AN OVERVIEW OF CYSTATIN C AND EGFR

Lesley Stevens MD MS

Tufts Medical Center, Boston

Acknowledgements

Investigators

- Andrew Levey, Josef Coresh, Tom Greene, Christopher Schmid, Harold Feldman, Fred Van Lente, Jane Manzi, Richard Landis, Liang Li, Yaping Zhang

Collaborators

- **African American Study of Kidney Disease and Hypertension (AASK)**: Gabriel Contreras, Julia Lewis.
- **Baylor University Medical Center:** Goran Klintmalm.
- **Captopril in Diabetic Nephropathy Study (CSG):** Roger Rodby, Richard Rohde.
- **Chronic Renal Insufficiency Cohort (CRIC)**: Harold Feldman, Lawrence Appel, Jing Chen, Alan Go, Lee Hamm, Chi-yuan Hsu, James Lash, Akinlolu Ojo, Mohboob Rahman, Raymond Townsend, Matthew Weir, Jackson Wright
- **Cleveland Clinic Foundation (CCF)**: Phillip Hall, Emilio Poggio.
- **Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)**: Vicente Torres.
- **Dallas Nephrology Associates (DNA)**: Larry Melton, Ruben Velez.
- **Diabetes Control and Complications Trial (DCCT)**: Saul Genuth, Michael Steffes
- **Diabetic Renal Disease Study Group (DRDS)**: Robert G. Nelson.
- **Groningen Renal Hemodynamic Cohort Study Group (GRECO)**: Gerjan Navis.
- **Inter Diabetes; Renin-Angiontensin System Study (RASS)**: Michael Mauer,
- **Lund:** Anders Grubb, Omran Bakoush.
- **Mayo Clinic**: Andrew D. Rule, Timothy Larson, Fernando Cosio.
- **Modification of Diet in Renal Disease (MDRD) Study**: Gerald Beck.
- **NephroTest**: Jerome Rossert, Marc Froissart.
- **Steno Diabetes Center**: Hans-Henrik Parving, Peter Rossing.

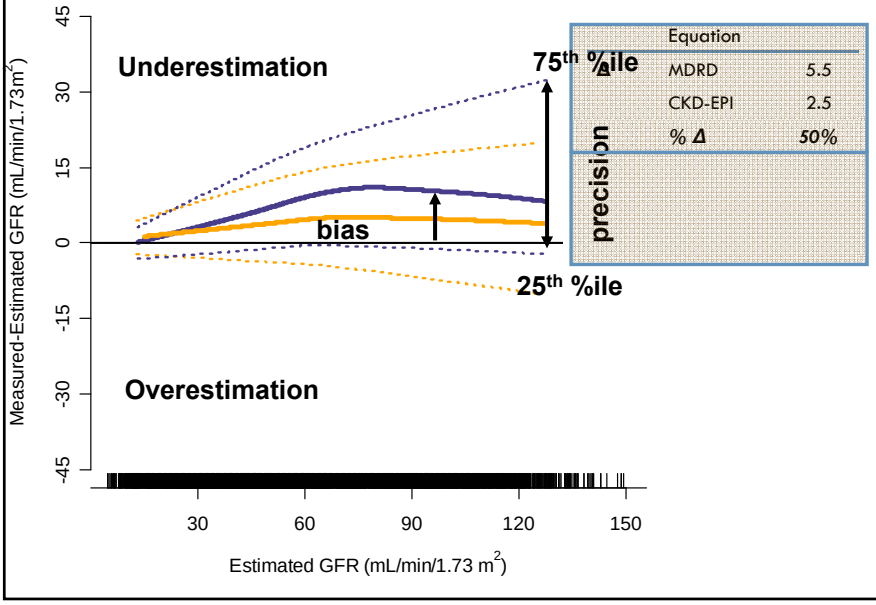
NIDDK

- Josie Briggs, Robert Starr, John Kusek, Paul Eggers

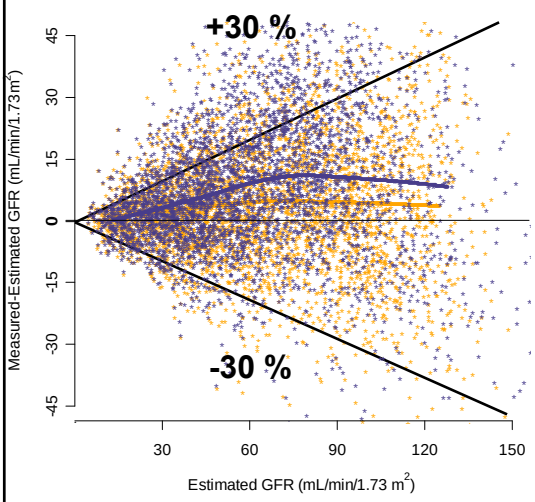
Outline

- Current state of eGFR with creatinine
- Cystatin as predictor of risk
- Cystatin as a filtration marker
  - Physiology
  - Assay
  - Estimating equations
- Strategies for use in practice
- Conclusions

