3. Use of cystatin C measurement in evaluating 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)

- **Serum cystatin C appears to be superior to serum creatinine for detecting reduced kidney function, particularly in the early stages. (Level III evidence, multiple small-to-large cohort studies in community and institutional settings, surrogate outcomes, inconsistent effects)**
- **The advantage of serum cystatin C compared with serum creatinine for the detection of kidney failure is no longer apparent when measurements are adjusted or stratified for age, gender and weight. (Level III evidence, large community cohort study, surrogate outcomes, strong effect)**
- **There is no convincing evidence that serum cystatin C measurement offers any clinical advantage over estimated glomerular filtration rate (eGFR) (Level III evidence, small-to-medium observational cohort studies, surrogate outcomes, weak effect) except that serum cystatin C appears to be superior to both serum creatinine and eGFR as a predictor of cardiovascular events in the eldely (age $\geq$ 65 years). (Level III evidence, large population cohort study, clinically important outcomes, strong effect)**
- **Serum cystatin C is not as sensitive as serum creatinine at detecting changes in the same individual. (Level III evidence, small cohort studies in healthy volunteers, surrogate outcomes, moderate effect)**
- **Serum cystatin concentrations are significantly influenced by a number of factors other than GFR, including age, gender, body size, current cigarette smoking, serum C-reactive protein (CRP) levels, corticosteroid treatment, cyclosporine A, thyroid dysfunction, physical activity, certain malignancies and pregnancy. (Level III evidence, multiple small-to-medium–sized cohort studies, surrogate outcomes, moderate-to-strong effects)**
- **Routine clinical use of serum cystatin C measurement cannot presently be recommended until there are further studies investigating the test's cost-effectiveness, turn-around time in a**

clinical setting, generalisability to non-Caucasian populations, effectiveness in detecting CKD in the community compared with automated eGFR reporting, and clinical utility in particular sub-groups in whom serum creatinine measurements are most unreliable (e.g. extremes of body size, people with paralysis, amputees, children, the elderly, etc).

Background

The need for a simple, accurate, and rapid endogenous marker of GFR has been a major limiting factor in clinical nephrology practice and research. Creatinine is the most commonly used filtration marker in clinical practice, but, as was described in the guideline titled 'Use of serum creatinine concentration to assess level of kidney function', its accuracy is significantly hampered by assay interference, unreliability of urine collection, and the confounding influences of diet, age, gender and muscle mass. A number of low molecular weight serum proteins, including β_2-microglobulin, retinol-binding protein and cystatin C, have been proposed as suitable alternative endogenous filtration markers (Grubb et al 1985, Donadio et al 2001, Filler et al 1997). Of these, cystatin C has received the most interest in the published literature.

Cystatin C is a 122 amino acid, 13 kDa protein that is a member of a family of potent, non-covalent, competitive inhibitors of mammalian lysosomal cysteine proteinases that are conserved throughout evolution (Barrett 1985). It has multiple biological functions including controlling extracellular proteolysis via inhibition of cysteine peptidases (especially cathepsins B, H, L and S) (Abrahamson et al 1988), modulation of the immune system (Warfel et al 1987), exertion of antibacterial and antiviral activities (Mussap and Plebani 2004), and modification of the body's response to brain injury (Mussap and Plebani 2004).

The clinical use of serum cystatin C concentration as a measure of GFR was first proposed in 1985 by Grubb et al (1985) and Simonsen et al (1985). The properties of cystatin C that make it a potentially more 'ideal' endogenous marker of GFR than creatinine include a constant rate of production by a 'housekeeping' gene expressed in all nucleated cells (Abrahamson et al 1990), the reported lack of effect of age, gender or muscle mass on cystatin C generation (Finney et al 2000a, Finney et al 2000b, Norlund et al 1997, Vinge et al 1999), free filtration at the glomerulus because of its small size and basic pI (Grubb 1992), complete reabsorption and catabolism by the proximal tubule cells (Tenstad et al 1996), lack of renal tubular secretion (Tenstad et al 1996), lack of reabsorption back into the bloodstream, and absence of problems with analytical interference (Kyhse-Andersen et al 1994).

The diagnostic value of serum cystatin C in clinical nephrology was not extensively investigated until 1994 because of general difficulties in standardising immunometric methods. More recently, automated homogeneous immunoassays using latex or polystyrene particles coated with

cystatin C-specific antibodies have been developed based on turbidimetry (particle-enhanced turbidimetric immunoassay, PETIA) (Kyhse-Andersen et al 1994) or nephelometry (particle-enhanced nephelometric immunoassay, PENIA) (Finney et al 1997). The PETIA method generally produces reference values that are 20%–30% higher than those from the PENIA method and a recent meta-analysis demonstrated that the correlation between GFR and the reciprocal of cystatin C was significantly stronger when cystatin C was measured by the PENIA method (14 studies including 1698 subjects) rather than when it was measured by other methods (21 studies involving 1953 subjects) (Dharnidharka et al 2002). However, this finding must be balanced against the potential limitations of the studies of cystatin C as a GFR marker to date, which include lack of assay standardisation (due to differences in antibodies, calibrators and technologies) (Mussap and Plebani 2004), lack of standardisation of statistical analyses, and higher intra-individual variance of cystatin C compared with creatinine (Keevil et al 1998).

