The Misguided Efforts to Perfect eGFR Equations: History and Future Directions for Using Creatinine, CysC, and eGFR

OR

Fool me once, shame on you;
Fool me four times, shame on us.

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Disclosures for JT

- **Receive consultation fees from B-D Life Sciences, and Werfen (formerly IL).**

(No products will be mentioned in this talk)

Learning Objectives

- Describe why the goals of creatinine, cystatinC, eGFR and mGFR should be to improve clinical detection of kidney disease at an early stage, not necessarily to improve agreement between eGFR and mGFR
- Describe the shortcomings of all measured GFR techniques and why they are not “gold standard” methods
- Assess that the ultimate marker for chronic kidney disease is the number of functional nephrons, not the GFR
- Identify the many advantages of following longitudinal changes of creatinine in a person, especially that this eliminates the variables of sex, race, nationality, and largely age
- State that serum creatinine absolutely changes early in the course of declining kidney function, even while in the reference interval
- Describe the future needs for improving the clinical value of serum creatinine and cystatin C

Polling Questions

- Do you report an eGFR with creatinine results?
- Are you familiar with high-sensitivity troponin?
- Have you heard of Drs Rob Christenson, Alan Wu, and/or Fred Apple? (select all that apply)

Historical Development of Cardiac Markers in an Alternate Universe

- **In 1960: Professor Herman Sheistkopf declares that cardiac output (CO) is the "gold standard" for detecting cardiac disease.**
  - **Based on CO being the most important physiologic function of the heart.**
  - **However measuring CO is highly invasive, difficult, and expensive.**
  - **Nevertheless, virtually every publication has to compare serum markers to measured CO.**
    - **because CO is always considered "Correct", the serum markers are never as good and are deemed "erroneous".**

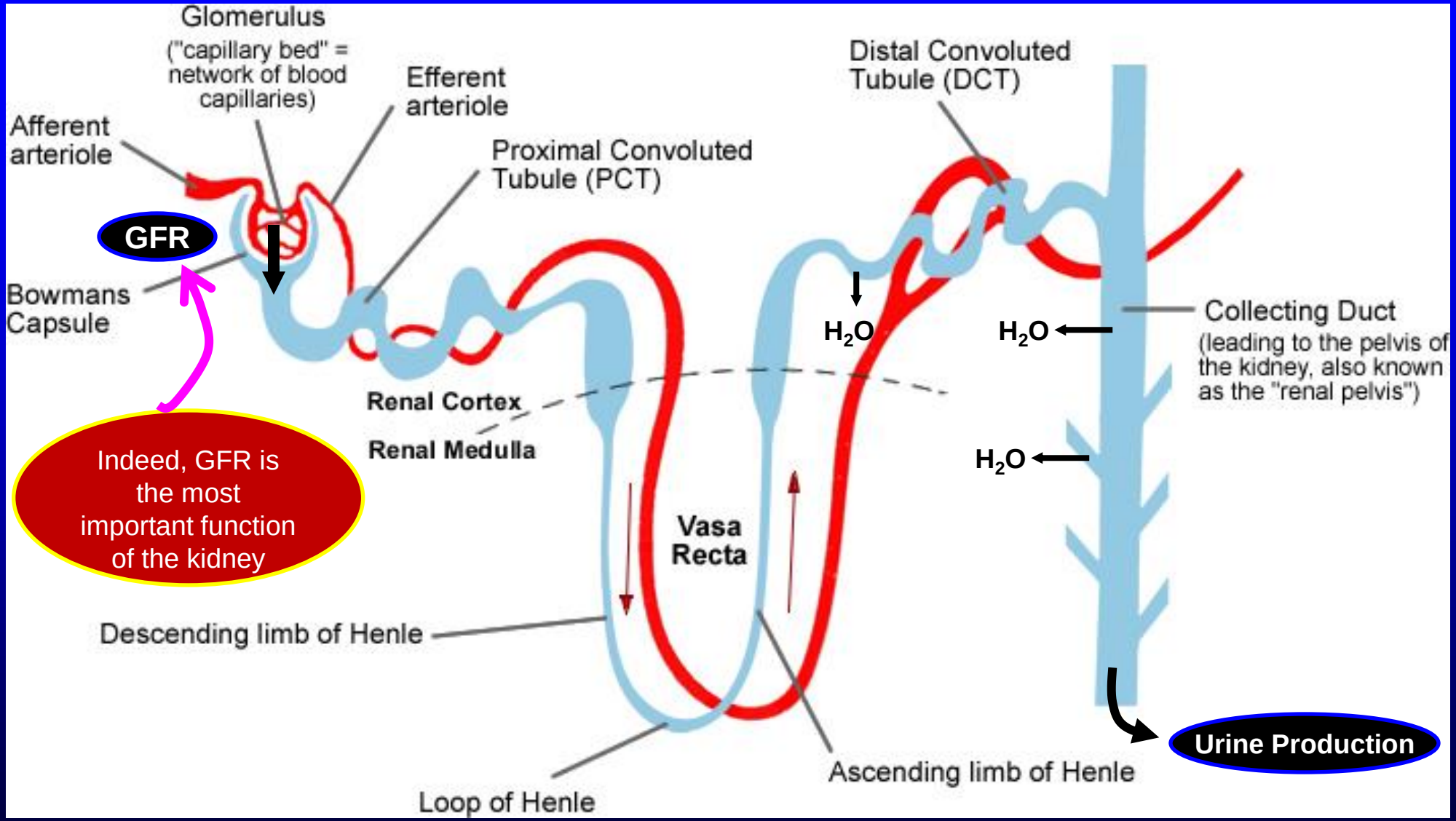
Historical Development of hs-Troponin in an Alternate Universe (continued)

- **From 1970 to 1995, CK-MB, then later, hs-Tn come along as surrogates to detect myocardial damage.**
  - **In 1985, Professor Sheistkopf develops equations using CK-MB to estimate Cardiac Output (eCO):**
  - **eCO = 1/ CK-MB x 0.95 Age x 1.1 *(if female)* x 1.2 *(if Black)***
  - **In 2010, Professor Sheistkopf develops the CHD eCO equation based on Tn, claiming it is more accurate at estimating CO.**
  - **eCO = (1/ Tn) x 0.97 x Age x 1.08 *(if female)* x 1.14 *(if Black)***
    - **All clinical labs have to modify their reports to use this new eCO equation.**
    - **Few, if any, studies show *m*CO is clinically superior to serum markers.**
  - **Professor Sheistkopf becomes very famous and reportedly owns several yachts, homes in Malibu, Swiss Alps, French Riviera, and a high-rise condo in NYC, and is seen driving a stable of Ferraris, Porsches, and Rolls.**

Historical Development of hs-Troponin in an Alternate Universe (Epilogue)

- ***However…***
- **In 2018, Professors Christenson, Wu, and Apple disagree with this approach. They:**
  - **believe hs-Tn is a much more sensitive clinical indicator of myocardial damage than *m*CO**
  - **encourage hs-Tn to be used by itself**
  - **Furthermore, they encourage that *within-patient CHANGES* of hs-Tn over 2 hours should become the optimal diagnostic parameter.**
  - **They publish many reports showing the clinical superiority of short-term changes hs-Tn over *m*CO.**
- **Unfortunately, *m*CO is so engrained in publications, that Profs Christenson, Wu, and Apple have to live in their $700K homes in suburbia and drive Toyotas, Hondas, and Fords.**

Diagram of a Human Nephron



What Would be the Ideal Marker for Chronic Declining Kidney Function?

