Estimated GFR Based on Creatinine and Cystatin C

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Chronic Kidney Disease-Epidemiology Collaboration

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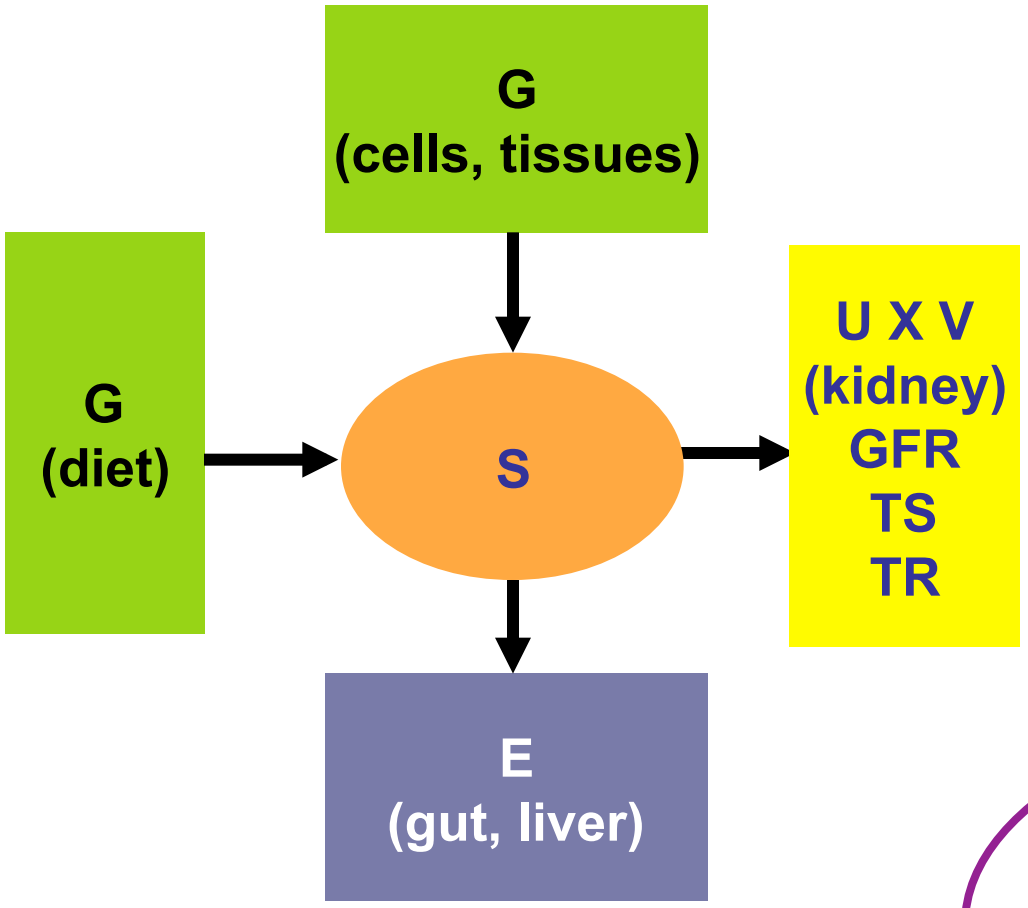
Background

