eGFR — use beyond the evidence

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ABSTRACT

- The estimated glomerular filtration rate (eGFR) algorithm has some advantages over serum creatinine concentration for estimating GFR.
- There are a number of caveats around the use of eGFR, predominantly because it assumes subjects are of average body size and similar lean body weight.
- eGFR has not been validated as a safe method of adjusting drug dosing, nor as a screening test for impaired renal function in the general population.
- eGFR has not been validated as a robust measure of kidney function in many groups (eg, older people, inpatients, differing racial groups, obese people).
- eGFR is inaccurate in many settings, such as in high, low or rapidly changing GFRs.
- Until evidence of safety and efficacy is provided, eGFR should not be used for calculating drug doses, and use of the Cockcroft–Gault formula or other validated methods should continue.

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Routine measurement of serum creatinine (SCr) concentration is one of the most frequently requested laboratory tests. Most of these requests are unrelated to chronic kidney disease (CKD) or even a specific investigation of renal function, but an abnormal result prompts consideration of these issues.[1,2] However, using SCr to diagnose renal impairment can be inaccurate, as the steady-state concentration is related to both muscle mass (production) as well as glomerular filtration rate (GFR) (elimination). Health authorities in several countries, including Australia, have recently tried to improve detection of renal impairment by advocating that each SCr measurement be accompanied by an estimated GFR (eGFR).[3] In Australia, the eGFR is derived from the four-parameter Modification of Diet in Renal Disease (MDRD) algorithm,[4] calculated using SCr and age and, if applicable, modified for sex (female) and African American race:

$$\text{eGFR (mL/min/1.73 m}^2) = 186 \times (\text{SCr}/88.4)^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if African American}]$$

There is no direct assessment of weight or lean body mass.

Two benefits were anticipated to arise from the introduction of this formula into routine practice. The first was that a single cut-off value for the diagnosis of CKD, in particular Stage 3 CKD (GFR of 30–59 mL/min), would be possible, enabling earlier detection than by measurement of SCr alone[5] and presumably enabling interventions that would reduce the incidence of end-stage renal failure. The second anticipated benefit was that the use of the eGFR would enable drug dosing to be optimised in people using drugs that are predominantly cleared unchanged by the kidneys.[6]

However, clinical concerns appear to be emerging with the use of this formula for both of these applications (Box). Additionally, although there was known to be an absence of comparative data supporting the benefit of MDRD eGFR over other methods of estimating GFR before the introduction of the formula, this has not been emphasised by the Australasian Creatinine Consensus Working Group, who devised the recommendations for automatic reporting of eGFR.[6] We believe that eGFR should not be used per se as a screening test or as a method of adjusting drug dosages until safety and efficacy evidence is provided.

Use of eGFR as a screening tool

If we examine the use of eGFR as a screening tool for detecting impaired renal function, two facts become evident. First, there is a paucity of data to evaluate whether use of eGFR would be helpful clinically or even cost-effective as a screening tool; and, second, the evidence with which to assess whether eGFR is better than the already available SCr in detecting changes in renal function over time is sparse.

In a screening situation, the sensitivity and specificity of the test, and hence the predictive values of positive and negative tests in the tested population (using the prevalence of the disease in the population where the test is being applied), need to be known. As these have not been measured, let alone rigorously analysed or meta-analysed as they have been for other estimates of GFR[7] (although we note that since acceptance of this article, the Cochrane Renal Review Group have registered a title for meta-analysis[8]), the value of algorithm-estimated GFR as a screening tool is uncertain. Screening an asymptomatic population for renal impairment ought not to be confused with early detection of renal disease in high-risk groups, for which there is some supporting literature. However, it should be noted that the Australian CARI (Caring for Australasians with Renal Impairment) guidelines state:

> There is currently no evidence to support the mass screening of the general population for kidney disease by urine dipstick, blood sampling or other means.[9]