- **Measured GFR (mGFR) ?**
  - **Has large physiologic variation and very cumbersome test.**
  - **However, measured GFR is a well-recognized parameter by physicians, and it has history.**
- **Serum marker ?**
  - **Creatinine, cystatin C: these are good.**
- **Number of lost functioning nephrons?**
  - **This is the ultimate test, but we cannot measure this.**
- **This has led to the eGFR (estimated GFR) calculated from the plasma creatinine and/or cystatin C.**

Why Do We Even Need to Calculate an estimated GFR?

Why not simply measure the GFR?

Answer: It's because the measured GFR is a &*X$bz@ process!

Methods for Measuring GFR:

Require bolus injection or plasma infusion, urine collection, and measurements of marker

- **Inject or infuse inulin, iothalamate, iohexol, ^{51}Cr-EDTA, etc) or use endogenous marker (creatinine).**
- **Collect multiple blood samples and sometimes also collect accurately-timed urine samples.**
- **GFR calculated by various methods:**
  - **"Clearance": Urine vol (mL/min) X [urine] / [plasma]**
  - **Plasma disappearance: Rate of decay in plasma: GFR = V_D X (0.69 / $T_{1/2}$)**
- **Procedures are all tedious, slow, expensive, and imprecise.**

Brief History of Developing eGFR Equations for Adults

- **1976: Cockroft and Gault develop equation to predict GFR from serum creatinine. Based on 249 persons ages 18-92y. Other factors are age, sex, and weight (race not included).**
- **1999: The MDRD eGFR equation for predicting mGFR from serum creatinine is published.**
- **2009: The CKD-EPI equation is developed. It is touted as "more accurate" than the MDRD equation for predicting measured GFR.**
- **2017: Some call attention to the bias inherent in these eGFR equations that include a factor based on race.**
- **2020-21: An NKF and ASN task force examine how the inclusion of race in eGFR equations affects persons = the CKD-EPI (2021) eGFR.**

GFR vs Stage of Chronic Kidney Disease:

Original and Some Recent Changes

CKD Stage	Description	GFR (mL/min/1.73m²)
1	Kidney damage with normal GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

New stages:
3a: 45 - 59
3b: 30 - 44

New Albuminuria Categories:
A1: <30 mg/g
A2: 30-300
A3: >300

Normal Range for GFR is 67-135

Reportable Range for MDRD eGFR

Clin Chem 2013; 59: 462-465.

KDIGO 2012 Classification for CKD based on GFR and Albuminuria (mg Alb/g Creat)

Use eGFR as an initial benchmark for further workup

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Kidney Inter., Suppl. 2013; 3: 1–150

eGFR Creatinine Equations for Adults

Cockcroft-Gault Equation (Nephron 1976;16:31):

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{Weight}}{72 \times S_{Cr}} \times 0.85 \text{ (if female)}$$

MDRD Equation (Ann Intern Med 1999;130:461):

$$\text{eGFR} = 175 \times (S_{Cr})^{-1.15} \times (\text{Age})^{-0.20} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

The new CKD-EPI equation (Ann Intern Med 2009;150:604):

$$\text{eGFR} = 141 \times \mathit{min}(S_{Cr}/k,1)^{a} \times \mathit{max}(S_{Cr}/k,1)^{-1.21} \times (0.99)^{\text{Age}} \times (1.018 \text{ if female}) \times (1.16 \text{ if black})$$

The new CKD-EPI 2021 equation (JASN 2021);

$$\text{eGFR} = 142 \times \mathit{min}(S_{Cr}/k,1)^{a} \times \mathit{max}(S_{Cr}/k,1)^{-1.20} \times (0.994)^{\text{Age}} \times (1.012 \text{ if female}) \sout{\times (1.16 \text{ if black})}$$

Is the eGFR Useful? YES!

- **Physicians are tuned in to understanding what a GFR number means.**
- **It is useful as a general guide for evaluating kidney function in a patient:**
  - ***Especially for initial evaluations***
- **Compared to mGFR, it is much more convenient, less invasive, and less expensive.**
  - **Remember, the eGFR is really a creatinine or cystatin C that has been numerically changed to look like a mGFR.**

What Were Recommendations for JASN 2021 Report?

- **Immediately implement the CKD-EPI 2021 creatinine equation without race variable.**
- **Increase national efforts to facilitate routine and timely use of cystatin C, especially to confirm eGFR in clinical decision making.**
- **Encourage and fund research to develop new more accurate eGFR equations based on new endogenous filtration markers.**
- **Utilize these to eliminate racial and ethnic disparities.**

Polling Question

- Do you look forward to changing to a new eGFR equation?

  a. No

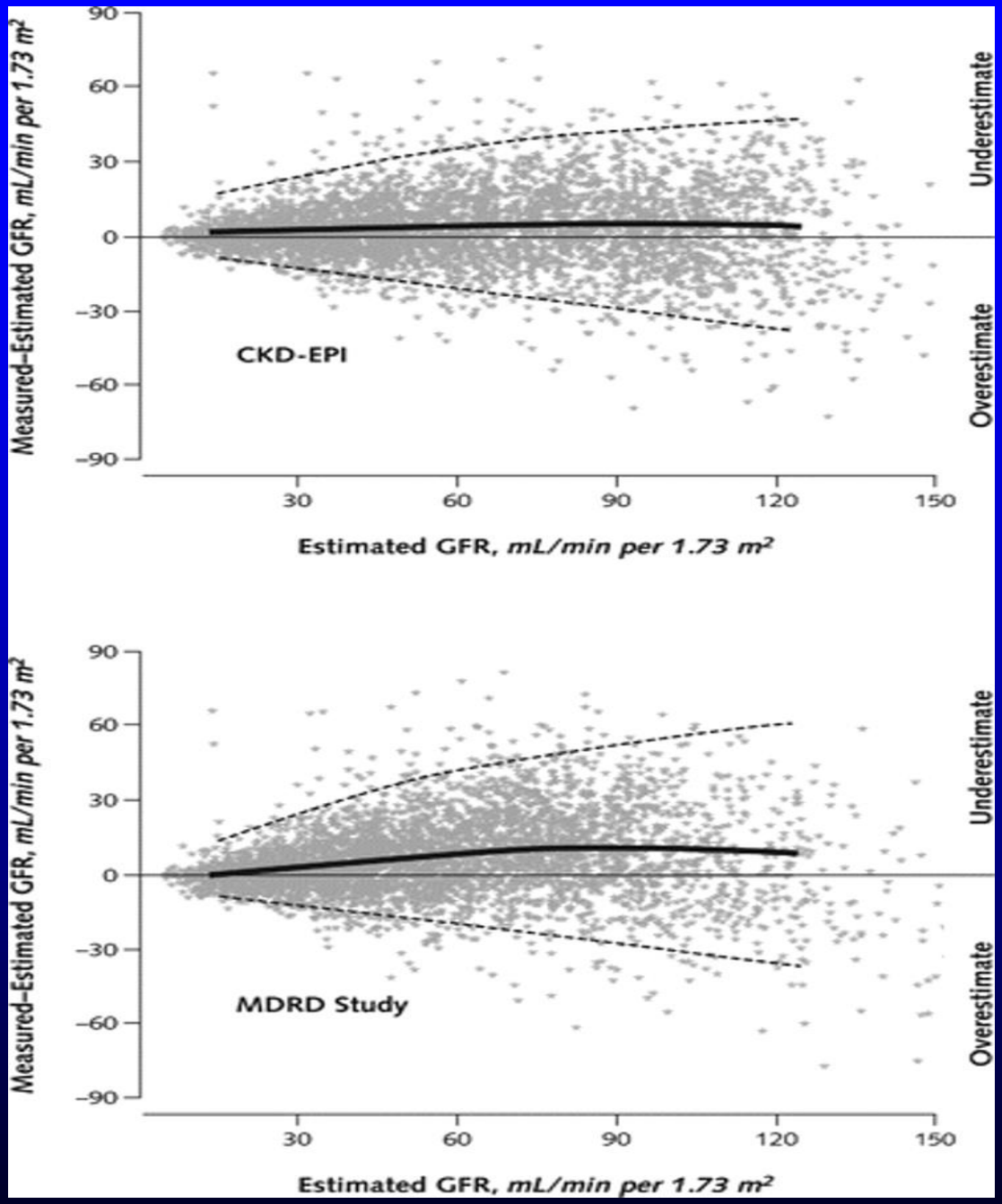
  b. Yes

  c. I still don't know what an eGFR is

What has been the continual goal of these eGFR equations from 1999 to 2021?

