

2. Use of estimated glomerular filtration rate to assess level of kidney function

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Several glomerular filtration rate (GFR) prediction equations that take into account the serum creatinine concentration and certain patient variables (age, gender, body size and/or race) have been shown to generate sufficiently precise, unbiased and accurate estimates of GFR (eGFR) to be clinically useful for evaluating kidney function in a broad range of clinical settings. (Level III evidence, multiple large cohort studies in community and institutional settings, clinically relevant outcomes, strong effects)**
- **In adults, the abbreviated (4-variable) MDRD, 6-variable MDRD and Cockcroft-Gault equations generally provide reliable eGFRs.**
- **In children, the Schwartz and Counahan-Barratt equations generally provide reliable eGFRs.**
- **Automated laboratory reporting of eGFR with each request for serum creatinine concentration (combined with a primary care physician education program) has been shown to substantially improve the clinical detection of chronic kidney disease (CKD) in the community. (Level III evidence, medium-sized before-and-after trial, clinically relevant outcome, strong effect)**
- **Clinical laboratories should therefore report an eGFR using a prediction equation in addition to reporting the serum creatinine concentration measurement. (Level III evidence, medium-sized before-and-after trial, clinically relevant outcome, strong effect)**
- **Overall, 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 patients with a GFR < 60**

mL/min/1.73 m² and its greater practicality (weight information and body surface area correction not required). (Level III evidence, multiple large cohort studies in community and institutional settings, clinically relevant outcome, strong effect)

- **There have been no randomised controlled trials (RCTs) comparing the effect of using eGFR versus other measures of kidney function on relevant clinical outcomes, such as prevention of end-stage kidney disease (ESKD), prevention of cardiovascular disease or reduction in medication-related adverse events.**
- **GFR prediction equations have generally been shown to provide more reliable estimates of GFR than creatinine clearance measurements. (Level III evidence, multiple large cohort studies in community and institutional settings, clinically relevant outcome, strong effect)**

Direct measurement of GFR (e.g. by creatinine clearance or one of the GFR reference methods) may be required in several circumstances.

a) Situations in which eGFR may be unreliable:

- **Extremes of body size**
- **Extremes of age (especially low BMI for MDRD formula)**
- **High or low dietary intake of creatinine or creatine (dietary supplements, vegans/vegetarians)**
- **Patients with muscle diseases or atrophy (muscular dystrophy, amputation, paralysis, malnutrition)**
- **Particular ethnic groups (Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders, Indo-Asians)**

b) Situations in which a high degree of accuracy in GFR estimation is required:

- **Prior dosing with renally-excreted medications that have high toxicity**
- **Evaluation of renal function in potential live kidney donors. (Level III evidence, multiple small-to-medium sized cohort studies, clinically relevant outcome, strong effect)**

Background

Measuring GFR is widely accepted as the best overall index of kidney function (K/DOQI 2002, Johnson et al 2004). 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 (Johnson et al 2004).

More recently, calculation of eGFR using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing

kidney function (John et al 2004, Akbari et al 2004, Levey et al 1999). There are no fewer than 46 different prediction equations currently available, although the two most commonly in use are the Cockcroft-Gault (Cockcroft et al 1976) and the abbreviated Modification of Diet in Renal Disease (MDRD) formulae (Levey et al 1999) (Table 1). 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 on the internet (<http://www.kidney.org.au/calculator.php> or http://www.kidney.org/kls/professionals/gfr_calculator.cfm).

Recently, the K/DOQI and KDIGO guidelines recommended that eGFR should be reported automatically with each request for serum creatinine using an equation based on serum creatinine and patient variables following assay calibration (K/DOQI 2002, Levey et al 2005). A similar recommendation using the abbreviated MDRD formula has recently been endorsed in a position paper published by the Australasian Association of Clinical Biochemists, Royal College of Pathologists of Australasia and the Australian and New Zealand Society of Nephrology (Australasian eGFR Working Party 2005).

The objective of this guideline is to review the evidence pertaining to the use of eGFR from empiric equations based on serum creatinine concentration and other demographic variables to reliably detect CKD and prevent its sequelae.

Search strategy

Databases searched: Text words for estimated glomerular filtration rate and glomerular filtration rate were combined with MeSH terms and text words for prediction formula and prediction equation. The search was carried out in Medline (1966 – 18 April 2005). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994–2004 were also searched for trials.

Date of searches: 18 April 2005.

What is the evidence?

No RCTs are available which address this issue.

There have been no RCTs comparing the effect of using eGFR versus other measures of kidney function on relevant clinical outcomes, such as detection or prevention of CKD, prevention of cardiovascular disease or reduction in medication-related adverse events.

To date, at least 46 prediction equations or nomograms have been developed to estimate GFR based on serum creatinine concentration with or without other patient variables. These are summarised in Table 1.

The most extensively validated formulae to date in adults are the Cockcroft-Gault, MDRD and abbreviated MDRD equations. The results of validation studies involving these formulae are summarised in Table 2.

All other formulae have been validated in a smaller number (< 1000 and often < 100) and more narrow range of patients, and have generally been found to have inferior precision and accuracy compared with the Cockcroft-Gault and MDRD formulae. The ability to compare or combine reported results of prediction equations is significantly hampered by the lack of standardisation of reporting of precision, bias and accuracy as well as failure to report how closely the serum creatinine assay employed reflected the 'true' serum creatinine level (i.e. calibration bias), as determined by an appropriate reference method.

Several formulae for eGFR in children have also been developed, including the Schwartz, Counahan-Barratt, modified Counahan-Barratt, Morris, Shull, Traub, Rudd, Dechaux, Ghazali-Barratt and van den Anker equations (see Table 1). The Schwartz and the Counahan-Barratt equations, which both provide an eGFR based on a constant multiplied by a child's height/length divided by serum creatinine, have been the most extensively validated and commonly used. The results of validation studies involving these 2 formulae are summarised in Table 3.

Cockcroft-Gault and MDRD formulae

The Cockcroft-Gault formula was originally derived in 249 consecutive hospitalised patients (96% male, age range 18–92 years) at the Queen Mary Veterans' Hospital in Canada, based on the means of two 24-hour creatinine clearances (Cockcroft et al 1976). Serum creatinine concentrations were determined by Jaffé reaction using an autoanalyzer (N-11B, Technicon Instruments Corp, NY). The derived formula was then used to predict creatinine clearance in a second validation cohort consisting of 236 patients (206 males, mean creatinine clearance 72.7 ± 36.6 mL/min). Mean predicted creatinine clearance by the Cockcroft-Gault formula was 75.8 mL/min with an r^2 of 0.69. Predicted and mean measured values differed by 35% or less in 95% and by 20% or less in 67% of patients. The main limitations of the study were:

- The study had questionable external validity given that the training and validation samples consisted predominantly of hospitalised, white men, many of whom did not have CKD. Nevertheless, the Cockcroft-Gault formula has subsequently been extensively validated and found to exhibit satisfactory accuracy, precision and bias in diverse populations including women and various ethnic groups, and across a broad range of GFRs.
- The formula was originally validated against creatinine clearance, which is known to appreciably overestimate inulin clearance and vary from day to day by 10%–20% (Edwards et al 1969). Subsequent validation studies

have generally shown equivalent or superior performance of the Cockcroft-Gault equation against a variety of GFR measures (inulin, iothalamate, ⁵¹Cr-EDTA, DTPA, Mag III and iohexol clearances) (Table 2).

- The calibration bias of the creatinine assay used versus 'true' creatinine was not reported.
- The results of the Cockcroft-Gault formula were not corrected for body surface area.

