

# ***Utility of Old and New Clinical Laboratory Tests for Chronic and Acute Kidney Disease***

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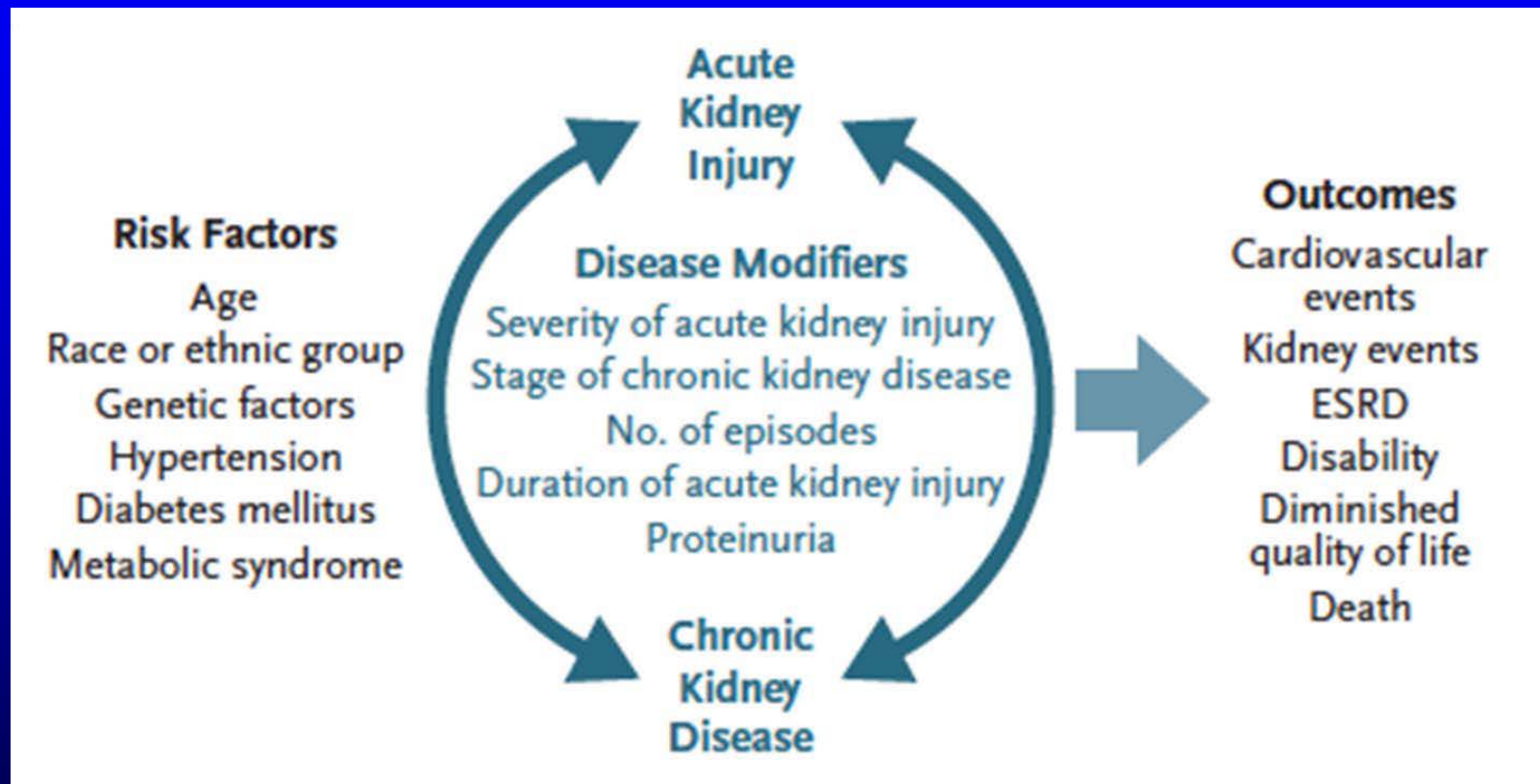
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# ***Acute Kidney Injury and Chronic Kidney Disease are Interconnected Syndromes***