- 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



$$U \times V = GFR \times S + TS - TR$$

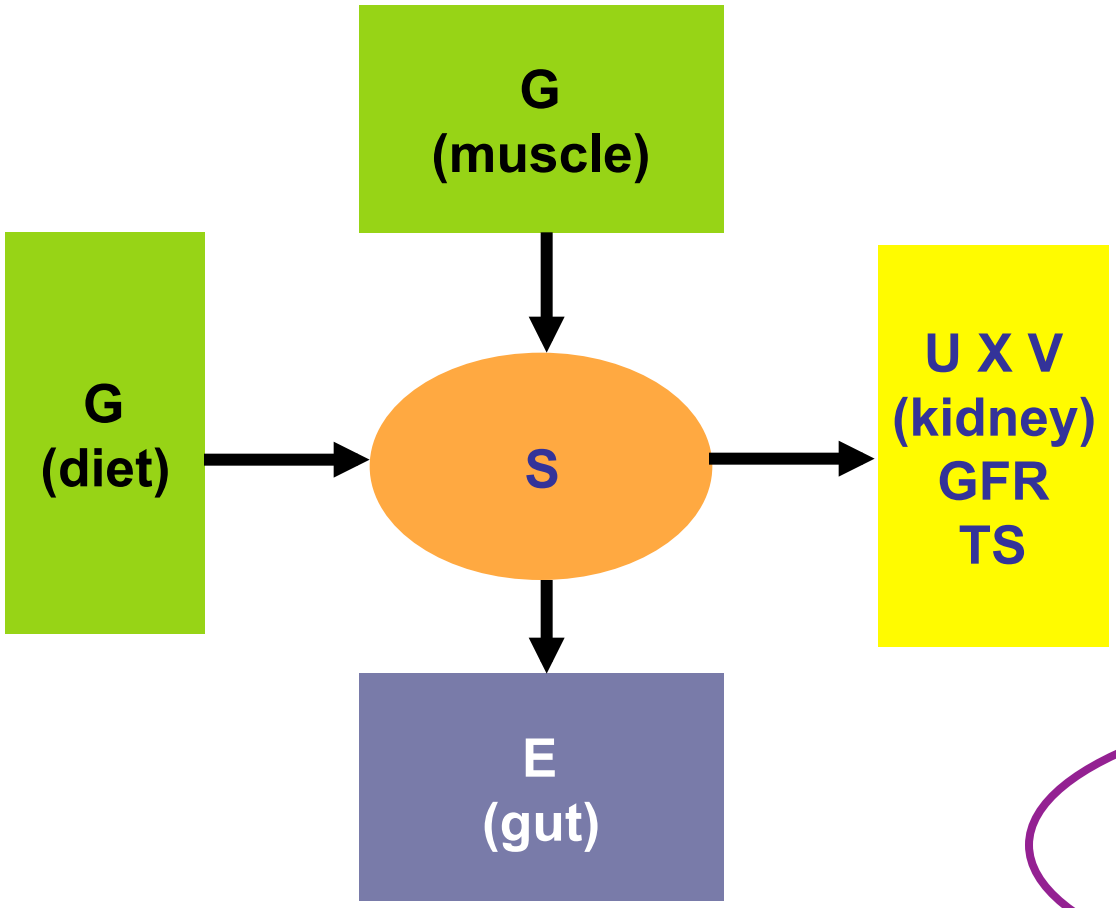
$$G\text{-}E = GFR \times S + TS\text{-}TR$$

$$S = (G - E - TS + TR) / GFR$$

$$GFR = (G - E - TS + TR) / S$$

Estimating equations substitute easily measured clinical surrogates for unmeasured physiological processes

