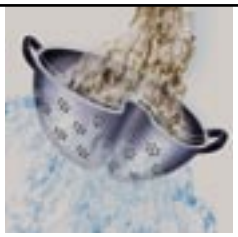

Automated reporting of GFR

Coming soon to a laboratory near you!

David W Johnson
MBBS, FRACP, PhD, is Director of Nephrology and Professor of Medicine, University of Queensland at Princess Alexandra Hospital, Brisbane, Queensland. david_johnson@health.qld.gov.au

Tim Usherwood
MD, FRACGP, FRCP, is Professor of General Practice, University of Sydney at Westmead Hospital, Sydney, New South Wales.

BACKGROUND Serum creatinine concentration is an unreliable and insensitive marker of chronic kidney disease (CKD). To improve CKD detection, Australasian guidelines have recently recommended that laboratories calculate and report an estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula with every request for serum creatinine concentration

OBJECTIVE This articles aims to provide timely information to health professionals about how to appropriately interpret and act upon eGFR reports. It also discusses the treatments shown to reduce renal and cardiovascular risk in CKD patients, and the indications for nephrologist referral.

DISCUSSION The accuracy and precision of eGFRs are reasonable in most adults in whom calculated values are <60 mL/min/1.73 m2. However, eGFRs should be interpreted with caution in some settings (particularly patients with eGFRs >60 mL/min/1.73 m2 and children). Automatic laboratory reporting of eGFR will enhance early detection of CKD, allow the timely institution of appropriate reno- and cardio-protective therapies, and better inform decisions regarding the prescription of renally excreted medications.

Chronic kidney disease (CKD) is a major public health problem in Australia and throughout the world. Based on data from the Ausdiab study,[1] it is estimated that over 1.7 million Australian adults have at least moderately severe kidney failure, defined as a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2. This pernicious condition is often not associated with significant symptoms or urinary abnormalities and is unrecognised in 80–90% of cases.[1–3] Chronic kidney disease progresses at a rate that requires approximately 1900 individuals each year in Australia to commence either dialysis or kidney transplantation.[4] Furthermore, the presence of CKD is one of the most potent known risk factors for cardiovascular disease, such that individuals with CKD have a 10–20 fold greater risk of cardiac death than age and sex matched controls without CKD.[5,6] Early detection of CKD in the primary care setting is therefore critically important for facilitating the timely institution of therapies proven to slow or prevent kidney failure progression, enhancing the appropriate assessment and modification of cardiovascular risk, and informing decisions regarding the prescription of drugs excreted by the kidneys.[7,8]

Assessment of kidney function

The role of eGFR

The most commonly used measure of overall kidney function in clinical practice is serum creatinine concentration. Unfortunately, this measurement is affected by many factors other than the level of kidney function and varies markedly with age, gender and muscle mass (*Figure 1*). Moreover, there are significant calibration issues associated with the measurement of serum creatinine that lead to inter-laboratory variation

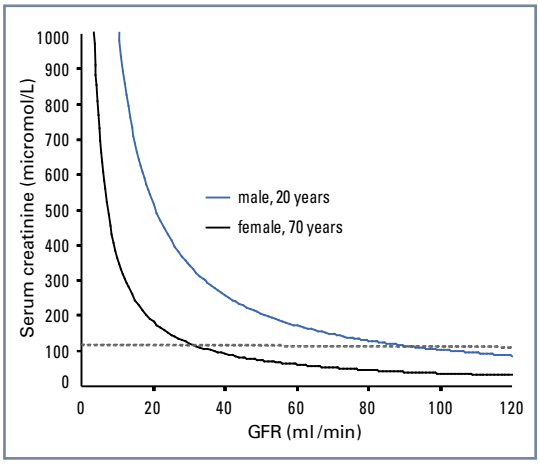

Figure 1. Normal serum creatinine measurements do not exclude serious loss of kidney function, especially in thin, elderly women. The relationship between serum creatinine and GFR is depicted for a man, aged 20 years weighing 70 kg, and a woman, aged 70 years weighing 50 kg. The upper limit of the serum creatinine reference range is shown as a broken line

Table 1. Equations for eGFR in adults based on serum creatinine concentration*

Abbreviated MDRD equation

GFR (mL/min/1.73 m2) = 186 x (SCr ÷ 88.4)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if Afro-American)

Cockcroft-Gault equation

GFR (mL/min) = (140 – age) x weight x 1.228 ÷ SCr x (0.85 if female)

