Old and New Biomarkers for Kidney Diseases: Creatinine, eGFR, Cystatin C & More

Dr Marielle Kaplan, Laboratory of Clinical Biochemistry, Rambam health Care Campus, Haifa, Israel
What are we measuring with kidney biomarkers

- **Glomerular filtration rate – GFR:** Glomerular filtration is the initial step towards urine production. GFR refers to the amount of filtrate formed in all the renal corpuscles of both kidneys each minute. In adults, the average is 125 mL/min for men and 105 mL/min for women.

- **Renal tubular cells injury** (caused by ischemic or toxic injury): leads to release of proteins, inflammatory mediators,
Why is early detection of kidney dysfunction important?

- Reduced renal function is associated with increased CV morbidity and mortality. 4 million deaths worldwide per year.
- Preventive and protective intervention is available
- No available therapeutic treatment after injury
Why is early detection of kidney dysfunction important?

- **Acute kidney injury (AKI)** is an abrupt reduction in kidney function (hours to days). It is associated with decreased GFR, and injured tubular cells. Diagnosis based on elevation of creatinine and oliguria. Loss of kidney function in AKI may be reversible, or may progress to end-stage renal disease (ESRD), necessitating permanent renal replacement therapy.

- **Chronic kidney disease (CKD)** refers to a progressive and usually irreversible decline in GFR. CKD occurs in stages, over a prolonged timeframe. A patient with CKD Stage 1 has an estimated GFR (eGFR) ≥ 90 mL/min. By CKD Stage 5, the GFR is diminished to 10% to 15% of normal (eGFR of < 15 mL/min). This final stage denotes ESRD, necessitating renal replacement therapy by dialysis or transplant.
Ideal endogenous marker for GFR

- Should have a production rate that is constant
- Should be cleared from the circulation only by glomerular filtration (excreted only by the kidneys)
- Should be freely filtered at the glomerulus
- Should neither be secreted nor reabsorbed by renal tubule.
- Not be metabolized
- Be stable in blood and urine
- Be easily measured
Production of creatinine

- Non-enzymatic breakdown product of phosphocreatinine in muscle
- Produced at a relatively constant rate based on age, gender, and muscle mass
- Not affected by diet
GFR Measurement by Creatine Clearance Test (CCT)

- The most frequently clearance test is based on the measurement of creatinine in blood and in urine.

- Clearance = \( \frac{U \times V}{P} \)
  - U: urinary creatinine concentration (\( \mu \text{mol/L} \))
  - V: Urine flow rate (ml/min)
  - P: Plasma creatinine concentration (\( \mu \text{mol/L} \))
  - reference range: 75-140 mil/min
Creatinine measurement

- 1886: Jaffe devised Alkaline Picrate assay for creatinine

- Creatinine + Picrate A = Colored chromogen

**Jaffe reaction**

Principle: serum/urine mixed with alkaline picrate solution in alkaline solution forms a yellow-orange complex of creatinine picrate which absorbs light at 520 nm, and is proportional to the amount of creatinine present
Jaffe assays

- Not specific for creatinine
- Interferences: protein, albumin, ketones, bilirubin, cephalosporins, ...
- Following Jaffe there has been over 100 years of modifications to the Jaffe reaction to improve specificity, interference
- Optimization of reaction condition
- NOT ALL JAFFE assays are the same
Jaffe Reactions

Absorbance-time curves for various analytes in Jaffe reaction
Enzymatic Creatinine

- Reduced Interference

Enzymatic methodology is a better clinical choice for the accurate measurement of creatinine, especially for neonates, pediatrics, and hematology units.

\[
\text{Creatinine} + \text{H}_2\text{O} \xrightarrow{\text{creatinase}} \text{creatinine}
\]

\[
\text{Creatine} + \text{H}_2\text{O} \xrightarrow{\text{creatinase}} \text{sarcosine} + \text{urea}
\]

\[
\text{Sarcosine} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{sarcosine oxidase}} \text{formaldehyde} + \text{glycine} + \text{H}_2\text{O}_2
\]