The objective of this guideline is to review the evidence pertaining to the reliability and clinical utility of serum cystatin C measurement in the evaluation of renal function.

Search strategy

Databases searched: Text words for cystatin were combined with MeSH terms and text words for renal function or kidney function. 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 randomised controlled trials (RCTs) are available which address this issue.

There have been no RCTs comparing the effect of using cystatin C with 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 109 studies (involving 16,831 subjects) have compared the accuracy of serum cystatin C and creatinine concentrations in relation to a reference standard for GFR. These are summarised in Table 1. The majority of these studies have found serum cystatin C to be comparable to or superior to serum creatinine determination. However, many of these studies also suffered from a number of potential weaknesses, including:

- Lack of assay standardisation (due to differences in antibodies, calibrators and technologies) (Mussap and Plebani 2004). In a meta-analysis of 54 studies, Dharnidharka and coworkers (2002) demonstrated that a lack of cystatin C over serum creatinine in some studies might reflect differences in assay methods (see below).

- Possible type 2 statistical errors due to inadequate sample sizes.

- Selection of an inappropriate reference standard for GFR (especially creatinine clearance, which is not only inaccurate as a GFR measure, but also mathematically coupled with serum creatinine concentration).

- Variable choice of GFR cut-off level discriminating normal from impaired kidney function (ranging from 30 to 90 mL/min/1.73 m^2).

- Lack of standardisation of GFR to body surface area (see guideline titled 'Use of estimated GFR to assess level of kidney function' for discussion of this issue).

- Inappropriate statistical analyses (e.g. evaluation of correlation without simultaneously assessing levels of agreement by Bland-Altman plots, determination of sensitivity and specificity at only 1 GFR cut-off point rather than over a range of GFRs, lack of assessment of statistically significant differences between correlation coefficients or areas under the ROC curves).

- Lack of adjustment of analyses for other factors (i.e. age, weight, gender, CRP level and cigarette smoking) that may affect serum creatinine and serum cystatin C by influencing the production of the marker. For example, Knight et al (2004) measured serum cystatin C, serum creatinine and creatinine clearance in 8058 patients in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort. On univariate analysis, the degree of correlation with creatinine clearance was higher for serum cystatin C ($r = 0.24$) than for serum creatinine ($r = 0.17$). However, after adjustment for age, weight and gender, the correlation was slightly higher for serum creatinine (0.65 vs 0.62, p = ns). Similarly, the AUC values for constructed ROC curves using a GFR cut-off of 60 mL/min were 0.71 for serum cystatin C and 0.66 for serum creatinine. However, these differences were no longer observed after adjusting for age, weight and gender (cystatin 0.79, creatinine 0.81). It was further observed that serum cystatin C levels were independently influenced by age, weight, gender, CRP level and smoking, independent of creatinine clearance.

- Uncertainty regarding generalisability of data. Nearly all of the studies to date have exclusively examined the clinical utility of serum cystatin C measurements in Caucasian populations. How well this filtration marker performs in other ethnic groups is presently uncertain. Moreover, there has

been insufficient study of the performance of cystatin C determinations in populations in which serum creatinine measurements are most unreliable and therefore where cystatin C has potentially the greatest utility (including paediatric and elderly populations, cirrhotics, and pregnant women). To date, there remains no clear evidence as to how and when serum cystatin C measurements should be applied to selected groups of patients.

- Lack of cost-effectiveness analyses.

- Lack of reporting of the turnaround time of cystatin C immunoassays.

- Lack of investigations and reports into the causes of false positives and false negatives in clinical studies of cystatin C.

Dharnidharka et al (2002) performed a meta-analysis of 54 studies (incorporating 4492 subject samples) of cystatin C as a GFR index, published in full or in abstract form up until 31 December 2001. They observed that the reference standard of GFR correlated significantly better with the reciprocal of serum cystatin C ($r = 0.816$, 95% CI 0.804–0.826) than with the reciprocal of serum creatinine ($r = 0.742$, 95% CI 0.726–0.758, $p < 0.001$). The correlation between GFR and the reciprocal of cystatin C was significantly stronger when cystatin C was measured by the PENIA (14 studies including 1698 subjects) than when it was measured by other methods (21 studies including 1953 subjects). Furthermore, the mean area under the ROC curve was greater for cystatin C (0.926, 95% CI 0.892–0.960) than for creatinine (0.837, 95% CI 0.796–0.878, $p < 0.001$). They concluded that serum cystatin C was clearly superior to serum creatinine as a marker of GFR. The limitations of this meta-analysis included those detailed above for the individual studies, as well as the fact that not all available published studies were included in the analysis (the reasons for exclusion of studies are not specified).

