An Improved Way To Screen For Chronic Kidney Disease

INNOVATIONS IN CLINICAL DIAGNOSTICS
“Our data suggests that estimated GFR based on serum Cystatin C could be used as a confirmatory test for chronic kidney diseases.”
- “Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C”
  Lesley A. Inker, M.D et al.

“Creatinine eGFR is affected by gender, ethnicity, muscle mass, diet, and drugs that affect tubular secretions.”
- Michael G. Shlipak, MD, MPH, chief,
  Division of General Internal Medicine,
  San Francisco VA Medical Center
  Cap Today Sept 2012

“One approach, which I think is a conservative approach, is to say in the creatinine range of around 60 where there’s some uncertainty and we really want to know the answer and avoid false-positives, the addition of cystatin C as a confirmatory test would help us get the right answer.”
- “Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C”
  Lesley A. Inker, M.D et al.

“Cystatin C works as a check because the cystatin C-based equations are not strongly affected by age, sex, or race. And race, in particular, is a problem, because many computer systems, such as ours, don’t include race in patient information. If you use cystatin C, you don’t seem to need to include race in the eGFR calculation.”
- John H. Eckfeldt, MD, PhD, vice chair for clinical affairs in the Department of Laboratory Medicine and Pathology,
  University of Minnesota Medical Center,
  Cap Today Sept 2012

“So in populations at pretty high risk for CKD, I think they should be screened with cystatin C so we know we’re not missing anything.”
- Michael G. Shlipak, MD, MPH, chief,
  Division of General Internal Medicine,
  San Francisco VA Medical Center
  Cap Today Sept 2012
Recent epidemiological studies in the United States report that there has been a 40% increase in the prevalence of CKD in recent years with a corresponding doubling of the incidence of end-stage renal disease and a tripling of Americans on dialysis. The prevalence of chronic kidney disease has reached epidemic proportions now affecting 13.8 to 15.8 percent of the general population.¹

The Importance of Early Detection and Treatment of CKD

The National Kidney Disease Education Program (NKDEP) was initiated by the National Institutes of Health in an effort to address this major public health issue. The NKDEP’s objective is “to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk (those with diabetes, high blood pressure, or a family history of kidney failure), and the availability of treatment to prevent or slow kidney failure.”³ There is a growing body of evidence that indicates that some of the negative outcomes of chronic kidney disease can be averted with early diagnosis and treatment. Unfortunately, it has also been reported that chronic kidney disease is significantly underdiagnosed and undertreated.⁴ In an effort to improve early diagnosis, the National Kidney Foundation has issued standardized clinical practice guidelines according to the Kidney Disease Outcomes Quality Initiative (K/DOQI). In these guidelines and recommendations the primary measure of renal function is the glomerular filtration rate (GFR).

### Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

- **Green**: low risk (if no other markers of kidney disease, no CKD);
- **Yellow**: moderately increased risk;
- **Orange**: high risk;
- **Red**: very high risk.

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
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<tbody>
<tr>
<td>G1 Normal or high</td>
<td>A1 Normal to mildly increased</td>
<td>≥90</td>
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<tr>
<td>G2 Mildly decreased</td>
<td>A2 Moderately increased</td>
<td>30-300 mg/g</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>A3 Severely increased</td>
<td>&gt;300 mg/g</td>
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<tr>
<td>G3b Severely decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4 Severe decreased</td>
<td></td>
<td></td>
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<tr>
<td>G5 Kidney failure</td>
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² The Epidemic of Chronic Kidney Disease (CKD)
The GFR is a measure of the rate at which water and dissolved substances (low molecular weight, ultrafiltrateable compounds) are filtered out of the blood per unit time.

- Normal GFR’s for males is approx. 150 mL/min per 1.73 m²
- Normal GFR’s for females is approx. 130 mL/min per 1.73 m²

Procedures for determining GFR with high accuracy require the injection of exogenous substances which are known to be only filtered at the glomerulus and not absorbed or secreted by the renal tubules. These gold standard procedures include

- Cr-EDTA
- Radiological contrast media (Iohexol)
- Inulin

Procedures determining GFR using exogenous substances are invasive and carry some risk to the patient which usually are considered too expensive and time consuming for routine clinical use. Historically, creatinine has been considered the renal marker of choice because it is a naturally occurring endogenous compound that is freely filtered at the glomerulus and has relatively minor absorption and secretion by the renal tubules. Even though serum creatinine determination remains the most commonly used renal marker for estimation of GFR, it is known to have a number of inherent difficulties which limit its clinical reliability.⁵,⁶

Even though creatinine based GFR equations such as the Modification of Diet in Renal Disease (MDRD), improve the accuracy of serum creatinine measurements, concentrations of creatinine can be within the normal range even with a GFR of around 40 mL/min/1.73 m² resulting in a so called “creatinine blind” range. This is due to the fact that MDRD understates normal and elevated GFR’s and overstates decreases in GFR⁵.