The MDRD equation was developed in 1628 CKD patients enrolled in the baseline period of the Modification of Diet in Renal Disease (MDRD) study, of whom 1070 were randomly selected as the derivation sample and the remaining 558 patients constituted the validation sample (Levey et al 1999). The exclusion criteria for the MDRD study were patients with body weight extremes (< 80% or > 160% of standard body weight), dubious compliance, insulin-dependent diabetes mellitus or heavy proteinuria (> 10 g/day). GFR was directly measured as iothalamate clearance and serum creatinine was measured by means of a modified kinetic Jaffé reaction using a Beckman Astra CX3 autoanalyzer (Brea, CA).

Using multiple regression analysis, a 6-variable equation (equation 7) was developed, which included the variables of serum creatinine, age, gender, ethnicity (African-American or other), serum urea and serum albumin. The equation was validated against GFR corrected for body surface area (BSA) and so, unlike the Cockcroft-Gault formula, the predicted GFR is expressed as mL/min/1.73 m² and does not require subsequent BSA normalisation. Compared with the BSA-corrected Cockcroft-Gault formula, the MDRD equation was more precise (r² 0.90 vs 0.84), less biased (3% vs 23%) and exhibited greater accuracy within 30% (91% vs 65%) and within 50% (98% vs 83%). The accuracy of GFR values was worst for Cockcroft-Gault GFR (non-BSA-corrected), intermediate for BSA-corrected GFR, and best for MDRD GFR (John et al 2004). The precision, accuracy and bias of the MDRD GFR has been validated in 5069 subjects over 16 studies and generally found to be superior to those of the Cockcroft-Gault formula (Table 3).

An abbreviated, 4-variable MDRD equation (age, gender, African-American ethnicity and plasma creatinine) has subsequently been developed (K/DOQI 2002, Levey et al 2000).

The precision, accuracy and bias of the MDRD GFR has been validated in 8654 subjects over 13 studies and generally found to be comparable to those of MDRD GFR and superior to those of Cockcroft-Gault GFR (Table 3).

The largest study to date was conducted by Froissart et al (2005) in a cohort of 2095 non-black European adults (863 females, 1232 males, mean age 52.8±16.5 years, mean measured GFR 61.1±32.7 mL/min/1.73 m²) referred

for ^{51}Cr -EDTA measurements at the Georges Pompidou Hospital, Paris, between January 1990 and April 2004. Among this cohort, 1933 had CKD and 162 were healthy potential kidney donors. Serum creatinine measurements were performed in the one laboratory via a modified kinetic Jaffé reaction using a Bayer RA-XT and a Konelab 20 analyzer. Cockcroft-Gault GFR predictions were corrected for BSA. Both the MDRD and Cockcroft-Gault equations showed minimal bias (-0.99 and 1.94 mL/min/ 1.73 m², respectively). The biases were always larger for Cockcroft-Gault GFR than MDRD GFR in selected age, gender and BMI subgroups (except individuals with a BMI < 18 kg/m² where the absolute difference between MDRD and measured GFR was larger than for Cockcroft-Gault GFR). In all cases, the MDRD formula was at least as accurate as the Cockcroft-Gault one. The Cockcroft-Gault formula principally lacked accuracy in subjects who were younger than 65 years and had GFR values below 60 mL/min/ 1.73 m². Both formulae lacked precision (standard deviation of bias for MDRD 13.7 mL/min/ 1.73 m² vs Cockcroft-Gault 15.4 mL/min/ 1.73 m²). When staged according to the K/DOQI classification of CKD, only 70.8% and 67.6% of subjects were classified in the correct stage by the MDRD and Cockcroft-Gault formulae.

Pierrat et al (2003) studied 198 children and 116 adults referred for inulin clearances for evaluation of CKD, post-nephrectomy, pre-chemotherapy or post-renal transplantation. Estimations of GFR (BSA-corrected Cockcroft-Gault, MDRD, Schwartz) and direct measurements of GFR (creatinine and inulin clearances) were compared. In younger children (< 12 years), no prediction equation demonstrated satisfactory precision and accuracy. In adults, the dispersion of 95% of the population on Bland-Altman plots was slightly more precise for MDRD than Cockcroft-Gault (± 23 vs ± 30 mL/min/ 1.73 m², respectively).

Several other studies have confirmed that the abbreviated MDRD equation shows generally greater precision and accuracy than the Cockcroft-Gault formula in patients with CKD (GFR < 60 mL/min/ 1.73 m²) (Poggio et al 2005, Lamb et al 2003, Lewis et al 2001), but tends to be more biased with significant underestimation of measured GFR in patients with normal or near-normal renal function (Rule et al 2004a, Rule et al 2004b, Lin et al 2003, Ibrahim et al 2005).

Recently, Marshall et al (2005) reported a comparison of prediction errors associated with the MDRD formula versus eGFR using a dynamic evolving neuro-fuzzy interference system (DENFIS) compared with 441 ^{18}Cr -EDTA clearance measurements in 178 CKD patients (mean GFR 22.6 mL/min/ 1.73 m²) from 12 centres in Australia and New Zealand. Both the MDRD formula and evolving connectionist system (ECOS) used the same predictive variables, and both were optimized to the study cohort by stepwise regression and training, respectively. Different datasets (randomly selected from the original) were used for ECOS training and validation. The bias and precision of the MDRD formula were 3.5 mL/min/ 1.73 m² and 34.5%, respectively,

improving to -1.2 mL/min/ 1.73 m² and 31.1% after maximal optimization of the formula to study data. The bias and precision of the ECOS were 0.7 mL/min/ 1.73 m² and 32.6%, respectively, improving to -0.1 mL/min/ 1.73 m² and 16.6% after maximal optimization of the system to study data. The prediction of GFR using ECOS was improved by accounting for the centre from where clinical and laboratory measurements originated within the connectionist model. The authors concluded that ECOS was superior to algebraic formulae, such as the MDRD. They have developed a web-based version of GFR^{DENFIS} and will be evaluating its performance characteristics.

The major limitations of this study were: a) its small sample size; b) the inclusion of multiple GFR measurements from each patient (thereby biasing results towards patients with more frequent measurements); c) the application of the MDRD African-American racial origin correction to Maori and Pacific Islanders (for which there is no evidence of validity); and d) the validation study only involved a relatively narrow range of GFRs (22.6 ± 10.7 mL/min/ 1.73 m²). Nevertheless, additional studies of the clinical utility of ECOS are warranted.

Impact of eGFR on CKD detection and other clinical endpoints

To date, there has only been one pre-test post-test study, which has evaluated whether automatic laboratory reporting of eGFR with each request for serum creatinine level has an impact on detection of CKD.

Akbari et al (2004) conducted a before-and-after study of 324 patients ≥ 65 years at an outpatient family medicine practice. From the original cohort of 854 patients, 530 were excluded because a Cockcroft-Gault GFR could not be calculated within the 3 years prior to intervention ($n = 154$), Cockcroft-Gault GFR < 30 mL/min ($n = 39$), no serum creatinine level was measured during the intervention period ($n = 322$) or the patient was lost to follow-up ($n = 15$). The intervention consisted of automatic laboratory reporting of Cockcroft-Gault eGFR together with an educational intervention directed at primary care physicians. Recognition of CKD (GFR < 60 mL/min) by the primary care physician was the primary outcome measure and was significantly increased by the intervention increasing from 22.4% to 85.1% of patients with CKD. The main limitations of this study were the potential for co-intervention, ascertainment and selection biases.