- Enzymatic method with significantly reduced interference compared to the Jaffé method
- Superior onboard and calibration stability and doesn’t stain cuvettes like the Jaffé method
- Requires only eight (8) μL of sample ideal for pediatric
CAP, 2003, Fresh Frozen Serum, N = 5624
Creatinine = 0.90 mg/dL (79.7 μmol/L)

VERTICAL BARS = ±1.96*SD for distribution of participant results

Peer group mean bias vs. IDMS, mg/dL

1 2 3 4 5 6 7 8 9 0 0 0 0

Instrument/method peer group

In 2008, the (NKDEP) in collaboration with the IFCC and the European Communities Confederation of Clinical Chemistry launched the Creatinine Standardization Program:

1. To reduce inter-laboratory variability in creatinine assay calibration
2. To enable more accurate estimates of glomerular filtration rate
NKEDP Recommendations
originally published in Clinical Chemistry 2006;52(1):5-18

Clinical laboratories are crucial partners in the successful implementation of the Creatinine Standardization Program. For clinical laboratories, the following steps are necessary:

1. Use a creatinine method that has calibration traceable to an IDMS (Isotope Dilution Mass Spectrometry) reference measurement procedure. Methods based on either enzymatic or Jaffe method principles should have calibration traceable to IDMS.

The National Institute for Standards and Technology (NIST) released a standard reference material (SRM 967 Creatinine in Frozen Human Serum) for use in establishing calibrations for routine creatinine measurement procedures
Creatinine Limitations

- Creatinine levels are affected by age, race and gender
- High inter- and intra-individual variability
- Creatinine levels are altered in dystrophy, e.g. muscle wasting, anorexia, liver cirrhosis, neuromuscular disease, etc
- Blood creatinine levels are proportional to muscle mass. This makes creatinine particularly unsuitable for measuring GFR in children
- Common laboratory measurements are influenced by Hb, glucose and bilirubin
- Only one of 4 conditions: freely filtered at the glomerulus
  - Production affected by muscle mass and dietary intake
  - In addition to renal excretion also cleared through the gut
  - Tubular secretion: inversely proportional to GFR, leads to overestimation of TRUE GFR
Abnormal serum creatinine concentration: Non-renal factors

- **Increased creatinine (usually transient)**
  - Massive muscle necrosis
  - Prolonged strenuous exercise

- **Decreased creatinine**
  - Severe loss of muscle mass
  - Small body size
  - Young age
Gold-Standard methods for GFR

**Inulin** (continuous iv infusion, multiple, timed urine collections)

Iohexol

$^{125}\text{I}$ iothalamate

$^{99}\text{Tc}$ DTPA

$^{51}\text{Cr}$ EDTA

*intra-individual values may vary by +/-30%

Grubb A, Scand J Clin Lab Invest 2010
Estimated e-GFR

- Use of a formula to estimate GFR by calculation on the basis of serum creatinine levels

**Advantages:**
- It is based on a very commonly ordered test – serum creatinine.
- It is far more sensitive than creatinine alone for the early detection and monitoring of CKD.
- Currently, there are about 46 different equations for estimating GFR using creatinine, the most common being the MDRD

- **Cockcroft and Gault Formula (adults):**  
  Creatinine Clearance (ml/min) = \((140 - \text{age}) \times \text{body weight (kg)} \times 0.85 \text{ (for women)} \)  
  \(72 \times \text{serum creatinine (mg/dL)}\)
# Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR Range* (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased GFR</td>
<td>60 – 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30 – 59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>
The MDRD Equations:

The equation requires four variables:
- Serum, or plasma, creatinine ($S_{cr}$)
- Age in years (18 years or older)
- Gender
- Race (African American or not)