Laterza et al (2002) performed a meta-analysis of 20 studies that examined the diagnostic accuracy of serum cystatin C versus serum creatinine. Summary ROC curves were generated by plotting the claimed sensitivities or specificities (or the optimal points from the depicted ROC curves) from each of the investigations. This approach suggested that cystatin C was superior to creatinine, since the areas under the summary ROC curves were 0.95 and 0.91, respectively ($p = 0.003$). However, the difference was of doubtful clinical significance. Sub-group analyses revealed a significantly greater diagnostic accuracy of cystatin C over creatinine in adults (AUC 0.96 vs 0.91, $p = 0.024$), but not in children (AUC 0.97 vs 0.96, $p = 0.37$) or renal transplant recipients (AUC 0.91 vs 0.82, $p = 0.23$). The latter results were likely limited by inadequate sample size. Moreover, the meta-analysis did not include all published studies, but the criteria for selecting 'credible studies' were not specified.

There is no convincing evidence as yet that serum cystatin C measurements are superior to eGFR (Daniel et al 2004, Hojs et al 2004, Reinhardt et al 2004,

Hoek et al 2003, Burkhardt et al 2002a, Chantrel et al 2000, Oddoze et al 2001), O'Riordan et al 2003, Perlemoine et al 2003, Tan et al 2002, Harmoinen et al 2003, Laterza et al 2002, Gabutti et al 2004, Visvardis et al 2004, Wasen et al 2004, Schuck et al 2004b, Van Den Noortgate et al 2002, O'Riordan et al 2002, Mussap et al 2002, Akbas et al 2004).

Sources of error/bias in serum cystatin C measurements

There have been 2 studies to date which have investigated the biological variability of serum cystatin C, as measured by PETIA (n = 12) (Keevil et al 1998) and EIA (n = 8) (Pergande & Jun 1993). Despite their different methodological approaches, the respective results were strikingly similar:

- analytical variability (CV_A) 8.9% vs 8.8%,
- within-subject variability (CV_I) 13.3% vs 15%,
- between-subject variability (CVG) 8.1% vs 5.7%,
- index of individuality ($IoI = SD_I/SD_G$)) 1.64 vs 2.63, and
- biological mean difference or critical difference ($2.77[CV_I^2 + CV_A^2]^{0.5}$) 36.8% vs 48.2%, respectively.

These results suggest that, because of its high individuality (IoI > 0.60), conventional population-based reference intervals for cystatin C are of greater value for the detection of a low GFR for a particular individual than serum creatinine (which typically has an IoI around 0.27). However, the Critical Difference for cystatin C (approximately 37% or 0.24 mg/L) is much greater than that for creatinine (approximately 14% or 12 µmol/L), suggesting that serum creatinine is still the better assay for following sequential changes in an individual with confirmed renal disease. In other words, although cystatin C appears to be better at detecting the onset of an abnormal GFR than serum creatinine, it is not as sensitive as serum creatinine for detecting changes in the same individual. However, it should also be emphasised that these conclusions are based on 2 studies in small numbers of healthy patients.

Several studies have demonstrated that, like creatinine, serum cystatin concentrations are significantly influenced by a number of factors other than GFR, including age, gender, body size, current cigarette smoking, serum CRP levels, corticosteroid treatment, cyclosporine A, thyroid dysfunction, physical activity, certain malignancies and pregnancy (Knight et al 2004, Laterza et al 2002, Galteau et al 2001, Cataldi et al 1999, Risch & Huber 2002, Cimerman et al 2000a, Cimerman et al 2000b, Fricker et al 2003, Wiesli et al 2003, den Hollander et al 2003, Schmitt & Bachmann 2003, Kos et al 1998a, Kos et al 1998b).

Applicability of cystatin C to patient sub-groups

a) Children

- The use of cystatin C measurement in paediatric populations, in which reliance on serum creatinine may be problematic because of body growth, has been examined in at least 14 studies involving 1682 subject samples (ranging from normal to severely impaired renal function). These studies are summarised in Table 1. Although there is no clearly demonstrable superiority of cystatin C over creatinine, there are insufficient studies to exclude a type 2 statistical error. This particularly applies to childer under 4 years old (for whom it has been hypothesised that cystatin C may be most effective).

- Although serum cystatin C concentrations are elevated in the early months of life (Finney et al 2000b, Harmoinen et al 2000), the plasma concentration of cystatin C appears to be relatively constant in children older than 1 year and similar to that of adults (Bokenkamp et al 1998, Filler et al 1997, Randers et al 1999, Helin et al 1998).