There are no data available to determine whether routine reporting of eGFR will improve CKD outcomes in the community, although several RCTs are currently underway. There is some circumstantial evidence however, that the prognosis of patients with unreferred CKD may be better than those referred to renal units for their CKD.

John et al (2004) aimed to identify individuals with significant CKD in a community population ($n = 688,193$; 51.4% female, 98.7% Caucasian, 14% > 70 years) who had not been referred to a renal service. They queried

databases of two pathology laboratories using the same serum creatinine assays on a monthly basis. CKD was defined according to NIH criteria as a serum creatinine level $\geq 180 \mu\text{mol/L}$ in men or $135 \mu\text{mol/L}$ in women. Patients who were unknown to renal services were identified and followed up to establish survival, rate of referral, and change in GFR. A total of 84.8% of patients were unknown to renal services. The majority of unreferred patients were elderly (> 70 years).

During a mean follow-up period of 31.3 months, 8.1% of patients were referred. Median survival of the unreferred population was slightly lower than that of referred patients (27.4 vs 29.1 months, respectively, $p < 0.001$). The standardised mortality rate of the unreferred patients was only marginally increased in the elderly (< 60 years 34.5, 60–70 years 8.8, 70–80 years 3.2, > 80 years 1.2). Non-referral was an independent predictor of survival. Most unreferred patients had stable kidney disease (80% had a GFR decline $< 2\text{mL/min/year}$). The authors concluded that referral of all patients with CKD is unrealistic and inappropriate. In particular, their study's results suggest that the prognosis of unreferred patients is different from that of referred patients.

Applicability of eGFR to patient sub-groups

a) Children

- A considerable number of studies have shown that the Cockcroft-Gault equation is too imprecise in children to be clinically useful (Pierret et al 2003).
- The MDRD equation has been poorly studied in children. One investigation in 198 children found that the mean MDRD eGFR overestimated mean inulin clearance by 30% (Pierret et al 2004). Results were also over-dispersed with 95% of the mean differences in eGFR and inulin clearance distributed in the range of $\pm 60 \text{ mL/min/1.73 m}^2$.
- Eleven prediction formulae have been specifically developed for estimating GFR in children (Schwartz, Counahan-Barratt, modified Counahan-Barratt, Morris, Shull, Traub, Rudd, Dechaux, Ghazali-Barratt, van den Anker, and Paap) (Table 1) (Schwartz et al 1976, Counahan et al 1976, Morris et al 1982, Shull et al 1978, Traub et al 1980, Rudd et al 1980, Van der Anker et al 1995, Ghazali and Barratt 1974, Dechaux et al 1978, Paap et al 1995). Most of these formulae have been validated against creatinine clearance and many use the proportionality between GFR and height/serum creatinine.
- The two most common and most extensively validated prediction formulae in children are the Schwartz and Counahan-Barratt equations

(Table 3). Both equations have been observed to have acceptable accuracy and bias, although they are somewhat imprecise. Available data suggest that the bias of Schwartz eGFR increases at lower levels of GFR (Seikaly et al 1996, Seilaly et al 1998). The disparity in proportionality constants between the Schwartz and Counahan-Barratt formulae has been attributed to the different assays used to measure serum creatinine concentration in the validation studies (modified Jaffé reaction versus Jaffé reaction after adsorption onto ion-exchange resin to remove non-creatinine chromogens, respectively).

- These data suggest that the Cockcroft-Gault and MDRD equations are unreliable in children. The Schwartz and Counahan-Barratt formulae can provide rapid and convenient estimates of GFR, although clinicians should be aware of their imprecision in this setting.

b) The elderly

- Since the elderly are at greatly increased risk of CKD, it is important to ensure the validity of eGFRs in this population.
- Most of the studies generally indicate that MDRD eGFRs have acceptable performance characteristics in the elderly that are comparable or superior to Cockcroft-Gault eGFRs.

In the study by Froissart and coworkers (2005), 595 (28.4%) of 2095 subjects were over the age of 65 years. Compared with the Cockcroft-Gault formula, MDRD eGFR display superior precision and accuracy with less bias overall in gender as well as GFR subcategories. Similar findings were observed in the study by Levey et al (1999) (41.8% > 55 years).

Lamb et al (2003) tested the precision, accuracy and bias of a number of prediction equations (Cockcroft-Gault, MDRD, abbreviated MDRD, Jelliffe 2 and Baracsay) in 52 elderly volunteers (27 men, 25 women, mean age 80 years, range 62–92 years) with a variety of medical diagnoses. Predicted GFRs obtained by Cockcroft-Gault and Baracsay formulae were corrected for BSA. ¹⁸Cr-EDTA was used as the reference method (mean GFR 53.3 mL/min/1.73 m², range 15.9–100.2 mL/min/1.73 m²). The MDRD, abbreviated MDRD and Cockcroft-Gault equations showed the greatest precision (r^2 0.84, 0.83 and 0.84, respectively) with minimal bias (8.0%, 8.1% and -10.4%, respectively). MDRD and Cockcroft-Gault eGFRs represented an improvement in estimation of kidney function over creatinine clearance measurement. By contrast, the Baracsay formula, which was specifically developed in an older population, lacked sufficient precision to be clinically useful ($r^2 = 0.56$).

Apart from the Baracsay formula (Baracsay et al 1997), Sanaka et al (1996) attempted to improve the predictive ability of prediction formulae for GFR in 90 elderly individuals with sarcopenia, by including albumin as an explanatory

variable. They found that their new formula (Table 1) was more accurate (lower root mean square error), less biased and more precise than the Cockcroft-Gault equation. However, a major limitation of this study was that the new prediction equation was not validated in an independent cohort.

One of the current controversies with respect to applying GFR prediction equations to the elderly is how to take account of the age-related decline in renal function. After the age of 30 years, GFR progressively declines at an average rate of 8 mL/min per decade (Coresh et al 2003). Based on North American data (Coresh et al 2003), 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 (Lindeman et al 1985). Data from the only longitudinal study to address this issue (Boston Longitudinal Study of Aging) (Lindeman et al 1985) suggest that the decline in GFR with increasing age is largely attributable to hypertension. Another study showed that heart failure was a significant contributing factor (Fliser et al 1997). The Italian Longitudinal Study on Ageing (ILSA) similarly demonstrated that age-associated decline in renal function in elderly subjects is associated with co-existing cardiovascular diseases and risk factors (Baggio et al 2005). Moreover, a reduced GFR remains a strong predictor of all-cause and cardiovascular mortality, even in elderly populations (Fried et al 1998, Shlipal et al 2002, Manjunath et al 2003, Shlipak et al 2005).

The Australasian eGFR Working Group has suggested that automatic laboratory reporting of eGFR may include age-related reference intervals for individuals aged ≥ 65 years. 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.

c) Diabetics

Both the Cockcroft-Gault and the MDRD equations were developed in predominantly non-diabetic individuals, thereby raising questions regarding their applicability to patients with diabetes mellitus.

Poggio and coworkers (2005) studied 249 CKD patients with diabetes and observed that the abbreviated MDRD equation performed better than the Cockcroft-Gault equation with respect to bias (1% vs 22%, $p < 0.05$) and accuracy within 30% (63% vs 53%, $p < 0.05$) and within 50% (87% vs 70%, $p < 0.05$).