SCr = serum creatinine concentration

* For each equation, SCr is (micromoles/L, age in years, weight in kg

eGFR derived by the Cockcroft-Gault formula should subsequently be corrected for body surface area (multiply by 1.73 then divide by calculated body surface area)

Table 2. Guideline recommendations of the Australasian eGFR Working Party of the Australasian Association of Clinical Biochemists (AACB), Australian and New Zealand Society of Nephrology (ANZSN), Kidney Health Australia (KHA) and Royal Australasian College of Pathologists (RCPA)

- An eGFR using the abbreviated MDRD formula shall be automatically calculated for every request for serum creatinine concentration in individuals aged >18 years
- GFR values that calculate to be in excess of 60 mL/min/1.73 m2 should be reported as '>60 mL/min/1.73 m2' and not as a precise figure
- Automatic reporting of eGFR may include age related reference intervals for individuals aged >65 years
- The implementation of automatic eGFR reporting will require a timely educational program that ensures information is available to health professionals to aid in interpretation of eGFR values

of up to 20%.[9] Serum creatinine concentration is notoriously insensitive for detecting mild to moderate kidney failure, such that patients must lose 50% or more of their kidney function before the serum creatinine value rises above the upper limit of normal (*Figure 1*). This situation of a 'normal' creatinine masking a significant decline in kidney function is especially important in elderly patients, in whom the age related decline in kidney function is not reflected by an increase in serum creatinine level because of a concomitant decrease in muscle mass.

Measuring GFR is widely accepted as the best overall index of kidney function.[10,11] The most common method for assessing GFR in the past was performing a timed urine collection for evaluation of creatinine clearance. However, this test was inconvenient and frequently inaccurate as a result of improper collection and overestimation of GFR due to kidney tubular secretion of creatinine.[11]

More recently, calculation of estimated GFR (eGFR) using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing kidney function.[3,7,12] In most cases, eGFR is at least as accurate as measuring creatinine clearance.[10] There are no fewer than 47 different prediction equations currently available, although the two most common in use are the Cockcroft-Gault[13] and the abbreviated Modification of Diet in Renal Disease (MDRD) formula[12] (*Table 1*). The Cockcroft-Gault equation has the advantages of being more widely known, easier to remember and more extensively validated than the MDRD formula. However, the MDRD formula does not require knowledge of the patient's weight (making it far more suitable for automated laboratory reporting), does not need correction for body surface area (and therefore does not require knowledge of the patient's height) and has been shown to be more precise and accurate than the Cockcroft-Gault equation when the GFR is below 60 mL/min/1.73 m2.[12,14] The Cockcroft-Gault formula is widely available on medical software and specialised semi-automated calculators. An automated calculator for the MDRD formula can be accessed at www.kidney.org.au.

Australasian guidelines for automated laboratory reporting of eGFR

In North America, the National Kidney Foundation Kidney and Dialysis Outcomes Quality Initiative (K/DOQI) guidelines have recommended that serum creatinine concentration alone is sub-optimal

Table 3. Classification of CKD stage

CKD stage	GFR (mL/min)	Comments
1	≥90	• Diagnosis requires evidence of kidney damage (eg. scarring on renal ultrasound, proteinuria)
2	60–89	• Diagnosis requires evidence of kidney damage (eg. scarring on renal ultrasound, proteinuria)
3	30–59	• Moderate kidney failure • Treat kidney and cardiac risk factors (esp. blood pressure, cholesterol, blood sugar, smoking, obesity) • Antiproteinuric drugs (angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers) if appropriate • Avoid nephrotoxic drugs • Correct anaemia, acidosis and hyperparathyroidism • Ensure drug dosages appropriate for level of kidney function • Consider referral to nephrologist (mostly not required)
4	15–29	• Severe kidney failure • As above + refer to nephrologist • Prepare for dialysis or transplantation if appropriate
5	<15	• End stage kidney failure • As above + refer to nephrologist • Institute dialysis or transplantation if appropriate

for assessing the level of kidney function and that pathology laboratories should concomitantly report eGFR, as determined by a prediction equation such as the MDRD formula.[10] Similar recommendations have been made by other organisations, including the British Renal Association[15] and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[16] These recommendations are based on observations that laboratory reporting of eGFR significantly enhances CKD detection[7] and that timely intervention can reduce the risk of progressive kidney failure and cardiovascular disease in CKD patients.[17]

Recently, an Australasian eGFR Working Group convened by representatives of the Australasian Association of Clinical Biochemists (AACB), Australian and New Zealand Society of Nephrology (ANZSN), Kidney Health Australia (KHA) and the Royal Australasian College of Pathologists (RCPA) unanimously endorsed and published recommendations that laboratories calculate and report an eGFR using the MDRD formula with every request for serum creatinine concentration[18] (*Table 2*). It is likely that most, if not all laboratories, will adopt these recommendations over the next few years, making it imperative that health professionals receive adequate information about how to appropriately interpret and act upon eGFR reports.

