

History of GFR and practical issues related to implementation

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Although creatinine clearance has been the mainstay for estimating glomerular filtration rate (GFR) in laboratories for the past half-century, prediction equations based on serum creatinine and other routine serum analytes are now available which enable reporting of a calculated GFR using the Modification of Diet in Renal Disease equations.

These urine-free estimates of GFR can now be made available on routine serum chemistry requests in an automated manner without technologist interaction in contrast to earlier prediction equations, which required patient height or weight.

Issues in implementing calculated GFR relate to the choice of formulas, laboratory information system reporting, standardization of serum creatinine measurements and clinical application of these formulas to a range of population groups.

Recent guidelines by the National Kidney Education Program now provide some direction to laboratories for implementing these calculations, and efforts are now in progress to standardize serum creatinine measurements.

These efforts will hopefully improve the clinical utility of serum creatinine measurements and facilitate identification of patients with chronic renal disease in our aging population.

A review in acute^{care}testing.org in April, 2006 by Miller and fellow members of the Laboratory Working Group of the National Kidney Disease Education Program (NKDEP) discussed initiatives to standardize serum creatinine measurements and develop recommendations for estimating glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) equation.

Additionally, web-accessible guidelines are now available

from the National Institutes of Health for laboratories and instrument/reagent manufacturers to standardize creatinine measurements and calculate GFR [1]. Detailed guidelines from the NKDEP Laboratory Working Group are also now available [2].

National guidelines for the diagnosis of chronic kidney disease (CKD) from the UK (www.renal.org) and Australia [3] have appeared also.

This review will look at the history of GFR measurements based on endogenous creatinine clearance (CrCl) as well as calculated GFR (eGFR) and discuss some practical issues related to implementation, some of which are based on almost four years of reporting eGFR in our laboratory.

Historical

GFR can be measured by administration of exogenous substances. Markers such as inulin, isotopic and non-isotopic iothalamate, Cr-51 EDTA and iohexol have been used with clearance determined from serum kinetics using multiple blood draws or blood and timed urine measurements.

These procedures tend to be very labor-intensive both from an analytical and preanalytical perspective and costly to provide on a routine basis.

Clearance of endogenous substances, principally creatinine and urea, have thus been the mainstay in laboratories for the past half-century based on collecting both serum and a 24-hour urine sample.

Urea clearance is compromised by virtue of tubular reabsorption, which lowers urine urea excretion, leading to underestimation of clearance.

Additionally, urea is very sensitive to blood volume status. Creatinine clearance, on the other hand, is influenced by tubular secretion of creatinine, causing overestimation of GFR by 10-15 mL/min and significantly impacting the reliability of this test in patients with compromised renal function for GFRs in the critical 30-70 mL/min range.

Serum creatinine is also influenced by physiologic variables such as muscle mass (age-dependent, lower in women, higher in African-Americans) and diet (lower in vegans, higher with ingestion of cooked meats).

Early serum methods were also influenced by various drugs (cimetidine, cephalosporins) and endogenous metabolites (acetoacetic acid, bilirubin). Additionally, the vagaries associated with collection of a 24-hour urine sample and the resulting patient inconvenience has generated interest in finding means to estimate GFR from strictly serum measurements.

Finally, across-laboratory variability of creatinine clearance remains largely unknown. While proficiency-testing (PT) programs have focused on selected calculations such as LDL-cholesterol and free testosterone, PT providers have ignored performance standards for the calculation of creatinine clearance.

Accordingly, NKDEP guidelines for standardizing at least one of the creatinine specimen types, namely serum, are indeed timely.

“Urine-free” creatinine clearance and GFR estimates

The Cockcroft-Gault equation (**TABLE, Eq. 1**) for estimating GFR has been available from the mid-70s [4]. Likewise, clinical application using this equation and other urine-free estimates of creatinine clearance were examined more than two decades ago [5, 6].

However, Cockcroft-Gault (which is correlated to creatinine clearance rather than GFR) and similar equations frequently require either patient height and/or patient weight, metrics not readily available to laboratory staff without querying either the patient's medical record or those responsible for initiating a laboratory test.

Ideally, such information could be provided by the ordering staff electronically as a free-text comment, but compliance in our experience is poor.

The MDRD equations developed by Levey and coworkers [7] in 1999 provided the first real opportunity for laboratorians to routinely include calculation of a urine-free GFR estimate using metrics readily available to computerized labs based on age, gender and routine analytes such as creatinine, albumin and (TABLE, Eq. 2) in conjunction with all Renal Function and Comprehensive Metabolic Profiles.