When $S_{cr}$ is in mg/dL (conventional units):

$$eGFR \text{ (mL/min/1.73 m$^2$)} = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

NKEPD Recommendations (2)
2. Use the IDMS-traceable MDRD Study equation for estimating GFR for adults using creatinine results from a method that has calibration traceable to IDMS.
The MDRD Study equation

- MDRD Study equation (1999)
  - Derived from 1628 participants with predominantly non-diabetic CKD (mean GFR 40 ml/min/1.73 m²)
  - Age, sex and race as surrogates for non-GFR determinants

- Reasonable accuracy in CKD populations

- Systematic bias (underestimation) of measured GFR at higher levels

- Imprecision throughout the GFR range
Limitations of the MDRD equation: Study Population Bias

- Should not be used in patients < 18 years or in pregnancy.
- Agreement with measured GFR is poorer for:
  - Patients with acute kidney failure-AKI
  - People with normal renal function
- The MDRD equation is not reliable for values >60ml/min
- By definition, the MDRD cannot detect stage 1 or 2 CKD
3. Use the IDMS-traceable version of the Schwartz equation for estimating GFR for children <18 years using creatinine results from a method that has calibration traceable to isotope dilution mass spectrometry (IDMS).

This equation has been referred to as the "bedside" Schwartz equation.

\[
GFR (\text{mL/min/1.73 m}^2) = (0.41 \times \text{Height in cm})/\text{Creatinine in mg/dL}
\]
The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a new equation, published in 2009, to estimate glomerular filtration rate (GFR) from serum creatinine, age, sex, and race for adults age $\geq 18$ years.

**Goal:** Develop and validate improved estimating equations

- Diverse dataset of individuals with & without kidney disease, and across range of measured GFR and age

CKD-EPI Equation

\[
GFR = 141 \times [\min(\text{Scr}/\kappa,1)^\alpha \times \max(\text{Scr}/\kappa,1)\times 1.018 \ [\text{if female}] \times \ [1.157 \ [\text{if Black}]]
\]

- \( \kappa \) is 0.7 for females and 0.9 for males
- \( \alpha \) is 0.329 for females and 0.411 for males;
- \text{min indicates minimum of Scr/}\kappa\text{ or 1, and}
- \text{max indicates maximum of Scr/}\kappa\text{ or 1}
The National Kidney Disease Education Program has not made a recommendation on general implementation of this equation.

The equation is still being validated and, while offering some improvement for eGFR between 60 and 120 mL/min/1.73 m², it is not clear that implementing CKD-EPI in place of the MDRD equation would alter clinical detection or management of patients with CKD.

However, a laboratory that reports eGFR numeric values > 60 mL/min/1.73 m² should consider using the CKD-EPI equation.
Figure 1. Accuracy of the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). Both panels show the difference between measured and estimated (y-axis) vs. estimated GFR (x-axis). A smoothed regression line is shown with the 95% CI for the distribution of results, using quantile regression, excluding the lowest and highest 2.5% of estimated GFR. From Ann Intern Med 2009;150:604-612, used with permission.
### Equations for estimating GFR.

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>Cockroft–Gault</td>
<td>eCrCl (mL/min) = (140 − age in years) × (weight in kilograms/72 × SCr) × (0.85 if female)</td>
</tr>
<tr>
<td>MDRD (4-variable, not IDMS-traceable)</td>
<td>eGFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 186 × (SCSr)⁻¹.¹⁵⁴ × (age in years)⁻⁰.²⁰³ × (0.742 if female) × (1.212 if African American)</td>
</tr>
<tr>
<td>MDRD (IDMS-traceable creatinine)</td>
<td>eGFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 175 × (Scr)⁻¹.¹⁵⁴ × (age in years)⁻⁰.²⁰³ × (0.742 if female) × (1.212 if African American)</td>
</tr>
<tr>
<td>CKD-EPI (IDMS traceable)</td>
<td>eGFR [mL · min⁻¹ · (1.73 m²)⁻¹] = 141 × min (Scr/κ,1)² × max(Scr/κ,1)⁻¹.²⁰⁹ × 0.⁹⁹³age × (1.⁰₁⁸ if female) × (1.₁⁵⁹ if African American), where κ is 0.7 for females and 0.9 for males, α is −0.₃₂⁹ for females and −0.₄₁₁ for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>Modified Schwartz</td>
<td>eGFR [mL · min⁻¹ · (1.73 m²)⁻¹] = (0.₄₁₃ × height in centimeters)/(Scr)</td>
</tr>
</tbody>
</table>
Creatinine Formulae Limitations