Ibrahim et al (2005) evaluated the performances of the abbreviated MDRD and Cockcroft-Gault equations against iothalamate GFR measurements in 1286 individuals with Type 1 diabetes mellitus from the Diabetes Control and Complications Trial (DCCT). Both formulae lacked precision (r^2 0.13 vs 0.11, respectively) but showed reasonable accuracy within 30% (78% vs 88%) and within 50% (98% vs 97%). To improve accuracy of the MDRD formula, the authors took the predictors of MDRD eGFR (serum creatinine, age and gender) and refitted the same linear regression equation on a randomly selected training subset of the DCCT data ($n = 815$). The refitted equation, shown in Table 1, was then applied to the remaining validation subset ($n = 456$) and showed superior accuracy within 10% compared with the MDRD and Cockcroft-Gault equations (56%, 25% and 39%, respectively).

The above studies suggest that the MDRD equation can provide reasonable estimates of GFR in diabetic subjects.

c) Those with normal and near-normal renal function

A number of studies have suggested that the performance of the MDRD and Cockcroft-Gault prediction formulae is impaired at higher levels of GFR (especially with respect to precision). This particularly applies to the MDRD equation, which was originally derived in CKD patients (GFR < 60 mL/min/1.73 m²). In contrast, the Cockcroft-Gault equation was initially derived in a population with a higher mean GFR (mean creatinine clearance 72.7 ± 36.6 mL/min).

Lin et al (2003) reported that the MDRD and abbreviated MDRD equations were more precise (r^2 0.15 and 0.14) and accurate within 30% (both 78%) than the Cockcroft-Gault formula (r^2 0.04, within 30% accuracy 45%) in 117 healthy potential kidney donors. However, the MDRD equations consistently underestimated iothalamate and DTPA GFR (-15.2 and -18.3 mL/min/1.73 m²), while Cockcroft-Gault consistently overestimated GFR (16.8 mL/min/1.73 m²).

Similarly, Froissart and coworkers (2005) demonstrated that the performance of the MDRD equation, as judged by precision, bias and combined root mean square error, was comparable or superior to Cockcroft-Gault at measured GFRs above 60 mL/min/1.73 m².

Poggio and coworkers (2005) observed that the MDRD equation significantly underestimated the iothalamate GFR when compared with the Cockcroft-Gault formula (bias -9.0 vs 1.9 mL/min/1.73 m²) in 457 healthy potential kidney donors. The respective accuracies within 30% were 86% and 85%.

Rule et al (2004) demonstrated significant imprecision of the abbreviated MDRD ($r^2 = 0.07$) and Cockcroft-Gault equations ($r^2 = 0.12$) compared with iothalamate GFR in 365 healthy potential kidney donors.

These studies suggest that prediction equations should be used with caution in patients with GFRs > 60 mL/min/1.73 m².

d) *Extremes of body size*

The use of actual body weight in the Cockcroft-Gault formula overestimates GFR in obese subjects and underestimates GFR in underweight individuals. Several authors have advocated calculating eGFR using lean body weight rather than actual body weight (Gault et al 1992, Sawyer et al 1982, Hallynck et al 1981). Unfortunately, this requires separate prediction equations and the use of these alternative formulae have not been well validated.

Another significant problem is the lack of consensus regarding whether or not GFR should be corrected for body surface area (BSA). The MDRD equation estimates GFR normalised to BSA as mL/min/1.73 m². In contrast, the Cockcroft-Gault equation estimates GFR in mL/min and requires a separate adjustment for estimated BSA (which is not often done). The principal rationale behind indexing GFR is that kidney weight and basal metabolic rate are proportional to BSA in normal individuals (Rustad 2004). However, it is uncertain whether indexing GFR to BSA might lead to underestimation of renal function in obese patients, since there are conflicting data regarding whether obese subjects have higher absolute GFRs (Anastasio et al 2000, Ribstein et al 1995, Brochner-Mortensen et al 1980). Other investigators have suggested alternative indexing parameters to BSA, such as height (Anastasio et al 2000) or metabolic rate (Singer et al 2000). GFR in mammals weighing from 30 g to 503 kg scales to [body weight]^{0.77}, which is close to the relationship for metabolic rate ([body weight]^{0.75}), such that GFR per unit body weight (or Kt/V) decreases significantly with increasing body size. Others have suggested an intuitive, but unproven, hypothesis that smaller body size engenders lower metabolic demand such that smaller individuals (e.g. women and the elderly) don't need as high a GFR as larger subjects (Rustad 2003).

The largest and best-performed study of the influence of body size on the predictive ability of eGFR equations has been that by Froissart et al (2005). When patients were divided into BMI groups according to the WHO classification (< 18.5 kg/m² n = 94, 18.5–25 kg/m² n = 1010, 25–30 kg/m² n = 712, > 30 kg/m² n = 279), the MDRD formula was less biased, more precise and more accurate than the BSA-corrected Cockcroft-Gault formula in all patients with BMI ≥ 18.5 kg/m². The mean magnitude of bias was less than 2.5 mL/min/1.73 m² with the abbreviated MDRD equation in each of the subcategories. However, the MDRD formula largely overestimated kidney function in underweight subjects (observed bias 12.2 ± 24.8 mL/min/1.73 m²).

Salazar and Corcoran (1998) developed an eGFR prediction formula based on estimated fat-free body mass (Table 1) in 12 obese and 9 normal-weight subjects. They reported that their formula provided eGFRs that were as accurate as the Cockcroft-Gault and Jelliffe formulae for estimating creatinine clearance in the normal-weight population and far superior to these methods when applied to obese subjects. However, the Salazar-Corcoran formula has not been sufficiently well validated to determine whether it may be a satisfactory alternative prediction equation in obese subjects. A similar argument applies to the GFR prediction formula developed in obese subjects

by Saracino et al (2004).

The studies to date suggest that the abbreviated MDRD equation still demonstrates acceptable performance characteristics in overweight and obese subjects, but should be applied with caution to underweight individuals (BMI < 18.5 kg/m²).

e) Renal transplant recipients

Nankivell et al (1995) developed a new prediction equation for estimating GFR in renal transplant recipients (Table 1). The study was based on 751 DTPA GFR measurements in 146 consecutive renal transplant recipients at a single centre. A total of 256 randomly selected GFR measurements were selected for derivation of three new formulae and then tested on a separate, independent group of randomly selected GFR measurements (n = 255). The performance characteristics of the new formulae were compared with the Cockcroft-Gault, Mawer, Hull, Jelliffe¹, Jelliffe² and Siersbaek-Nielson methods and found to provide better precision and less overall scatter than these previously published equations. Formula B was proposed to replace other published formulae for calculating GFR in renal transplant recipients. The major weakness of this study was the fact that the prediction equations were not tested in a large independent cohort, making the external validity of this study questionable.

Mariat and coworkers (2004) evaluated the performance characteristics of the Nankivell, MDRD, Cockcroft-Gault, Walser, and Jelliffe equations against creatinine and inulin clearances in 294 renal transplant recipients at a single institution in France. In terms of accuracy, the MDRD, Walser and Jelliffe equations were quite similar and were superior to the other tested models. Nevertheless, all equations displayed appreciable lack of agreement with the reference method (inulin clearance). The proportion of predicted GFR differing from inulin clearance by ± 10 mL/min/1.73 m², ranged from 34% for the Jelliffe formula (best) to 53% for the Nankivell formula (worst) (Cockcroft-Gault 48%, MDRD 41%).

Rodrigo and associates (2003) validated the Cockcroft-Gault, MDRD and Nankivell formulae against a reference method of averaged urinary urea and creatinine clearances in 125 deceased donor renal transplant recipients. The MDRD formula showed the best correlation ($r^2 = 0.55$), the lowest bias (-1.65 ± 4.4 mL/min/1.73 m²) and the narrowest limits of agreement (-10.61 to 7.31 mL/min/1.73 m²). The major weakness of this study was the use of a suboptimal reference method.