Furthermore, the performance of any new test should be evaluated using a receiver operating characteristic (ROC) plot to measure the test accuracy in regard to sensitivity and specificity, both alone and, if possible, as compared with the existing test. Because eGFR underestimates renal function in people without known kidney disease, and because of the enormous variation between individuals, there is an overlap in eGFR values when testing patients with and without CKD. This compromises the ability of eGFR to separate these two groups, making the decision about whether someone does or does not have renal disease (ie, false positives) difficult.[10] False positives are acceptable in screening tests if simple confirmatory tests can distinguish between true and false positives, and if patients are unharmed while the uncertainty is resolved. The problem here is that the follow-up "test" may be referral to a renal clinic, which is a limited and expensive resource.[11] In addition, affected patients are labelled as having CKD, which may result in difficulty getting insurance and being prescribed medications, all on the basis of an unvalidated test. Until the natural history of CKD and the difference between the impact on GFR of normal ageing versus disease, and obesity versus undernutrition, are understood, the significance of an

abnormal eGFR and the subsequent management plan are not clear and have the potential to cause harm.

Lastly, the way in which eGFR has been accepted into use as a screening tool for CKD is in stark contrast to the methodical way in which Australia's breast, cervical and bowel cancer screening programs assessed and evaluated the evidence for screening (eg, <http://www.breastscreen.info.au/internet/screening/publishing.nsf/Content/pilot>). In effect, a screening test has been introduced without reference to criteria for screening programs.[12]

Use of eGFR to optimise drug dosing

The second issue arising from the eGFR recommendations[6] is the statement that eGFR enables drug dosing to be optimised. Again, there was no evidence of this at the time the test was introduced, despite claims that eGFR has recently been proven to be predictive in dosing enoxaparin safely.[13] In fact, this now much-quoted study (PROPHRE.75) was actually conducted to estimate the distribution parameters of antifactor Xa activity in patients aged >75 years.[14] Furthermore, enoxaparin clearance (which is also different to patient-related endpoints such as safety or efficacy) was found to be related to a number of variables, including body weight, consistent with standard teaching and other studies in this area.[15,16]

The Australasian Creatinine Consensus Working Group suggests that using eGFR for drug dosing is a safe practice, as it has been endorsed by a number of drug bodies.[13] In fact, the National Prescribing Service has recently released a *RADAR* statement advising of the risks of using eGFR for dose adjustment and stating that there is not yet enough evidence to support its safety.[17] The statement outlines a number of renally cleared drugs for which eGFR should not be used. However, the list of exclusive body sizes and "safe" drugs is very confusing to medical practitioners who may perform this dose-adjustment task infrequently.

The information on dose adjustment in the British National Formulary (BNF) is based on creatinine clearance. The BNF adds that eGFR is now being reported in the United Kingdom, yet:

> Although the two measures of renal function are not interchangeable, in practice, for most drugs and for most patients of average build and height, eGFR (MDRD) can be used to determine dosage … For potentially toxic drugs with a small safety margin and in some patients … the absolute glomerular filtration rate or creatinine clearance should be used or dosage should be adjusted according to plasma-drug concentration and clinical response.[18]

As most patients requiring dose adjustments in renal disease are not of average build and height, and in the absence of evidence, we cannot see how eGFR can ever be safe for this purpose. Of note, the Australian equivalent of the BNF (the *Australian medicines handbook*) has not endorsed eGFR as safe for dosing. The United States Food and Drug Administration similarly states:

> Currently, creatinine clearance is used widely in patient care settings as a measure of renal function. Consequently, it is more practical than most other alternatives as a criterion for adjusting dosage in outpatient and inpatient settings.[19]

While we recognise that the Cockcroft–Gault formula has limitations, it does at least take some measure of body size into account when estimating GFR. Other markers of GFR used in drug development and dosing recommendations (eg, 1/SCr or estimated creatinine clearance [CrCl] using either Cockcroft–Gault or some variant) are commonly reported for dosing and dose adjustment in product information, peer-reviewed drug pharmacokinetics publications, and medical texts. We surmise that the use of the term "GFR" in the eGFR formula, as opposed to a term such as "adjusted SCr" or "estimated CrCl", may be a major reason for the inappropriate interpretation of the use of this formula for drug dosing.