Current State of GFR Estimation with Creatinine



Current State of GFR Estimation with Creatinine



Bias	MDRD	5.5
	CKD-EPI	2.5
	%	50%
IQR	MDRD	18.3
	CKD-EPI	16.6
	%	9%
P_{30}	MDRD	80.6
	CKD-EPI	84.1
	%	4%
$1-P_{30}$	MDRD	19.4
	CKD-EPI	15.9
	%	18%

Levey et al Annals 2009

Cystatin C and the Risk of Death and Cardiovascular Events among Elderly Persons

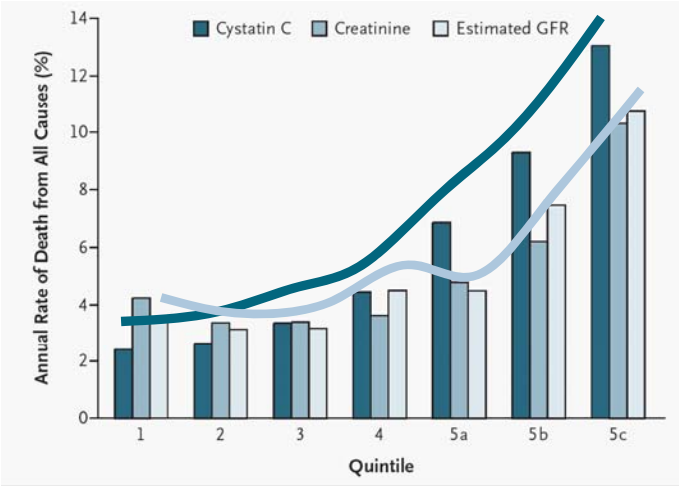
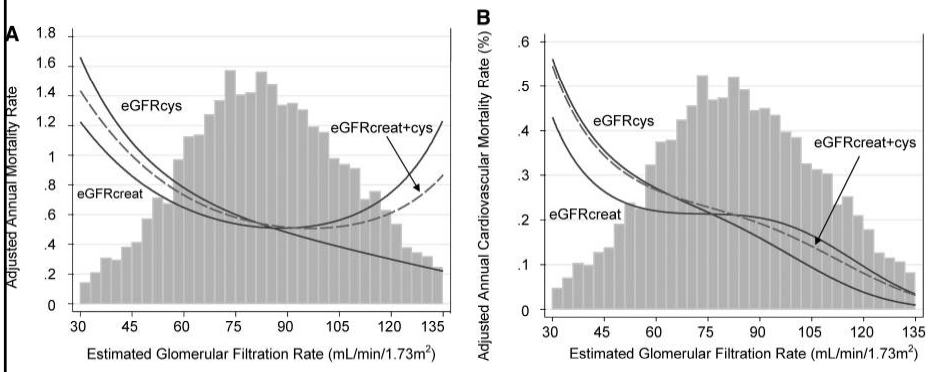


Figure 1. Mortality from All Causes According to Quintile of Measures of Renal Function.

Shlipak et al. N Engl J Med. 2005;352(2):2049-60.