This action was based on the finding that this equation gave the best agreement with iothalamate-measured GFR among all serum-based prediction equations [7]. Subsequently in 2002, Levey and coworkers proposed in abstract form the more familiar “simplified” or “abbreviated” 4-parameter MDRD equation [8] involving only creatinine (TABLE, Eq. 3), a formula that correlates well with the 6-parameter equation.

More importantly, the simplified equation accords the opportunity to apply a GFR estimate to all creatinine results rather than combinations of tests.

Laboratory implementation of eGFR

Method comparisons

Method comparison of eGFR with creatinine clearance and internal validation studies are useful as an educational tool and to facilitate buy-in among clinicians and laboratory staff.

Comparisons can be done by “mining” historical data from prior creatinine clearance worksheets. In doing so in our laboratory, several observations were apparent. First of all, MDRD GFR correlated well with creatinine clearance in the 30-60 mL/min range, but less well in the <30 mL/min range, likely due to overestimation of GFR by creatinine clearance at low levels. In the >60 mL/min range, MDRD GFR was significantly lower than creatinine clearance.

This trend reflects the finding that the MDRD formula is based on a patient population with compromised renal function and the equations considerably underestimate GFR in the normal range, underscoring the recommendation to simply report high MDRD values as “>60”.

Finally, outliers were evident where eGFR values were markedly higher than creatinine clearance on patients with relatively low 24-hour urine volumes and low 24-hour urinary creatinine excretions. This suggests an incomplete 24-hour urine collection and a falsely low creatinine clearance.

Additionally, several subjects had creatinine-clearance levels markedly higher than eGFR with an increased 24-hour urinary creatinine excretion, likely reflecting over-collection of urine.

Equation	GFR Estimate (mL/min/1.73m ²)	Ref. & Notes
1 Cockroft-Gault	= [Weight (kg) × (140 - age) / (72 × SCr)] × 0.85 (if female)	[4], a
2 6-Parameter Extended MDRD	= 170 × (SCr) ^{-0.999} × (Age) ^{-0.176} × (BUN) ^{-0.17} × (Alb) ^{+0.318} × 0.762 (if female) × 1.18 (if AfrAmer)	[7], b
3 4-Parameter Simplified MDRD	= 186 × (SCr) ^{-1.154} × (Age) ^{-0.203} × 0.742 (if female) × 1.21 (if AfrAmer)	[8]
4 IDMS-Traceable MDRD	= 175 × (SCr) ^{-1.154} × (Age) ^{-0.203} × 0.742 (if female) × 1.21 (if AfrAmer)	[2]
5 Pediatric GFR	= K × Height (cm) / SCr where K = 0.55 (Schwartz) or K = 0.43 (Counahan-Barrat)	[13]
(a) an estimate of creatinine clearance (and indirectly GFR)		
(b) Alb = albumin in g/dL using a bromocresol green method; BUN in mg/dL N		

TABLE: GFR prediction equations for serum creatinine (in mg/dL), patient age in years and ethnicity (African-American)

Choice of equations

The guidelines now focus primarily on the 4-parameter equation involving creatinine as the sole measured analyte. This original equation (Eq. 3) was based on creatinine measurements using the Beckman Synchron CX3 analyzer.

A new 4-parameter equation (**TABLE, Eq. 4**) based on standardization of creatinine measurements to isotope-dilution mass spectrometry (IDMS) has now been proposed in the NKDEP guidelines.

Laboratorians thus have to decide whether to 1) delay implementation of eGFR while awaiting vendor-initiated standardization to IDMS; 2) implement eGFR by adjusting calibration set points independently to an IDMS standard using external reference materials [2, 9], taking into account reporting of PT data with an appropriate peer group; or 3) as suggested in the current guideline [2] implement eGFR (using Eq. 3) even though the assay may not yet be standardized to IDMS.

Laboratory Information System (LIS) and reporting issues
Implementation of eGFR may impose some challenges in either reporting or LIS implementation:

1. Capability for exponentiation and IF-THEN logic for gender is required.
2. Can your LIS use age in a calculation? Our LIS is unable to use a demographic variable such as age in a direct calculation but does support Boolean logic. Our workaround was to use bracketed ages using the average patient age within a 5- or 10-year interval as part of a series of IF-THEN statements. This created a small bias of 1-2 mL/min in eGFR, which was considered a reasonable compromise.
3. Ability to suppress the calculation when age is <18 years. As noted, the MDRD equation has not been validated in a pediatric population. The original MDRD study [7] also did not include subjects >70 years although a subsequent study by Lamb using a chromium-51 EDTA reference method in subjects

from 69-92 years did find the MDRD calculation to be reliable and superior to measured creatinine clearance [10].