- Creatinine-based equations are not ideal for CKD patients with co-morbid conditions.
- Creatinine-based equations are not ideal for elderly patients, obese patients or patients with only mild renal impairment.
# Biomarkers: AMI versus AKI

<table>
<thead>
<tr>
<th>Period</th>
<th>Acute Myocardial infarction</th>
<th>Acute Kidney Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>LDH, AST</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1970s</td>
<td>CPK, Myoglobin</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1980s</td>
<td>CKMB</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1990s</td>
<td>Troponin T</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>2000s</td>
<td>Troponin I</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>2010s</td>
<td>High sensitive Troponin</td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>
The Future: Cystatin C?

- Cystine protease inhibitor, ) is a low-molecular weight (13 kDa) produced by all nucleated cells.
- Not affected by muscle mass (synthesized at constant rate)
- 13 Kda (freely filtered)
- Immunoanalysis
- Not secreted or reabsorbed in tubuli.
- Completely metabolized by proximal renal tubular cells (no detectable Cystatin C in urine).
- Good inverse correlation between GFR and serum Cystatin C.
Cystatin C: An attractive alternative to creatinine for GFR estimation?

- Produced at a constant rate
- Less physiologically variable than creatinine.
- No reabsorption or secretion in the proximal or distal renal tubules
- Completely metabolized by proximal renal tubular cells (no detectable Cystatin C in urine).
- Steady-state serum levels reflect the GFR
- Easier to measure accurately.
- Equations exist for expressing results as an e-GFR that may be superior to MDRD.
- Elevated Cystatin C is a better early predictor of CKD than e-GFR.
Some Features of Cystatin C

- $T_{1/2} = 1.5 - 2$ hours

- Average individual daily variation $(CV_i)^*$ is $\sim 13\%$ ($\sim 3\%$ in diabetics)
  
  * A low $CV_i$ is a requirement for serial monitoring

- Serum levels are fairly constant from 1 – 50 years of age

- Unique Reference Range for children above 1 and to adults up to 50

- The concentration in blood not affected by diet
Tan GD et al, Diabetes Care, 2002
Fig. 1. Accuracy of plasma markers cystatin C and creatinine to estimate GFR in transplanted patients.

GFR was measured by the $^{51}$Cr-labeled EDTA clearance (lower reference limit, 80 mL·min$^{-1}$·1.73 m$^{-2}$) in 25 kidney transplant patients 3 months after surgery. Changes in plasma cystatin C and creatinine concentrations are presented as the relative increase vs the upper reference limit (creatinine, females, 100 μmol/L; males, 109 μmol/L; cystatin C, 0.94 mg/L) (1). Horizontal and vertical dashed lines represent the upper and lower reference limits, respectively.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR Range* (ml/min/1.73 m²)</th>
<th>Cystatin C (Siemens) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or increased GFR</td>
<td>≥ 90</td>
<td>≤ 0.85</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased GFR</td>
<td>60 – 89</td>
<td>0.86–1.25</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30 – 59</td>
<td>1.26–2.34</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15 – 29</td>
<td>2.35–4.16</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15</td>
<td>&gt; 4.16</td>
</tr>
</tbody>
</table>
Cystatin C Formulae