Risk for Mortality and CVD Mortality in NHANES III by eGFRcreat vs eGFRcys



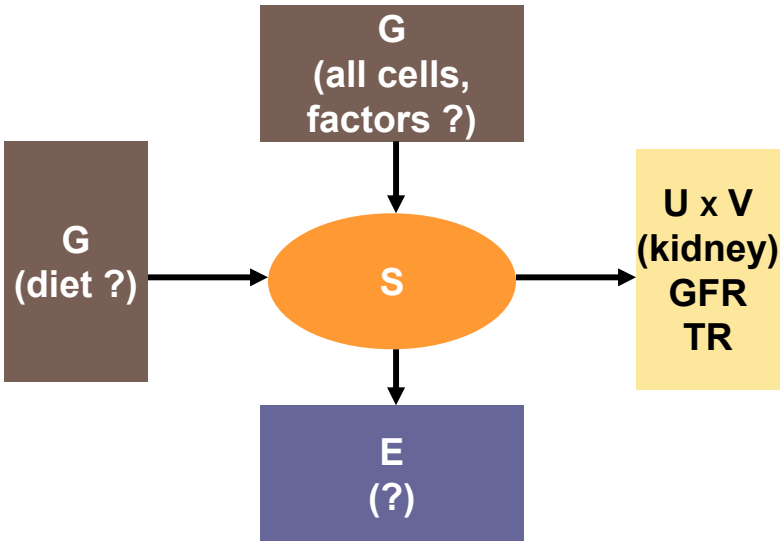
Astor et al JASN 2009 20 (10) 2214–2222.

Cystatin C as a Risk Factor for Outcomes in Chronic Kidney Disease (MDRD Study)

	1/creatinine	Measured GFR	1/cystatin
Mortality	1.22	1.26	1.39
CVD Mortality	1.24	1.27	1.60
Kidney failure	2.82	2.43	2.35

Menon et al Annals Int Med 2007

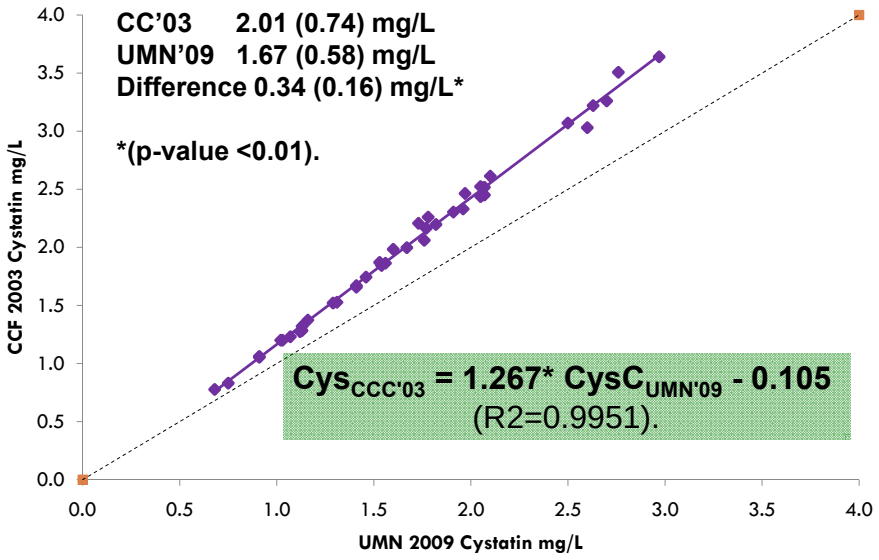
Relationship of Plasma Level and GFR for Cystatin C



Assay

- Variation among cystatin assays is well recognized, and these differences lead to variation in the estimated GFR
- Reference methods for assay of cystatin C were recently developed by the IFCC
- Manufacturers have not yet calibrated their assay to reference methods, and this will likely occur over 2-3 time frame
- Research laboratories can calibrate to these reference standards. Investigators should use standardized values and equations developed for these standardized values

Comparison of Cystatin C Assay CCF'03 & UMN'09



Cystatin C equations

Author	Population	N	Assay	Manufacturer/ Instrument
Hoek 2003	Clinical population	93	PENIA	Dade ProSpec
Filler 2003	Children (1-18 year)	536	PENIA	Dade Pro Spec
Larsson 2004	Healthy adults	100	PENIA	Dade ProSpec
Grubbs 2005	Clinical population (Adults & Children)	536	PETIA	Hitachi P Mod Dako
Sjostrom 2005	Clinical population (including patients on hemodialysis)	381	PETIA	Hitachi P Mod Dako
Rule 2006	CKD	204	PENIA	Dade BN II
	Transplant	103		
Stevens 2008	CKD	3184	PENIA	Dade BNII

CKD-EPI Diverse Dataset Clinical Characteristics

	Development	External Validation
	5352	*1119*
Age (years) mean (SD)	47 (15)	50 (17)
Female, N (%)	2245 (42)	456 (41)
Blacks, N (%)	2123 (40)	30 (3)
Diabetes, N (%)	1726 (32)	594 (53)
BMI (kg/m^2), mean (SD)	28 (6)	25 (4)
BSA (m^2), m,ean (SD)	1.9 (0.2)	1.9 (0.2)
GFR (mL/min/1.73 m^2), mean (SD)	68 (39)	70 (41)
Serum cystatin (mg/dL), mean (SD)	1.5 (0.8)	1.6 (0.9)
Serum creatinine (mg/dL). mean (SD)	1.6 (0.9)	1.6 (1.1)