Creatinine Physiology



U X V = GFR x S + TS

G-E = GFR x S + TS

S= (G - E - TS) /GFR

GFR= (G - E - TS)/S

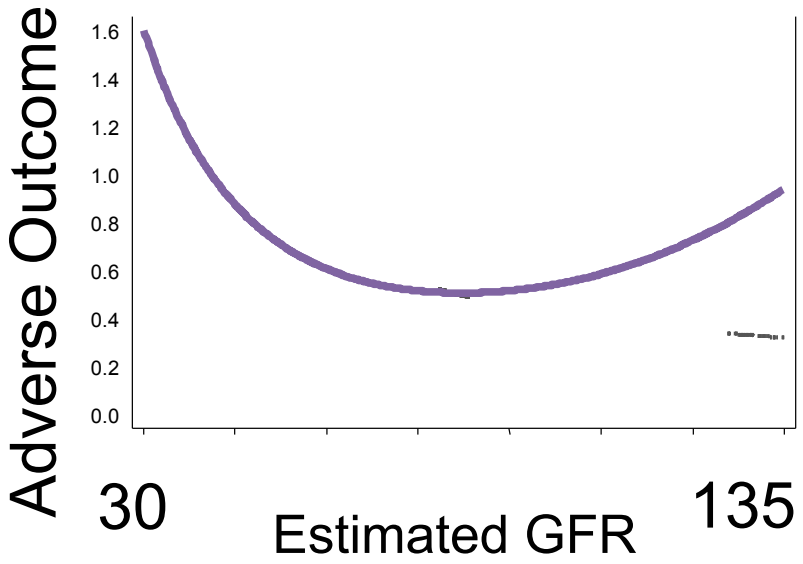
Age, sex, race, weight

The MDRD Study equation

- MDRD Study equation
  - Derived from 1628 participants with predominantly non-diabetic CKD (mean GFR 40 ml/min/1.73 m^2)
  - 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



Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)

- **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*	**Category 2 (16 studies)** ***External validation***
N	8254	3896
