Formula estimation of glomerular filtration rate: have we gone wrong?

Paul D Giles and **David A Fitzmaurice** argue that the introduction of estimated glomerular filtration rate to screen for chronic kidney disease in primary care will lead to pressure on specialist services and create patient anxiety without clear proof of benefit

Chronic kidney disease is a public health problem worldwide.¹ The estimated prevalence of established renal failure is around 1400 per million in the United States and more than 600 per million in the United Kingdom. Patients with chronic kidney disease have increased risk of cardiovascular disease. A test that reliably detects early kidney disease could help minimise cardiovascular disease and renal failure.

Estimating glomerular filtration rate

The best known function of the kidneys is plasma filtration—measured by the glomerular filtration rate (GFR). Many of the kidney's functions are related to GFR (box 1). Inulin clearance and modern isotopic methods are not practical for measuring GFR in routine practice. Creatinine based tests are used instead but have several disadvantages. Creatinine clearance involves timed urine collection and is prone to error. Measuring serum creatinine is easier but this test cannot detect early kidney disease.² Routine reporting of estimated GFR using formulas based on serum creatinine concentration plus age, sex, and racial group was first advocated in the US and has now been recommended in many other countries.

In the UK the second part of the national service framework for renal services,⁴ published in 2005, required clinical biochemistry laboratories to develop automatic reporting of formula based GFR estimates. In 2006 the quality and outcomes framework⁵ asked primary care to establish registers of patients with

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Classification of chronic kidney disease⁷

Stage	Description
1	Normal GFR (>90 ml/min/1.73 m ²) with other evidence of chronic kidney damage
2	Mildly impaired GFR (60-89 ml/min/1.73 m ²) with other evidence of chronic kidney damage
3	Moderately impaired GFR (30-59 ml/min/1.73 m ²)
4	Severely impaired GFR (15-29 ml/min/1.73 m ²)
5	Established renal failure (GFR <15 ml/min/1.73 m ²)

GFR=glomerular filtration rate

estimated GFR worse than 60 ml/min/1.73 m² (chronic kidney disease stages 3-5 in the international classification; table).^{6,7} Many registers have been populated using computer programs that find serum creatinine results in general practitioners' information systems and then calculate estimated GFR using the "four variable version of the modification of diet in renal disease" (MDRD) formula (box 2).⁸

Labelling patients as having chronic kidney disease in this way has caused controversy.² We challenge some of the applications of GFR estimated from this formula.

Clinical indications for assessing glomerular function

Glomerular function is assessed for three different reasons, which have an important bearing on the qualities required of the test.

Box 1 | Functions of the kidneys related to glomerular filtration rate³

Excretion of nitrogenous waste, sodium, free water, potassium, phosphate, and water soluble medicines (such as digoxin and gentamicin)
Control of blood pressure
Acid-base balance
Secretion of erythropoietin
Hydroxylation of vitamin D1 (activation)
Gluconeogenesis in the fasting state
Catabolism of peptide hormones (including insulin)

Box 2 | Estimating glomerular filtration rate (GFR) using the four variable version of the modification of diet in renal disease equation

$GFR (ml/min/1.73 m^2) = 186 \times \{[S_{cr}/88.4]\}^{-1.154}$

$\times age$ in years^{-0.203}

$\times 0.742$ if female

$\times 1.21$ if African American

Where S_{cr} is serum creatinine in $\mu mol/l$

Detecting changes in renal function over time

A test to monitor change in renal function over time in individual patients will need to be reproducible. Serial serum creatinine measurements are useful in this context because they are analytically precise and vary little over time in patients with stable disease, although meat rich meals and other non-renal factors can interfere.⁹ Because formula estimated GFR is a mathematical transformation of serum creatinine that takes into account three factors that have no measurement error and that do not change (sex and ethnic group) or change slowly (age), it is just as sensitive as serum creatinine at detecting change over time. It does not, however, provide a more reliable measure, except in the longer term, as changes in estimated GFR mirror changes in creatinine, and errors in measuring creatinine or interference in serum creatinine by non-renal factors translate into errors in estimated GFR.

Fig 1 | Association of estimated glomerular filtration rate (GFR) with GFR measured by isotopic reference method. Below 60 ml/min/1.73 m² the two methods are tightly associated, with limited scatter of the points. At higher filtration rates scatter becomes worse, and in kidney donors estimated GFR underestimates renal function. Adapted from Poggio et al¹⁰

Disease staging in patients with chronic kidney disease

The classification of chronic kidney disease is based on GFR,⁶ so a reproducible and accurate method is needed for correct staging. Formula estimates of GFR must agree closely with reference method determinations, not just on average across a tested population but for each individual being tested. In stages 3-5 of disease estimated GFR has no bias against isotopic reference methods, and in plots of the two methods the scatter between individuals decreases as GFR decreases. Estimated GFR is arguably accurate enough to stage patients with known chronic kidney disease with a GFR less than 60 ml/min/1.73 m² (fig 1).¹⁰ Different patients with the same serum concentration of creatinine can have widely divergent degrees of renal impairment, so the formula can clarify loss of function in a way that is not directly apparent from the creatinine concentration itself. As estimated GFR improves, however, the scatter of estimated GFR plotted against reference GFR becomes progressively wider, and some biochemistry departments do not specify actual values for estimated GFRs higher than 60 ml/min/1.73 m².⁹ It should be noted that the average serum creatinine concentration in the original MDRD data was around 200 µmol/l, the average GFR was about 40 ml/min/1.73 m² (disease stage 3), and few patients had serum creatinine within the reference range (≤124 µmol/l).