# ***Conditions Associated with Acute Kidney Injury and/or Chronic Kidney Disease***

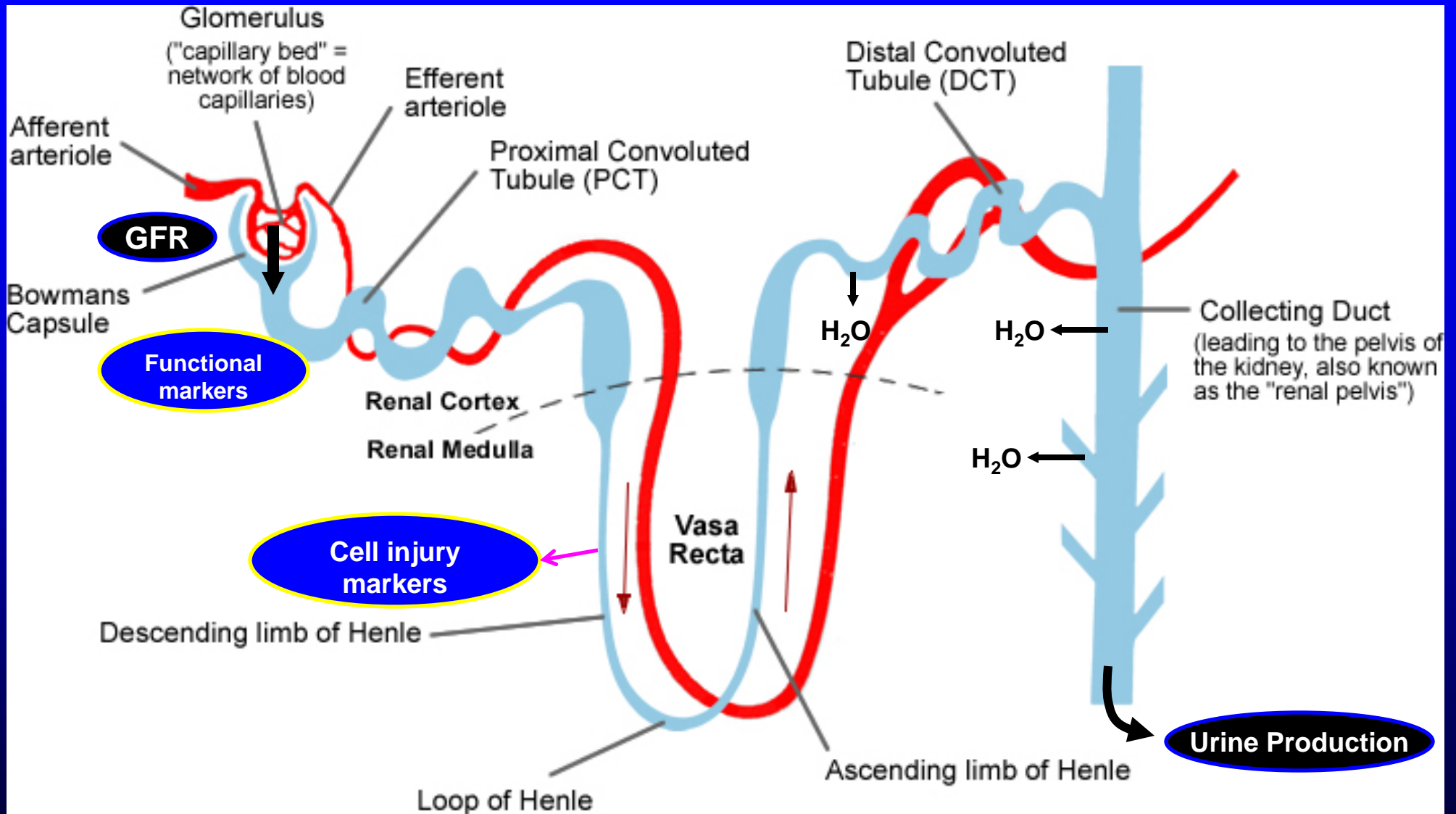
## **Conditions That May Cause or Increase Susceptibility to: Acute Kidney Injury / Chronic Kidney Disease**

Hyper-inflammatory response (sepsis);  
Diabetes; Autoimmune reaction; Advanced age;  
Toxins/Nephrotoxic Drugs;  
Chronic diseases; Critical illness;  
Major surgery, especially with CP Bypass;  
Trauma, Burns, Radiocontrast agents, Dehydration.

# ***Lab Tests Discussed Today***

- **Creatinine**
- **eGFR**
- **measured GFR**
- **Cystatin C**
- **NGAL:** neutrophil gelatinase-associated lipocalin
- **KIM-1:** kidney injury molecule
- **IGFBP7:** insulin-like growth factor binding protein 7  
(a cell-cycle arrest molecule)