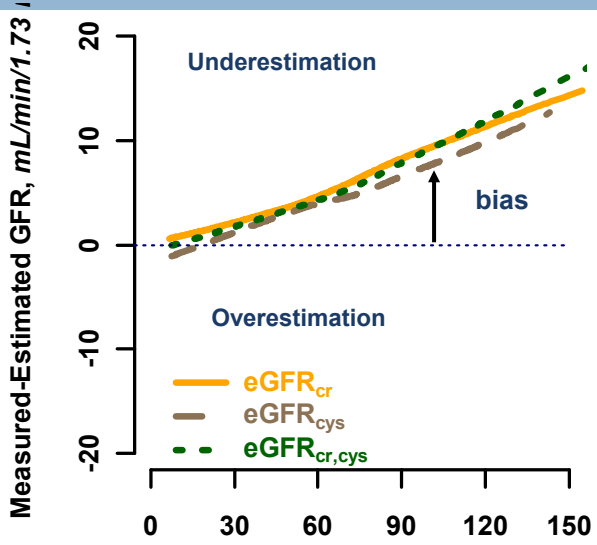
CKD-EPI: Performance in Overall Dataset

Model name	Markers + variables	Bias	Precision	Accuracy	
		Difference	IQR	RMSE	P_{30}
Equations in CKD populations					
MDRD Study	Log Creat	5.4	18	0.252	83
AJKD 2008	Log Cys	6.0	19	0.258	84
AJKD 2008*	Log creat-Log cys	4.2	14	0.200	92
Equations in a diverse population					
CKD-EPI**	Spline Creat	3.1	14	0.221	87
CKD-EPI^	Spline Cys	3.2	17	0.235	86
CKD-EPI^	Spline Creat-Log Cys	3.0	13	0.188	92
	Average of eGFRcreat+eGFRcys	3.5	14	0.190	92

A, age; S, sex; R, race; RMSE, root mean square error; IQR=Interquartile range: 25th and 75th percentile of mGFR-eGFR; P30=percentage of eGFR within 30% of mGFR

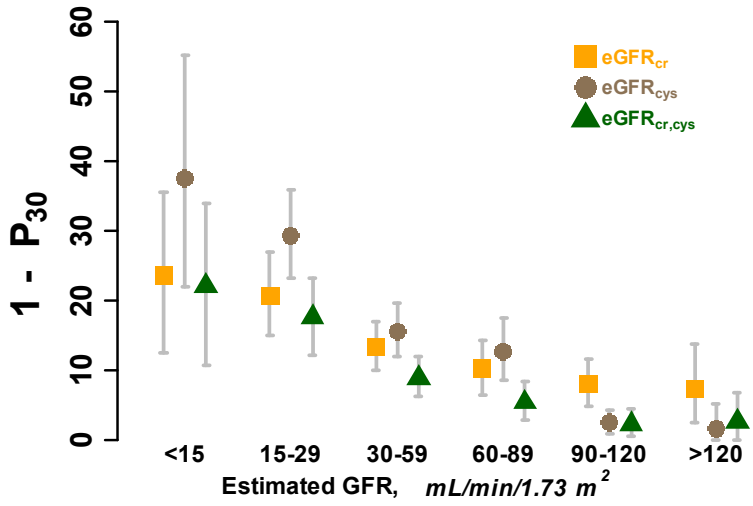
*Stevens et al *AJKD* 2008 **Levey et al *Ann Int Med* 2009
^In preparation. Stevens et al *ASN Free communication 2009*

CKD-EPI: Median difference by Level of eGFR (Validation Dataset)