- A meta-analysis of 5 studies of cystatin C versus creatinine in children showed no statistically significant difference between areas under the ROC curves (AUC 0.97 vs 0.96, p = 0.37) (Laterza et al 2002). The meta-analysis did not include all available studies and the number of subject samples was inadequate to confidently exclude a type 2 statistical error.

b) The elderly

- There have been five studies of cystatin C involving 1370 elderly patients (Table 1).

– Burkhardt et al (2002b) performed a secondary analysis of data from a cross-sectional study to evaluate the diagnostic efficiency of cystatin C as a marker of the GFR in 30 elderly individuals (mean age: 75.4 ± 7.1 years). Compared with Cockcroft-Gault eGFR, serum cystatin C measurement did not significantly improve the diagnostic efficiency in detecting a reduced GFR (measured by inulin clearance).

– Similarly, Van Den Noortgate et al (2002) found that serum cystatin C did not offer any significant advantages over serum creatinine for detecting a reduced GFR.

– O'Riordan et al (2003) compared the diagnostic accuracy of cystatin C against creatinine in 53 elderly patients (mean age: 79.6 years) recruited from hospital outpatient clinics. ^{51}Cr-EDTA clearance was the reference method for GFR measurement and it was reasonably well correlated with Cockcroft-Gault eGFR (r = 0.91), serum cystatin C (r = 0.89), serum creatinine (r = 0.87) and creatinine clearance (r = 0.85). However, regression modelling predicted that the upper limit of normal for serum cystatin C would be exceeded as GFR fell below 64 mL/min/1.73 m^2, compared with 44 mL/min/1.73 m^2 for serum creatinine. This suggests that

serum cystatin C is a more sensitive test for detecting early chronic kidney disease in the elderly than is serum creatinine.

- In contrast, Fliser & Ritz (2001) observed that the correlation between serum cystatin C concentration and inulin clearance ($r = -0.65$, $p < 0.001$) was considerably better than between plasma creatinine concentration and inulin clearance ($r = -0.30$, $p < 0.02$).

- Wasen and associates (2004) assessed renal function by serum creatinine, serum cystatin C, Cockcroft-Gault eGFR and MDRD eGFR in a cross-sectional communiy-based survey of 1246 elderly residents (mean age: 74 years, range: 64–100 years) in Lieto, Finland. Serum cystatin C correlated significantly with serum creatinine (r=0.61), Cockcroft-Gault eGFR (r=0.45), BSA-corrected Cockcroft-Gault eGFR (r=0.61) and MDRD eGFR (r=0.69). This study was seriously limited by the lack of a gold standard GFR measurement and the failure to undertake analysis of agreement between cystatin C and creatinine.

c) Renal transplant recipients

- There have been 14 studies of cystatin C in 708 adult renal transplant recipients (RTRs) and 1 study in 24 paediatric RTRs (Table 1). A number of studies have shown that serum cystatin C concentrations may be falsely increased in renal transplant patients leading to a significant underestimation of GFR by 14%–25% (Le Bricon et al 2000, Bokenkamp et al 1999). The explanations for this observation are unknown, but one possible reason is interference by immunosuppressive agents. Investigations have shown that corticosteroids can increase serum cystatin C levels whereas cyclosporine decreases cystatin concentrations (Laterza et al 2002).

- A meta-analysis of 3 studies of cystatin C in RTRs revealed no significant differences between ROC AUCs for cystatin C (0.91) and serum creatinine (0.82, $p = 0.23$). However, the meta-analysis did not include all available studies and the number of subject samples was inadequate to confidently exclude a type 2 statistical error. Among 24 paediatric RTRs, cystatin C did not predict acute rejection any sooner than did serum creatinine in the 9 patients who developed acute rejection (Bokenkamp et al 1999). Hence, it remains unclear whether cystatin C offers a significant advantage in RTRs.

d) The obese

- There has been 1 study of the clinical utility of cystatin C (PENIA) in 33 obese patients with CKD (Schuck et al 2004a) compared with 78 non-obese individuals. The correlation between serum cystatin and inulin clearance was comparable between obese patients ($r = 0.96$) and non-obese patients ($r = 0.90$). Using a cut-off value for inulin clearance of 30

mL/min/1.73 m^2, ROC curve analysis did not show significant differences in AUC, sensitivity or specificity between obese and non-obese subjects. The principal weakness of this study was a lack of comparison with serum creatinine.

e) Patients with hepatic cirrhosis

- There have been at least five studies of cystatin C involving 320 patients with hepatic cirrhosis (Table 1). Although the total number of studies is too small to permit definitive conclusions to be drawn, the findings of these investigations suggest that serum cystatin C may predict reduced GFR with greater accuracy than creatinine. This observation may be explained by the fact that patients with advanced cirrhosis and CKD can present with normal serum creatinine concentrations because of their decreased muscle mass and enhanced tubular secretion of creatinine (Caregaro et al 1994, Takabatake et al 1988).