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Comments</th>
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<tr>
<td>Non-Renal Factors</td>
<td>Gender, Ethnicity, Diet, Muscle mass, Drugs which affect tubular secretion of creatinine</td>
</tr>
<tr>
<td>Clinical Utility</td>
<td>Poor sensitivity for CKD “creatinine blind range”</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine remains in the normal range until 50% of renal function is lost. Insensitive to loss of GFR in Stage 2 and Stage 3 of CKD.</td>
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<tr>
<td>Analytical Problems</td>
<td>Non-specific bias frequently reported with the commonly used Jaffé Assay Method (alkaline picrate)</td>
</tr>
<tr>
<td></td>
<td>Use of enzymatic assays for creatinine such as Diazyme’s enzymatic creatinine method can significantly improve test performance by eliminating many sources of analytical error.</td>
</tr>
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It is in this area of small to moderate decrease in kidney function that Cystatin C provides its greatest utility in the detection of both acute and chronic kidney disease.
A substantial body of evidence has developed over the past several years which supports the use of Cystatin C as an alternative and more sensitive endogenous marker for the estimation of GFR than serum creatinine and serum creatinine based GFR estimations. Cystatin C is a small 13-kDa protein that is a member of the cysteine proteinase inhibitor family that is produced at a constant rate by all nucleated cells. Due to its small size it is freely filtered by the glomerulus, and is not secreted but is fully reabsorbed and broken down by the renal tubules. This means the primary determinate of blood Cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker. A recent meta-analysis demonstrated that serum Cystatin C is a better marker for GFR than serum creatinine.

A significant advantage of Cystatin C based formulas, unlike creatinine based equations, is that Cystatin C based estimated GFR formulas are not biased according to GFR and there is no GFR blind area with Cystatin C.

<table>
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<tr>
<td>Virtually unaffected by non-renal factors</td>
<td>Muscle Mass / Weight / Height / Age (&gt;1 year) – Cystatin C parallels age related decreases in GFR and may be used reliably with children, Gender, Diet, Less inter individual variation than creatinine</td>
</tr>
<tr>
<td>Primary determinate of Cystatin C levels are renal factors</td>
<td>Cystatin C is not secreted but is fully absorbed and broken down by tubular cell. Since there is no tubular secretion of Cystatin C, it is extremely sensitive to small changes in GFR in the earliest stages of CKD.</td>
</tr>
<tr>
<td>Sensitive to changes in the so-called creatinine blind GFR range (40-70 ml/min/1.73 m²)</td>
<td>Enables early detection and treatment of CKD.</td>
</tr>
<tr>
<td>Demonstrates higher diagnostic accuracy than MDRD, or C-G equations in patients with diabetes</td>
<td>Enables early detection and treatment of CKD in both Type 1 and Type 2 diabetes.</td>
</tr>
<tr>
<td>Can be used to detect and monitor kidney disease in patients with hepatic disease</td>
<td>Creatinine based GFR measurements are not reliable and are not recommended in hepatic disease. Cystatin C is reliable in cirrhotic patients.</td>
</tr>
<tr>
<td>Has been advocated as the preferred endogenous marker for dosing medication eliminated by the kidneys</td>
<td>May detect mild to moderate decreases in GFR that are not evident with serum creatinine based measurements, thus avoiding unnecessarily high drug doses which may pose an increased risk to the patient and the associated cost of possible resulting side effects.</td>
</tr>
<tr>
<td>Correlates to the appearance of microalbumin</td>
<td>Recent studies suggest that very early renal failure may be the first clinical indication of the progressive kidney damage associated with diabetes.</td>
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Cystatin C Estimated GFR

A number of very simple formulas have been introduced which can be used to obtain an estimated GFR using Cystatin C. Multiple studies have found Cystatin C to be more sensitive to actual changes in GFR in the early stages of CKD than creatinine based GFR estimates. An example of a Cystatin C estimated GFR formula is the one proposed by Larson and Grubb et al. In their study a cystatin C-based prediction equation using only concentration in mg/L and a factor: GFR (ml/min) = 99.43 x (cys C)-1.5837 provided reliable and readily available GFR data based on single measurements of Cystatin C concentrations. As with all new test methods the actual formula used for conversion should be evaluated by the laboratory prior to introduction.18

Cystatin C and the MDRD

The creatinine based MDRD underestimates GFR in healthy subjects and shows decreased accuracy in older patients (with decreased muscle mass) and patients with body mass indexes (BMI) <21 and >30. While MDRD and serum creatinine show good diagnostic accuracy in severe renal failure (GFR <15 mL/min per 1.73 m²) creatinine based measurements show a lack of sensitivity in stage 2 and stage 3 renal disease when early intervention may improve outcomes.11 Cystatin C based estimates of GFR have been reported to be a more sensitive marker of decline in GFR especially in the earliest stages of CKD.

Cystatin C for Early Detection of CKD in Diabetes

Multiple reports indicate that Cystatin C is a reliable marker of GFR in patients with mild to moderate impairment of kidney function (stages 2-3 of CKD).10 This high degree of sensitivity has been demonstrated in both Type 1 and Type 2 Diabetes.13,14 In addition, several studies indicate that although clinical proteinuria was associated with both MDRD and Cystatin C estimates of GFR only Cystatin C was associated with microalbuminuria. This finding supports the enhanced sensitivity of Cystatin C based formulas for the early detection of kidney damage. Elevated serum Cystatin C levels have also recently been identified as a significant prognostic indicator for the development of cardiovascular disease in people with diabetes.

(n = 451) Population GFR = 83.93 × cystatin C [mg/L]^ - (1.68)
Dose Adjustments of Medications

GFR is commonly determined in clinical practice to guide the dosage of potentially toxic drugs including digoxin, chemotherapy medications and aminoglycoside antibiotics. Serum Creatinine often does not increase until the GFR has moderately decreased (about 40 ml/min/1.73 m²). This insensitivity to small to moderate decreases in GFR in the so called creatinine blind GFR area (40–70 ml/min/1.73 m²) may result in an unnecessarily high drug dose thus increasing the risk to the patient and the cost of possible resulting side effects. Some studies have advocated the preferential use of Cystatin C based GFR estimations for establishing the appropriate dose adjustment of drugs that are mainly eliminated by the kidneys.

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