A cohort study of 40 lung transplant recipients (2000) found that the MDRD equation performed better than reciprocal creatinine or Cockcroft-Gault eGFR against iothalamate clearance.

Overall, the current evidence suggests that the MDRD formula is the best available equation for estimating GFR in transplant recipients and has reasonable performance characteristics.

f) Non-steady state of creatinine

The use of serum creatinine concentration to estimate GFR relies on the individual being in steady state and the ability to estimate the average rate of creatinine generation. eGFR from any prediction equation will therefore be unreliable in the settings of acute renal failure, muscle breakdown or fluctuating dietary intake.

Hallynck et al (1981) modified their original equation to contain a correction factor for acute changes in renal function (Table 1). This required 2 separate measurements of serum creatinine concentration spaced over time. However, this equation has not been sufficiently validated to recommend its use for calculating GFR in non-steady state situations.

g) Certain ethnic groups

Data from NHANES III (Clase et al 2002) show that, for any given age and sex stratum, serum creatinine levels are higher among blacks than whites. The reason for this racial variation is unknown, but may be the result of lower GFR, lower renal tubular secretion of creatinine and/or increased creatinine generation (e.g. increased muscle mass) (Coresh et al 1998, Jones et al 1998, Goldwasser et al 1997). The MDRD equation is the only eGFR prediction formula which contains a race variable (African-American or not) and has been shown in several studies to provide better precision and accuracy of eGFR than other published formulae in African-American subjects. Using the data from the African-American Study of Hypertension and Kidney Disease (AASK), Lewis et al (2001) developed a new five-term AASK formula (Table 1) for estimating GFR that exhibited comparable performance to the MDRD formula in the African-Americans in AASK.

The influence of ethnicity on the performance characteristics of eGFR formulae has been poorly studied. In particular, none of the equations has been adequately validated in Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders and Indo-Asian populations. GFR prediction equations should therefore be applied with caution in these groups.

h) Certain disease states

Significant alterations of muscle mass (e.g. muscular dystrophies, paraplegia, quadriplegia, amputations) will result in the excretion of much less creatinine per kilogram of body weight than predicted, thereby reducing the accuracy of eGFR formulae. The performance characteristics of prediction equations in these settings have been poorly studied and should therefore be applied with caution.

Mirahmadi et al (1983) compared measured endogenous creatinine clearance with Cockcroft-Gault predicted clearance in 22 paraplegic, 36 tetraplegic and 11 ambulatory male individuals, as well as 11 ambulatory females, all of whom had normal renal function. While the predicted and measured values

were closely concordant in the ambulatory patients, the predicted values in the spinal cord injured patients consistently exceeded the measured values. They suggested a modification of the Cockcroft-Gault formula by using a correction factor of 0.8 in paraplegics and 0.6 in tetraplegics. This modified formula has not been formally validated in an independent cohort.

Other disease states, such as malnutrition and liver cirrhosis, would also likely undermine the performance of GFR prediction equations.

Orlando and coworkers (1999) evaluated the accuracy and precision of measured and Cockcroft-Gault calculated creatinine clearances as indices of GFR by comparing their values to those of inulin clearance in 10 healthy subjects and 20 patients with either Child's class A or Child's class C liver cirrhosis. A significant correlation was observed between Cockcroft-Gault and inulin GFR in the normal and Child's A groups ($r = 0.73$, $p < 0.02$ and $r = 0.69$, $p < 0.025$, respectively). However, in Child's class C cirrhotics, Cockcroft-Gault GFR significantly overestimated inulin GFR (predicted-to-true GFR ratio 1.23, CV 20%) and no significant correlation was found between predicted and true GFR ($r = 0.58$, $p > 0.05$). The poor performance of the Cockcroft-Gault formula in the Child's C group was attributed to their lower muscle mass, reduced ability to convert creatine to creatinine, and the presence of ascites. The major weaknesses of this study were its small size and the lack of any subsequent independent validation in other cirrhotic populations.

Summary of the evidence

There have been no RCTs comparing the effect of using eGFR versus other measures of kidney function on relevant clinical outcomes, such as detection or prevention of CKD, prevention of cardiovascular disease or reduction in medication-related adverse events. However, automated laboratory reporting of eGFR with each serum creatinine request has been shown in one before-and-after study to substantially improve the detection of CKD in the community by primary care physicians.

At least 46 GFR prediction equations have been developed. The most precise, accurate and extensively validated of these formulae in adults are the Cockcroft-Gault, MDRD and abbreviated MDRD methods. 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. Neither equation performs well enough to be clinically confident of estimating GFR in patients with normal or near-normal renal function (e.g. assessment of potential living kidney donors). Lack of calibration of serum creatinine assays

can represent a source of significant error in the estimation of GFR by empiric formulae.

Both the Cockcroft-Gault and MDRD equations have generally been shown to be superior to creatinine clearance measurements for measuring GFR. However, direct measurement of GFR may be warranted in certain situations when eGFRs might be unreliable, including extremes of age, extremes of body size, certain disease states (e.g. muscle disorders, paraplegia, quadriplegia, amputations) and certain ethnic groups where the MDRD formula has not yet been validated (e.g. Asians, Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders).

For children, the Schwartz and Counahan-Barratt equations have been the most extensively validated. These formulae are convenient, but are limited by imprecision.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Estimates of GFR are the best overall indices of the level of kidney function.

- The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size. The following equations provide useful estimates of GFR:
 - a) in adults, the MDRD Study and Cockcroft-Gault equations, and
 - b) in children, the Schwartz and Counahan-Barratt equations.
- The serum creatinine concentration alone should not be used to assess the level of kidney function.
- Clinical laboratories should report an estimate of GFR using a prediction equation, in addition to reporting the serum creatinine measurement.
- Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard.
- Measurement of creatinine clearance (for example, 24 hours) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for:
 - o estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, creatinine supplements) or muscle mass (amputation, malnutrition, muscle wasting);
 - o assessment of diet and nutritional status;
 - o assessment of need to start dialysis.

British Renal Association: Kidney function in patients with CKD should be assessed by formula-based estimation of GFR using either the 4-variable MDRD or Cockcroft and Gault equations. Level of evidence III.

All clinical laboratories should report estimates of GFR alongside measurements of serum creatinine. Laboratories should communicate to their users (possibly using the laboratory report) the following information:

- a) which formula has been used in the estimation
- b) that GFR estimates between 60 and 89 mL/min/1.73 m² do not indicate CKD unless there is other clinical / laboratory evidence of disease
- c) that, where information on ethnic origin is unavailable, MDRD-based GFR estimates may be approximately 20% higher in African-Caribbeans.

There is no need to collect 24-h urine samples to measure creatinine clearance in primary care. Level of evidence III.

A renal network, which may or may not be co-terminous with a pathology network, should provide comparable creatinine results, ideally by the use of identical methodology. This should be audited by internal quality control procedures across the network and satisfactory performance in a national quality assessment scheme. Renal/pathology networks should agree a common approach to the estimation of GFR.

Canadian Society of Nephrology: GFR estimated from the average of urea and creatinine clearance is the preferred method of following changes in residual renal function.

For a predialysis patient:

$$\text{GFR (L/wk per 1.73 m}^2\text{)} = (54.6 \times \text{weekly Kt/V}_{\text{urea}}) + 17.48$$

There are no data to suggest a level of GFR at which dialysis should be recommended regardless of symptoms, but as residual renal function decreases, clinical follow-up should increase in frequency.