# Diagram of a Human Nephron



# ***Chronic Kidney Disease***

***A slow, progressive loss of functional nephrons lasting over three months that leads to:***

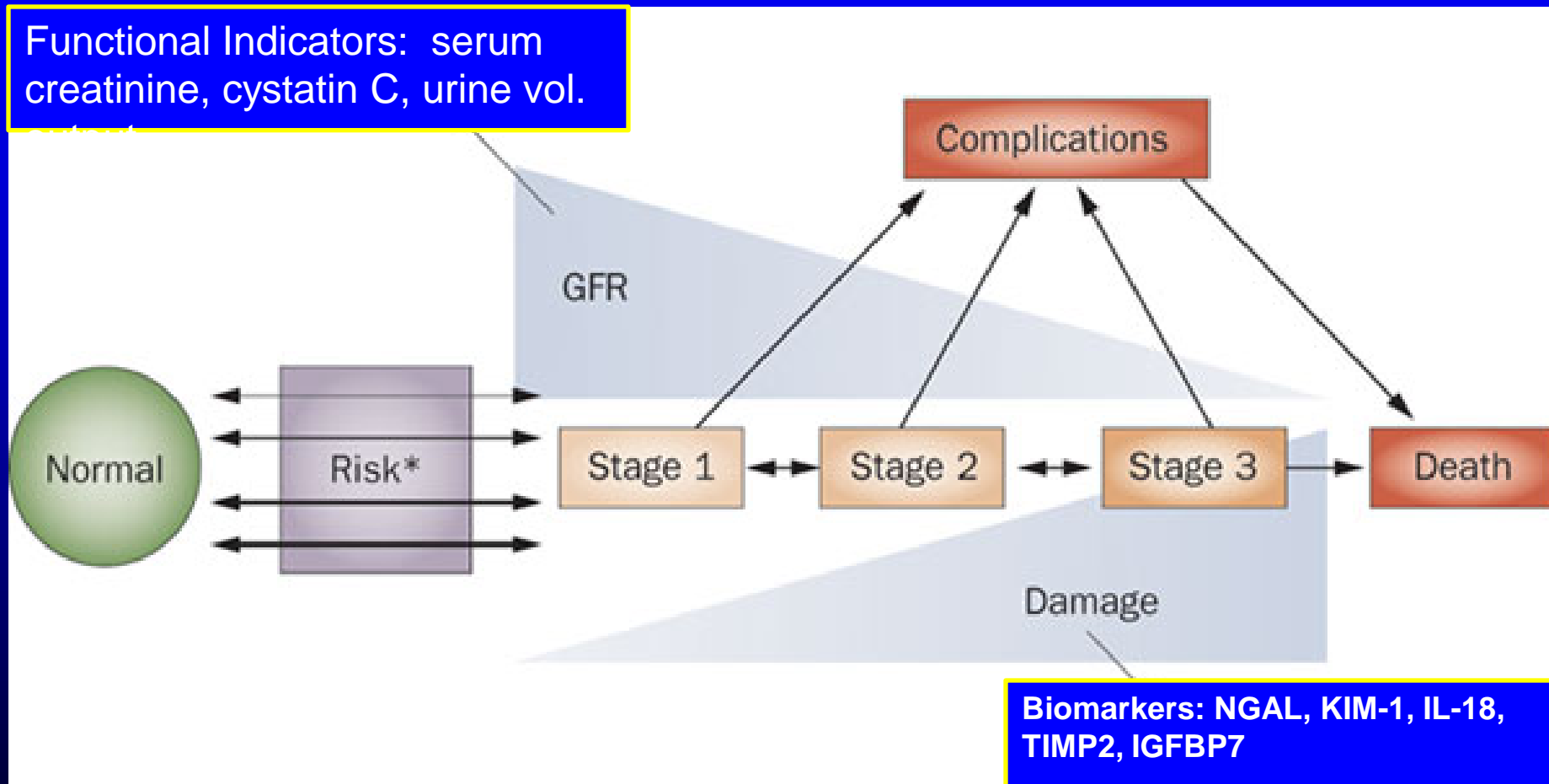
- **Proteinuria:**
  - Progresses from occasional (early stages) to persistent.
- **Gradual decrease in GFR:**
  - rise of serum creatinine and cystatin C.
- **Hypertension, bone disease due to poor ion regulation, 2<sup>o</sup> hyperparathyroidism.**

