Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

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ABSTRACT

- Since publication of the Australasian Creatinine Consensus Working Group's position statement in 2005, most Australasian laboratories now automatically report an estimated glomerular filtration rate (eGFR) (based on the Modification of Diet in Renal Disease [MDRD] formula) with results of serum creatinine tests in adults.
- Anecdotal evidence suggests that automatic reporting of eGFR helps to identify asymptomatic kidney dysfunction at an earlier stage and to develop rational and appropriate management plans.
- Changes to the measurement and calibration of serum creatinine assays and issues regarding implementation of eGFR in clinical practice led the Australasian Creatinine Consensus Working Group to reconvene in 2007.
- The recommendations contained here build on the original 2005 position statement and consolidate the role of eGFR in clinical practice.
- The Working Group recommends that the eGFR upper reporting limit be extended to 90 mL/min/1.73 m^2, with eGFR values above this amount being reported as "> 90 mL/min/1.73 m^2", rather than as a precise figure.
- The Working Group has concluded that it is currently premature to recommend age-related decision points for eGFR. However, it is appropriate to advise medical practitioners that, in people aged ⩾ 70 years, an eGFR in the range 45–59 mL/min/1.73 m^2, if stable over time and unaccompanied by other evidence of kidney damage, may be interpreted as consistent with a typical eGFR for this age group and is unlikely to be associated with chronic kidney disease-related complications.
- Pending publication of validation studies, the Working Group recommends that Australasian laboratories continue to automatically report eGFR in Aboriginal and Torres Strait Islander peoples and other ethnic groups.
- The Working Group supports the use of eGFR to assist drug dosing decision making in general practice.

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The Australasian Creatinine Consensus Working Group recommended in June 2005 that Australasian laboratories automatically report an estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula each time a serum creatinine test was requested.[1] Survey findings and anecdotal information indicate that the vast majority of laboratory reports now include an eGFR. In addition, standardisation of μmol/L as the unit for serum creatinine concentration has largely been achieved. The response of clinicians to the introduction of eGFR has been strongly positive, with easier identification of chronic kidney disease, better decision making for affected patients, and more appropriate referral patterns being identified as outcomes.

Issues that have arisen since the publication of the 2005 position statement include changes to the measurement and calibration of serum creatinine assays that have had implications for eGFR, questions about the use of eGFR in different ethnic populations (such as Aboriginal and Torres Strait Islander people), the use of eGFR for decisions on drug dosing, and the possible introduction of age-related eGFR decision points.

The Australasian Creatinine Consensus Working Group reconvened on 11 December 2006 to consider these issues. The Working Group consisted of 12 nephrologists and six pathologists nominated by the parent bodies of this process (the Australian and New Zealand Society of Nephrology, Kidney Health Australia, the Australasian Association of Clinical Biochemists, and the Royal College of Pathologists of Australasia). All recommendations contained in this position statement are endorsed by these organisations.

This revised statement should be read in conjunction with the original consensus statement (see Box 1 for a summary of the principal changes).[1] The recommendations in this document are in addition to and do not replace the original recommendations.

Recommendations

1. Measurement of serum creatinine concentration and consideration of the revised (MDRD "175") eGFR formula

Recommendation: The calculation of eGFR should be changed to use the MDRD "175" formula for assays aligned to the international reference method.

Since the original MDRD article[2] was published, there has been considerable focus on the variability in results derived from assays in routine use for measuring serum creatinine concentration. An international process of assay standardisation has been undertaken, led by the National Kidney Disease Education Program in the United States and supported by other national and international bodies.[3,4] Isotope dilution mass spectrometry (IDMS) has been accepted as the reference method, and diagnostic companies are producing revised assays to give results aligned to this method. As most assays in routine use in Australasia are variations of the non-specific Jaffe reaction,[5] this generally involves an adjustment for the expected effects of non-creatinine chromogens in an average sample. The results from IDMS-aligned assays are different from those derived from the assay used to establish the MDRD equation, and so a revised version of the equation has been published, known as the "175" formula:

The revised MDRD formula (the "175" formula)[6]

$$eGFR = 175 \times (S_{CR} \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ [if female]})$$

where MDRD = Modification of Diet in Renal Disease,[2] eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), S_{CR} = serum creatinine concentration (μmol/L), and age is expressed in years.