European Best Practice Guidelines: GFR should only be estimated using a method validated in patients with advanced renal failure. The preferred method for calculating GFR in advanced renal failure is the mean of urea and creatinine clearance. The latter is best calculated from a 24-h urine collection and normalised to 1.73 m².

Other examples of validated GFR estimations are: MDRD equation, Indicator decay methods (e.g. Iohexol, Iothalamate, EDTA, inulin), Creatinine clearance after oral cimetidine.

International Guidelines: Kidney Disease Improving Global Outcomes:

II.B.1 Estimated GFR should be reported automatically using an equation based on serum creatinine and patient variables following assay calibration. Clinical laboratories are critical for the implementation. This recommendation does not preclude reporting GFR estimates prior to calibration.

II.B.2. GFR estimates have been reported successfully using several different models.

a. Interpretation of GFR estimates in the context of CKD definition:

- “GFR < 60 ml/min/1.73m² for 3 or more months is consistent with CKD”
- “GFR > 60 ml/min/1.73m² and kidney damage that is present for 3 or more months is consistent with CKD”
- “GFR > 60 ml/min/1.73m² without kidney damage is not consistent with CKD”

b. Accounting for imprecision of GFR estimates at higher values:

- If creatinine assay is calibrated, numerical value of GFR should be reported for GFR < 90 or “GFR > 90” for higher values
- If creatinine assay is not calibrated, numerical value of GFR should be reported for GFR < 60 or “GFR > 60” for higher values.
- Numerical value of GFR at all GFR levels, with qualification that levels of GFR > 60 are imprecise

c. For all of the above, GFR levels of < 60 should be highlighted as abnormal.

II.C GFR Estimating Equations

II.C.1. Estimating equations for GFR should have the following characteristics:

- Developed in a large cohort
- Evaluated in an independent cohort
- Validated to have adequate precision and low bias against a gold standard measure of GFR (not creatinine clearance)
- Practical to implement taking into consideration cost, required data elements, generalisability, calibration and reliability of the assay.

II.C.2. Abbreviated MDRD Study equation meets these criteria. The MDRD Study equation has been validated in patients with diabetic (type 2) and non-diabetic kidney disease and in kidney transplant recipients. It has been validated in U.S. whites and African-Americans, European whites, but requires verification for other groups, countries and racial and ethnic groups.

II.C.3. Cockcroft-Gault formula is more difficult to implement in clinical laboratories. It requires weight (and height for body surface area adjustment). Furthermore, the calibration of serum creatinine cannot be performed because the serum samples laboratory are not available.

II.C.4. Both MDRD Study and Cockcroft-Gault equations are imprecise at high values for GFR (low values for serum creatinine). This may cause misclassification in these groups, including:

- normal individuals

- children
- pregnant women
- conditions associated with hyperfiltration.

II.D. Clinical Circumstances in which Clearance Measurements May Be Necessary to Estimate GFR (Table 6)

II.D.1. Situations in which GFR estimation may be unreliable:

- Patients with grossly abnormal muscle mass (e.g. amputation, paralysis, muscular disease)
- Low body mass index ($<18.5 \text{ kg/m}^2$)
- High or low intake of creatinine or creatine (e.g. dietary supplements, vegetarians)

II.D.2. A high degree of accuracy is needed for:

- Potential kidney donors
- Prior to dosing with medications that have high toxicity that are excreted by the kidneys

II.D.3. Methods for measurement of GFR:

- Exogenous filtration markers including inulin, iothalamate (^{125}I -labeled or unlabeled), ^{51}Cr -EDTA, ^{99}Tc -DTPA and iothexol provide good accuracy
- Urinary or plasma clearance of exogenous filtration markers can be used to measure GFR
- Urinary clearance of exogenous filtration markers is less susceptible to error than plasma clearance
- Timed creatinine clearance may be a useful alternative when exogenous filtration markers are not available.

II.E. Drug Dosing

II.E.1. Drug dosing should be based on GFR estimates without surface area adjustment. This is most important for individuals with body size substantially different from 1.73 m^2 (children, obese, very large or small adults).

- Cockcroft-Gault equation provides unadjusted creatinine clearance.
- MDRD Study equation provides adjusted GFR.

II.E.2. Recommendations for drug dosing should be based on methods for measuring or estimating GFR that were used in pharmacokinetic studies. This is most important for narrow ranges of GFR or for drugs with significant toxicity. Otherwise, either MDRD Study or Cockcroft-Gault equation provides reasonable estimates.

II.E.3. Most studies are based on creatinine clearance. Many pharmacies use Cockcroft-Gault equation to estimate creatinine clearance before dispensing drugs. Future studies should provide drug dosing information based on both GFR and creatinine clearance. This will facilitate use of GFR estimates.

Implementation and audit

The ANZDATA registry and its participating renal units should be adequately resourced to establish and maintain a CKD registry. Information on serum creatinine and eGFR should be collected and collated against cardiovascular, renal and overall survival outcomes.

Suggestions for future research

1. Estimation equations for GFR should be validated in more diverse groups, including:
 - Patients with BMI > 35 kg/m² and < 18.5 kg/m²
 - Elderly patients
 - Specific ethnic groups (Asians, Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders).
2. The accuracy of formulae to follow progression of CKD should be determined in longitudinal studies.
3. A database of research studies and clinical populations with GFR measurements and measurements of serum creatinine should be established from a variety of countries, racial and ethnic groups, to develop improved GFR estimating equations.
4. Further evaluation of the clinical utility and diagnostic accuracy of evolving connectionist systems (ECOS) are warranted.
5. The within and between method variability in GFR measurement should be assessed and agreement on protocols developed to reduce this variation.
6. Formulae for estimating GFR not corrected for BSA, suitable for drug dosing, should be assessed. The process of 'uncorrecting' MDRD estimates of GFR has not been validated and may not be valid.

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Appendices

Table 1 Equations for estimated glomerular filtration rate (eGFR) in adults based on serum creatinine concentration*

Cockcroft-Gault (1976)

GFR (mL/min) = (140 – age) x weight x 1.228 / S_{Cr} x (0.85 if female)

MDRD (1999)

GFR (mL/min/1.73 m²) = 170 x (sCr / 88.4)^{-0.999} x age^{-0.176} x (Ur x 2.78)^{-0.17} x alb^{0.318} x (0.762 if female) x (1.18 if African-American)

Abbreviated MDRD (2000)

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

Quadratic (Rule) (2004)

GFR (mL/min/1.73 m²) = exp(1.911 + 464 / sCr – 2.186.9 / (sCr)² – 0.00686 x age – (0.205 if female))

If S_{Cr} < 71 µmol/L, use 71 µmol/L for S_{Cr}

Jelliffe (2004) (1971)

For men, C_{Cr} (mL/min) = 8840 / S_{Cr} – 12

For women, C_{Cr} (mL/min) = 7072 / S_{Cr} – 7

Modified Jelliffe (1973)

C_{Cr} (mL/min) = (98 – 0.8 x (age - 20)) x (0.9 if female) / (S_{Cr} / 88.4)

Siersbaek-Nielsen nomogram (1971)

A nomogram is used to read creatinine clearance, based on Age, weight and S_{Cr}.

Tougaard nomogram (1976)

A nomogram is used to read GFR, based on 2 separate measurements of S_{Cr}.

Jadrony nomogram (1965)

A nomogram is used to read creatinine clearance, based on weight and S_{Cr}.