It has been to improve the agreement of eGFR results to measured GFR results.

What did that "improved accuracy" of the CKD-EPI 2009 equation look like?



84.1% agree within 30%

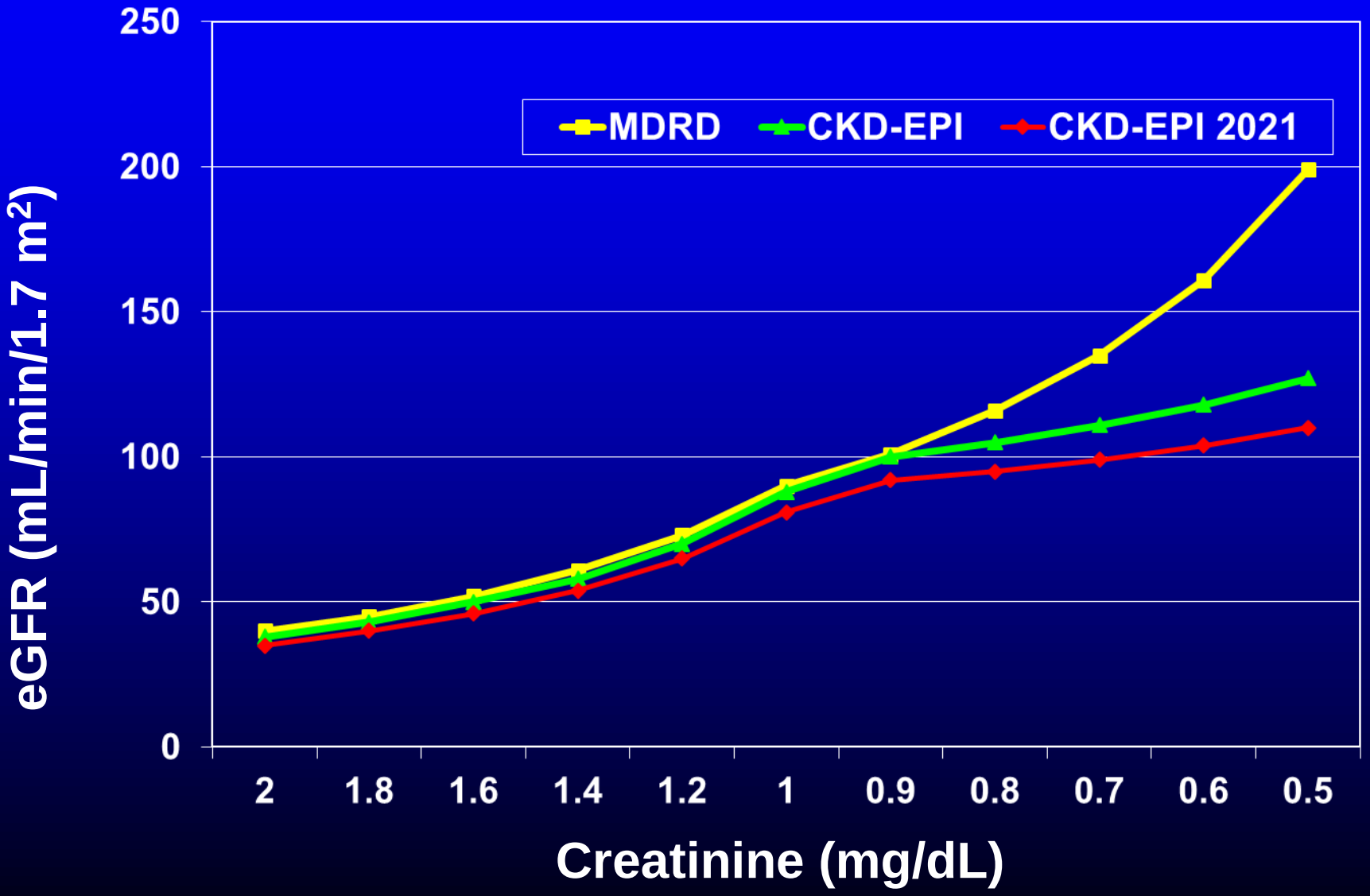
Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the validation data on patients.

A ± 30% error had to be accepted

80.6% agree within 30%

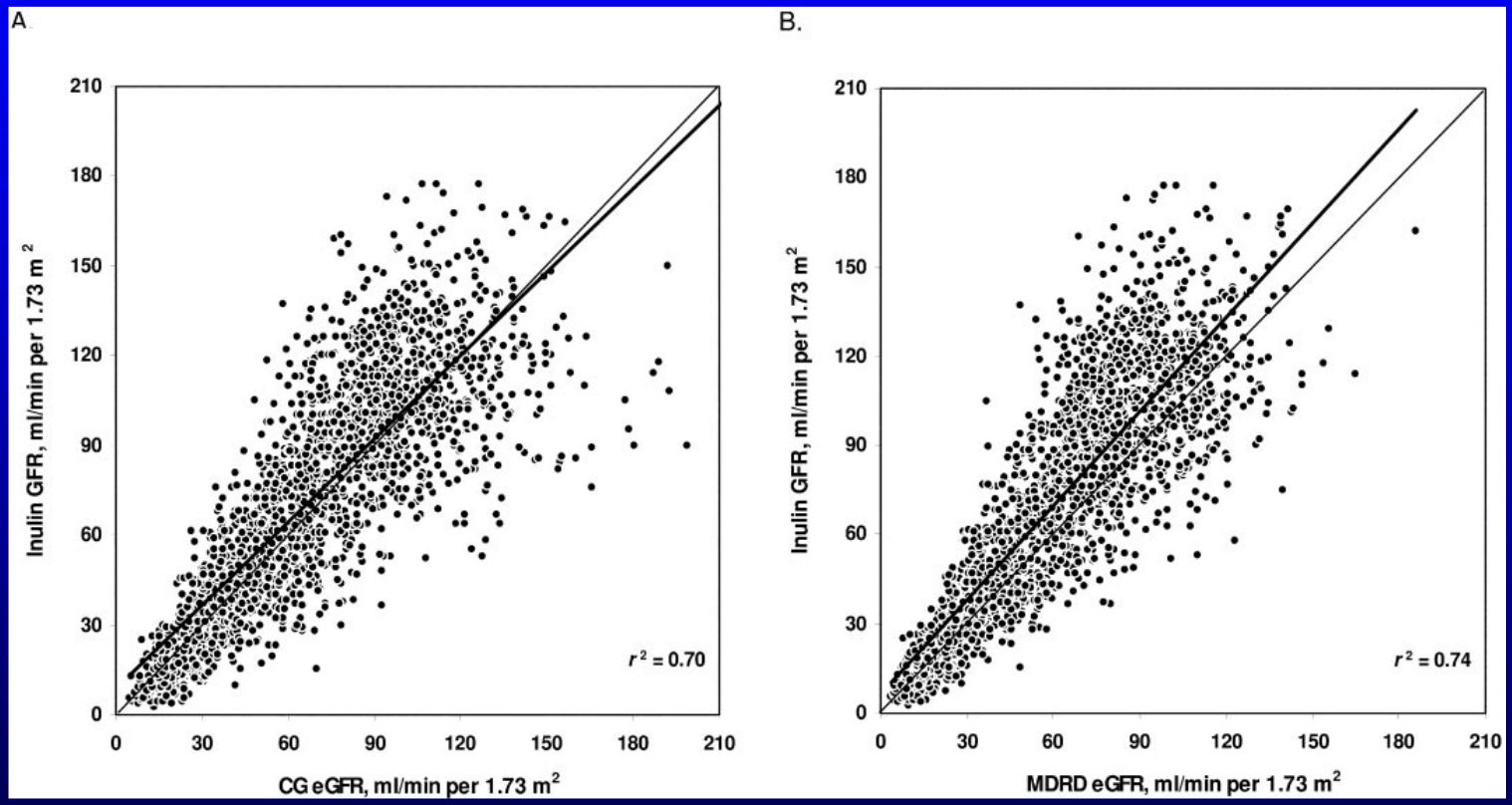
Levey AS, Stevens LA, Coresh J, et al.
Ann Intern Med 2009;150:604-612