- There are some 14 different equations using cystatin C to derive an eGFR
- In most cystatin C estimating equations, inclusion of age or sex does not substantially improve performance
- Cystatin C-based eGFR formulae without anthropometric data show lower bias and higher accuracy vs iohexol-GFR compared to CG- or MDRD-based eGFR
  
  Grubb A et al, Scand J Clin Lab Invest, 2005

- GFR based on cystatin C alone is equivalent to that based on adjusted creatinine. Adjusted cystatin C gives the most accurate estimation of GFR
  
  Stevens, L et al, AJKD, 2008

- Combining cystatin C and creatinine equations further improves sensitivity and specificity by ROC analysis
  
Acute Kidney Failure + Rhabdomyolysis

Creatinine 0.5-1.3 mg/dl
Cystatin >0.95 mg/L
eGFR 75-125 ml/min
GFR and Cystatin C

In critically ill, ICU patients, using various criteria for measuring GFR, cystatin C picks up a GFR <80 ml/min earlier than creatinine.

Delanaye P et al, Int Care Med 2004 (24-hour creat. clear. + CG)
Villa P et al, Crit Care 2005 (24-hour creat. clear.)
Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*
Panel A shows the median difference between measured and estimated GFR. The bias is similar with the equation using creatinine alone, the equation using cystatin C alone, and the combined creatinine–cystatin C equation. Panel B shows the accuracy of the three equations with respect to the percentage of estimates that were greater than 30% of the measured GFR (1−P30). I bars indicate 95% confidence intervals.
Pediatrics

- GFR based on serum cystatin C in children is not affected by age, body composition, height or gender
  Bokenkamp A et al, Pediatrics, 1998

- Cystatin C is recommended as a marker of renal dysfunction in children with liver disease or following liver Tx. Sensitivity of cystatin C = 91%, specificity 81% @ cut-off of 1.06 mg/ml
  Samyn M et al, Liver Transpl. 2005

- Cystatin C can be used for follow-up in renal Tx in children and is clinically equivalent to the Schwartz formula
  Podracka L et al, Pediatr. Transpl. 2005

- Cystatin C + β2-microglobulin is very useful in critically ill children
  Goldstein SL, Critical Care, 2007
Around 30% of Type 1 diabetics develop a diabetic nephropathology. In these patients, cystatin C is superior to creatinine clearance and plasma creatinine and the eGFR correlates well with a gold standard.

Tan GD et al, Diabetes Care, 2002

In Types 1 and 2 (mixed), cystatin C discriminates better than serum creatinine regarding eGFR.

Buysschaert M et al, Diabetes Metab., 2003
Factors that may influence cystatin C production or catabolism

- Gender, weight and height
  In extreme cases, lean body mass may affect the rate of cystatin C production
  Bakoush O et al, Clin Nephrol 2008

- CRP levels

- Smoking
  Knight EL et al, Kidney Intl. 2004
  Stevens LA et al, Kidney Intl. 2009
Cystatin C as a marker in acute renal dysfunction

“Serum Cystatin C Concentration as a Marker of Acute Renal Dysfunction in Critically Ill Patients”
Villa P. et al. (Critical Care, 2005; 9:R139-143)

- This study comprised 50 patients with different pathologies, in the age of 21 to 86 years who were all admitted to intensive care.
- All patients were at risk for developing renal failure.
- Renal dysfunction was defined as creatinine clearance ($C_{cr}$) below 80ml/min/1.73m$^2$
- Cystatin c (Cys C) and serum creatinine (sCrea) were compared to the $C_{cr}$
Cystatin C as a marker in acute renal dysfunction

- Cystatin C displayed a much higher sensitivity and specificity for detecting renal dysfunction in the ROC plot.

- The area under the curve was 0.972 for Cys C but only 0.694 for creatinine.

Villa et al., Critical Care 2005
Cystatin C as a marker in acute renal dysfunction

Key findings

↑ Cystatin C correlated much better to the creatinine clearance (C_{cr}) than serum creatinine (sCrea)!