Interpretation of eGFR values on pathology reports

The normal GFR in young adults is around 120 mL/min/1.73 m2. Glomerular filtration rate values below 90 mL/min/1.73 m2 are abnormal and generally indicate the presence of CKD if present for more than 3 months. The K/DOQI guidelines have classified five stages of CKD based on the level of GFR and/or the presence of kidney damage (as evidenced by urinary abnormalities or the presence of scarring on radiological imaging) (*Table 3*).[10] As eGFR is based on serum creatinine concentration, the errors associated with creatinine measurement similarly apply to eGFR.

Limitations of eGFR

There are a number of limitations associated with eGFR that include the errors associated with serum creatinine measurement as discussed above. Moreover, prediction formulae for eGFR have been poorly validated in children[19] and so their use is currently only recommended in adults (≥18 years). After the age of 30 years, GFR progressively declines at an average rate of 8 mL/min per decade.[20] Based on North American data,[20] it is estimated that 25% of the Australian population over the age of 70 years will have an eGFR below 60 mL/min/1.73 m2. There is ongoing debate as to whether this age related GFR decline is

'normal' or pathological. Approximately one-third of the population does not experience a decline in GFR with age.[21] Moreover, a reduced GFR remains a strong predictor of all cause and cardiovascular mortality, even in elderly populations.[22–24] The Australasian eGFR Working Group has suggested that automatic laboratory reporting of eGFR may include age related reference intervals for individuals aged 65 years or over. However, the definition of CKD is not modified according to age. This scenario is analogous to that for hypertension. Even though blood pressure levels rise with age and are highly prevalent in the elderly, the threshold for diagnosing hypertension based on blood pressure level is not altered in older individuals because hypertension in this age group is still strongly associated with adverse outcomes. Similarly, severely reduced eGFR values in elderly patients below 60 mL/min/1.73 m2 should be considered significant.

In addition to extremes of age, there are a number of other clinical situations where reported eGFR results should be interpreted with caution due either to lack of appropriate validation or to demonstrated lack of precision or accuracy (eg. with eGFR values above 60 mL/min/1.73 m2). These conditions are listed in *Table 4*. Under such circumstances, it may be worth considering direct assessment of kidney function (such as timed urine collections for creatinine clearance).

Management of patients with significantly reduced eGFRs

All patients with substantially reduced eGFRs (<60 mL/min/1.73 m2) should undergo cardiovascular and kidney disease risk factor modification.[10,15] There is strong randomised controlled trial evidence that timely intervention in this group of patients can substantially reduce kidney failure progression and cardiovascular risk by up to 50%.[17] The most important goal in patients with CKD is to reduce arterial blood pressure to target levels (<130/85 mmHg if proteinuria <1 g/day or <125/75 mmHg if proteinuria >1 g/day).[25] Based on the weight of accumulated evidence to date, angiotensin converting enzyme inhibitors remain the first line therapy,[26] although recent new evidence in type 2 diabetic nephropathy suggests that angiotensin receptor antagonists may provide comparable renoprotection.[27–29] In order to reach currently recommended blood pressure targets, multiple (often 3–4) antihypertensive medications are frequently required.[17] Other strategies found to be effective in a limited number of studies include statins,[30–32] and correction of uraemic anaemia with erythropoietin.[33,34] Smoking is strongly associated with renal disease, and cessation has been shown to reduce progression in diabetic patients; of course, cessation of smoking is also important in reducing cardiovascular risk. Intensive glycaemic control reduces the risk of renal complications in both type 1 and 2 diabetes mellitus, although there is currently no evidence that it improves renal outcomes once overt nephropathy has developed.[17] Dietary protein restriction provides modest benefits in CKD, but these are generally outweighed by deleterious nutritional consequences and therefore not recommended.[35]