eGFR: MDRD, CKD-EPI, and 2021 eGFRs vs Creatinine: 70 yr old black male



Do ANY Equations Provide an eGFR (from Creatinine) that Accurately Predicts mGFR?

Plots of Inulin mGFR vs C-G eGFR and MDRD eGFR



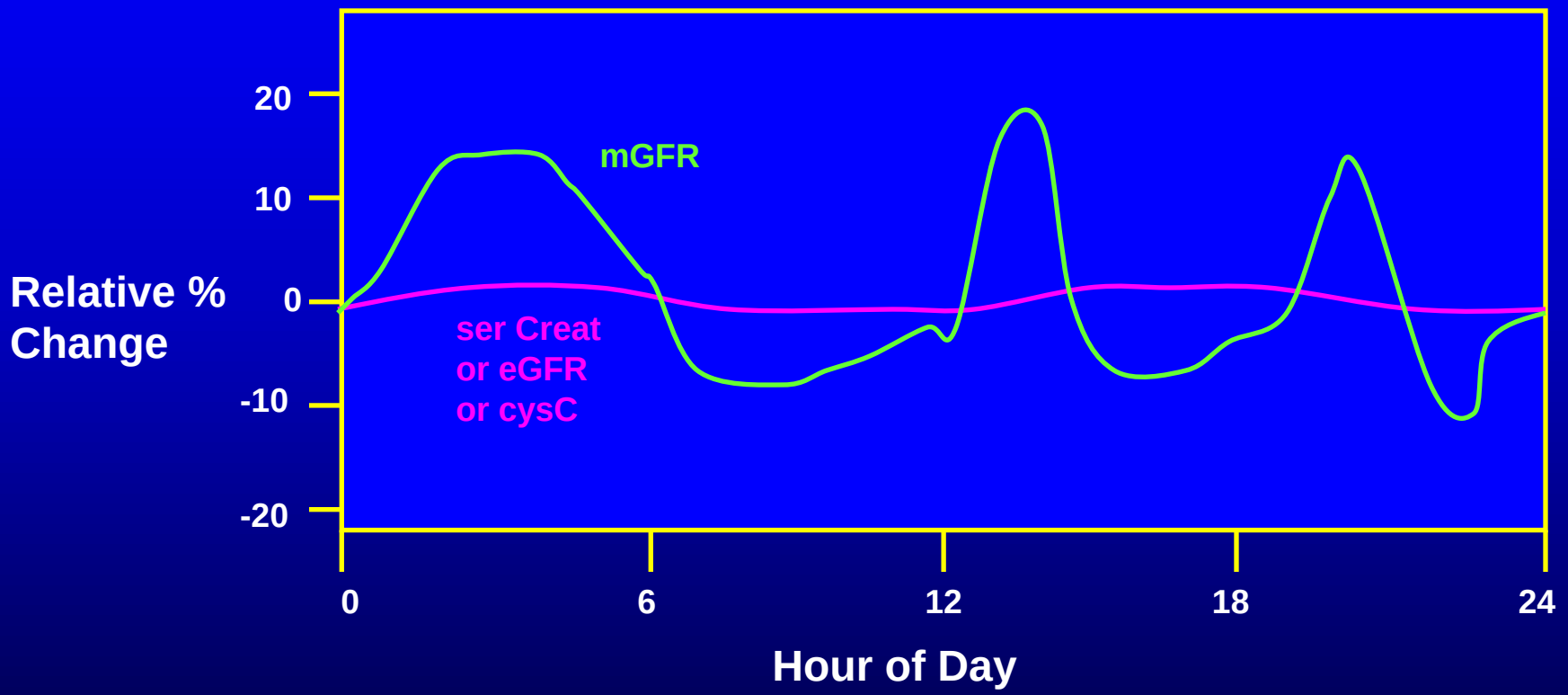
From Figure 2 in: Botev R, et al. Clin J Am Soc Nephrol 2009; 4: 899-906.

So, is the creatinine, cysC, or eGFR the culprit… or is the measured GFR the culprit?

Is Measured GFR* Really a "Gold-Standard"?

**By Inulin, Iothalamate, Iohexol, Creatinine, Cr-EDTA, etc*

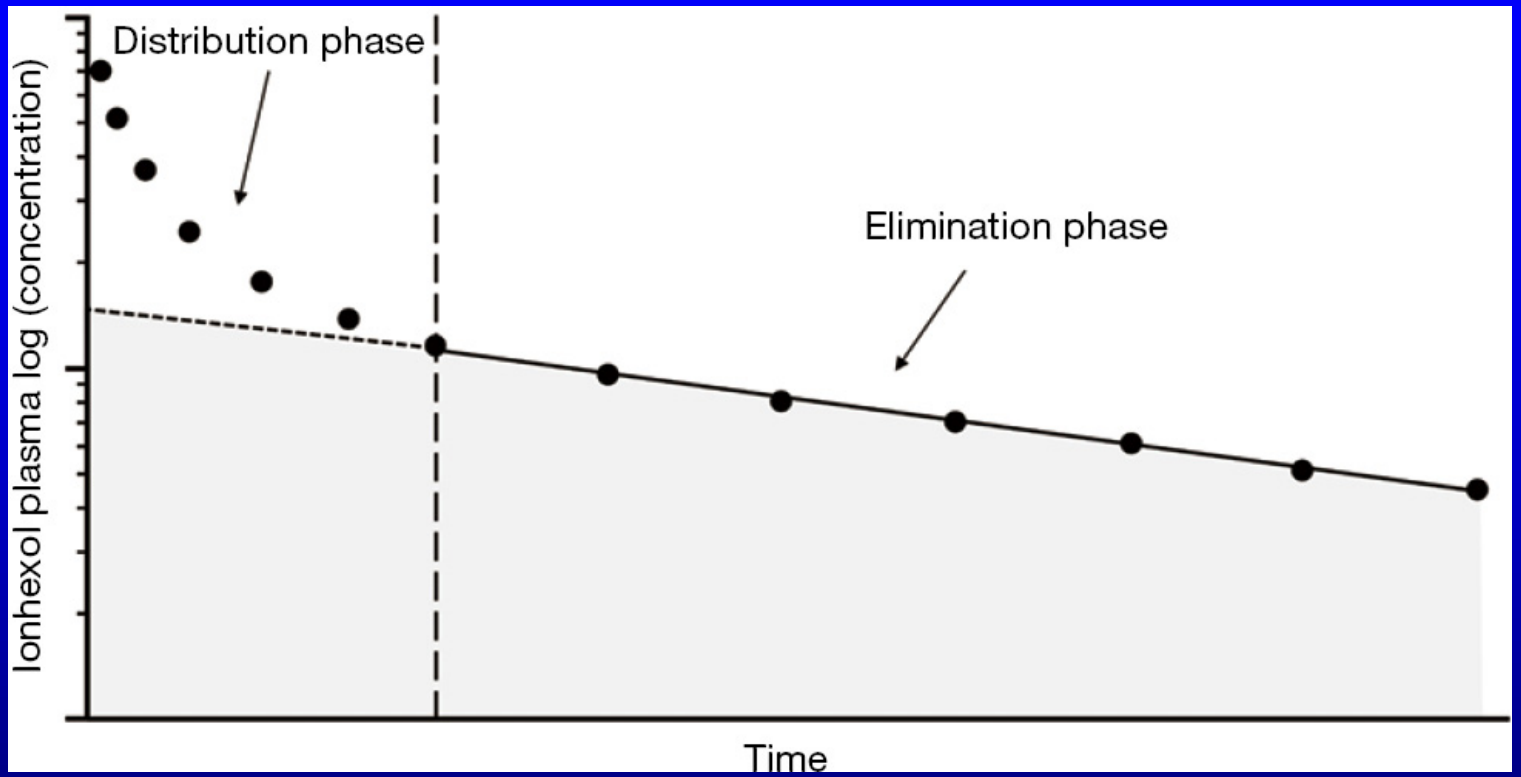
My Conclusion: Measured GFR and Serum Creatinine/eGFR Have Inherently Different Regulation Patterns