f) Patients receiving chemotherapy

- Stabuc et al (2000) measured serum cystatin C in 72 patients receiving cisplatinum chemotherapy for malignant melanoma, gastric carcinoma or ovarian cancer. Cystatin C correlated significantly better with ^{51}Cr-EDTA clearance (r = 0.84) than did serum creatinine (r = 0.74, p = 0.01). Moreover, cystatin C exhibited greater sensitivity (100% vs 60%) but poorer specificity (87% vs 98%) for predicting a GFR below 78 mL/min. They concluded that cystatin C may be more useful than serum creatinine for monitoring renal function during cisplatinum therapy. However, this finding requires confirmation. Furthermore, the same group has previously demonstrated significantly higher serum cystatin C levels in patients with colorectal carcinoma or metastatic melanoma in the absence of renal disease when compared with patients with primary melanoma (Kos et al 1998), raising the possibility that increased turnover of nucleated cells in cancers may lead to an increase in cystatin C levels in the serum, independent of GFR.

Cystatin C as a predictor of cardiovascular events

- There has been 1 study of the predictive value of serum cystatin C as a cardiovascular risk factor.

- Shlipak et al (2001) compared serum cystatin C, serum creatinine and abbreviated MDRD eGFR as predictors of death and cardiovascular events in 4637 participants in the Cardiovascular Health Study (a community-based, prospective, longitudinal observational cohort study of North American adults who were 65 years or older at the study's inception). Higher cystatin C levels were independently predictive of all-

cause mortality, cardiovascular mortality, myocardial infarction and stroke. Cystatin C was a stronger predictor of death and cardiovascular events than either creatinine or eGFR. It was uncertain whether the association of cystatin C with the outcomes studied solely reflected its association with kidney function or whether other associations were also operating.

– The limitations of this study included the significant possibility of residual confounding, lack of calibration of serum creatinine measurements, and the exclusion of patients younger than 65 years (so it is uncertain whether cystatin C would be a stronger predictor of mortality than serum creatinine or eGFR in a younger population, in whom lean body mass makes up a greater proportion of body mass).

Summary of the evidence

There are no RCTs on this topic.

There have been no RCTs comparing the effect of using cystatin C 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 109 studies (involving 16,831 subjects) have compared the accuracy of serum cystatin C and creatinine concentrations in relation to a reference standard of GFR. The vast majority of these studies have found serum cystatin C to be comparable or superior to serum creatinine determination.

A meta-analysis of a selected subset of these studies concluded that serum cystatin C was a more accurate measure of GFR than serum creatinine. However, many of these studies suffered from a number of potential weaknesses, including lack of assay standardisation, inadequate sample sizes, selection of an inappropriate reference standard for GFR, variable choice of GFR cut-off level discriminating normal from impaired kidney function, lack of standardisation of GFR to body surface area, inappropriate statistical analyses, uncertain generalisability of data and a lack of cost-effectiveness analyses.

Serum cystatin concentrations are significantly influenced by a number of factors other than GFR, including age, gender, body size, current cigarette smoking, serum CRP levels, corticosteroid treatment, cyclosporine A, thyroid dysfunction, physical activity, certain malignancies and pregnancy. There is insufficient evidence yet to justify replacing creatinine with cystatin C in clinical practice, although the test may have a role in detecting impaired GFR in certain groups of patients in whom serum creatinine is particularly likely to be misleading (e.g. young children and cirrhotics). Whether it becomes more commonly used will ultimately depend on the results of outcome-based studies.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association: There are alternatives to the use of serum creatinine in the assessment of kidney excretory function that are less dependent on variations in muscle mass. The most promising of these is serum cystatin C concentration. Concentrations become increased at milder degrees of kidney dysfunction than for serum creatinine, and the test may therefore be useful in the detection of mild to moderate CKD, including amongst older people and those with spinal cord injury. However, the use of this test awaits further validation in the routine clinical setting.

Candadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Kidney Disease Improving Global Outcomes: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

1. Serum cystatin C measurements should be validated against serum creatinine and MDRD eGFR in selected groups, including:

- patients with BMI > 35 kg/m^2 and < 18.5 kg/m^2
- spinal cord injured patients
- amputees
- specific ethnic groups (Asians, Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders)
- paediatric patients
- elderly patients.

2. Studies also need to be undertaken to examine the test's cost-effectiveness and turn-around time in a clinical setting.

3. Investigators who have previously published cystatin C studies should re-analyse their data to evaluate the diagnostic accuracy of this test compared with abbreviated MDRD eGFR relative to the reference GFR method.

4. Additional studies of the value of serum cystatin C as a predictor of death and cardiovascular events, especially in young and middle-aged populations, are warranted. Such studies should compare the predictive value of cystatin C with other measures of kidney function (including serum creatinine and eGFR).