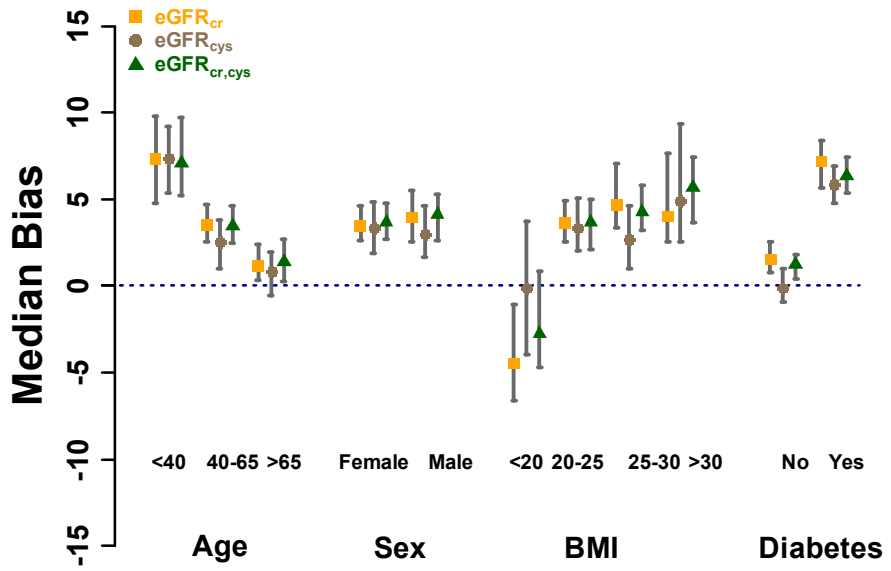


Unpublished data.

Outliers by level of GFR



Bias by subgroups



Cystatin C in Special Populations

Adv for cystatin	Population	Bias	Precision	Reference (e.g)
Changes in Muscle (Adults)	Elderly	**Mixed**	**Mixed**	O'Riordan, S.E 2003; Burkhardt 2002; Ferholm
	Cirrhosis	**Mixed**	**Mixed**	Xirouchakis 2010, Woitas 2000, Poge 2006, Chu 2004
	MM	**Similar**	**Similar**	Lamb 2004
	Anorexia	**Cys**	**Similar**	Delanaye
	Cystic fibrosis	**Similar**	**Cys**	Beringer 2009
Changes in Muscle (Pediatrics)	Pediatrics	**Creat**	**Creat**	Schwartz 2009
	Mitocondrial	**Cys**	**Cys**	Lee 2009
	DMD	**Cys**	**Cys**	Viollet 2009
Drugs affect creatinine	Kidney Tx	**Mixed**	**Mixed**	Maillard 2008;White 2007, Zahran 2007, Akbas 2004
	Liver Tx	**Creat**	**Creat**	Boudville 2009
High level of GFR	General population	**Similar**	**Similar**	Eriksen 2010

eGFR cys vs eGFRcreat to evaluate GFR change over time

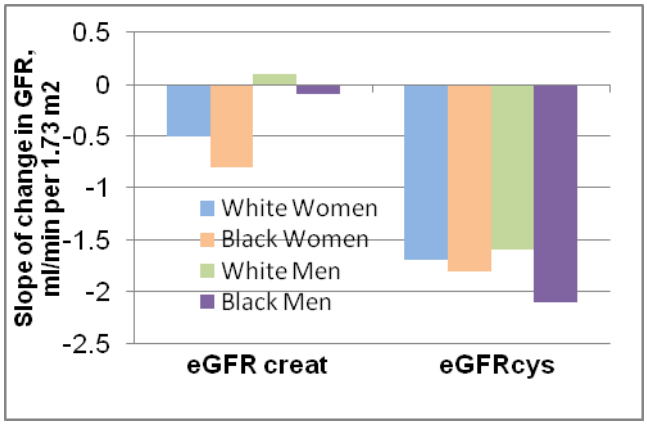
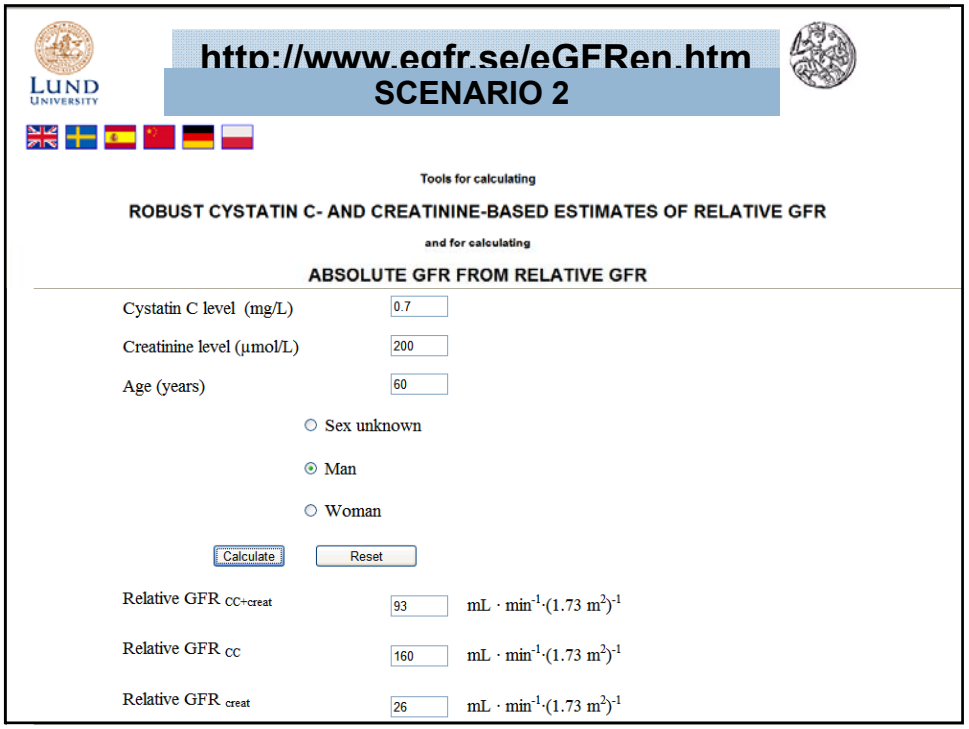