Methods for Measuring GFR:

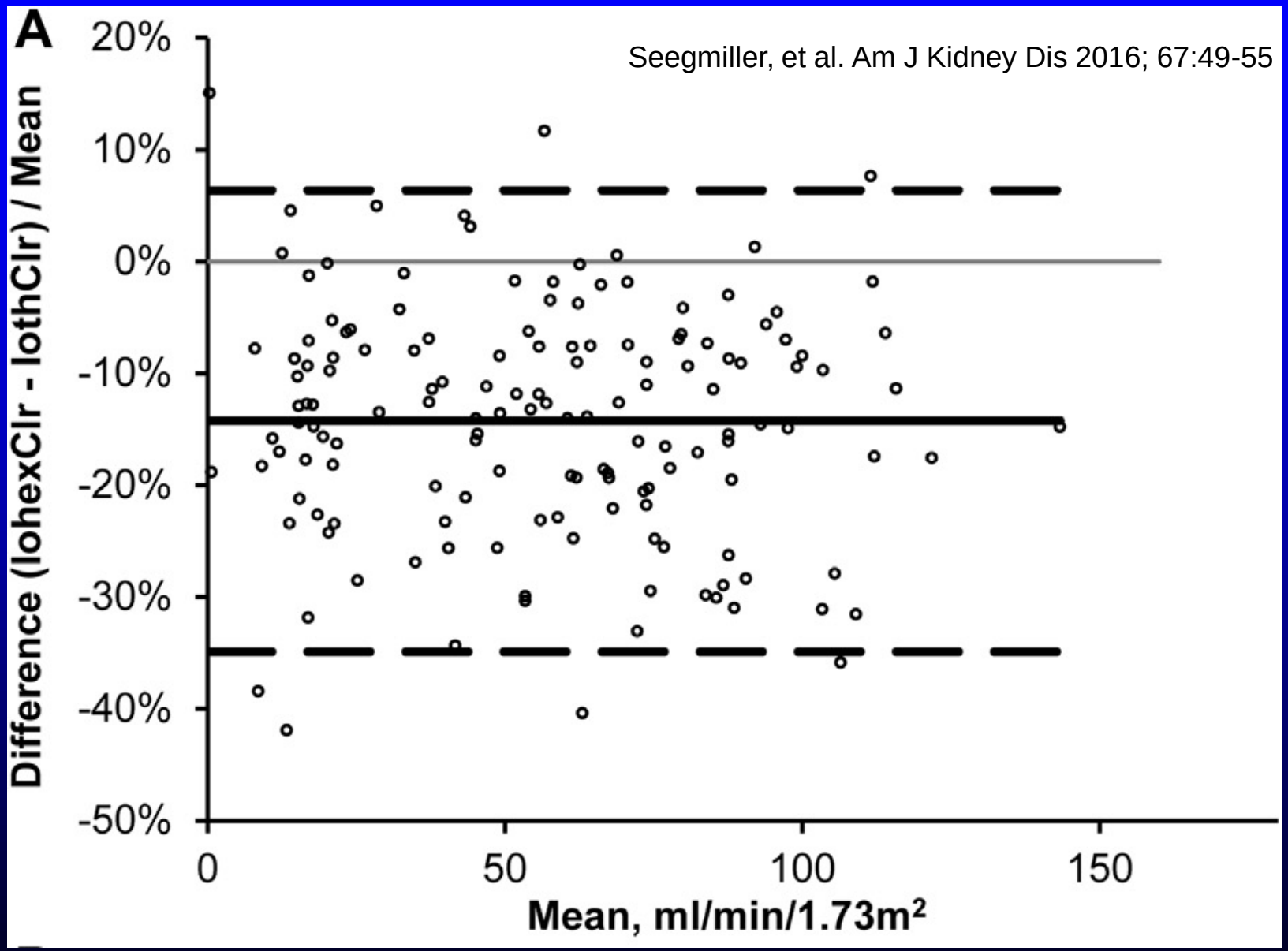
- ***Remember:***
- **mGFRs require injection or infusion of a marker, urine collection w/ accurate time and volume, and measurements of marker**
- **Procedures are all invasive, tedious, slow, and expensive.**
- **Precision and agreement are variable among methods.**