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Appendix

Table 1 Summary of studies investigating the relative clinical utility of serum cystatin C vs creatinine

Population	Methods		N	Correlation with GFR		Impaired clearance definition (mL/min)	Sensitivity		Specificity		Area under ROC curve		Reference
	GFR	Cys		Cys	Cr		Cys	Cr	Cys	Cr	Cys	Cr	
Adult CKD	Inulin	PENIA	161	0.70	0.74	< 90	75	72	92	94	0.88	0.88	Chantrel et al 2000
Adult CKD	EDTA	PETIA	123	0.82	0.68	< 60	ND	ND	ND	ND	0.96	0.96	Christensson et al 2004
Adult CKD	Iothala-mate	PENIA	61	0.77	0.73	< 88	93	87	100	100	ND	ND	Coll et al 2000
Adult CKD	DTPA	PENIA	110	0.65	0.65	ND	ND	ND	ND	ND	0.84	0.82	Donadio et al 2001
Adult CKD	EDTA	SRID	135	0.95	NS	ND	ND	ND	ND	ND	ND	ND	Grubb et al 1985
Adult CKD	Inulin	PENIA	26	0.87	ND	ND	ND	ND	ND	ND	ND	ND	Hayashi et al 1999
Adult CKD	CrCl	PENIA	226	ND	ND	< 83	97	83	65	89	ND	ND	Herget-Rosenthal et al 2000a
Adult CKD	Iothala-mate	PENIA	146	0.87	0.80	ND	ND	ND	ND	ND	0.96	0.88	Hoek et al 2003

Adult CKD	EDTA	PENIA	144	0.90	0.80	ND	ND	ND	ND	ND	ND	ND	Hojs et al 2004
Adult CKD	DTPA	ELISA	31	0.81	ND	< 80	88	53	86	100	ND	ND	Jung & Jung 1995
Adult CKD	Na thio-sulphate	PENIA	212	0.82	0.73	< 80	88	ND	95	ND	0.96	ND	Kazama et al 2002
Adult CKD	CrCl	PENIA	8058	0.23	0.08	< 60	ND	ND	ND	ND	0.71	0.66	Knight et al 2004
Adult CKD	Iohexol	PETIA	51	0.87	.71	< 80	100	100	75	0	ND	ND	Kyhse-Andersen et al 1994
Adult CKD	Inulin	PENIA	NS	0.95	0.92	ND	ND	ND	ND	ND	ND	ND	Larsson et al 2004
Adult CKD	C-G	PENIA	75	ND	ND	< 87.5	0.94	0.94	0.95	0.80	ND	ND	Meier et al 2001
Adult CKD	Iohexol	PETIA	47	0.87	0.71	ND	ND	ND	ND	ND	ND	ND	Nilsson-Ehle & Grubb 1994
Adult CKD	Inulin	PENIA	26	0.87	0.66	ND	ND	ND	ND	ND	ND	ND	Nitta et al 2002
Adult CKD	DTPA	ELISA	31	0.89	NS	< 82	88.2	ND	52.9	ND	ND	ND	Pergande & Jun 1993
Adult CKD	DTPA	PETIA	76	0.91	0.89	ND	ND	ND	ND	ND	0.97	0.96	Randers et al 1998

Adult CKD	Inulin	PENIA	67	0.81	0.81	ND	ND	ND	ND	ND	ND	ND	Schuck et al 2003
Adult CKD	CrCl	ELISA	68	0.85	0.90	ND	ND	ND	ND	ND	ND	ND	Tian et al 1997
Adult CKD	Inulin	PENIA	62	0.69	0.39	< 70	78	65	100	87	0.88	0.65	Woitas et al 2001
Adult CKD	DTPA	PENIA	51	0.74	0.66	< 68	ND	ND	ND	ND	0.89	0.75	Xia et al 2004
Adult Diabetes	EDTA	PETIA	123	0.82	0.68	< 80	ND	ND	ND	ND	0.93	0.68	Christensson et al 2004
Adult Diabetes	EDTA	PETIA	123	0.82	0.68	< 60	ND	ND	ND	ND	0.96	0.96	Christensson et al 2004
Adult Diabetes	EDTA	PETIA	47	0.77	0.56	NS	92	67	100	91	0.99	0.86	Harmoinen et al 1999
Adult Diabetes	CrCl	PETIA	77	ND	ND	< 80	40	12	100	100	ND	ND	Mojiminiyi et al 2000
Adult Diabetes	C-G	PETIA	105	0.63	0.76	< 60	87	53	88	100	0.90	0.79	Mojiminiyi & Abdella 2003
Adult Diabetes	EDTA	PENIA	52	0.84	0.65	< 80	97	62	81	89	0.94	0.81	Mussap et al 2002
Adult Diabetes	EDTA	PETIA	52	0.84	0.65	< 80	0.92	0.98	0.50	0.83	ND	ND	Mussap et al 2002
Adult Diabetes	EDTA	PENIA	49	0.65	0.77	< 80	50	55	100	96	0.78	0.91	Oddoze et al 2001