Once eGFR is substantially reduced, the natural history is a continuing decline. The steps outlined above will slow the decline, but regular monitoring (at least every 3 months) is essential. Also

Table 4. Clinical situations where eGFR results may unreliable and/or misleading

- Rapidly changing kidney function
- Dialysis dependent patients
- Exceptional dietary intake (eg. vegetarian diet, high protein diet, creatine supplements)
- Extremes of body size
- Diseases of skeletal muscle, paraplegia
- Amputees
- Certain ethnic groups (eg. Asians, Aboriginal and Torres Strait Islanders)
- Children
- eGFR values above 60 mL/min/1.73 m2

Table 5. Frequently used drugs that may damage the kidneys

- Nonsteroidal anti-inflammatories, COX-2 inhibitors
- ACE inhibitors and angiotensin 2 receptor antagonists
- Beware, especially, the 'triple wammy' of NSAID/COX-2 inhibitor, ACE inhibitor and diuretic
- Radiographic contrast agents
- Diabetes and kidney impairment or proteinuria

Table 6. Indications for referral of CKD patients to a nephrologist

- eGFR <30 mL/min/1.73 m2
- Rapidly declining kidney function (>15% ↓ in GFR over 3 months)
- Significant proteinuria >1 g/24 hours
- Glomerular haematuria
- Kidney impairment and hypertension that proves difficult to control

essential is the avoidance of potentially nephrotoxic medications (*Table 5*).

Indications for referral

With over 1.7 million adults with stage 3 CKD (GFR 30–60 mL/min) in Australia and only 180 nephrologists, it is clear that the majority of these patients will need to be managed in the primary health care setting. Nevertheless, the Caring for Australians with renal insufficiency (CARI) guidelines recommend that patients with severe kidney failure (eGFR <30 mL/min, stage 4 or 5 CKD), diabetic nephropathy, rapidly deteriorating renal function or features suggestive of an underlying glomerulonephritis (eg. heamaturia, casts or proteinuria in excess of 1g/day) should be referred to a nephrologist (*Table 6*). A number of studies[36–38] have demonstrated that early referral of patients with severe CKD to a multidisciplinary renal unit is associated with reduced rates of kidney failure decline, decreased need for and duration of hospitalisation, increased likelihood of permanent dialysis access created before dialysis onset, reduced initial costs of care following the commencement of dialysis, increased likelihood of kidney transplantation, and decreased patient morbidity and mortality. The CARI guidelines recommend that patients should be referred to renal units at least 12 months before the anticipated commencement of dialysis and/or kidney transplantation (ie. eGFR ≥30 mL/min/1.73 m^2). Nevertheless, in spite of this, approximately 30% of CKD patients in Australia are referred 'late' to nephrologists (ie. within 3 months of needing to commence kidney replacement therapy). Such 'late referred' patients have markedly reduced survival rates on dialysis and are much less likely to receive a kidney transplant.[39]

Conclusion

Automatic laboratory reporting of eGFR on each occasion a serum creatinine concentration is ordered will significantly increase the likelihood of early detection of CKD, allow the institution of appropriate management strategies to reduce the risks of kidney failure progression and cardiovascular death in the community, and inform decisions regarding the prescription of renally excreted medications. General practitioners need to be aware of the limitations of eGFR results (particularly patients with eGFR values >60 mL/min/1.73 m2 and children), treatments shown to reduce renal and cardiovascular risk in CKD patients, and indications for nephrologist referral.

Summary of important points

- Serum creatinine concentration alone is inadequate for assessing a patient's level of kidney function.
- Australasian guidelines recommend that laboratories calculate and report an eGFR using the MDRD formula with every request for serum creatinine concentration.
- eGFR reports may be unreliable and/or misleading in certain settings, including rapidly changing kidney function, dialysis dependent patients, extremes of body size, diseases of skeletal muscle, paraplegia, amputees, certain ethnic groups, children, and eGFR values above 60 mL/min/1.73 m2.
- Interventions proven to reduce the risk of kidney disease progression by up to 50% include reduction of blood pressure, prescription of statins, cessation of smoking, correction of anaemia and intensive glycaemic control in diabetics before the development of macroalbuminuria. Nephrotoxic drugs should be avoided.
- Renal function should be checked at least every 3 months in patients with eGFR <60 mL/min/1.73 m2.
- The indications for referral of a CKD patient to a nephrologist include eGFR <30 mL/min/1.73 m2, rapidly declining kidney function, proteinuria >1g/24 hours, glomerular haematuria and proteinuria, kidney impairment and uncontrolled hypertension, and diabetes and kidney impairment or proteinuria.