1 Comparison between original and revised recommendations: summary

Original key recommendations	Revised recommendations
An eGFR shall be calculated and reported with every request for serum creatinine concentration	No change
eGFR values over 60 mL/min/1.73 m^2 should be reported as "> 60 mL/min/1.73 m^2", rather than as a precise figure	eGFR values over 90 mL/min/1.73 m^2 should be reported as "> 90 mL/min/1.73 m^2", rather than as a precise figure
Automatic reporting of eGFR may include age-related reference intervals for people aged ⩾ 65 years	In the absence of agreed age-related reference intervals, eGFR values in the range 45–59 mL/min/1.73 m^2 in people aged ⩾ 70 years should be interpreted with caution. If no other signs of kidney damage (eg, proteinuria, haematuria) are present, a stable eGFR in this range may be consistent with typical GFR for this age and an absence of CKD-related complications
Drug dosing — no recommendation was made, but it was noted that "an uncorrected eGFR may be preferred for clinical use in some situations, such as drug dosing"	In most out-of-hospital settings, particularly general practice, where an eGFR (based on the MDRD formula) is on hand and no other measure of GFR is known or readily accessible, it is clinically appropriate to use eGFR to assist drug-dosing decision making
Use of eGFR in various ethnic populations — no recommendation was made, but it was noted that "specific clinical settings in which eGFR is not appropriate for use and GFR should be measured directly include . . . populations in which the MDRD equation is not validated (eg, Asian people) or in which validation studies have not been performed (eg, Aboriginal and Torres Strait Islander populations)"	Pending publication of validation studies, it is recommended that Australasian laboratories continue to automatically report eGFR in Aboriginal and Torres Strait Islander peoples and other ethnic groups

CKD = chronic kidney disease. eGFR = estimated glomerular filtration rate. MDRD = Modification of Diet in Renal Disease.[2] ◆

The Working Group has validated the revised equation using data from two local centres and recommends the introduction of this formula for laboratories using assays aligned to the IDMS international standard. Peake and Whiting[5] have evaluated the assays in common use in Australia against the reference preparation SRM 967 and shown that the majority of assays are acceptable by comparison with this standard. Revised versions of other assays are expected in 2007.

The change to the 175 formula leads to a fall in eGFR results of 5% at all creatinine concentrations if no change is made in the assay system. As this is a small change compared with the overall accuracy of the eGFR result (±30%), it is not recommended that laboratories necessarily inform all users at the time of implementing the new formula. However, laboratories are encouraged to communicate the change to nephrologists, as this modification may be significant for some patients being monitored closely over time. Any significant changes in creatinine results due to changes in the assays themselves would require notification to all doctors.

It is important to recognise that improvements in the trueness of assays for serum creatinine do not reduce the potential for assay interference. Peake and Whiting[5] have demonstrated the effects of common interfering substances such as albumin, glucose, pyruvate, bilirubin, haemoglobin F and cephalosporins (especially cefpirome) on a commonly used Jaffe creatinine assay, but the interferences are likely to be different for each manufacturer. Where interference is considered to be likely, the use of an enzymatic method may be better. Some biological influences on creatinine are not assay-related — for example, the effect of a cooked meat meal, which may cause a temporary increase of over 20 μmol/L in measured creatinine concentration that can last several hours.[7]

2. Extension of upper reporting limit of eGFR to 90 mL/min/1.73 m^2

Recommendation: eGFR values over 90 mL/min/1.73 m^2 should be reported as "> 90 mL/min/1.73 m^2" rather than as a precise figure.

The original recommendation, similar to that adopted in the United States, that eGFR values greater than 60 mL/min/1.73 m^2 should be reported as "> 60 mL/min/1.73 m^2" rather than as a numerical result was based on evidence available at the time (summarised in the original statement[1]). After considerable discussion, the Working Group agreed to recommend that Australasia now adopt the United Kingdom's approach,[8] which is for laboratories to report numerical values up to 90 mL/min/1.73 m^2, with results of over 90 mL/min/1.73 m^2 to be reported as "> 90 mL/min/1.73 m^2".