Figure C.8: Rate of decline in eGFR using creatinine and cystatin by race and sex [167]

Shlipak et al Am J Nephrol 2009

Strategies for use

- Scenario 1: Both used in combination to report eGFR
  - Advantages: Most accurate estimate; Less confusing to the clinician
  - Disadvantages: Cost; Combination not appropriate for all
- Scenario 2: eGFRcr, eGFRcys and eGFRcr-cys reported separately
  - Advantages: Most flexibility
  - Disadvantages: Not clear indications for when to use
- Scenario 3: Cystatin used as confirmatory test
  - Advantages: Most cost efficient; able to use when appropriate
  - Disadvantages: Complicated decisions for when to order; May prevent timely decision making

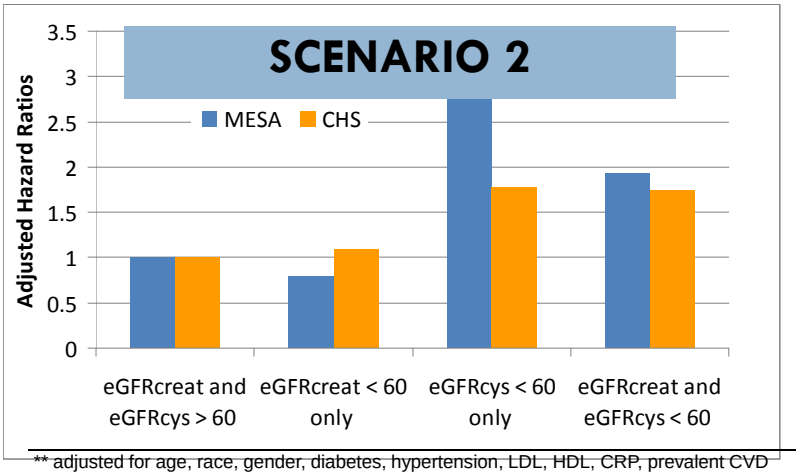


Does eGFR reporting using cystatin improve outcomes?

- eGFRcys and eGFRcreat were used to assess safety for patients on Li
- After 14 months, iohexol GFR was performed in 111/182 patients
- Agreement with GFR was better for eGFRcreat vs eGFRcys
- Repeatability was better for eGFRcreat vs eGFRcys
- The authors concluded that the results do not justify replacing eGFRcreat w eGFRcys

SCENARIO 2

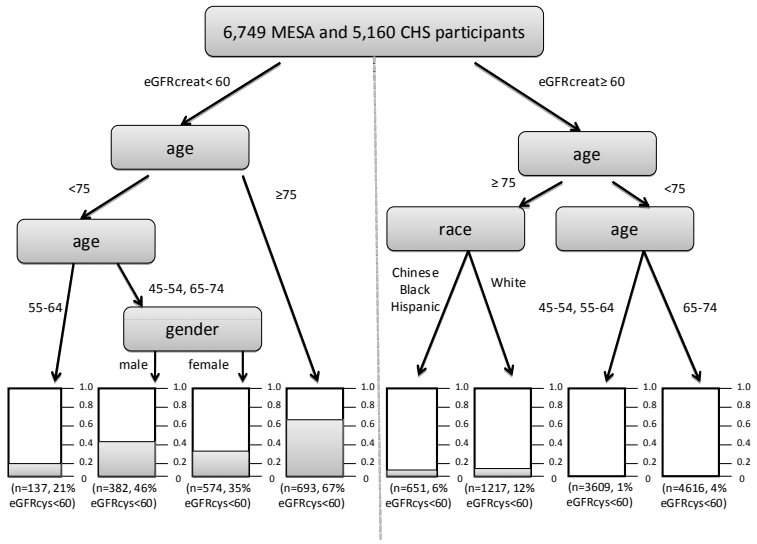
Role of Cystatin for Detection of High Risk Patients