***Early diagnosis and treatment can save kidney function!***

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

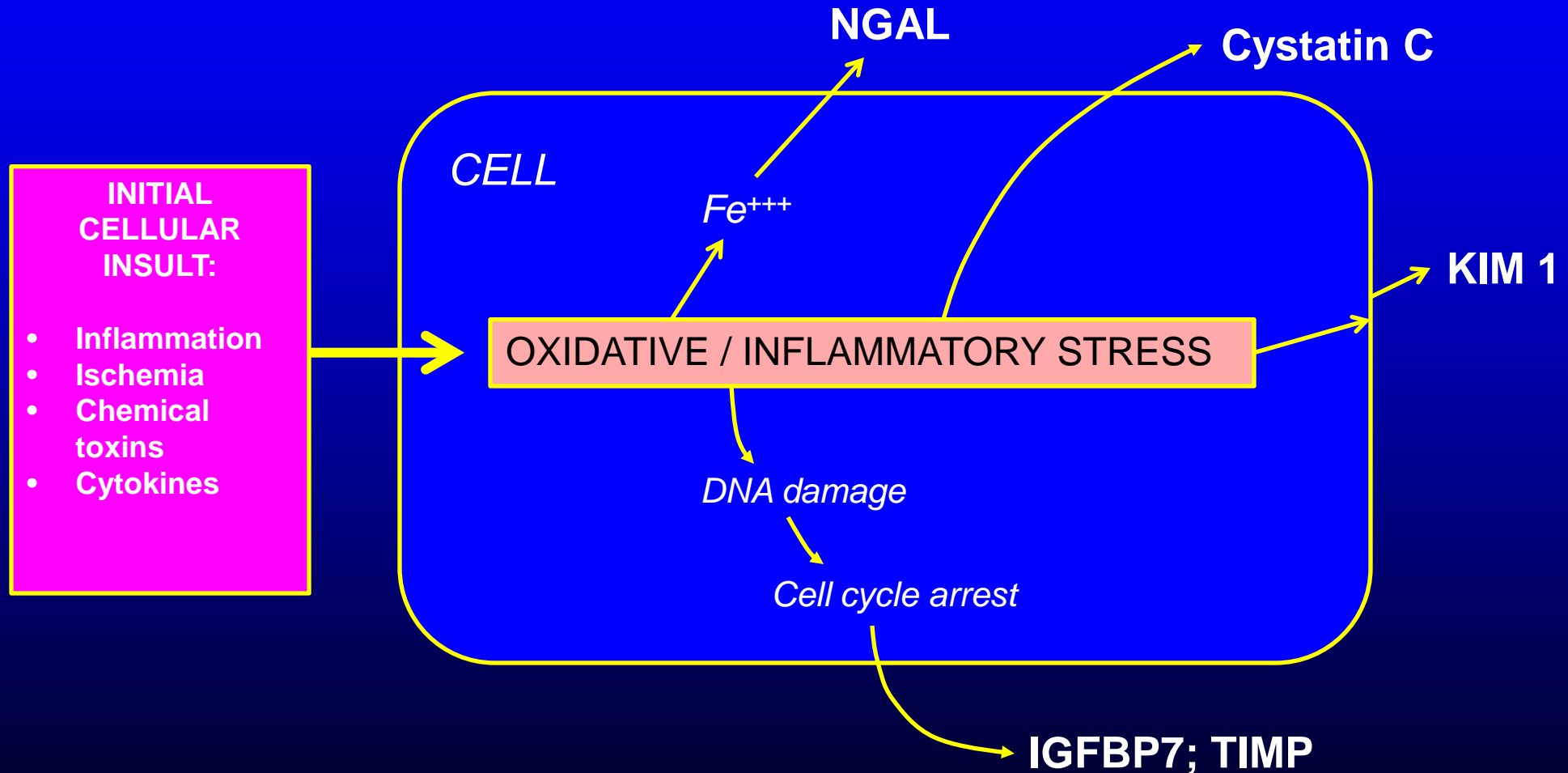
- **GFR ?**
  - Has large individual and population variation.
  - Very cumbersome test.
- **Serum marker ?**
  - Creatinine, cystatin C
- **Number of lost functioning nephrons?**
  - Yes, but we cannot measure this, so we are stuck with GFR or serum marker. This has led to the development of the eGFR (estimated GFR) calculated from the plasma creatinine.

# Model for Progression of Acute Kidney Disease





# ***Cellular Production of Molecules Associated with Acute Kidney Injury***



# RIFLE Criteria for Acute Kidney Injury

	Serum Creatinine Criteria	Urine Output Criteria
Risk (Stage 1)	Creatinine increased X1.5 above baseline; or creat rise $\geq 0.3$ mg/dL in 48 hr.	UO < 0.5 mL/kg/hr for 6 hr
Injury (Stage 2)	Creatinine increased X 2 above baseline	UO < 0.5 mL/kg/hr for 12 hr
Failure (Stage 3)	Creatinine increased X 3 or creatinine $\geq 4$ mg/dL	UO < 0.5 mL/kg/hr for 24 hr or anuria for 12 hours
Loss	Persistent AKI for > 4 weeks may lead to complete loss of renal function.	
ESRD	End Stage Renal Disease	

# ***What Would be the Ideal Marker for Acute Kidney Injury?***

- **GFR ?**

- Neither sensitive nor practical: time consuming and too much variation.

- **Serum marker of lost nephrons or GFR?**

- Creatinine and cystatin C (**these are useful**).

- **Marker for some insult to kidney cells:**

- Cystatin C, NGAL, KIM, urinary IGFBP7 and TIMP (cell cycle arrest molecules).

- **These might change earlier than creatinine, but specificity for kidney disease has been difficult.**

# ***Cystatin C in Renal Function***

- **Cystatin C is a small protein (MW ~13,000) that:**
  - Is produced at a constant rate by all nucleated cells.
  - Is freely filtered by the glomerulus, then is catabolized by the renal tubules.
- **It is also affected by a few non-renal conditions and factors:**
  - Inflammation and other factors that affect cell function
  - Diabetes
- **Serum levels are supposed to be less affected by muscle mass, age, diet, gender or race than is creatinine. However:**
  - Reference ranges change with age:  
< 1y: 0.65-1.50 mg/L; 1-17y: 0.50-1.27 mg/L; > 17y: 0.53-0.95 mg/L

# ***Cystatin C vs Creatinine***

- Serum cystatin C levels correlate inversely with GFR. However, cystatin C is no more sensitive for decreased GFR than serum creatinine.
- Cystatin C was initially reported to have much smaller population variation than serum creatinine. This does not appear to be true:
  - Both within-individual and between-individual variations were slightly larger for cystatin C than for creatinine:
    - » Scand J Clin Lab Invest 2009; 69: 831-836 (adults)
    - » Scand J Clin Lab Invest 2010; 70: 54-59 (children)
    - » Both studies concluded that serum creatinine would be better for serial monitoring of renal function.
- Cost, availability, and familiarity are also issues.