GFR (mL/min/1.73 m^2)	67 (40)	68 (36)
Diagnosed CKD, N (%)	6004 (73)	2143 (55)
Age (years) N, (SD)	47 (15)	50 (15)
Female, N (%)	3606 (44)	1753 (45)
Black, N (%)	2602 (32)	384 (10)
Diabetes, N (%)	2406 (29)	1091 (28)
Transplant recipient, N (%)	360 (4)	1130 (29)
BMI (kg/m^2) N (SD)	28 (6)	27 (6)

Levey et al *Ann Int Med* 2009; 150: 604 612

CKD-EPI Equation

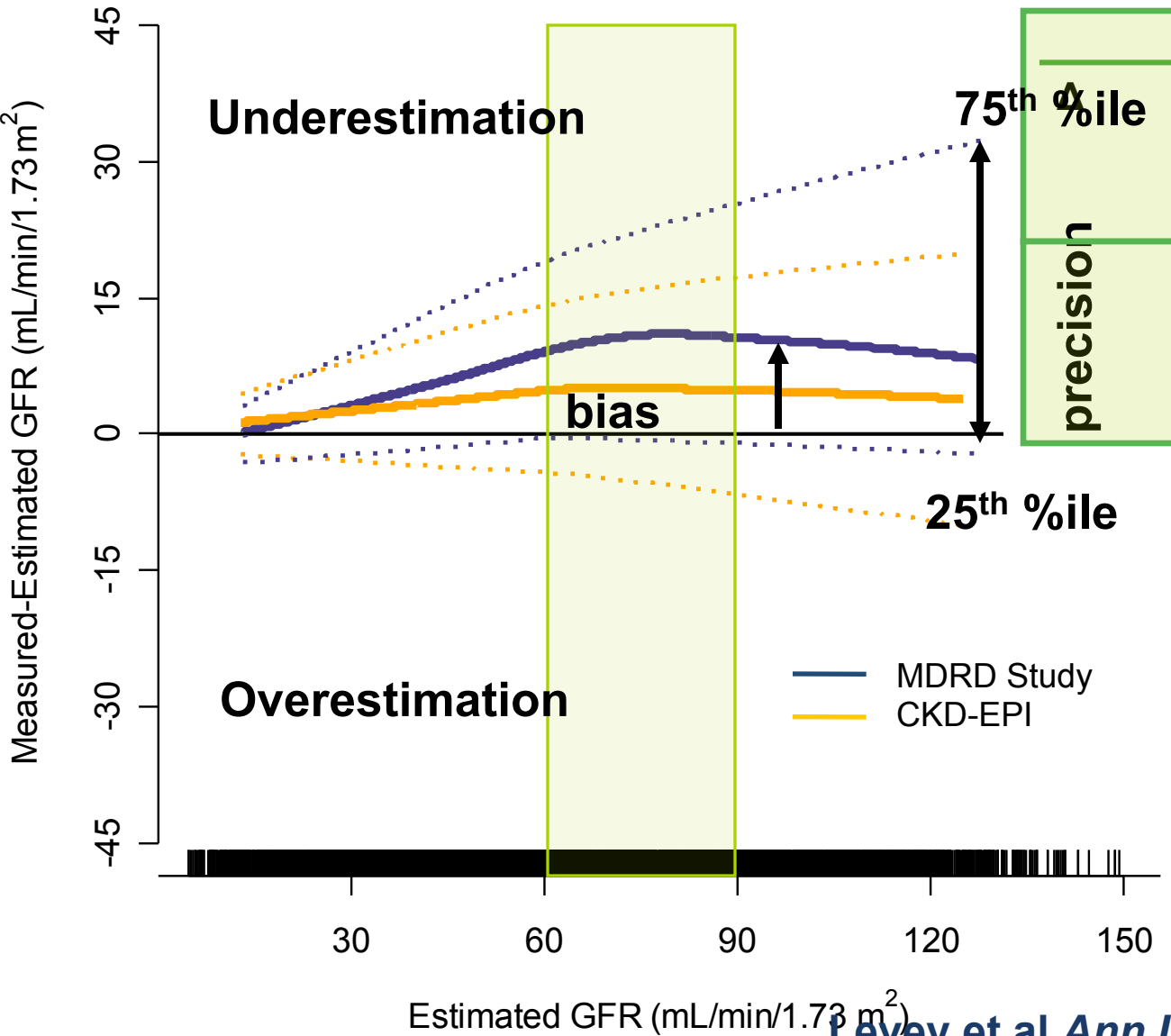
$$GFR = 141 \times [\min(Scr/\kappa),1)^{\alpha} \times \max(Scr/\kappa),1)^{-1.209}] \times Age^{-0.993} \times 1.018 \text{ [if female]} \times [1.157 \text{ if Black}]$$