4. Calculation using creatinine results to two decimal places in mg/dL. Of concern is reducing roundoff error in estimating eGFR by having an additional decimal place available for creatinine in mg/dL. Although the guidelines also suggest reporting to two decimal places (in mg/dL), this decision should likely include clinician input.
5. eGFR reporting units. Although not intuitive, MDRD eGFR is correlated to a body-surface-area-corrected method. Additional body-surface-area calculations are not required. Identifying eGFR as a normalized calculation by incorporating the "1.73 sq. m" or "1.73 m²" in the reporting units is thus desirable.
6. Reference ranges. Current guidelines suggest reporting values >60 as simply a "greater than" value. This may also be used as the reference range with lower values reported numerically. Earlier NKDEP guidelines suggested using textual comments for the average GFR by age in decades based on Third National Health and Nutrition Examination Survey [11].
7. Ethnicity variable. Use of the MDRD equation for Caucasians will give a falsely low eGFR for African-Americans; accordingly reporting of two eGFRs has been proposed as ethnicity is rarely available. This may require two textual comments displaying eGFR for each ethnicity, or alternatively having two independent result fields with different calculations for each ethnicity. Laboratorians will need to weigh the merits of having multiple textual comments for ethnicity (and possibly reference ranges) vs. possible information overload on cumulative reports when displaying serial data for such a frequently-ordered analyte as creatinine, particularly for an LIS which generates the same repetitive comments for each serial result. Accordingly, clinician feedback regarding the reporting format is essential.

8. Inpatients vs. outpatients. In our 400-bed trauma center, we have had no clinician objections to reporting of inpatient eGFR during the past several years. In facilities with transplant services, however, the utility of eGFR in patients with rapidly changing renal function remains unclear and suppressed reporting may be desirable.
9. Annual authentication of formulae (College of American Pathologists accrediting requirement). The NKDEP website [1] provides calculators for verification of calculations.

Should we still perform measured creatinine clearance

A 24-hour urine collection and a conventional measured creatinine clearance is preferred in the following patient groups [12]:

- Exceptional dietary intake (vegan, creatine supplementation, high meat intake)
- Muscle mass abnormalities (malnutrition, amputation, muscle wasting)
- Rapidly changing renal function
- Before starting dialysis
- Children and pregnant women

In our laboratory, we continue to provide measured creatinine clearance but the availability of eGFR has significantly impacted on the volume of creatinine clearance requests, decreasing some 60 % currently from a peak volume of 2400 requests annually in 2001.

Issues with eGFR

Concerns with eGFR relate to three major issues: 1) lack of standardization of creatinine measurements as addressed in a prior acute-care-testing.org review; 2) limitations of the abbreviated MDRD prediction equation in particular population groups; and 3) clinical limitations of creatinine as a metric.

Regarding subpopulations, GFR estimation in pediatric patients is a concern. A recent guideline suggests the

equations (**TABLE, Eq. 5**) of Schwartz or Counahan-Barrat [13].

Underrepresentation of certain ethnicities remains an on-going concern both on a national and international level [3]. Of significant concern is the applicability of MDRD GFR in the general population with minimal renal involvement.

Rule and colleagues note that the abbreviated MDRD GFR will classify 4 % of the US population as having an eGFR of <60 mL/min, giving rise to a disproportionately high incidence of renal disease [14].

Since MDRD GFR was developed from a population with chronic renal disease, they further argue that healthier subjects may have more muscle mass than subjects with chronic renal disease, resulting in a higher serum creatinine level at the same GFR.

To address this concern, an alternative prediction equation has been proposed [15] using a mix of subjects consisting of healthy kidney donors and subjects with chronic renal disease.

Finally, because of the dependence of creatinine on diet and muscle mass, interest has been generated in serum cystatin C and GFR prediction equations using this analyte.

Cystatin C is largely independent of age, gender and muscle mass, enabling use of a simple, "1-parameter" GFR prediction equation, and five versions of cystatin C-based equations now exist for at least one instrument system [16, 17].

Summary

In summary, laboratory estimation of GFR using serum creatinine and the MDRD equation is clearly an important first step in identifying patients with chronic renal disease and will continue to evolve with standardization efforts and broader experience with a variety of population groups.

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