Interpreting the Iohexol Clearance Test for mGFR

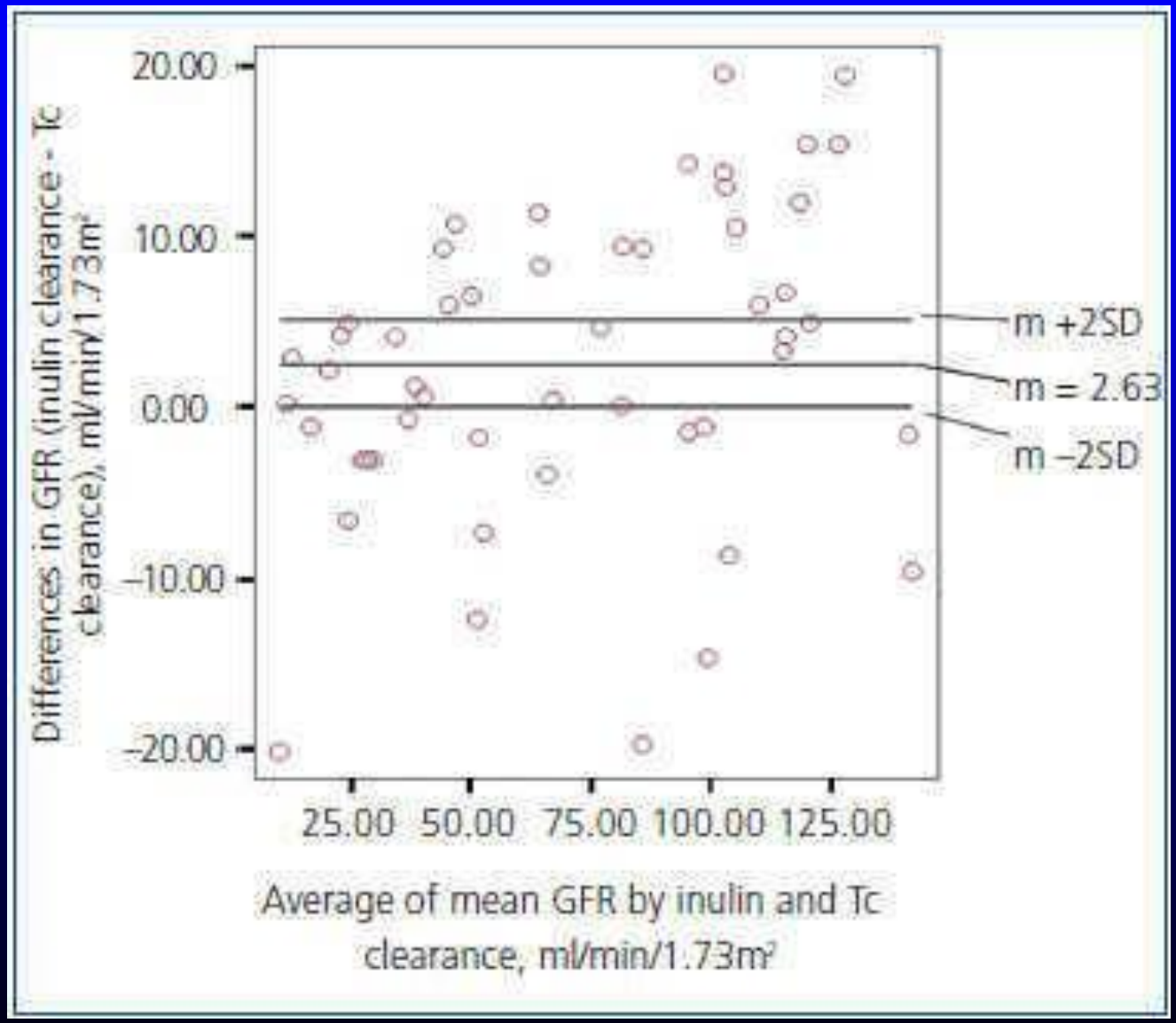


- Inject 5–10 mL of iohexol solution.
- Collect multiple blood samples to measure plasma iohexol disappearance.
- The early phase (fast component) reflects the distribution between the intra- and extra-vascular volumes
- The late (slow component) corresponds to elimination by the kidney.

Differences Between Iohexol mGFR and Iothalamate mGFR



Discordance Between GFR Measured by Inulin Clearance and Technetium Clearance



Nephrologia 2010; 30(3): 324-30.

Soveri I, et al. Measuring GFR: A Systematic Review. Am J Kidney Dis. 2014;64(3):411-424

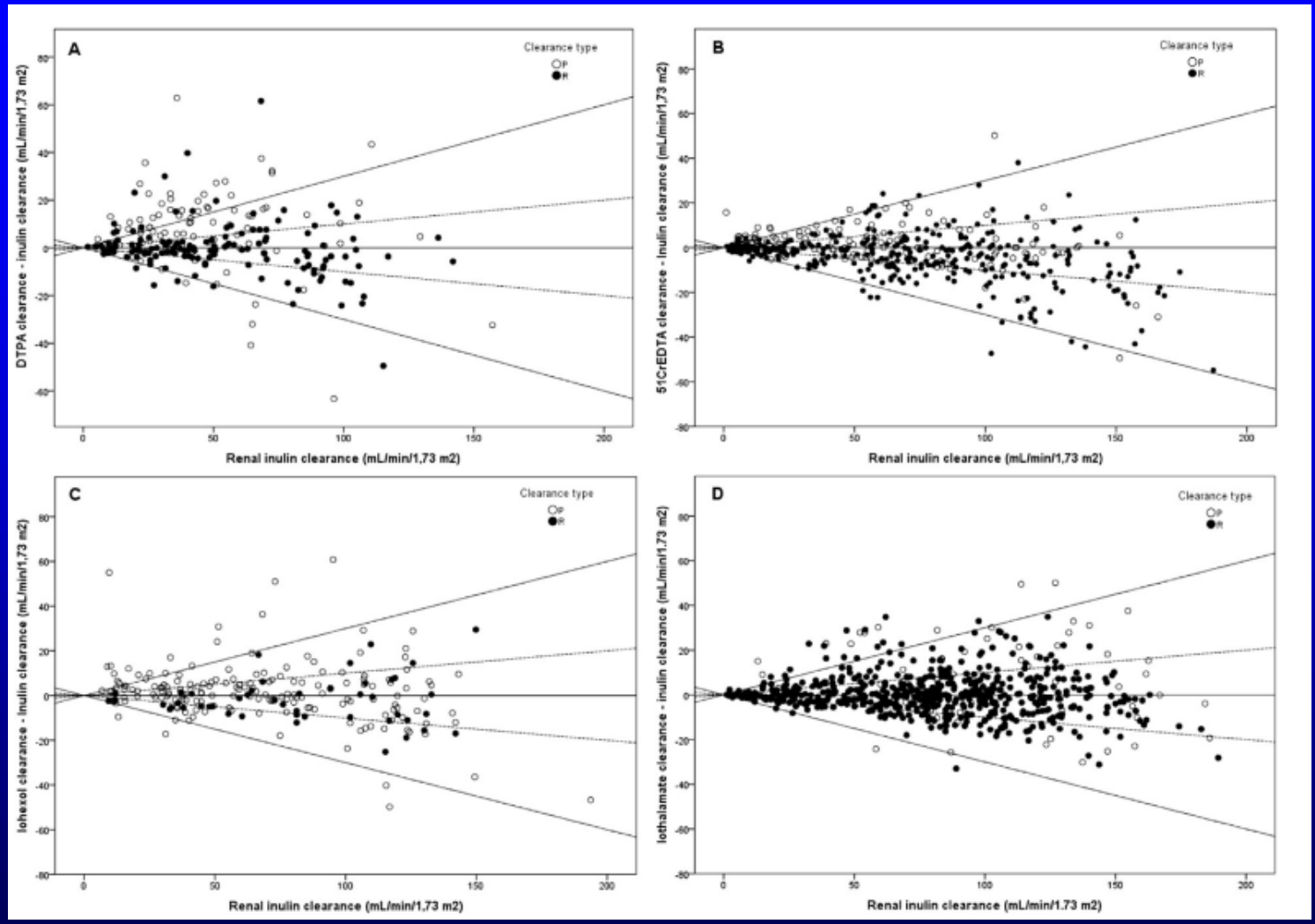
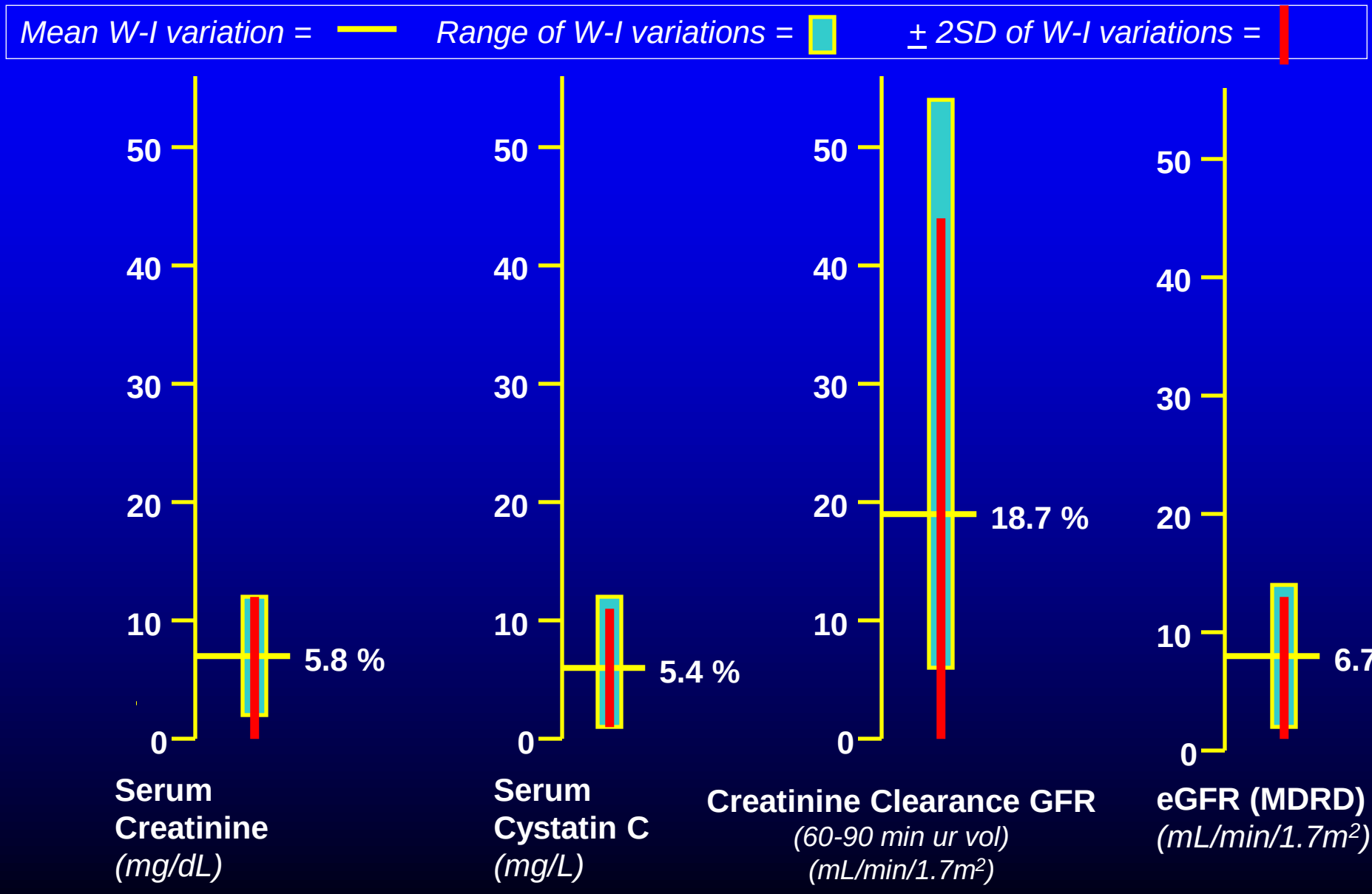