α is 0.329 for females and 0.411 for males; min indicates minimum of Scr/κ or 1, and max indicates maximum of Scr/κ or 1

Female	≤0.7 →	$GFR = 144 \times (Scr/0.7)^{-0.329}$	$\times Age^{-0.993}$	$\times 1.157$ [if black]
	>0.7 →	$GFR = 144 \times (Scr/0.7)^{-1.209}$		
Male	≤ 0.9 →	$GFR = 141 \times (Scr/0.9)^{-0.411}$		
	>0.9 →	$GFR = 141 \times (Scr/0.9)^{-1.209}$		

Levey et al *Ann Int Med* 2009; 150: 604 612

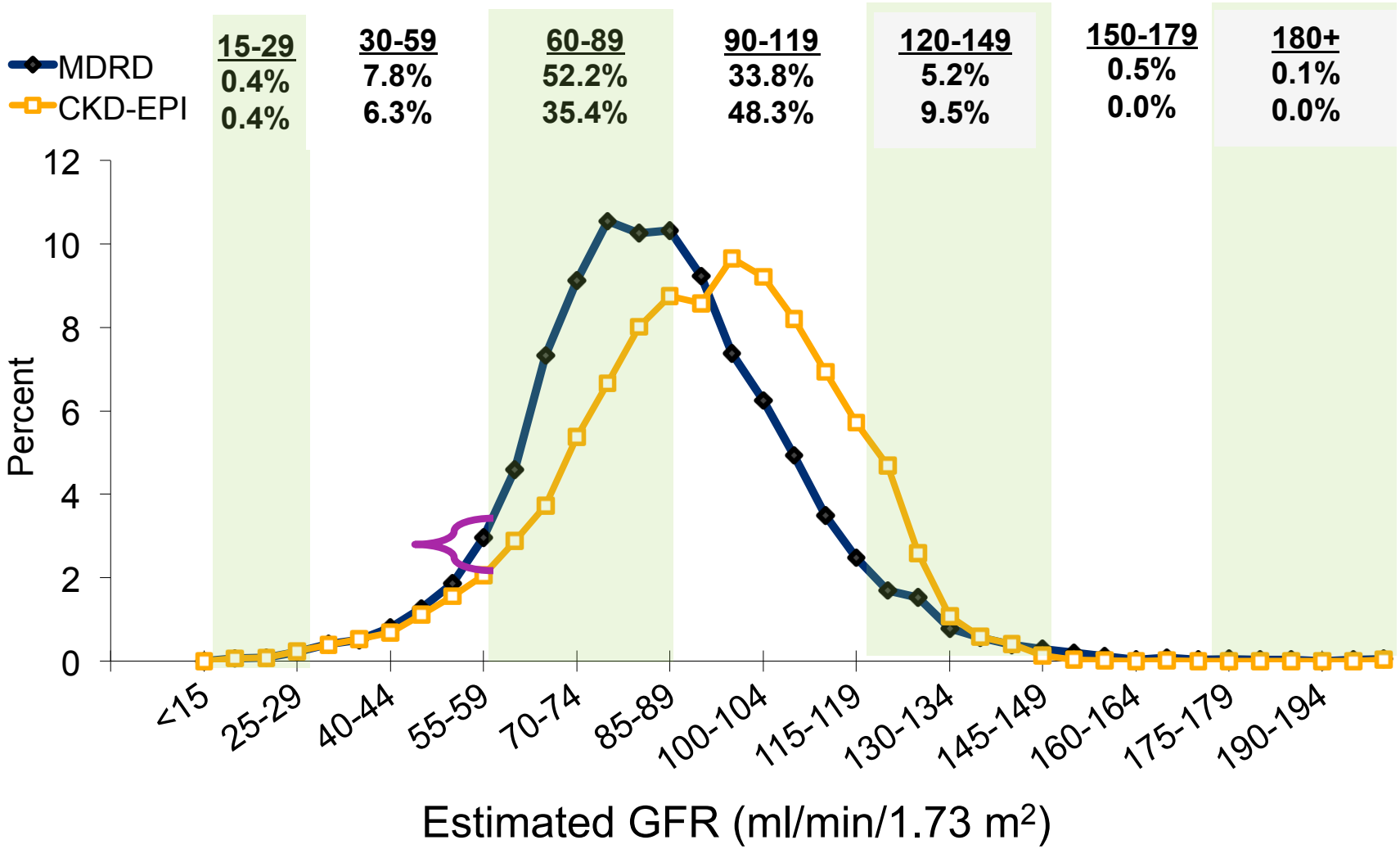
Comparison of the Performance of the MDRD Study and CKD-EPI equations (Validation dataset)