# ***Cystatin C Has Clinical Usefulness***

- Recommended to confirm CKD when eGFR is 45-59 mL/min/1.7m<sup>2</sup>.
- Is a better predictor of mortality in patients with CKD, HF, or CVD.
- Rises sooner than creatinine in AKI:
  - Among 442 general ICU patients, cys C indicated **acute** kidney injury earlier than did serum creatinine (*Nephrol Dial Transplant* 2010; 25: 3283-3289) :
  - In 342 pts, neither increased
  - In 17 pts, creat increased before cys C
  - In 66 pts, cys C increased before creat
  - In 17 pts, both increased at same time

# ***NGAL (Neutrophil Gelatinase-Associated Lipocalin)***

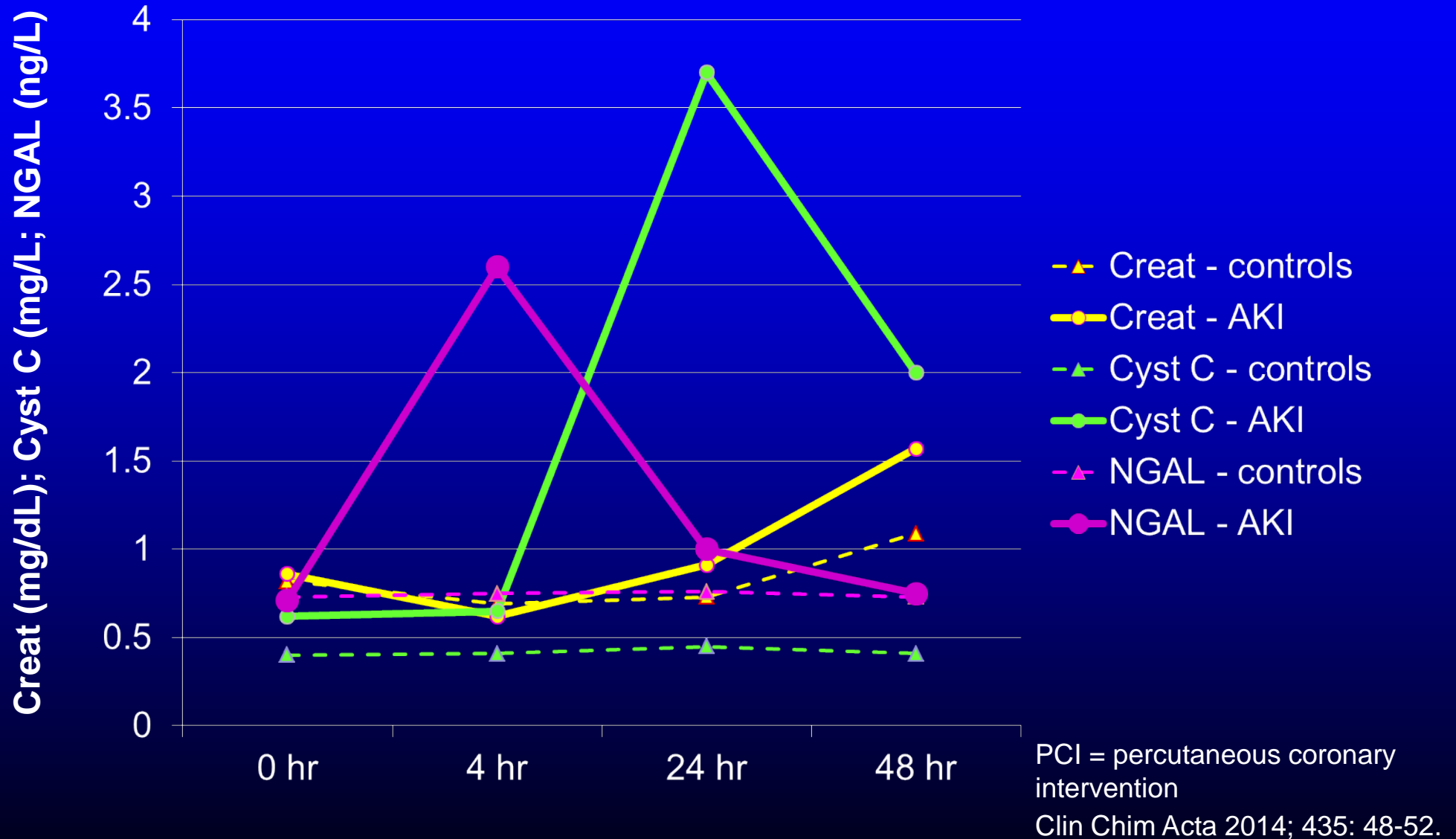
- NGAL is normally expressed at very low levels.
- NGAL expression is markedly enhanced by renal tubular cells, lymphocytes, and other cells in response to free iron ions that are liberated in response to ischemic or toxic injury.
- Some studies show that plasma (and urine) NGAL might be an early marker for AKI, especially when the timing of the kidney insult is known, such as post cardiac surgery, sepsis, trauma, or radiocontrast exposure.