Additionally, the argument by the Australasian Creatinine Consensus Working Group that eGFR should be used for dosing because it is more easily available to general practitioners than the Cockcroft–Gault formula (ie, "better than nothing") is dangerous.[13] The Cockcroft–Gault formula *is* accessible to GPs as it is readily available in Medical Director (Health Communication Network, Sydney, NSW), a computer program widely used by Australian GPs. It is also a simple formula that can be added to analysers in the same way as eGFR, and, although it requires a weight measurement to be taken, it is arguably a test with greater overall prognostic value than eGFR. While it is possible to get a more predictive eGFR by calculating the patient's actual body surface area (BSA) and incorporating this into the eGFR, this extra calculation is not making it simpler for the clinician.

The eGFR is an evolving tool and it is possible that it might become the appropriate standard recommendation for calculating drug doses in the future. However, until it is known whether eGFR is superior or even equivalent to the Cockcroft–Gault formula for calculating drug doses,[20] Cockcroft–Gault or actual GFR measurements are the preferred methods for calculating any renally cleared drug dose.

Concerns with use of the MDRD eGFR

- eGFR has not been validated as a screening test for impaired renal function for the general population in Australia
- There are no specificity and sensitivity data to accompany the introduction of this test
- It is unknown where the capacity constraints are for patient follow-up after an "abnormal" eGFR result
- eGFR has not been studied to ascertain its safety or efficacy as a tool to aid in drug dosing

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

What is the place of eGFR?

Although there are many publications suggesting, for example, that both eGFR and the Cockcroft–Gault formula are statistically similar to "gold standard" methods such as ^{51}Cr-EDTA in diseased populations with normal body mass index (BMI) or moderately abnormal GFR,[21] we do not yet have good comparative data on how eGFR performs in other situations and populations or the population in which the MDRD algorithm was derived. We agree that SCr is a poor marker for GFR, but we are unsure if eGFR is better than the other estimations of GFR that are available to clinicians. Indeed, a recent dataset consisting of very large outpatient (N = 93 404) and hospitalised patient (N = 35 572) groups compared the diagnostic performance of eGFR and SCr to estimate the uncertainty and imprecision of eGFR. It demonstrated that adding the three factors in the MDRD algorithm (age, sex and race) to SCr did not improve on the measurement of SCr as a method of detecting impaired renal function — in fact, it was found to have inferior performance![22] The combined uncertainty of the measured

values for eGFR was estimated at 15%, about three times that of the SCr concentration results. Additionally, it was shown that the diagnostic capacity of eGFR, as it stands, had no added value compared with SCr — even the sex and age differences of the SCr concentrations in the dataset persisted after applying the MDRD eGFR algorithm.

So, if it performs no better than SCr in a diagnostic head-to-head comparison, why was the eGFR introduced into clinical practice? There are certainly theoretical reasons why it might have been expected to perform better than SCr. Adding age, sex and African American race to SCr adds population-derived surrogates for changes in muscle mass, directly related to creatinine production. Perhaps the poor performance of this formula in practice is due to the fact that the eGFR takes the SCr measurement back to a population mean BSA of 1.73 m^2, yet many subjects have a larger BSA as a result of a large BMI (ie, relatively less muscle as a percentage of total body weight). Yet the assumptions in the eGFR (correcting for the biological variation between population groups of sex, race and age) and standardising concentrations to that of a specific population group with a BSA of 1.73 m^2 could just as easily have been applied to the SCr (and called eSCr), and would give a standardised result with a universal reference range. Cut-off concentrations would identify the same group of patients as the eGFR, but without the same misinterpretation of what is actually being measured.