Conflict of interest: none declared.

References

1. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. J Am Soc Nephrol 2003;14:S131–8.
2. McClellan WM, Knight DF, Karp H, Brown WW. Early detection and treatment of renal disease in hospitalised diabetic and hypertensive patients: important differences between practice and published guidelines. Am J Kidney Dis 1997;29:368–75.
3. John R, Webb M, Young A, Stevens PE. Unreferred chronic kidney disease: a longitudinal study. Am J Kidney Dis 2004;43:825–35.
4. McDonald S, Russ G. New patients commencing renal replacement therapy in 2003. In: McDonald S, Russ G, editors. ANZDATA Registry Report 2003. Adelaide, SA: Australian and New Zealand Dialysis and Transplant Registry, 2005;8–15.
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:S112–9.
6. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all cause mortality: a pooled analysis of community based studies. J Am Soc Nephrol 2004;15:1307–15.
7. Akbari A, Swedko PJ, Clark HD, et al. Detection of chronic

kidney disease with laboratory reporting of estimated glomerular filtration rate and an educational program. Arch Intern Med 2004;164:1788–92.
8. Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: Part I. Definition, disease stages, evaluation, treatment, and risk factors. Am Fam Physician 2004;70:869–76.
9. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002;39:920–9.
10. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.
11. Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: part II. Glomerular filtration rate, proteinuria, and other markers. Am Fam Physician 2004;70:1091–7.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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;130:461–70.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
14. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459–66.
15. Joint Specialty Committee of the Royal College of Physicians of London and the British Renal Association. Guidelines for identification, management and referral of adults with chronic kidney disease. London: Department of Health for England, 2005;20–3.
16. Eknoyan G, Lameire N, Barsoum R, et al. The burden of kidney disease: improving global outcomes. Kidney Int 2004;66:1310–4.
17. Johnson DW. Evidence based guide to slowing the progression of early renal insufficiency. Intern Med J 2004;34:50–7.
18. The Australasian eGFR Working Party. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. Med J Aust 2005; in press.
19. Pierrat A, Gravier E, Saunders C, et al. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. Kidney Int 2003;64:1425–36.
20. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.
21. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 1985;33:278–85.
22. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5 year mortality in older adults: the Cardiovascular Health Study. JAMA 1998;279:585–92.
23. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555–62.
24. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int 2003;63:1121–9.
25. Johnson DW, Mathew T, Gillin A, et al. CARI guidelines: Prevention of progression of renal failure. Sydney: Australian and New Zealand Society of Nephrology. Available at: www.kidney.org.au/cari/drafts/new/prevention.html.
26. Giatras I, Lau J, Levey AS. Effect of angiotensin converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomised trials. Angiotensin Converting Enzyme Inhibition and Progressive Renal Disease Study Group. Ann Intern Med 1997;127:337–45.
27. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
28. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–8.
29. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;45:861–9.
30. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int 2001;59:260–9.
31. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 2003;41:565–70.
32. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004;57:728–34.
33. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anaemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron 1997;77:176–85.
34. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anaemia early in renal failure patients slows the decline of renal function: a randomised controlled trial. Kidney Int 2004;66:753–60.
35. Johnson DW, Mathew T, Gillin A, Thomas M, Nankivell B, Nicholls K, Haris DCH. CARI guideline: Prevention of progression of kidney disease. Sydney: Australian and New Zealand Society of Nephrology Available at: www.kidney.org.au/cari/drafts/new/prevention.html.
36. Churchill DN. An evidence based approach to earlier initiation of dialysis. Am J Kidney Dis 1997;30:899–906.
37. Binik YM, Devins GM, Barre PE, et al. Live and learn: patient education delays the need to initiate renal replacement therapy in end-stage renal disease. J Nerv Ment Dis 1993;181:371–6.
38. Curtis BM, Ravani P, Malberti F, et al. The short and long term impact of multidisciplinary clinics in addition to standard nephrology care on patient outcomes. Nephrol Dial Transplant 2005;20:147–54.
39. Cass A, Cunningham J, Snelling P, Ayanian JZ. Late referral to a nephrologist reduces access to renal transplantation. Am J Kidney Dis 2003;42:1043–9.

Email: afp@racgp.org.au