		All	60-89
precision	MDRD	5.5	11.9
	CKD-EPI	2.5	4.2
	% Δ	***50%***	***59%***

Levey et al *Ann Int Med* 2009; 150: 604 612

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

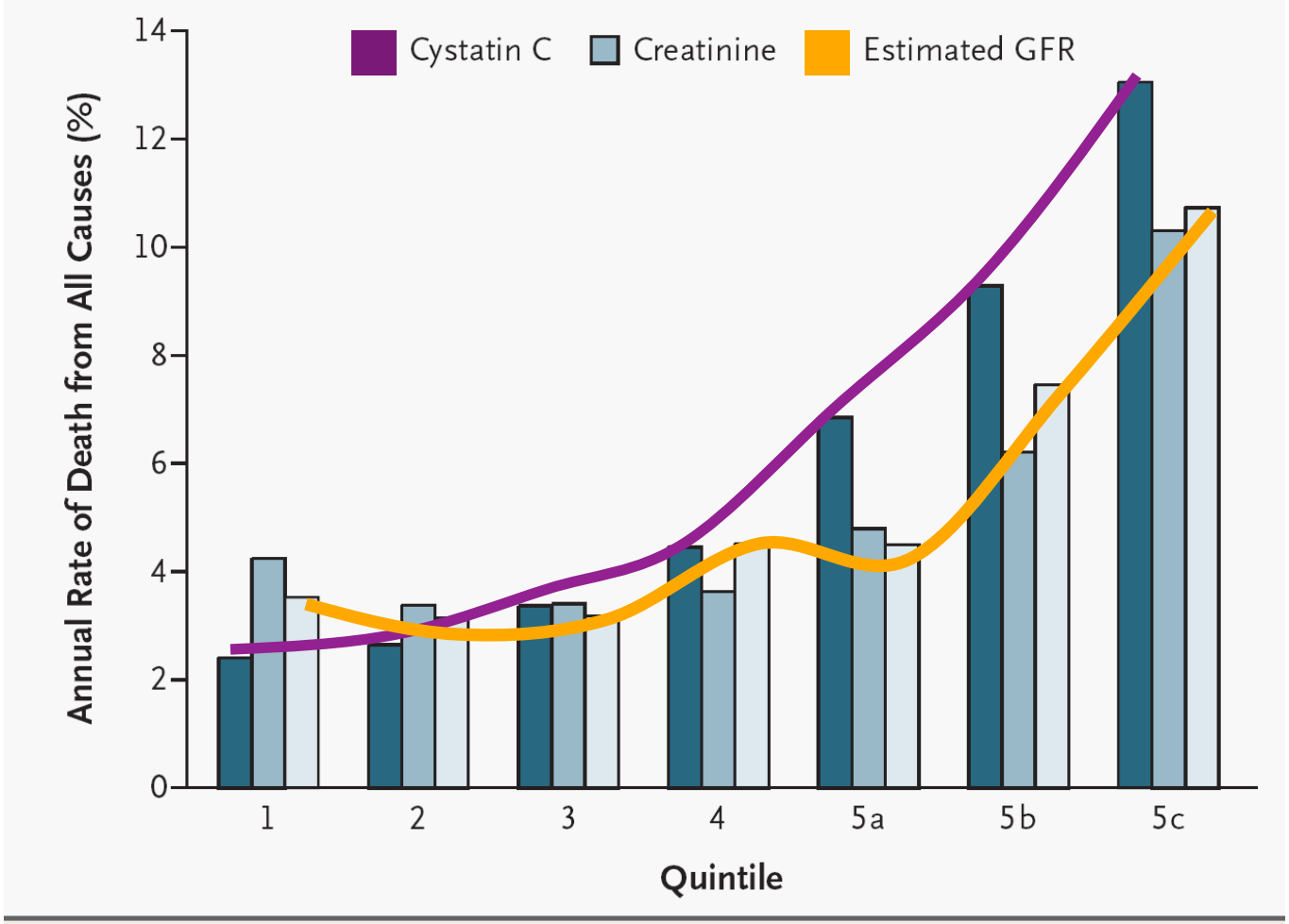
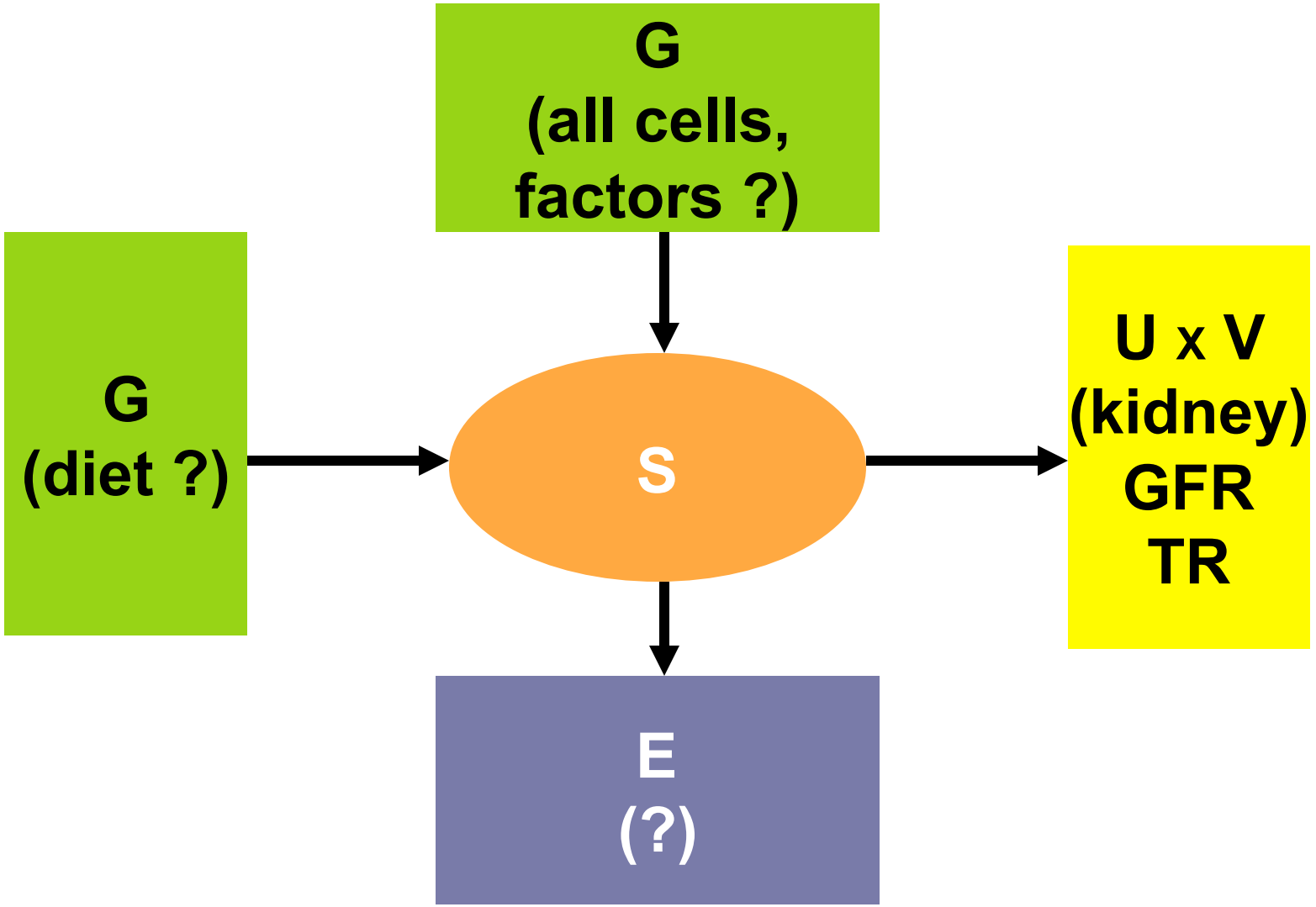