This decision took the following factors into account:

- There were some clinical situations in which knowing specific eGFR values in the range 60–90 mL/min/1.73 m^2 would be useful — for example, in providing earlier warning of declining eGFR and allowing trends over time to be monitored.
- The relative accuracy of eGFR compared with direct measurement of GFR was similar throughout the range 0–90 mL/min/1.73 m^2.
- Standardised creatinine assays would be likely to show better agreement with each other in the eGFR range 60–90 mL/min/1.73 m^2 than was the case with older assays.
- Advice would be offered to clinicians that further investigation was usually only required if the eGFR fell to < 60 mL/min/1.73 m^2. Clinical judgement could determine whether an eGFR in the range 60–90 mL/min/1.73 m^2 in a young adult required investigation.
- A substantial number of laboratories in some Australian states had already begun to report specific eGFR values up to 90 mL/min/1.73 m^2, which may have been a source of confusion and uncertainty among medical practitioners.

While it is commonly stated that the "normal range" for eGFR is > 90 mL/min/1.73 m^2, this does not reflect the distribution of eGFR values in the Australian community presenting to medical practitioners (Box 2). By the age of 40 years, the median eGFR in the Australian community is about 90 mL/min/1.73 m^2, and by the

age of 80 years, the median value is 70 mL/min/1.73 m^2. Thus, well over 50% of Australians aged over 40 years will have an eGFR of < 90 mL/min/1.73 m^2.

3. Age-related decision points for eGFR

Recommendation: eGFR values in the range 45–59 mL/min/1.73 m^2 in people aged ⩾ 70 years should be interpreted with caution. If there are no other signs of kidney damage (eg, proteinuria, haematuria), a stable eGFR in this range may be consistent with typical GFRs for this age group and an absence of chronic kidney disease (CKD)-related complications.

Age-related decision points have not been agreed for eGFR,[9] and the UK guidelines specifically state that "age-related reference intervals are not recommended".[8] While most studies show that GFR declines with age (Box 2), 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: the Baltimore Longitudinal Study on Ageing showed that the decline in GFR with age is largely the result of hypertension.[10] Although the impact of reduced GFR seems largely independent of age, one large study has demonstrated a weaker association between reduced GFR and mortality in people aged ⩾ 65 years than in younger people.[11]

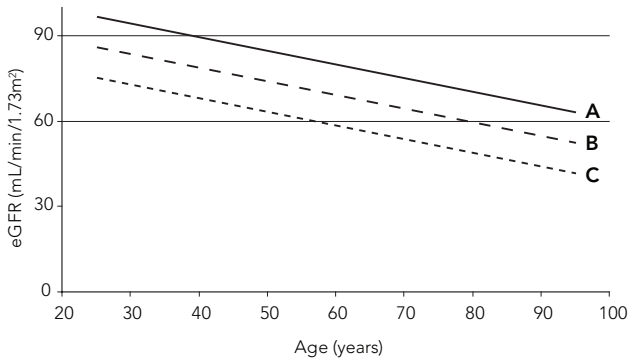
The Working Group concluded that, at this stage, it was premature to recommend age-related decision points for eGFR, but that it was appropriate to advise medical practitioners that, in people aged ⩾ 70 years, eGFR values in the range 45–59 mL/min/1.73 m^2, if stable over time and unaccompanied by other evidence of kidney damage, may be interpreted as typical for this age group and are unlikely to be associated with CKD complications. Importantly, this commonly found moderate reduction in eGFR in the elderly should always be considered when drug dosing decisions are being made about renally excreted drugs.

4. Reference intervals for serum creatinine concentration

Recommendation: Standardised reference intervals for serum creatinine concentration should be established when assays are IDMS-aligned. Separate reference intervals should exist for males and females.

