Automated reporting of eGFR: a useful tool for identifying and managing kidney disease

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ABSTRACT

- Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula has been shown to provide unbiased and acceptably accurate estimates of measured GFR across a broad range of individuals with impaired kidney function.
- eGFR is superior to measuring serum creatinine (SCr) concentration alone, more accurate than other prediction formulas (such as Cockcroft–Gault) in the setting of reduced kidney function, and more practical and reliable under most circumstances than measuring urinary creatinine clearance.
- Routine eGFR reporting with requests for SCr, in concert with clinician education, has been shown to enhance the detection of chronic kidney disease (CKD), resulting in improved cardiac and renal outcomes for patients.
- eGFR has been shown to effectively identify individuals at increased risk of adverse drug reactions (even when SCr concentration is in the normal range). For most drugs prescribed in primary care and for most patients of average age and body size, drug dosage adjustments based on eGFR should be similar to those based on Cockcroft–Gault. eGFR should not replace Cockcroft–Gault for determining dosage adjustments for critical-dose drugs that have a narrow therapeutic index.
- eGFR has resulted in important spin-off benefits, such as standardisation of laboratory creatinine assays and enhanced public and clinician awareness of CKD.
- Clinicians should be aware of the strengths, weaknesses and appropriate use of eGFR. Considerable research effort is being directed towards further refinement of eGFR.

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There is a substantial body of evidence that the Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) provides improved understanding of a patient's renal function, which is the only valid reason for which a serum creatinine (SCr) concentration measurement should be requested. Here, we summarise this evidence and outline the benefits associated with automated reporting of eGFR.

Accuracy of eGFR across a range of individuals

MDRD eGFR has been demonstrated to provide unbiased and acceptably accurate estimates of measured GFR across a broad range of individuals with impaired kidney function. The performance characteristics of different GFR-estimating formulas, compared against radioisotopically measured GFR, were comprehensively reviewed in the CARI (Caring for Australasians with Renal Impairment) guidelines in 2005.[1] The guidelines concluded that

> the current evidence suggests that the abbreviated MDRD formula is the best available equation for automated laboratory reporting of eGFR, based on its extensive validation in over 8000 subjects against appropriate GFR reference methods, its demonstrated superior precision and accuracy compared with the Cockcroft–Gault equation in CKD [chronic kidney disease] patients with a GFR < 60 mL/min/1.73 m^2 and its greater practicality (weight information and body surface area correction not required).

The superior performance characteristics of eGFR compared with the Cockcroft–Gault formula have been demonstrated in an array of important patient subgroups, including older people,[2,3] renal transplant recipients,[4,5] patients with diabetes mellitus,[6,7] and obese individuals.[2] Recently, the CKD Epidemiology (CKD-EPI) Collaboration pooled patient data from 5504 individuals participating in six research studies and four clinical populations to compare eGFR with iothalamate clearance.[8] They observed that eGFR provided unbiased and reasonably accurate estimates of GFR below 60 mL/min/1.73 m^2 across a wide spectrum of clinical characteristics, including age (< 40, 40–65 or > 65 years), race, sex, presence or absence of diabetes mellitus, presence or absence of a renal transplant, and variable body mass index (BMI) (< 20, 20–25, 26–30 or > 30 kg/m^2). Similar observations were reported in a cohort of 2095 European adults in whom eGFR was found to be less biased, more precise and more accurate than the Cockcroft–Gault formula in nearly all subgroups defined by age, sex, BMI and GFR level.[2] In this study, eGFR was found to have high sensitivity (93%), specificity (89%), positive predictive value (89%) and negative predictive value (93%) with respect to identifying individuals with ^{51}Cr-EDTA GFR measurements below 60 mL/min/1.73 m^2.[2] The prevalence of low measured GFR in this study was 49%. Other studies have demonstrated that, in patients with reduced kidney function, the probability that the GFR estimate is within 30% of the measured GFR (P_{30}) is 80%–90% for eGFR and 60%–70% for the Cockcroft–Gault formula.[1,9,10] Thus, eGFR has clinically acceptable accuracy for detecting patients with truly impaired kidney function and is superior in this respect to the Cockcroft–Gault formula. Furthermore, low eGFR and proteinuria provide independent and additive information for stratifying any given patient's risk for CKD progression[11] and cardiovascular events.[12]