# ***NGAL and Creatinine in Critically Ill Patients***

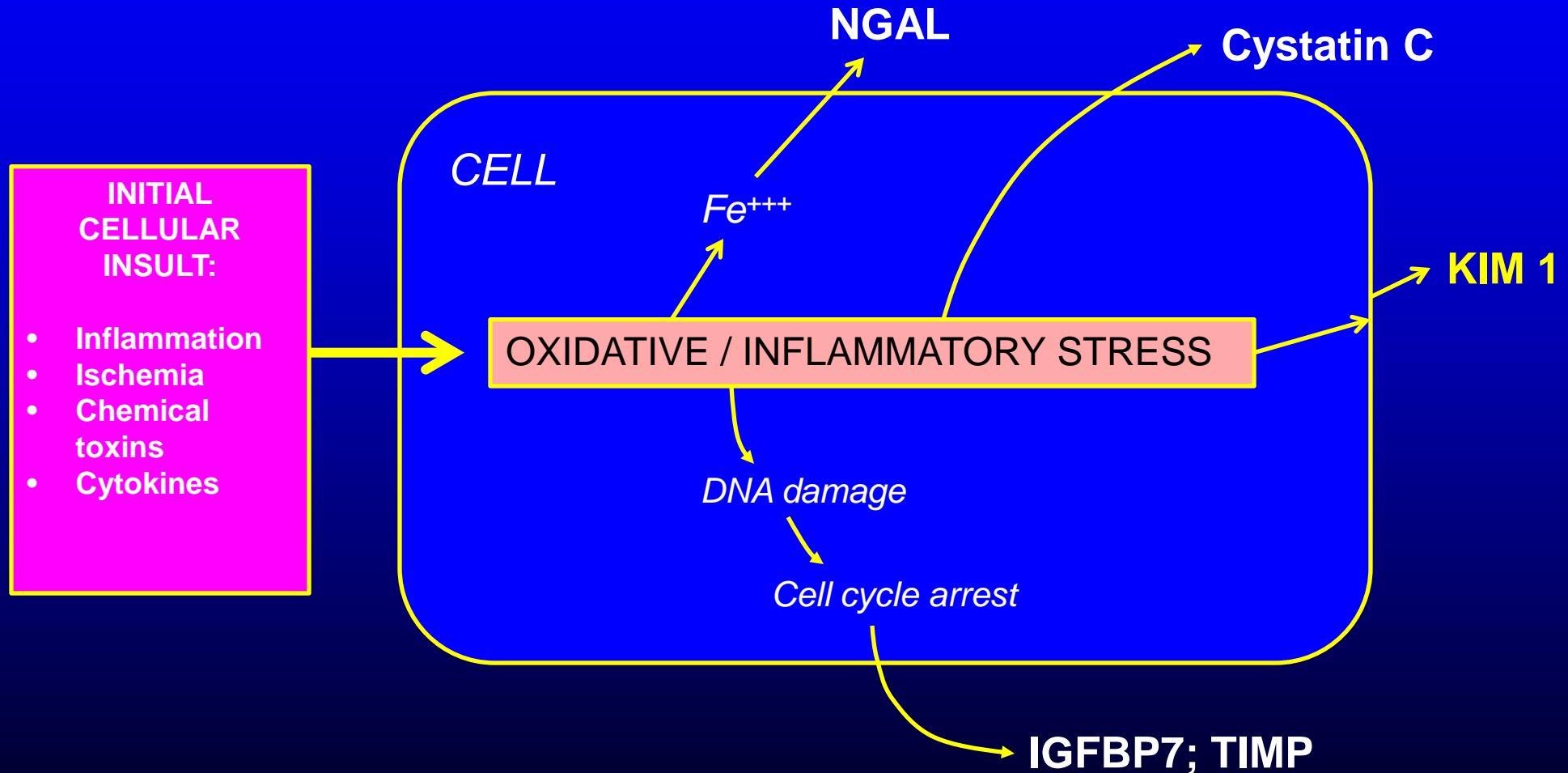
- In a multicenter study of 2322 patients, mostly with a cardiorenal syndrome, NGAL was able to detect subclinical AKI in some patients without an increase in serum creatinine:
  - 56%: Both NGAL and creatinine NEG
  - 19%: NGAL POS and creatinine NEG
  - 5%: NGAL NEG and creatinine POS
  - 20%: Both NGAL and creatinine POS