↑ Cystatin C was diagnostically superior (AUC-ROC analysis) to creatinine!

↓ 50% of the patients had acute renal dysfunction but only 20% revealed increased creatinine values whereas

↑ 76% of patients exhibited elevated Cystatin C values!

Authors’ conclusions

↑ Cystatin C is an accurate marker to detect even slight changes of the GFR

↑ Cys C may be superior to creatinine for GFR assessment in clinical practice in critically ill patients
Kidney biomarkers for AKI

Creatinine is not a good marker enough during acute changes, Up to 2-3 days after injury to detect AKI
⇒ Need for additional biomarkers:

- Neutrophil gelatinase-associated lipocalin (NGAL),
- Kidney injury molecule-1 (KIM-1),
- Cystatin C,
- interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18),
- N-acetyl-glucosaminidase (NAG),
- glutathione transferases (GST)
- liver fatty acid binding protein (LFABP)
Neutrophil Gelatinase Associated Lipocalin (NGAL)

- NGAL (neutrophil gelatinase-associated lipocalin, lipocalin-2, siderocalin) is a small protein expressed in neutrophils and certain epithelia, including the renal tubules.

- Renal expression of NGAL is dramatically increased in kidney injury after ischemic or nephrotoxic insult.

- NGAL is released into both urine and plasma.

- NGAL levels rise within 2 hours of the insult, making NGAL an early and sensitive biomarker of kidney injury.
  - as much as 24 hours or more before any significant rise in serum creatinine.
Neutrophil Gelatinase Associated Lipocalin (NGAL): Troponin of the Kidney

- Clinical research have proven that NGAL levels identify patients with AKI before any diagnostic change in serum creatinine.
  - Early diagnosis of AKI to allow earlier initiation of appropriate management
  - Risk stratification of AKI
  - Prediction of clinical outcomes (dialysis, in-hospital death, length of hospital stay, mortality)
  - Monitor response to therapy
  - Lower hospitalization costs
Urine NGAL Levels after Cardiac Surgery

Adapted from Mishra, *et al.* *Lancet* 2005
Normal urinary NGAL levels are not dependent on age, but are higher in women than men.
NGAL: Plasma levels versus Urine Levels?
uNGAL: Use of absolute value or ratio to creatinine?

uNGAL cut-off value values: 117.6 ng/mL, with an imprecision <5 CV%
Plasma cut-off value values: 100 ng/ml (PPV 100%, NPV 75%)
Thank you
Cystatin C Formulae

An estimated GFR combining cystatin C and creatinine measurements more accurately matches a reference GFR compared to other equations at all stages of CKD, particularly in patients with near-normal kidney function.

Ma YC et al, Kid Int 2007

It may be appropriate to provide both cystatin C and creatinine eGFR's, selecting the one most suitable for the individual patient.

e.g. high corticosteroids $\rightarrow$ creatinine

abnormal muscle mass $\rightarrow$ cystatin C

GFR and Cystatin C

- Cystatin C ↑ when GFR is 70 - 90 ml/min/1.73 m² i.e. mildly reduced
- Creatinine ↑ when GFR ≤50ml/min/1.73 m²

- The range 50 - 80 is the so-called “creatinine-blind range” or “below the creatinine radar”
Creatinine: endogenous marker for GFR?

✓ Should have a production rate that is constant: *Creatinine is produced endogenously at a constant rate*

✓ should be cleared from the circulation only by glomerular filtration (excreted only by the kidneys): *Creatinine is excreted by the kidneys by glomerular filtration (only??)*

✓ Should be freely filtered at the glomerulus: *113 Da molecule below*

✓ Should neither be secreted nor reabsorbed by renal tubule

✓ Not be metabolized: *creatinine is not metabolized in renal tubuli cells*

✓ Be stable in blood and urine

✓ Be easily measured