Nevertheless, it is important for clinicians to realise that there are certain populations or clinical settings in which both eGFR and the Cockcroft–Gault formula are inappropriate for estimating kidney function or where their use requires careful interpretation (Box). These include Aboriginal and Torres Strait Islander peoples, extremes of body size, and extremes of dietary protein intake. Concern has also been raised about the possibility that eGFR may overestimate CKD in older people (particularly women). While most studies show that GFR declines with age, accepting this as normal runs the risk of "normalising" a pathological state caused by age-related diseases rather than by age itself. A fall in GFR is not

an inevitable consequence of ageing, with the Baltimore Longitudinal Study of Aging showing that the decline in GFR with age can largely be accounted for by hypertension.[13] The impact of reduced GFR appears largely independent of age, although one large mortality study has demonstrated a weaker association of mortality in older people than in younger groups.[14] Consequently, the Australasian Creatinine Consensus Working Group concluded that it was premature to recommend age-related decision points for eGFR, but that it was appropriate to advise medical practitioners that, in people aged 70 years or older, an eGFR from 45 to 59 mL/min/1.73 m^2, when stable over time and unaccompanied by other evidence of kidney damage, may be interpreted as consistent with a typical eGFR for this age and unlikely to be associated with CKD complications.[15]

Enhanced detection of chronic kidney disease

Routine eGFR reporting, in concert with clinician education, has been demonstrated to enhance the detection of CKD in the community. A study in the United Kingdom demonstrated that automated laboratory reporting of MDRD eGFR with requests for SCr significantly increased the detection of CKD.[16] Although there was an initial increase (up to sevenfold) in nephrology referrals following the introduction of eGFR reporting, the establishment of a referral assessment program was shown to effectively ensure appropriate referral and to avoid exceeding the capacity of nephrology services. In Australia, results were recently published of a prospective audit of the impact of introduction of automated eGFR reporting and concomitant clinician education on the number, patterns and appropriateness of referrals of CKD patients to a tertiary institution, a regional (secondary) hospital and a single private practice servicing a catchment population of about 1.3 million.[17] Automated eGFR reporting significantly increased the referral of patients with CKD (especially Stage 3 CKD) to nephrology services, and most patients were referred appropriately within the framework of published guidelines. There was a 60% greater absolute number of CKD patients being appropriately referred for nephrologist review in the 12 months following eGFR reporting compared with baseline, such that the intervention was clearly of net benefit. Importantly, the services were able to shoulder the additional workload without any significant increase in outpatient appointment waiting times. There are presently no randomised controlled trials that have evaluated the effect of automated laboratory reporting of eGFR on CKD detection.

Improved outcomes for patients

Timely detection and management of CKD using eGFR has been shown to result in improved cardiac and renal outcomes for patients. The presence of a reduced eGFR is associated with an increased risk of progression to end-stage kidney failure.[11] Furthermore, such patients are at least 20 times more likely to die from cardiovascular disease than to survive to the point of needing dialysis or kidney transplantation.[18] Treatment of CKD by renin-angiotensin axis blockade, blood pressure lowering, statin therapy and a number of other measures, including optimising glycaemic control in diabetic patients, has been convincingly shown in numerous randomised controlled trials to reduce the risk of kidney failure progression and cardiovascular disease by 20%–50%.[19-22] Although the impact of renin-angiotensin axis blockade on progression of renal disease in patients with a low eGFR but normal proteinuria is still uncertain, there is randomised controlled trial evidence that patients with eGFR values < 60 mL/min/1.73 m^2 derive a greater cardiovascular protection benefit from angiotensin-converting enzyme inhibitors than those with eGFR values ⩾ 60 mL/min/1.73 m^2, even in the setting of normal albumin excretion.[23,24] A non-randomised controlled trial of 52 diabetic patients in whom CKD was detected in primary practice on the basis of an abnormal routine eGFR report and/or proteinuria demonstrated that patients who were subsequently referred to a nephrologist exhibited better preservation of renal function than those who remained treated by only their family doctors.[25] Moreover, another study demonstrated that the establishment of primary care-centred disease management of CKD based on eGFR reporting led to significant and clinically important improvements in both cardiovascular risk factors (particularly blood pressure and lipid levels) and reduction in the rate of decline of renal function in 483 patients with Stages 4 and 5 CKD.[26] The effects on cardiovascular events (rather than just risk factors) were not reported, although the study would not have had adequate statistical power for this outcome measure.