# ***Creatinine, Cyst C, and NGAL After PCI: Controls vs Patients Who Developed AKI***



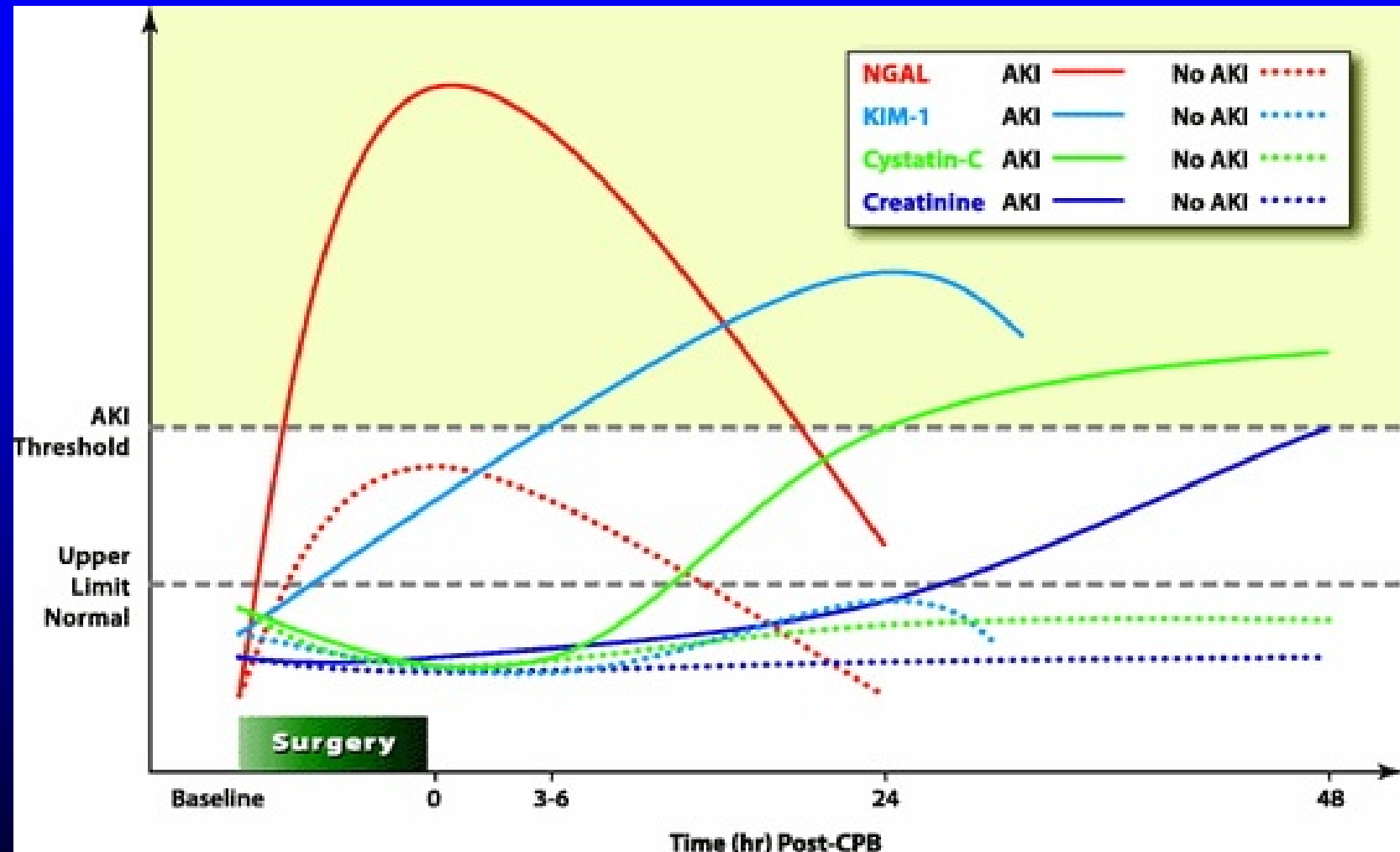
# ***Cellular Production of Molecules Associated with Acute Kidney Injury***



# ***Kidney Injury Molecule (KIM-1)***

- **KIM-1 is a membrane protein that is not produced in normal kidney cells.**
- **KIM-1 is up-regulated by ischemic or toxic injury.**
- **Appears to have clinical value as a marker for AKI.**