** adjusted for age, race, gender, diabetes, hypertension, LDL, HDL, CRP, prevalent CVD for CHS (persons with baseline CVD were excluded for incident CVD analyses)

Peralta et al JASN in press

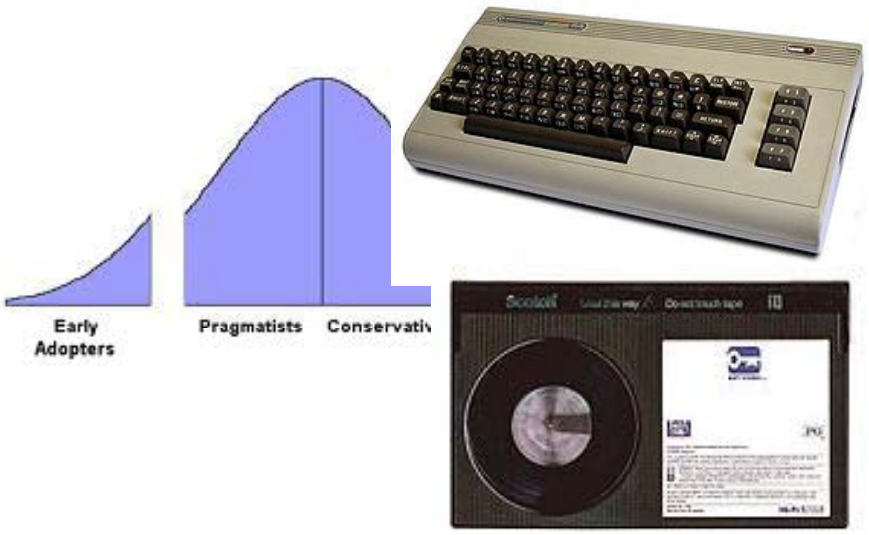
Role of Cystatin for Detection of High Risk Patients



Summary

- Filtration marker to estimate GFR
  - Probably some advantage over creatinine in some populations, but data are mixed and clinical indications can therefore not be developed
  - Combination of creatinine and cystatin appears to be more accurate
- Predictor of risk
  - Definite advantage over creatinine for mortality and CVD risk, needs to be more evaluated in combination with albuminuria
  - More assessment with other outcomes to define use for patient safety, AKI, drug dosing

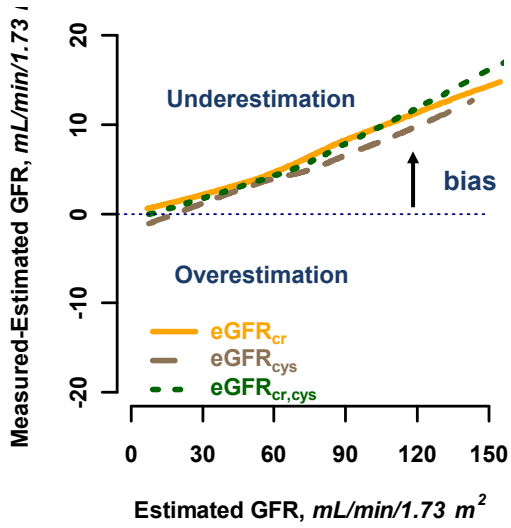
Should cystatin be implemented in clinical practice?



If cystatin is to be implemented ….