The increased accuracy of serum creatinine concentration measurements and their alignment with IDMS that will progressively apply in most laboratories in Australasia allows the possibility of uniform reference intervals to be developed. The Working Group decided that, in view of the well recognised variation in serum creatinine concentration between the sexes, separate reference intervals for males and females should be implemented. The establishment of age-stratified reference intervals for those aged 17 years and under was considered desirable and should be encouraged. Although some data show that serum creatinine levels rise slightly in many older Australians, it was agreed at this stage not to reflect this in serum reference intervals, because of the difficulty of establishing reliable intervals in older age groups and the fact that changes in kidney function will be identified by the use of the eGFR.

2 Relationship of estimated glomerular filtration rate (eGFR) to age*



*A: median (50% of subjects have eGFR above this line); B: 80% of subjects have eGFR above this line; C: 97.5% of subjects have eGFR above this line. These reference lines are derived from over 300 000 presentations to a large private pathology service, with exclusion of creatinine results lying outside a Gaussian distribution for each age decade (personal communication, Ken Sikaris, Chemical Pathologist, Melbourne Pathology Service, VIC). ◆

5. The use of eGFR in various ethnic populations

Recommendation: Pending publication of validation studies, Australasian laboratories should continue to automatically report eGFR in Aboriginal and Torres Strait Islander peoples and other ethnic groups.

The original MDRD formula contains a factor to be applied to African Americans, raising the possibility that other variations in the formula may be required for optimal performance in different ethnic groups. The publication of our initial consensus statement was interpreted by some to discourage the use of eGFR (MDRD) in Aboriginal and Torres Strait Islander peoples and led to correspondence in this Journal.[12] Our intention had simply been to highlight that in certain populations the MDRD formula for estimating GFR had not been validated, and that in those populations caution should be exercised in its application. To date, there have been no studies validating the use of the MDRD formula in any specific non-Caucasian groups in Australia or New Zealand.

It was not intended to deny the advantages of automatic reporting of eGFR to any section of the community. The sparse evidence available suggests that Indigenous Australians do not differ from non-Indigenous Australians in fat-free mass, and that a correction factor is unlikely to be required. There are also difficulties associated with the alternatives to an automatically calculated eGFR (eg, serum creatinine concentration alone, the Cockcroft–Gault formula, or formal measurement of creatinine clearance).

The real need is for the eGFR formula to be validated in Aboriginal and Torres Strait Islander peoples, Māori, Pacific Island peoples and other groups so that a firm basis for its use can be established. Until this evidence is available, it appears clinically appropriate for the eGFR to be calculated and used prudently in any racial group. Automatic reporting of eGFR is currently in regular use throughout Australia and New Zealand and has been reported to assist in clinical management of Aboriginal and Torres Strait Islander peoples. A validation study in Aboriginal and Torres Strait Islander peoples comparing eGFR to a "gold" standard GFR has been initiated.

6. The use of eGFR for adjusting drug dosing in patients with reduced kidney function

When adjusting drug doses for people with CKD, decision making is enhanced by an assessment of kidney function that takes into account both serum creatinine concentration and GFR.

Recommendation: In most out-of-hospital settings, particularly general practice, where an eGFR (MDRD) result is available and no other measure of GFR is known or readily accessible, it is clinically appropriate to use the eGFR to assist drug-dosing decision making in patients with CKD. However, when amending the dosing of critical-dose drugs, particularly in the hospital setting, it is important to adhere to published recommendations, which usually involve the use of the Cockcroft–Gault formula to estimate eGFR, or to measure creatinine clearance.

The original consensus statement noted that drug-dosing adjustments for patients with reduced kidney function are currently based mainly on creatinine clearance determination or the Cockcroft–Gault formula and that these results may differ significantly from the eGFR. Attention was also drawn to the eGFR value being corrected for body surface area and thus needing to be "uncorrected" if an actual GFR value was required for drug-dosing decisions in people of large or small body size. This cautious approach appeared justified at the time and has been emphasised in a recent publication.[13] A stricter approach has been taken in the *Australian medicines handbook*: "Be aware that the estimate of glomerular filtration rate (eGFR) automatically reported with electrolyte test results is not appropriate for use in dosage calculations."[14] As new drugs are introduced into clinical practice, we can expect to see a progressive increase in the use of eGFR as a guide to dose adjustment for patients with CKD. In the interim, the question arises as to whether it is appropriate to use eGFR for dose adjustment.

