Estimated GFR Based on Creatinine and Cystatin C

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Chronic Kidney Disease-Epidemiology Collaboration
UO1 DK 053869, UO1 DK 067651 and UO1 DK 35073.
Background

- GFR is essential to detection, management, and evaluation of CKD
- GFR is difficult to measure and is usually estimated from serum markers
- GFR estimates are used to:
  - Estimate measured GFR
  - Predict risk for adverse outcomes
- Interpretation of GFR estimates depends upon properties of the equations and the filtration markers
• Physiology of endogenous filtration markers

• Creatinine
  – Physiology
  – MDRD Study equation
  – CKD-EPI equation

• Cystatin C
  – Physiology
  – CKD-EPI equations
  – Predictors of serum levels
Physiology of Endogenous Filtration Markers

\[ U \times V = GFR \times S + TS - TR \]

\[ G-E = GFR \times S + TS-TR \]

\[ S = \frac{(G - E - TS + TR)}{GFR} \]

\[ GFR = \frac{(G - E - TS + TR)}{S} \]

Estimating equations substitute easily measured clinical surrogates for unmeasured physiological processes.
Creatinine Physiology

\[ \text{U} \times \text{V} = \text{GFR} \times \text{S} + \text{TS} \]

\[ \text{G-E} = \text{GFR} \times \text{S} + \text{TS} \]

\[ \text{S} = \frac{(\text{G} - \text{E} - \text{TS})}{\text{GFR}} \]

\[ \text{GFR} = \frac{(\text{G} - \text{E} - \text{TS})}{\text{S}} \]

Age, sex, race, weight
The MDRD Study equation

- MDRD Study equation
  - 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
The MDRD Study equation

- Predicts higher risk for adverse outcomes at lower eGFR
- Paradoxical higher risk observed in people at higher eGFR
• **Goal:** Develop and validate improved estimating equations
  – Diverse dataset of individuals with & without kidney disease, and across range of measured GFR and age
  – Additional surrogates for non-GFR determinants

• **Inclusion criteria:** study population >250; availability of serum samples; quality control data

• **Final studies**
  – Category 1: 10 studies; equation development (random selection of 2/3 of data) and internal validation (remaining 1/3 of data)
  – Category 2: 16 studies; external validation

Levey et al *Ann Int Med* 2009; 150: 604 612
# Clinical Characteristics of CKD-EPI Datasets

## Category 1 (10 studies)  
**Development and Internal Validation**

|                          | N     | Category 2 (16 studies)  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>________________________</td>
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</tr>
<tr>
<td><strong>N</strong></td>
<td>8254</td>
<td>3896</td>
</tr>
<tr>
<td><strong>GFR (mL/min/1.73 m²)</strong></td>
<td>67 (40)</td>
<td>68 (36)</td>
</tr>
<tr>
<td><strong>Diagnosed CKD, N (%)</strong></td>
<td>6004 (73)</td>
<td>2143 (55)</td>
</tr>
<tr>
<td><strong>Age (years) N, (SD)</strong></td>
<td>47 (15)</td>
<td>50 (15)</td>
</tr>
<tr>
<td><strong>Female, N (%)</strong></td>
<td>3606 (44)</td>
<td>1753 (45)</td>
</tr>
<tr>
<td><strong>Black, N (%)</strong></td>
<td>2602 (32)</td>
<td>384 (10)</td>
</tr>
<tr>
<td><strong>Diabetes, N (%)</strong></td>
<td>2406 (29)</td>
<td>1091 (28)</td>
</tr>
<tr>
<td><strong>Transplant recipient, N (%)</strong></td>
<td>360 (4)</td>
<td>1130 (29)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) N (SD)</strong></td>
<td>28 (6)</td>
<td>27 (6)</td>
</tr>
</tbody>
</table>

Levey et al *Ann Int Med* 2009; 150: 604 612
CKD-EPI Equation

\[
GFR = 141 \times \left[ \min \left( \frac{\text{Scr}}{\kappa}, 1 \right)^\alpha \times \max \left( \frac{\text{Scr}}{\kappa}, 1 \right)^{-1.209} \right] \times \text{Age}^{-0.993} \times 1.018 \text{ [if female]} \times [1.157 \text{ if Black}]
\]

\[\alpha\] is 0.329 for females and 0.411 for males; \(\min\) indicates minimum of \(\frac{\text{Scr}}{\kappa}\) or 1, and \(\max\) indicates maximum of \(\frac{\text{Scr}}{\kappa}\) or 1