Figure 2. Differences between **measured glomerular filtration rates** (mGFR) by (A) DTPA, (B) ^{51}Cr-EDTA), (C) Iohexol, or (D) Iothalamate in relation to renal inulin clearance (P, plasma clearance, R, renal clearance). The proportion of errors that did not exceed 30% (P_{30}) limits (solid lines) and P_{10} limits (dashed lines) are shown.

Within-Individual Variation (%CV) of Renal Function Tests on 31 Healthy Persons *(Clin Chim Acta 2008; 395: 115-9)*



Reference Intervals (Ranges) for mGFR as Wide as for Serum Creatinine

Parameter	Healthy Persons *(n = 501)*	
	Mean + 2 SD	***Range***
Serum creatinine *(mg/dL)*	**0.73 – 1.37** ***(Ratio = 1.88)***	**0.6 – 1.6**
Iothalamate GFR *(mL/min/1.73 $m^{2)}$*	**67 – 135** ***(Ratio = 2.01)***	**63 – 177**

Rule AD, et al. Using serum creatinine to estimate GFR: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004; 141: 929-937.

We Must Correct the Perception that Serum Creatinine Does not Increase Until 50% of Nephrons are Lost

- **This originates from an often-referenced 1985 study by Shemesh et al. concluding that:**
  - **large decreases in mGFR are associated with insignificant changes in sCr in early kidney impairment.**
  - **Unfortunately, this has been widely cited as fact, even in the CKD-EPI 2021 study.**
- **The Shemesh study was an excellent work on the physiology of creatinine handling by kidney tubules, but…**
- **The authors' clinical conclusion was based more on physiology than clinical study.**
  - **Their Table 3 shows serum creatinine increased from 1.4 to 2.3 mg/dL as inulin clearance mGFR decreased from 61 to 32 mL/min/1.73 m^2 in glomerulopathic patients.**

Here are Several Studies that Demonstrate how Creatinine, eGFR, etc should be evaluated

These evaluate their clinical utility

They studies clearly show that serum creatinine does change in the early stages of nephron loss

Onuigbo and Agbasi concluded that within-individual trajectories of a patient's sCr are a most useful diagnostic tool for management of patients

- **They illustrated this with cases from a variety of patients with acute kidney injury and/or CKD.**
- **Seemingly small changes in serum creatinine allowed earlier identification of patients with milder kidney impairment.**
- **Following within-individual changes are independent of variables such as age, sex, race, or nationality.**

Diabetic nephropathy and CKD – Analysis of individual patient serum creatinine trajectories: A forgotten diagnostic methodology. J Clin Med 2015;4:1348–68.

Bhavsar et al. followed over 800 African Americans with hypertensive CKD for a mean of 103 months

- **They compared mGFR, sCr, eGFR, sCysC, and β-trace protein (BTP) concentrations to predict end-stage renal disease (ESRD).**
- **For 246 participants who developed ESRD during follow-up, higher concentrations of each marker were strongly and significantly associated with higher risk of ESRD.**

Bhavsar NA, et al. Am J Kidney Dis 2011;58:886–93

Kim et al. evaluated over 1300 patients in stages 3 to 5 CKD (eGFR <60 mL/min/1.73 m^2)

- **134 of the 1300 patients progressed to ESRD, requiring either dialysis or kidney transplant.**
- **They concluded that slope of eGFR calculated from either sCr or sCysC were equivalent in predicting which patients in CKD stages 3 to 5 progressed to ESRD.**

Creatinine-and cystatin C-based estimated glomerular filtration rate slopes for the prediction of kidney outcome: a comparative retrospective study. BMC Nephrol 2019;20:214.

Spanaus et al. followed changes of sCr, cysC, BTP, and mGFR by iohexol in 177 patients during progression of CKD