Figure 1. Mortality from All Causes According to Quintile of Measures of Renal Function.

Shlipak et al. *N Engl J Med* 2005;352:2049-60

Relationship of Plasma Level and GFR for Cystatin C



CKD-EPI Pooled Cystatin Database (4 studies, N=3134)

Age, mean (SD), years	52.0 (13.2)
Female, N (%)	1006 (32.1)
Black, N (%)	1677 (53.5)
Diabetes, N (%)	436 (13.9)
Transplant, N (%)	0
BMI, mean (SD), kg/m^2	28.7 (6.1)
GFR, mean (SD), $ml/min/1.73\ m^2$	48.7 (25.7)
Standardized Scr, mean (SD), mg/dl	2.0 (1.0)
Cystatin C, mean (SD) mg/l	1.8 (0.8)

Stevens LA, et al. *Am J Kidney Dis*. 2008;51:395-406

Cystatin C vs Creatinine Equation

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

Equation	Δ		P_{30}
	Median	IQR	
Creatinine age, sex and race*	0.1	10.8	85
Cystatin alone	0.2	11.7	81
Cystatin age, sex and race	0	11.2	83
Both age, sex and race	**0.1**	**9.2**	**89**

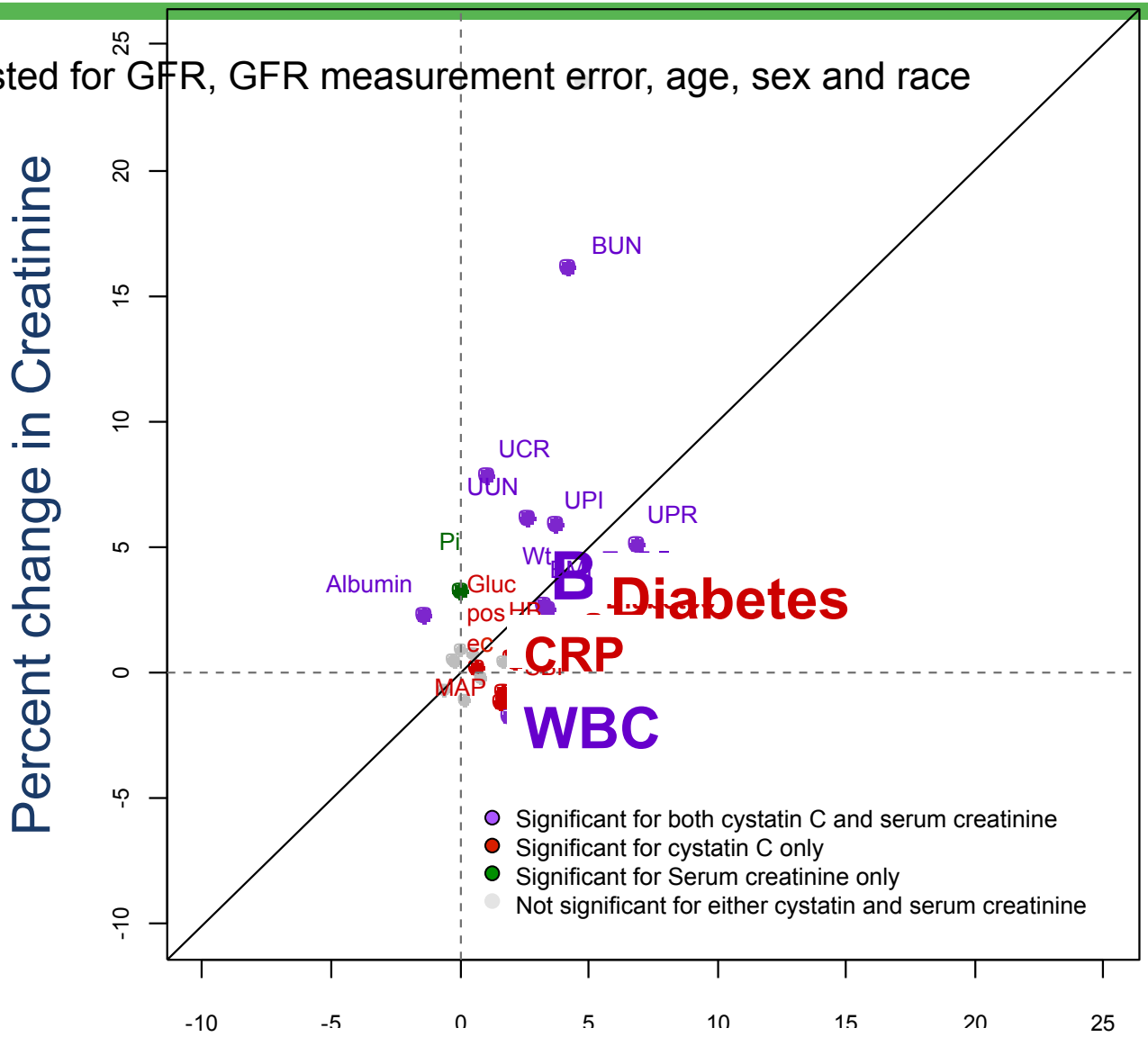
Δ =mGFR-eGFR. Positive value indicates underestimate
IQR, interquartile range
P_{30}, percentage of esteimates within 30% of measured GFR

***Refit MDRD Study equation**

Stevens LA, et al. *Am J Kidney Dis.* 2008;51:395-406

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

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



Stevens et al *KI* 2008

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