Salazar-Corcoran (1988)

For men, C_{Cr} (mL/min) = (137 – age) x (0.285 x weight) + (12.1 x height²) / (0.916 x S_{Cr})

For women, C_{Cr} (mL/min) = (146 – age) x (0.287 x weight) + (9.74 x height²) / (0.679 x S_{Cr})

Gates (1985)

For men, C_{Cr} (mL/min) = (89.4 x (S_{Cr} / 88.4)^{-1.2}) + (55 - age) x (0.447 x (S_{Cr} / 88.4)^{-1.1})

For women, C_{Cr} (mL/min) = (60 x (S_{Cr} / 88.4)^{-1.2}) + (56 - age) x (0.3 x (S_{Cr} / 88.4)^{-1.1})

Mawer (1972)

For men, C_{Cr} (mL/min) = 100 x weight x (29.3 – 0.203 x age) x (1 – S_{Cr} / 2947) / (16.29 x S_{Cr})

For women, C_{Cr} (mL/min) = 100 x weight x (25.3 – 0.175 x age) x (1 – S_{Cr} / 2947) / (16.29 x S_{Cr})

Hallynck (1981)

C_{Cr} (mL/min) = 88.4 x E / S_{Cr} (where E is age-dependent urinary creatinine excretion read off a nomogram)

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Hallynck 2 (1981)(contains correction factor for acute changes in renal function)

$$C_{Cr} \text{ (mL/min)} = 88.4 \times E / S_{Cr} + (600 \times (S_{Cr1} - S_{Cr2})) / (t \times S_{Cr})$$

(where E is age-dependent urinary creatinine excretion read off a nomogram; S_{Cr} is the average of 2 separate serum creatinine measurements S_{Cr1} and S_{Cr2} ; t is the time interval in hours between S_{Cr1} and S_{Cr2})

Davis-Chandler (1996)

$$\text{GFR (mL/min)} = (140 - \text{age}) \times (\text{weight})^2 / 72 \times 1.228 / S_{Cr} \times (0.85 \text{ if female})$$

Mogensen-Heilskov (1980)

$$\text{GFR (mL/min)} = ((10000 / S_{Cr}) - 14) / 0.90$$

Effersee (1957)

$$\text{For men, } C_{Cr} \text{ (mL/min)} = 10^{(-1.09 \times \log(S_{Cr} / 88.4) + 1.9)}$$

$$\text{For women, } C_{Cr} \text{ (mL/min)} = 10^{(-1.06 \times \log(S_{Cr} / 88.4) + 1.78)}$$

Edwards-Whyte (1959)

$$\text{For men, } C_{Cr} \text{ (mL/min)} = 8336 / S_{Cr} - 1.8$$

$$\text{For women, } C_{Cr} \text{ (mL/min)} = 6179 / S_{Cr} + 2.2$$

Sanaka (1996)

$$\text{For men, } C_{Cr} \text{ (mL/min)} = (1.9 \times \text{alb} + 32) \times \text{weight} / (1.13 \times S_{Cr})$$

$$\text{For women, } C_{Cr} \text{ (mL/min)} = (1.3 \times \text{alb} + 29) \times \text{weight} / (1.13 \times S_{Cr})$$

Couchoud creatinine cut-off points (1999)

$$\text{GFR } 80 \text{ mL/min} = S_{Cr} \text{ } 115 \text{ } \mu\text{mol/L (males), } 90 \text{ } \mu\text{mol/L (females)}$$

$$\text{GFR } 60 \text{ mL/min} = S_{Cr} \text{ } 137 \text{ } \mu\text{mol/L (males), } 104 \text{ } \mu\text{mol/L (females)}$$

$$\text{GFR } 30 \text{ mL/min} = S_{Cr} \text{ } 177 \text{ } \mu\text{mol/L (males), } 146 \text{ } \mu\text{mol/L (females)}$$

AASK (2001) (African Americans)

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 222 \times (S_{Cr} / 88.4)^{-0.974} \times (\text{age})^{-0.267} \times (0.757 \text{ if female}) \times (\text{Ur} \times 2.78)^{-0.108} \times (\text{albumin})^{0.372}$$

Toto (1997) (African Americans)

$$\text{GFR (mL/min/1.73 m}^2\text{)} = -0.29 \times (\text{age} - 52) + 7780 / S_{Cr} - 0.77 \times (\text{BMI} - 30)$$

Yukawa (1999) (Japanese)

$$C_{Cr} \text{ (mL/min)} = (470 - \text{age}) \times \text{weight} / ((3.26 \times S_{Cr}) + 98.7)$$

Bjornsson (1979)

$$\text{For men, } C_{Cr} \text{ (mL/min)} = (27 - 0.173 \times \text{age}) \times \text{weight} \times 6.188 / S_{Cr}$$

$$\text{For women, } C_{Cr} \text{ (mL/min)} = (25 - 0.175 \times \text{age}) \times \text{weight} \times 6.188 / S_{Cr}$$

Hull (1981)

$$C_{Cr} \text{ (mL/min)} = ((145 - \text{age}) - 3) \times (0.85 \text{ if female}) \times 88.4 / S_{Cr}$$

Reciprocal serum creatinine

$$\text{GFR (mL/min)} = 100 / S_{Cr}$$

Walser (1993)

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For men $GFR (mL/min/3m^2) = 669 / S_{Cr} - 0.103 \times age + 0.096 \times weight - 6.66$

For women $GFR (mL/min/3m^2) = 535 / S_{Cr} - 0.08 \times age + 0.08 \times weight - 4.81$

Mitch-Walser (1980)

For men, $C_{Cr} (mL/min) = ((2458 / S_{Cr}) - 0.04) \times 0.69 \times weight$

For women, $C_{Cr} (mL/min) = ((2089 / S_{Cr}) - 0.04) \times 0.69 \times weight$

Baracsay (1997) (elderly)

$C_{Cr} (mL/min) = 88 + 4909 / S_{Cr} - (1.06 \times age)$

Schwartz (1976) (children)

$C_{Cr} (mL/min) = K \times height / S_{Cr}$

K varies with age and gender (2920 pre-term infants; 3980 full-term infants; 4860 both sexes 2-12 yo; 4860 girls 13-21 yo; 6190 boys 13-21 yo)

Counahan-Barratt (1976) (children)

$GFR (mL/min/1.73 m^2) = 3800 \times height / S_{Cr}$

Morris (1982) (children)

$GFR (mL/min/1.73 m^2) = 4000 \times height / S_{Cr}$

Shull (1978) (children)

$C_{Cr} (mL/min/1.73 m^2) = ((0.035 \times age) + 0.236) \times 8840 / S_{Cr}$

Paap (1995) (children)

$C_{Cr} (mL/min/1.73 m^2) = 4600 \times height / S_{Cr} - 3.6$

Traub (1980) (children)

$C_{Cr} (mL/min/1.73 m^2) = 4243 \times height / S_{Cr}$

Rudd (1980) (children)

For males, $C_{Cr} (mL/min) = weight \times (11.173 + (0.879 \times age)) \times 0.12 / ((S_{Cr} / 88.4) \times BSA)$

For females, $C_{Cr} (mL/min) = weight \times (10.106 + (0.795 \times age)) \times 0.12 / ((S_{Cr} / 88.4) \times BSA)$

Dechaux (1978) (children)

$C_{Cr} (mL/min) = (46 \times height / S_{Cr}) - 3.6$

Ghazali-Barratt (1974) (children)

$C_{Cr} (mL/min/1.73 m^2) = 10.6 \times (15.4 + (0.46 \times age)) \times weight / (S_{Cr} \times BSA)$

Van den Anker (1995) (pre-term infants)

$GFR (mL/min) = 0.29 + 40 / S_{Cr}$

Ibrahim (2005) (Type 1 diabetics)