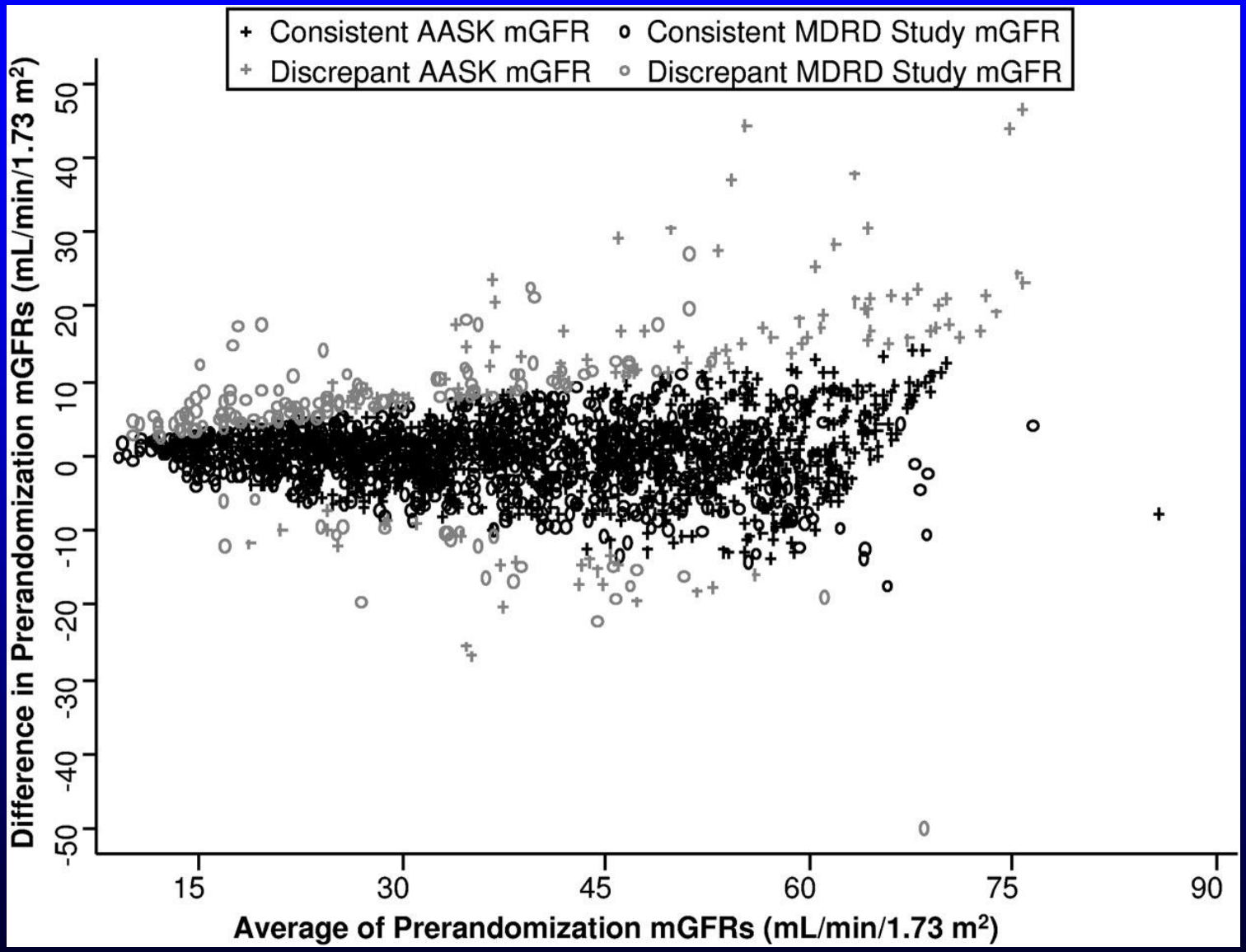
- **Patients were studied for periods of 3 to 84 months.**
- **All 3 markers increased progressively with decreasing mGFR:**
  - **Their diagnostic performance for detecting even minor decreases in kidney function were similar, with BTP slightly better**
- **Creatinine, even within the reference interval, increased in the early stages of declining kidney function as detected by iohexol mGFR.**
- **They concluded that changes of each serum biomarker, including sCr, strongly correlated with mGFR, and that each was useful for diagnosing early changes in kidney function as mGFR decreased from >120 to < 60 mL/min/1.73 m^2.**
  - *Clin Chem 2010;56:740–9.*

Study of Imprecision of Iothalamate mGFR

- **Evaluated data from 1995 participants in the MDRD and AASK studies with at least 2 baseline iothalamate mGFRs.**
  - **mGFRs averaged 62 days apart**
- **Found that mGFRs had substantial variability across visits:**
  - **8% varied by > 30%; 4% varied by 25 – 30%; 87% varied by ≤ 25 %.**
  - **They defined "consistent results" between visits as ≤ 25% difference.**
- **While they did show the variation of mGFRs between these 2 visits ….**

Kwong D, Stevens LA, … Levey AS, Coresh J. Imprecision of urinary iothalamate clearance as a gold-standard mGFR decreases the diagnostic accuracy of kidney function estimating equations. Am J Kid Dis 2010; 56: 39-49.

Differences Between the 2 Baseline mGFRs



Study of Imprecision of Iothalamate mGFR

- …. they concluded that:
  - "… the variation in iothalalamate mGFR… substantially impacts the accuracy of these eGFRs."
- Unfortunately, they also concluded that:
  - "Nevertheless, this gold-standard mGFR performed better than eGFRs" (MDRD $_{Cr}$, CKD-EPI $_{CysC}$, and CKD-EPI $_{Cr\text{-}CysC}$ equations) ***in predicting itself!***
- When they averaged the 2 mGFRs, the agreement with eGFRs got better!
- *DUH!*

2019 report carrying the absurdity to a new level: "Validation of a metabolite panel for a more accurate estimation of GFR using LC-MS/MS"

- **Concluded that an equation based on 4 metabolites more accurately estimated mGFR.**
- **Metabolites were:**
  - **N-acetylthreonine, pseudouridine, phenylacetyglutamine, tryptophan**
- **Relative accuracy within ± 30% *(1 – P_{30})* compared to mGFR:**
  - **$eGFR_{Creat}$: 87%**
  - **$eGFR_{cysC}$: 88%**
  - **4 metabolite panel: 90%**
  - **$eGFR_{Cr\text{-}cysC}$: 91%**

Freed TA, Coresh J, Inker LA, …Levey AS.
Clin Chem 2019; 65(3): 406-418.

I've complained a lot, so let's look at…

Future Needs for sCr and eGFR

- **A national effort to encourage developing baseline creatinines, eGFRs and/or cystatin C on all appropriate persons.**
- **Improve precision of serum creatinine methods:**
  - **Requires improved methods; this is challenging!**
    - **enzymatic creatinine methods typically better**
  - **Note: IDMS standardization improves long-term method stability, but has little impact on method precision.**

More Future Needs for sCr and eGFR

- **Emphasize value of serial measurements:**
  - **Within-individual changes of creatinine and/or eGFR eliminate variables of race, sex, nationality, and age.**
- **Develop specific guidelines for interpreting within-individual changes in sCr, eGFR, and/or sCysC that warrant referral to nephrology:**
  - **An increase of 0.20 mg/dL (18 umol/L)?**
  - **An increase of 0.30 mg/dL (27 umol/L)?**
  - **An increase of 20% or 30%?**
    - **Shavit, et al noted each 0.20 mg/dL increase was associated with an increased mortality *(Kidney Blood Pressure Res 2012)***
  - **An appropriate time interval for changes: 3, 6, or 12 months?**
    - **These are similar to recommendations in AKI**

Summary of Points

- Creatinine is a good renal function test:
  - More precise than mGFR and increases early in disease.
- The eGFR is useful in calling attention to possible kidney disease.
- Measured GFR is not a “gold-standard” kidney function test:
  - Cumbersome, lengthy, invasive, and expensive, and has large population and individual variations.
- Cystatin C can be useful clinically:
  - When creatinine/eGFR are equivocal
  - Not going to replace creatinine measurements anytime soon.
- For both eGFR and creatinine measurements, the use of serial or longitudinal within-individual measurements needs to be encouraged.
  - This has been done for years to confirm AKI.
- No more eGFR equations, *please!*

Some Big Lies Through History

- **The Earth is flat** *(Homer, Thames, many others)*
- **I'll call you tomorrow** *(many men, some women)*
- **email will never catch on** *(Toffaletti, circa 1990)*
- **You'll go blind if you keep doing that** *(many mothers)*
- **It's simply plug and play** *(software experts)*
- **We got it all** *(many surgeons)*
- **Serum creatinine does not increase until 50% of nephrons are lost** *(many kidney experts)*
- **The gold standard for detecting kidney disease is the measured GFR** *(too many)***.**
- **We need more equations for eGFR** *(Levey, Inker, Coresh)*