Lastly, there are known anthropometrical differences between Americans (as in the MDRD) and other populations, and between African Americans and other Africans. Do we know what happens in other racial groups, such as people of Asian descent, or northern versus southern Europeans? These groups are often intermixed with other racial groups and cannot be assumed to have a homogeneous muscle mass for a set age or sex. Of specific concern to the Australian health care system are the possible inaccuracies in the eGFR in calculating true renal function in Indigenous people, many of whom have renal impairment. Similarly, the formula does not adjust for those patients who are obese, who are known to have a greater or lesser muscle mass, older people, and patients with low GFRs.

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Competing interests

None identified.

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References

1 Rainey PM. Automatic reporting of estimated glomerular filtration rate — jumping the gun? *Clin Chem* 2006; 52: 2184-2187.

2 Levey AS, Stevens LA, Hostetter T. Automatic reporting of estimated glomerular filtration rate — just what the doctor ordered. *Clin Chem* 2006; 52: 2188-2193.

3 Mathew TH; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.

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 (2 Suppl 1): S1-S266.

5 Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139: 137-147.

6 Mathew TH, Johnson DW, Jones GRD; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. *Med J Aust* 2007; 187: 459-463.

7 Roos JF, Doust J, Tett SE, Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children — a meta-analysis. *Clin Biochem* 2007; 40: 383-391.

8 Doust J. Cystatin C versus serum creatinine or MDRD eGFR for estimating the glomerular filtration rate in adults and children (Cochrane review registered title). http://www.cochrane.org/reviews/en/topics/89_titles.html (accessed Jan 2009).

9 Thomas MC; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Prevention of progression of kidney disease: early detection of patients with kidney disease. *Nephrology (Carlton)* 2007; 12 Suppl 1: S37-S40.

10 Giles PD, Fitzmaurice DA. Formula estimation of glomerular filtration rate: have we gone wrong? *BMJ* 2007; 334: 1198-1200.

11 Chadban SJ, Ierino FL. Welcome to the era of CKD and the eGFR [editorial]. *Med J Aust* 2005; 183: 117-118.

12 National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. London: NSC, 2003. http://www.library.nhs.uk/screening/ViewResource.aspx?resID=59772 (accessed Dec 2008).

13 Mathew TH, Johnson DW, Jones GRD; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations [letter]. *Med J Aust* 2008; 188: 429-430.

14 Berges A, Laporte S, Epinat M. Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old. *Br J Clin Pharmacol* 2007; 64: 428-438.

15 Green B, Greenwood B, Saltissi D, et al. Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; 59: 281-290.

16 Sanchez-Pena P, Hulot JS, Urien S, et al. Anti-factor Xa kinetics after intravenous enoxaparin in patients undergoing percutaneous coronary intervention: a population model analysis. *Br J Clin Pharmacol* 2005; 60: 364-373.

17 National Prescribing Service. Automatic eGFR reporting — its role in screening for kidney disease and drug-dosing decisions. *RADAR*, 1 Aug 2008. http://www.nps.org.au/health_professionals/publications/nps_radar/issues/current/august_2008/egfr (accessed Dec 2008).

18 British National Formulary. What's new in BNF 54? Renal function and drugs. http://www.bnf.org/bnf/extra/current/450035.htm (accessed Jan 2008; no longer available).

19 Center for Drug Evaluation and Research. Guidance for industry: pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling. Rockville, Md: United States Food and Drug Administration, 1998. http://www.fda.gov/cber/gdlns/renal.pdf (accessed Dec 2008).

20 Faull R. Prescribing in renal disease. *Aust Prescr* 2007; 30: 17-20.

21 Harmoinen A, Lehtimaki T, Korpela M, et al. Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft–Gault and Levey (MDRD) formulas. *Clin Chem* 2003; 49: 1223-1225.

22 Kallner A, Ayling PA, Khatami Z. Does eGFR improve the diagnostic capability of S-Creatinine concentration results? A retrospective population based study. *Int J Med Sci* 2008; 5: 9-17.

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