After a review of recent publications, the Working Group agreed that the present state of drug-dosing adjustment in patients with reduced kidney function can be summarised as follows:

- In most clinical situations (particularly in general practice), the prescriber is unaware of the patient's kidney function. Few general practitioners or specialists routinely calculate the GFR using the Cockcroft–Gault formula before prescribing. The availability of an eGFR value on a general chemistry report has increased the frequency with which practitioners have access to a measure of GFR before prescribing.
- The published recommendations are potentially confusing, with variation in terminology of kidney dysfunction and different decision making points for the same drug.[15]

There is variability in the recommended use of the Cockcroft–Gault formula with regard to use of estimated ideal body weight from height and build, and there has been no update to the formula to account for restandardisation of creatinine assays.

When dose adjustments are indicated because of reduced GFR, for most drugs the dose change is coarse (eg, halving the dose or changing to a once-a-day regimen from twice-a-day). This highlights the wide therapeutic index of these agents and indicates that assessment of GFR for this purpose need not be precise for safe and appropriate prescribing.

For critical-dose drugs requiring dose adjustment for reduced GFR, particularly in a hospital setting, careful attention to an accurate GFR to guide decision making is desirable. In such cases, the use of the Cockcroft–Gault formula or another measure of kidney function — rather than eGFR (MDRD) — is appropriate. In all situations involving critical-dose drugs, where drug-level monitoring is available the results should be used to guide dosing decisions.

Studies in general practice of the clinical value in drug dosing of using eGFR determined by MDRD compared with other formulas (eg, Cockcroft–Gault) and with measured creatinine clearance are urgently needed.

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Conclusion

The introduction of automatic reporting of eGFR each time a test for serum creatinine concentration is requested has increased the awareness of significant kidney dysfunction in clinical practice. It appears that eGFR is here to stay — it is already the basis of CKD staging and clinical management and of changes to the International classification of diseases (ICD-10-AM) coding of CKD that are currently under review. Further studies assessing the outcomes and impact of automatic reporting of eGFR are highly desirable.

One outcome of the recent focus on serum creatinine concentration and its use for eGFR determination has been the commitment to improve the accuracy of laboratory measurement and the reduction in the variability previously seen in Australasia and overseas. Undoubtedly, refinements in the measurement of serum creatinine concentration and the eGFR formula will continue to occur, leading to increased accuracy and thus improved application of this important new tool.

Competing interests

None identified.

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References

1 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.
2 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461-470.
3 Myers GL, Miller GW, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006; 52: 5-18.
4 National Kidney Disease Education Program. Creatinine Standardization Program. http://www.nkdep.nih.gov/labprofessionals/index.htm (accessed Apr 2007).
5 Peake M, Whiting M. Measurement of serum creatinine — current status and future goals. *Clin Biochem Rev* 2006; 27: 173-184.
6 Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247-254.
7 Preiss DJ, Godber IM, Lamb EJ, et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem* 2007; 44: 35-42.
8 Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, and the Royal College of General Practitioners. Chronic kidney disease in adults: UK guidelines for identification, management and referral. London: Royal College of Physicians, 2006. http://www.bgs.org.uk/Publications/Publication%20Downloads/RCPKidneyOrderForm.pdf (accessed Aug 2007).
9 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39 (2 Suppl 1): S1-S246.
10 Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984; 26: 861-868.
11 O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 2006; 17: 846-853.
12 Chronic kidney disease and automatic reporting of estimated glomerular filtration rate [matters arising]. *Med J Aust* 2007; 184: 41-43.
13 Faull R. Prescribing in renal disease. *Aust Prescr* 2007; 30: 17-20.
14 Prescribing in renal impairment. In: Bochner F, Buckley N, Del Mar C, et al, editors. Australian medicines handbook. Adelaide: AMH, 2007. http://amh.hcn.net.au (accessed Sep 2007).
15 Vidal L, Shavit M, Fraser A, et al. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005; 331: 263-266.

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