Clinical situations where MDRD eGFR or Cockcroft–Gault formula results should be interpreted with caution

Situations where eGFR results may be unreliable or misleading

- Rapidly changing kidney function (eg, acute kidney failure)
- Dialysis-dependent patients
- Exceptional dietary intake (eg, vegetarian diet, high-protein diet, recent consumption of cooked meat, creatine supplements)
- Extremes of body size
- Diseases of skeletal muscle, paraplegia, those with increased muscle mass and amputees
- Severe liver disease
- Children (under 18 years)

Situations in which eGFR has not been validated or shown to have acceptable accuracy

- Aboriginal and Torres Strait Islander peoples
- Asian populations
- Maori and Pacific Islander peoples

MDRD = Modification of Diet in Renal Disease. eGFR = estimated glomerular filtration rate. ◆

Identification of patients at increased risk of adverse drug reactions

eGFR has been shown to effectively identify individuals at increased risk of adverse drug reactions (even when SCr concentration is in the normal range). In an Italian study, data on 11 687 older hospitalised patients were analysed to assess the relationship between eGFR and adverse drug reactions.[27] Concealed kidney failure, defined as an eGFR < 60 mL/min/1.73 m^2 in the presence of a normal SCr concentration (⩽ 106 μmol/L), was detected in 1631 patients (13.9%) and was associated with a highly significant 61% increased risk of adverse drug reactions to hydrosoluble drugs. This increased risk was not significantly different from that observed in individuals with overt kidney failure (defined by reduced eGFR and an elevated SCr concentration). Recognising patients with impaired renal function is an obvious condition for

appropriate dosing, and this study demonstrated that eGFR was highly useful for this purpose.

Use of both the Cockcroft–Gault and MDRD eGFR formulas for drug dosing mostly results in concordant prescribing recommendations, but a recent study suggested that potentially important differences in clinical decision making occurred in 21%–37% of patients.[28] However, it is not yet known whether the use of the Cockcroft–Gault formula or the MDRD eGFR for drug dosing results in superior clinical outcomes. The MDRD formula clearly provides a more reliable estimate of GFR than does the Cockcroft–Gault formula, although Cockcroft–Gault is currently considered optimal for drug dosing because most of the renal dosing recommendations are based on this formula. On the other hand, there are concerns about the variability in the recommended use of the Cockcroft–Gault formula with regard to incorporation of estimated ideal or actual body weight,[1] and the fact that the Cockcroft–Gault formula has not taken into account variations in SCr assays or been revised to account for the restandardisation of SCr assays in recent times. Most guideline groups have recommended using the Cockcroft–Gault creatinine clearance formula for drug dosing until more clinical studies with the MDRD eGFR formula are conducted, although the Australasian Creatinine Consensus Working Group,[15] a 2008 National Prescribing Service *RADAR* statement[29] and the British National Formulary (BNF 54) recommend that for most drugs in primary care and for most patients of average age and body size, dosage adjustments based on eGFR should be similar to those based on creatinine clearance. It is currently advised that MDRD eGFR should not replace Cockcroft–Gault for determining dosage adjustments for critical-dose drugs that have a narrow therapeutic index until more studies of eGFR are conducted in this area. Nevertheless, at the very least, the MDRD eGFR alerts treating doctors to the possibility of reduced renal function to allow the use of other estimates, if desired, for informing drug-dosing decisions.

Spin-off benefits

The introduction of automated laboratory reporting of eGFR has resulted in other important benefits, including providing the impetus for universal standardisation of creatinine calibration. Before eGFR reporting, calibration of SCr measurements was not standardised, such that there was substantial variation between laboratories.[9] This variability has affected all research and routine laboratories, adding uncertainty to any comparisons of study results or patient data for creatinine or derived formulas when the creatinine results were obtained from different assays.

The advent of automated laboratory reporting of eGFR has also stimulated considerable public and clinician awareness of CKD, as well as CKD research.

The eGFR is now an established feature of pathology reports in Australia and has a considerable evidence base to support its use as an unbiased and accurate measure of kidney function, to enhance the detection and timely management of unrecognised CKD. It is not intended as a general population screening tool for CKD, but to provide improved understanding of a patient's renal function. eGFR has acceptable sensitivity and specificity in most patients, although clinicians should be aware that eGFR may be misleading in certain populations or situations. Some areas require additional research, including validation of eGFR in certain ethnic populations, and comparison of patient-level outcomes for drug-dosing decisions based on eGFR versus Cockcroft–Gault.

Debate about eGFR is healthy and will help stimulate further research and clinician awareness of the strengths, weaknesses and appropriate use of the MDRD formula. Further refinements to estimating GFR are being eagerly sought, and validation of eGFR in Aboriginal and Torres Strait Islander peoples is currently underway. In the meantime, it is important not to let perfect be the enemy of good.

Competing interests

Gavin Becker was previously on the Board of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO).

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