Adult Diabetes	EDTA	PENIA	49	0.65	0.77	< 60	90	90	90	90	0.93	0.92	Oddoze et al 2001
Adult Diabetes	EDTA	PENIA	89	0.74	0.67	< 80	87	77	72	81	0.86	0.81	Perlemoine et al 2003
Adult Diabetes	NS	PETIA	41	ND	ND	NS	82	48	88	86	ND	ND	Piwowar et al 1999
Adult Diabetes	Inulin	PENIA	115	ND	ND	< 80	95	49	62	96	0.89	0.77	Priem et al 2001
Adult Diabetes	CrCl	PENIA	174	ND	ND	ND	ND	ND	ND	ND	0.76	0.66	Shimizu et al 2003
Adult Diabetes	Iohexol	PETIA	40	0.80	0.54	ND	ND	ND	ND	ND	ND	ND	Tan et al 2002
Adult diabetic CKD	EDTA	PENIA	49	0.65	0.77	< 80	55	50	96	100	0.93	0.92	Oddoze et al 2001
Adult diabetic CKD	EDTA	PENIA	49	0.65	0.77	< 60	90	90	90	90	0.93	0.92	Oddoze et al 2001
Adult IgA	CrCl	PENIA	306	NS	NS	ND	ND	ND	ND	ND	ND	ND	Tomino et al 2001
Adult mixed	DTPA	PENIA	60	0.94	0.93	ND	ND	ND	ND	ND	0.94	0.93	Donadio et al 2003
Adult mixed	EDTA	PETIA	112	0.92	0.88	ND	ND	ND	ND	ND	0.88	0.71	Harmoinen et al 2003
Adult mixed	Iothala-mate	PENIA	123	0.87	ND	ND	ND	ND	ND	ND	0.93	ND	Hoek et al 2003

Adult mixed	EDTA	PETIA	206	0.81	0.5	< 80	71	52	95	92	ND	ND	Newman et al 1994
Adult mixed	EDTA	PETIA	206	0.81	0.50	< 72	78	57	ND	ND	ND	ND	Newman et al 1995
Adult mixed	DTPA	PENIA	46	0.87	0.77	ND	ND	ND	ND	ND	0.996	0.899	Randers et al 2000
Adult non-obese CKD	Inulin	PENIA	78	0.90	0.90	< 30	ND	ND	ND	ND	ND	ND	Schuck et al 2004b
Adult obese CKD	Inulin	PENIA	33	0.96	0.95	< 30	ND	ND	ND	ND	ND	ND	Schuck et al 2004b
Adult Rheumatoid Arthritis	CrCl	PENIA	56	0.49	0.31	< 90	ND	ND	ND	ND	ND	ND	Mangge et al 2000
Adult RTR	Iohexol	PETIA	125	0.89	0.81	< 60	92	72	78	79	0.94	0.90	Christensson et al 2003
Adult RTR	Inulin	PENIA	60	0.60	0.40	< 90	0.72	0.67	0.80	0.90	NS	NS	Daniel et al 2004
Adult RTR	Inulin	PENIA	60	0.60	0.40	< 60	0.60	0.61	0.87	0.83	NS	NS	Daniel et al 2004
Adult RTR	DTPA	PENIA	32	0.89	0.49	ND	ND	ND	ND	ND	ND	ND	Filler & Pham-Huy 2002
Adult RTR	CrCl	PENIA	110	0.87	0.85	< 80	95	83	31	67	ND	ND	Herget-Rosenthal et al 2000b

Adult RTR	DTPA	PETIA	19	0.76	0.80	ND	ND	ND	ND	ND	ND	ND	Krieser et al 2002
Adult RTR	EDTA	PENIA	25	0.88	0.78	< 80	ND	ND	ND	ND	ND	ND	Le Bricon et al 2000
Adult RTR	C-G	PETIA	21	0.79	0.91	ND	ND	ND	ND	ND	ND	ND	Leach et al 2002
Adult RTR	CrCl	PENIA	103	0.89	0.82	< 60	93	71	72	68	0.93	0.81	Li et al 2002
Adult RTR	CrCl	PETIA	40	0.66	0.56	< 60	75	80	87	41	ND	ND	Paskalev et al 2001
Adult RTR	Inulin	PETIA	12	0.67	ND	ND	ND	ND	ND	ND	ND	ND	Plebani et al 1998
Adult RTR	CrCl	PENIA	173	0.73	0.77	< 70	90	97	88	76	0.95	0.93	Pöge et al 2003
Adult RTR	Iothala-mate	PETIA	30	0.83	0.67	< 60	70	80	89	44	ND	ND	Risch et al 1999
Adult RTR	Iothala-mate	PETIA	30	0.83	0.67	< 60	65	35	100	100	ND	ND	Risch et al 2001
Adult RTR	C-G	NS	30	0.73	0.91	NS	ND	ND	ND	ND	ND	ND	Thervet et al 2000
Adult spinal cord injury	CrCl	PENIA	27	0.48	0.25	ND	ND	ND	ND	ND	ND	ND	Jenkins et al 2003
Adult spinal cord injury	EDTA	PENIA	31	0.72	0.26	ND	ND	ND	ND	ND	0.91	0.51	Thomassen et al 2002
Child CKD	Inulin	PETIA	83	0.88	0.72	< 84	90	ND	86	ND	0.97	0.89	Bokenkamp et al 1998