Detecting chronic kidney disease in mixed populations

This is what primary care has been asked to do by creating disease registers on the basis of estimated GFR less than 60 ml/min/1.73 m² and what a laboratory does if it reports estimated GFR with all adult creatinine results. Effectively, a screening test has been introduced without reference to the criteria for screening programmes.¹¹

GFR estimates based on the MDRD formula have been implemented in a setting far outside the original evidence base, with no proof of reliability in the new context, and without evaluating the balance of benefit to harm for tested individuals or the use of healthcare resources. This is in stark contrast to the methodical way in which the National Screening Committee assessed and rejected the evidence for urine testing to screen for bladder cancer and glomerulonephritis in 2002 (reconfirmed in 2006).¹²

In such a screening situation we need to know 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). Here, the value of formula estimated GFR is unclear.

Although estimated GFR reflects the true filtration rate in patients with chronic kidney disease, several studies have shown that formula estimated GFR underestimates renal function in people without known kidney disease. This problem is compounded by enormous variation between individuals, and this unpredictable scatter gets worse as GFR increases (fig 1).^{10 13-15} These effects increase the overlap in estimated GFR values when testing patients with and without chronic kidney disease and significantly compromise the ability of estimated GFR to separate these two patient groups.

The risk of many false positives occurring is high. 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 (a precious resource in limited supply); also, patients may be entered on a kidney disease register, which may result in their having difficulty getting life insurance and being prescribed drugs (including angiotensin converting enzyme inhibitors⁵) on the basis of an inadequate test. Primary care clinicians realise this and may not label people as having chronic kidney disease even when estimated GFR values are below 60 ml/min/1.73 m².

Analytical considerations

Numerous versions of the traditional method of determining creatinine concentrations (Jaffe chemistry) exist as well as more specific enzymatic methods. There are analytical differences between these techniques and a lack of standardisation.⁹ Figure 2¹⁴ shows a scatter plot of estimated GFR against GFR measured by an isotopic reference method in people with normal serum concentrations of creatinine. Two estimated GFR values were calculated for each patient—one using the Jaffe chemistry and one using results of an enzymatic method. Compared with the reference GFR method, the MDRD formula underestimated GFR for both creatinine assays, but more so for the Jaffe related results (about -27%) than those based on the enzymatic assay (about -10%).

Laboratories should obviously try to minimise variations between creatinine methods,⁹ but even if all analytical problems were resolved concerns remain

Fig 2 | Scatter plot of estimated GFR against isotopic reference GFR in subjects with normal serum creatinine using two different creatinine assays (enzymatic and Jaffe methods). Formula calculations underestimate GFR for both assays. The negative bias is less with the enzymatic assay, but the scatter of results is wide with both methods. Adapted from Verhave et al¹⁴

about using estimated GFR in patients with lower serum creatinine concentrations. Even within one enzymatic method, one study showed a significant overall negative bias and substantial interindividual scatter of results—an estimated GFR at the threshold value of 60 ml/min/1.73 m² could correspond to a reference method GFR between about 40 ml/min/1.73 m² and more than 100 ml/min/1.73 m².¹⁴

Conclusion

In some patients, the glomerular filtration rate may be half that seen in healthy people before serum creatinine rises above the population reference interval.¹⁶ Because serum creatinine is so insensitive for detecting early loss of renal function, it is tempting to suppose that estimated GFR is a better measurement. But this is not true.

Our view is that estimated GFR is useful for staging disease in patients with stage 3-5 chronic kidney disease, and many nephrologists use estimated GFR and serum

SUMMARY POINTS

Estimated glomerular filtration rate (GFR) has come into widespread use as a result of the recent UK recommendations

Estimated GFR is useful for staging progress in patients with established kidney disease but collection of blood samples and creatinine assays should be standardised

The use of estimated GFR to screen for chronic kidney disease in primary care needs careful evaluation

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PDG is consultant head of a district general hospital clinical biochemistry service that reports estimated GFR results to primary care. He also works with nephrologists in the local renal clinic and uses estimated GFR results to manage his patients. DAF is a general practitioner and professor of primary care; his primary research interest is in cardiovascular disease and its prevention. This paper was prompted by discussions with nephrology and clinical biochemistry specialists, and with primary care doctors at regional network level after estimated GFR was introduced through the national service framework for renal services. PDG wrote the first version of the article and DAF helped make it more understandable to readers from primary care. PDG is guarantor.

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creatinine to monitor progress in such patients. To make estimated GFR more reliable laboratories should work towards greater uniformity in the assay of serum creatinine,⁹ and sample collection should be standardised to minimise the impact of non-renal factors (such as meat intake) on serum creatinine results.¹⁷ Serial measurements of serum creatinine and estimated GFR in individual patients may help clinicians detect changes in renal function even when serum creatinine remains in the population reference interval.

However, none of these initiatives will overcome the underlying weak association between estimated GFR and GFR measured by reference methods in people with normal or near normal renal function. Creatinine is a fundamentally flawed filtration marker, as too many non-renal factors affect its concentration in serum; we need a more reliable indicator of early loss of GFR.² In the meantime, the uncritical introduction of estimated GFR in biochemistry laboratories and in primary care in adults with normal serum creatinine and no other indication of renal disease lacks a good scientific basis; it will lead to pressure on specialist services and create patient anxiety without clear proof of benefit.

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