR in adults has been updated to use coefficients appropriate for such methods (2). The updated Schwartz formula (based on height and creatinine) is the first pediatric GFR-estimating equation with coefficients suitable for use with IDMS-traceable creatinine methods. The Coulahan equation was found to have nearly the same performance as the updated Schwartz equation (1).

The specificity of creatinine methods remains a concern, particularly for pediatric patients. Although both the enzymatic and Jaffe methods have known specificity limitations, albumin, IgG, and hemoglobin F have recently been reported to influence Jaffe methods but not enzymatic methods (3, 4). These substances are important considerations in pediatric patients. Children, particularly younger children, have
lower albumin and IgG concentrations than adults. The techniques used to correct for protein interference in Jaffe methods have primarily been directed to adult concentrations and can be less effective at the lower concentrations found in children. Because children have lower creatinine concentrations than adults at a given GFR value, the percent error in eGFR can be large, irrespective of the creatinine-based estimating equation used.

Urea does not have a formal standardization program. An IDMS reference measurement procedure and a primary reference material are available for calibration traceability. All contemporary clinical laboratory methods for urea are based on enzymatic procedures, and the specificity of these methods is generally regarded as adequate.

Cystatin C measurement procedures are available from several manufacturers, but calibration has not been standardized. Different methods are known to give different results, as is exemplified by the different reported GFR-estimating equations that use cystatin C measurements (1). A working group of the IFCC is addressing cystatin C standardization (5). A serum-based reference material is expected to become available in 2009. Manufacturers will then need time to establish traceability to the reference material and deploy recalibrated methods to clinical laboratories. Consequently, GFR-estimating equations based on cystatin C are currently limited to the laboratory method that was used to derive the equation.

Differences in standardization among clinical laboratory methods have contributed to GFR-estimating equations with different performance characteristics. Creatinine calibration standardization is becoming uniform, but the lack of specificity for some measurement methods, as noted above, remains an important problem for pediatric patients. Older equations that were derived with creatinine measurements before the recent introduction of calibration standardization need to be revised for use with current clinical laboratory methods.

Cystatin C calibration standardization is being addressed but remains a barrier to the general use of GFR-estimating equations that include cystatin C. Current proposed estimating equations, including the CKID equation, will need to be revised to conform to standardized method calibration when it becomes available and to be validated in multicenter investigations that include a range of demographic and clinical situations.

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