<table>
<thead>
<tr>
<th>Gender</th>
<th>Scr</th>
<th>GFR Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>≤0.7</td>
<td>(GFR = 144 \times \left( \frac{\text{Scr}}{0.7} \right)^{-0.329})</td>
</tr>
<tr>
<td></td>
<td>&gt;0.7</td>
<td>(GFR = 144 \times \left( \frac{\text{Scr}}{0.7} \right)^{-1.209})</td>
</tr>
<tr>
<td>Male</td>
<td>≤0.9</td>
<td>(GFR = 141 \times \left( \frac{\text{Scr}}{0.9} \right)^{-0.411})</td>
</tr>
<tr>
<td></td>
<td>&gt;0.9</td>
<td>(GFR = 141 \times \left( \frac{\text{Scr}}{0.9} \right)^{-1.209})</td>
</tr>
</tbody>
</table>

Comparison of the Performance of the MDRD Study and CKD-EPI equations (Validation dataset)

Comparison of distribution of estimated GFR for MDRD Study and CKD-EPI equations (NHANES 1999-2004)

Values are plotted at the midpoint.

Levey et al Ann Int Med 2009; 150: 604 612
Cystatin C and the Risk of Death and Cardiovascular Events among Elderly Persons

Figure 1. Mortality from All Causes According to Quintile of Measures of Renal Function.

Relationship of Plasma Level and GFR for Cystatin C

\[ G \text{ (all cells, factors ?)} \]

\[ G \text{ (diet ?)} \]

\[ S \]

\[ U \times V \text{ (kidney) GFR TR} \]

\[ E \text{ (?)} \]
<table>
<thead>
<tr>
<th></th>
<th>Value</th>
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<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>52.0 (13.2)</td>
</tr>
<tr>
<td><strong>Female, N (%)</strong></td>
<td>1006 (32.1)</td>
</tr>
<tr>
<td><strong>Black, N (%)</strong></td>
<td>1677 (53.5)</td>
</tr>
<tr>
<td><strong>Diabetes, N (%)</strong></td>
<td>436 (13.9)</td>
</tr>
<tr>
<td><strong>Transplant, N (%)</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>BMI, mean (SD), kg/m^2</strong></td>
<td>28.7 (6.1)</td>
</tr>
<tr>
<td><strong>GFR, mean (SD), ml/min/1.73 m^2</strong></td>
<td>48.7 (25.7)</td>
</tr>
<tr>
<td><strong>Standardized Scr, mean (SD), mg/dl</strong></td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td><strong>Cystatin C, mean (SD) mg/l</strong></td>
<td>1.8 (0.8)</td>
</tr>
</tbody>
</table>

### Cystatin C vs Creatinine Equation

**CKD-EPI Cystatin Pooled Dataset; 4 studies; 3,134 individuals**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Δ</th>
<th>P₃₀</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Creatinine age, sex and race*</td>
<td>0.1</td>
<td>10.8</td>
</tr>
<tr>
<td>Cystatin alone</td>
<td>0.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Cystatin age, sex and race</td>
<td>0</td>
<td>11.2</td>
</tr>
<tr>
<td>Both age, sex and race</td>
<td>0.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Δ =mGFR-eGFR. Positive value indicates underestimate
IQR, interquartile range
P₃₀, percentage of estimates within 30% of measured GFR

*Refit MDRD Study equation

Non-GFR Determinants of Cystatin C vs Creatinine in patients with CKD

*Adjusted for GFR, GFR measurement error, age, sex and race

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Stevens et al, *KI* 2008

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* Significant for both cystatin C and serum creatinine
* Significant for cystatin C only
* Significant for Serum creatinine only
* Not significant for either cystatin and serum creatinine
Summary

• All endogenous filtration markers have non-GFR determinants that affects interpretation of their accuracy as well as prediction of risk

• The CKD-EPI equation is more accurate than the MDRD Study equation
  – Less bias at eGFR >60
  – Similar performance at eGFR <60
  – Imprecision remains

• Cystatin C based estimates
  – Provide similar or less accurate estimates of measured GFR in populations with CKD
  – Non-GFR determinants are not well understood but may explain some of the improved risk prediction