$GFR (mL/min/1.73 m^2) = \exp(5.27 - 0.3739 \times \log(S_{Cr} / 88.4) - 0.1472 \times \log(age) - (0.066 \text{ if female}))$

Tzamaloukas-Murata (2002) (CAPD patients)

Creatinine excretion (mg/day) = $302.15 - 4.38 \times age + (171.23 \text{ if male}) - (39.04 \text{ if diabetic}) + 11.73 \times weight$

Nankivell (1995) (Renal transplant recipients)

$GFR (mL/min) = 6700 / S_{Cr} + weight / 4 - Ur / 2 - 100 / (height)^2 + (35 \text{ if male or } 25 \text{ if female})$

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Saracino (2004) (obese subjects)

GFR (mL/min) = Cockcroft-Gault GFR x (1.25 - 0.012 BMI)

Wright (2001) (Cancer patients)

For Jaffe S_{Cr} , GFR (mL/min) = (6550 – (38.8 x age)) x (0.832 if female) x BSA / S_{Cr}

For enzymatic S_{Cr} , GFR (mL/min) = (6230 – (32.8 x age)) x (0.77 if female) x BSA / S_{Cr}

Martin (1998) (Cancer patients)

GFR (mL/min) = 163 x weight x (1 – (0.00496 x age)) x (0.748 if female) / S_{Cr}

Tsubaki (1993) (Cancer patients)

GFR (mL/min) = Cockcroft-Gault GFR x 0.75

Robinson (1990) (Cancer patients)

GFR (mL/min) = (2.11 – 0.007 x age – 0.014638 x S_{Cr} + 0.0166 x weight – (0.329 if female)) x 60

Mirahmadi (1983) (Paraplegics, Tetraplegics)

GFR (mL/min) = Cockcroft-Gault GFR x K (K = 0.8 for paraplegics, 0.6 for tetraplegics)

S_{Cr} = serum creatinine concentration; GFR = glomerular filtration rate; C_{Cr} = creatinine clearance

* For each equation, serum creatinine (S_{Cr}) is in $\mu\text{mol/L}$, serum urea (Ur) is in mmol/L , serum albumin (alb) is in g/L , age is in years, height is in metres, weight is in kilograms, body mass index is in kg/m^2 and body surface area (BSA) is in m^2 .

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Table 2 Accuracy and bias of the most extensively validated equations commonly employed to determine eGFR in adults

Equation	Initial validation			Subsequent validation studies			Groups tested in	Accuracy within		r ²	Bias %	Study ID (author, year)
	Year	N	Ref. method	No.	N	Validated against		30%	50%			
Cockcroft-Gault	1976	236	C _{Cr}	75	14,926	Inulin Iothalamate ⁵¹ Cr-EDTA DTPA Mag III Iohexol	CKD , Eld, NRF, RTx, DM, AA, KiD, Obese, CA, HIV, Tx, ICU, CLD	70 (58-100)	88 (77-100)	0.66 (0.06-0.94)	-4.9 (-27 to 30)	Lewis, 2001; Pierrat, 2003; Poggio, 2005; Lamb, 2003; Lewis, 2001; Lin, 2003; Gault, 1992; Saracino, 2004; Nankivell, 1995; Mariat, 2004; Rodrigo, 2003; Hallynck, 1981; Daniel, 2004; Gates, 1985; Toto, 1997; Hull, 1981; Durakovic, 1986; Rolin, 1984; Cochran, 1993; Bostom, 2002; Vervoort, 2002; Bertolatus, 2001; Lemann, 1990; Charleson, 1980; Waller, 1991; DeSanto, 1991; Bedros, 1998; Goerd, 1997; Wiczorowska-Tobis, 2004; Hojs, 2004; Reinhardt, 2004; Itoh, 2003; Hoek, 2003; Poole, 2002; Burkhardt, 2002; Burkhardt,

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												2002; Sanusi, 2000; Rule, 2004a; Rule, 2004b; Ibrahim, 2005; Salazar, 1988; Mirahmadi, 1983; Orlando, 1999; Robinson, 1990; Robert, 1993; Erley, 2001; Luke, 1990; Nicoll, 1991; Dooley, 2000; Perlemoine, 2003; Tan, 2002; Montgomery, 2000; Rhodes, 1987.
MDRD	1999	1070	lothalamate	16	5,069	Inulin ⁵¹ Cr-EDTA DTPA Mag III Iohexol CCr	CKD , Eld, NRF, RTx, DM, AA, KiD	81 (24-91)	97 (71-98)	0.56 (0.01-0.90)	-7.4 (-24 to 25)	Levey, 1999; Pierrat, 2003; Lewis, 2001; Lin, 2003; Rodrigo, 2003; Bostom, 2002; Vervoort, 2002; Bedros, 1998; Lamb, 2003; Ibrahim, 2005; Mariat, 2004; Broekroelofs, 2000; Bertolatus, 2001; Wieczorowska-Tobis, 2004; Harmoinen, 2003.
Abbreviated MDRD	1999	1070	lothalamate	13	8,654	Inulin DTPA Iohexol ⁵¹ Cr-EDTA	CKD , Eld, NRF, DM, AA, KiD	77 (28-91)	97 (82-98)	0.46 (0.02-0.90)	-6.2 (-38 to 8.1)	Levey, 1999; Levey, 2000; Poggio, 2005; Lewis, 2001; Lin, 2003; Harmoinen, 2003; Froissart, 2005; Lamb, 2003; Rule, 2004; Rule, 2004; Ibrahim, 2005.

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C_{Cr} = creatinine clearance; CKD = chronic kidney disease; Eld = elderly; NRF = normal renal function; RTx = renal transplant recipients; DM = diabetes mellitus; AA = African-Americans; KiD = kidney donors; CA = cancer patients; HIV = AIDS patients; Tx = trauma patients; ICU = intensive care unit patients; CLD = chronic liver disease.

Values for precision and bias represent the median (range) values for all studies in which data were provided.

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Table 3 Accuracy and bias of the most extensively validated equations commonly employed to determine eGFR in children

Equation	Initial validation			Subsequent validation studies			Accuracy within		r ²	Bias %	Study ID (author, year)
	Year	N	Ref. method	No.	N	Validated against	30%	50%			
Schwartz	1976	186	C _{Cr}	14	2,192	Inulin Iothalamate Iohexol Tc-DTPA C _{Cr}	75 (53-91)	89 (64-97)	0.70 (0.2-0.82)	10.4 (-7.9 to 32.3)	Schwartz, 1976; Seikaly, 1998; Seikaly, 1996; Filler, 1999; Hellerstein, 1998; Guignard, 1980; Pierrat, 2003; Springate, 1992; Waz, 1993; Filler, 2003; Skinner, 1994; Gbadegesin, 1997; Hjorth, 2002.
Counahan-Barratt	1976	108	C _{Cr}	6	574	Inulin EDTA C _{Cr}	83 (70-86)	93 (89-94)	0.62 (0.23-0.78)	1.3 (-6 to 11.7)	Counahan, 1976, Morris, 1982; Traub, 1980; Skinner, 1994; Hjorth, 2002; Bokenkamp, 1998.

C_{Cr} = creatinine clearance; CKD = chronic kidney disease; Eld = elderly; NRF = normal renal function; RTx = renal transplant recipients; DM = diabetes mellitus; AA = African-Americans; KiD = kidney donors; CA = cancer patients; HIV = AIDS patients; Tx = trauma patients; ICU = intensive care unit patients; CLD = chronic liver disease.

Values for precision and bias represent the median (range) values for all studies in which data were provided.