Child CKD	EDTA	PENIA	381	0.64	0.55	< 90	67	ND	95	ND	0.90	0.88	Filler et al 1999
Child CKD	EDTA or DTPA	PENIA	225	0.76	0.50	< 90	95	95	63	47	ND	ND	Filler & Pham-Huy 2002
Child CKD	DTPA	PENIA	536	0.82	0.55	ND	ND	ND	ND	ND	ND	ND	Filler & Lepage 2003
Child CKD	EDTA	PENIA	64	0.81	0.44	ND	ND	ND	ND	ND	ND	ND	Kilpatrick et al 2000
Child CKD	Inulin	PETIA	99	0.64	0.54	< 100	ND	ND	ND	ND	0.73	0.60	Martini et al 2003
Child CKD	Inulin	PENIA	66	0.94	0.92	< 80	97	86	89	100	0.97	0.98	Willems et al 2003
Child CKD	EDTA	PETIA	52	0.89	0.80	< 89	100	74	97	97	0.99	0.92	Ylinen et al 1999
Child CKD 12-19 yr	Inulin	PETIA	34	0.87	0.89	< 90	87	91	100	91	0.94	0.96	Stickle et al 1998
Child CKD 4-12 yr	Inulin	PETIA	26	0.76	0.84	< 90	80	67	91	100	0.88	0.79	Stickle et al 1998
Child mixed	EDTA	PETIA	69	0.83	0.67	< 75	100	NS	98	NS	NS	NS	Helin et al 1998
Child RTR	CrCl	PETIA	24	0.88	0.72	< 84	90	NS	86	NS	0.97	0.89	Bokenkamp et al 1999
Child Spina Bifida	DTPA	PENIA	27	0.45	0.16	< 90	100	ND	95	ND	0.95	0.88	Pham-Huy et al 2003

Elderly	Inulin	PENIA	30	ND	ND	< 70	67	33	56	78	0.66	0.76	Burkhardt et al 2002a, 2002b
Elderly	Inulin	PENIA	41	0.65	0.30	< 96	ND	ND	ND	ND	ND	ND	Fliser & Ritz 2001
Elderly	EDTA	PENIA	53	0.79	0.76	ND	ND	ND	ND	ND	ND	ND	O'Riordan et al 2003
Elderly	EDTA	PENIA	48	0.62	0.68	≤ 80	73	57	100	100	0.93	0.90	Van Den Noortgate et al 2002
Elderly Finnish community survey	MDRD	PENIA	1246	0.68	ND	ND	ND	ND	ND	ND	ND	ND	Wasen et al 2004
Hepatic Cirrhosis	DTPA	PETIA	26	0.52	0.37	ND	ND	ND	ND	ND	ND	ND	Demirtas et al 2001
Hepatic Cirrhosis	CrCl	PENIA	97	ND	ND	< 60	69	45	56	71	0.67	0.62	Gerbes et al 2002
Hepatic Cirrhosis	Inulin	PETIA	92	0.85	0.87	< 72	88	23	79	100	0.90	0.91	Orlando et al 2002
Hepatic Cirrhosis	EDTA	PENIA	36	ND	ND	ND	ND	ND	ND	ND	0.74	0.63	Randers et al 2002
Hepatic Cirrhosis	Inulin	PENIA	44	0.66	0.28	< 90	86	28	ND	ND	ND	ND	Woitas et al 2000

Hepatic Cirrhosis (Child-Pugh class C)	CrCl	PENIA	25	ND	ND	< 60	87	60	60	60	0.77	0.61	Gerbes et al 2002
Liver Transplant	EDTA	PENIA	62	0.73	0.51	ND	ND	ND	ND	ND	0.89	0.78	Samyn et al 2005
Neonates	Inulin	PETIA	20	0.77	0.85	ND	ND	ND	ND	ND	ND	ND	Montini et al 2001

Note: CKD = chronic kidney disease; Cr = serum creatine; CrCl = creatinine clearance; Cys = serum cystatin C; ND = not done; NS = not specified; PENIA = no particle-enhanced nephelometric immunoassay; PETIA = particle-enhanced turbidimetric immunoassay.