- Development of decisions tools to assist clinicians in interpretation of results
  - GFR estimate: Additional rigorous studies to test advantage in acute and chronically ill patients
  - Predictor of risk: Evaluation of whether cystatin C and albuminuria into new proposed classification systems
- Assay: Standardized values available in clinical laboratories

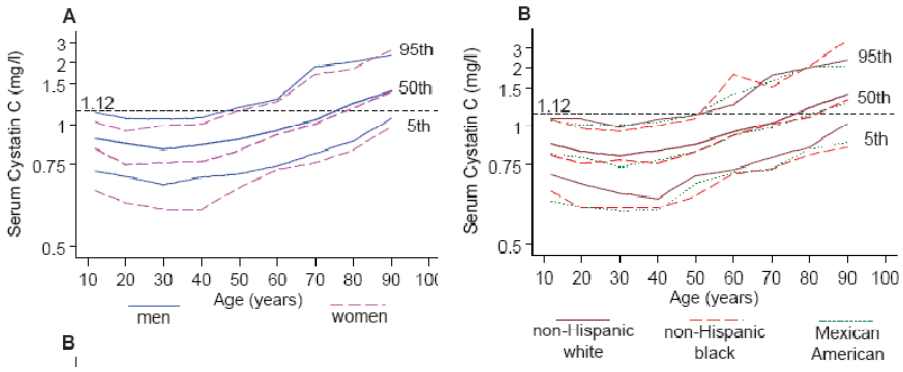
CKD-EPI: Median difference by Level of eGFR (Validation Dataset)



	<60	60-89	90-119
Creat	1.8	6.6	11.1
Cystatin	0.3	6.2	8.8
Creat-Cys	1.3	7.1	10.6

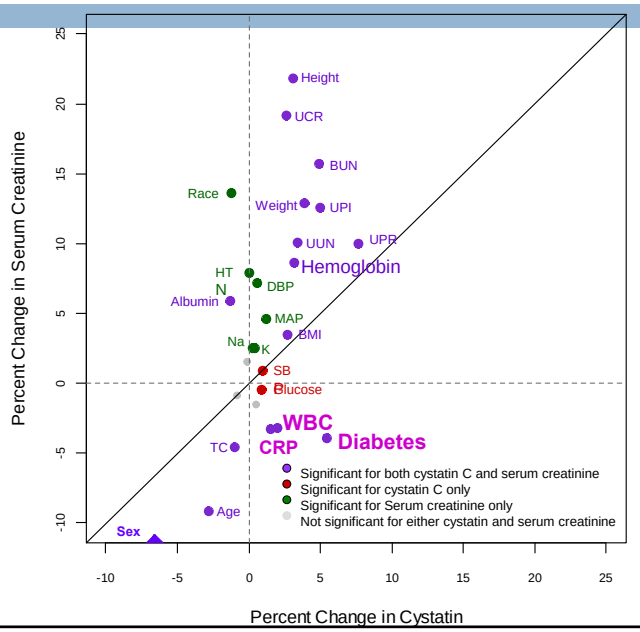
Unpublished data.

Serum Cystatin in NHANES



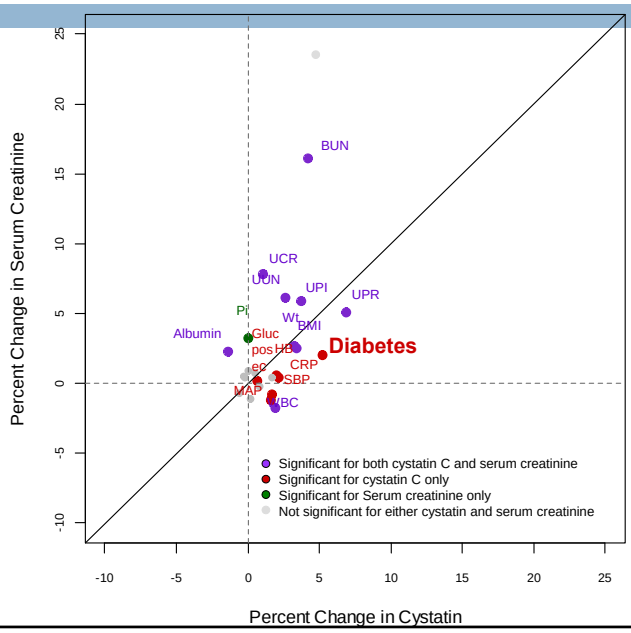
Kottagen et al, *AJKD* 2008

Non-GFR Determinants of Cystatin C



Stevens LA, et al. Kl. 2009; 75(6):652-60.

Non-GFR Determinants of Cystatin C



Summary of Cystatin as a Filtration Marker

- Equivalent to creatinine with respect to bias
- Less accurate at lower levels of GFR
- Most accurate in combination with creatinine
- Mixed results as to whether more accurate in populations with reduced muscle mass