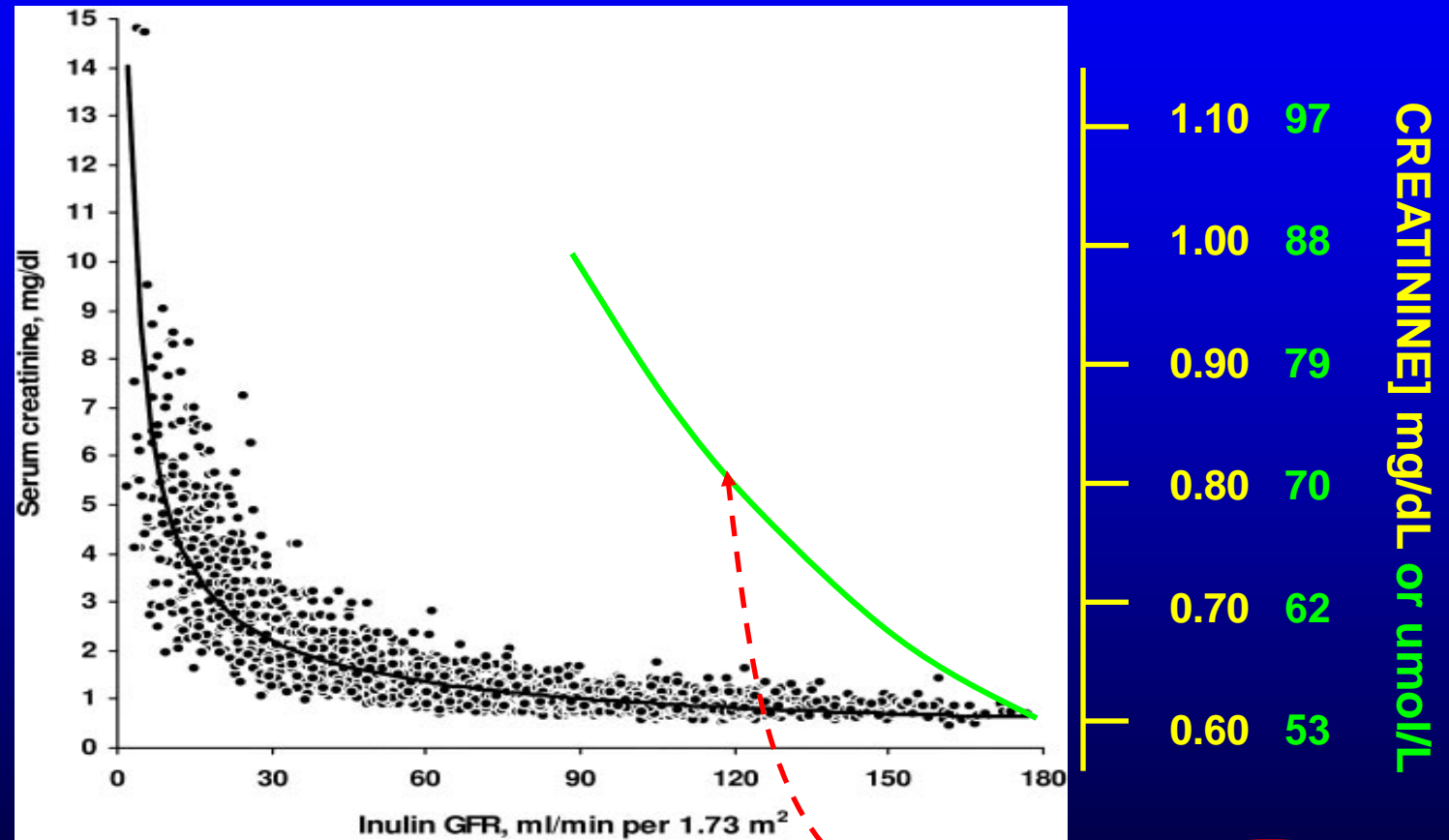
# ***AKI Biomarkers: Typical Time Courses after Cardiac Surgery***



# ***Some Big Lies Through History***

- **The Earth is flat** (*Homer, Thames, many others*)
- **We got it all** (*many surgeons*)
- **I'll call you tomorrow** (*many men, some women*)
- **You'll go blind if you keep doing that** (*many mothers*)
- **email will never catch on** (*Toffaletti, circa 1990*)
- **It's simply plug and play** (*software experts*)
- **Serum creatinine does not increase until 50% of nephrons are lost** (*many kidney experts*)

# Plot of Serum Creatinine vs GFR by Inulin Clearance



0.10 mg/dL scale  
makes Sensitivity appear  
much better!

From Figure 1 in: Clin J Am Soc Nephrol 2009; 4: 899-906.

# ***Plasma Creatinine as a Renal Function Test***

- Good: An increase is usually specific for diminishing renal function.
- Good: Within-individual variation is small.
- Bad: Population variation is large:
  - Creatinine varies by age, gender, and race (muscle mass)
  - *Protein intake*, drugs, and exercise may also affect blood levels of creatinine.
- Bad?: Lacks sensitivity for early detection of declining renal function (***Somewhat true, but is GFR any better?***).

# ***Clinical Usefulness of Creatinine in Kidney Disease***

- ***Within-individual*** changes in serum creatinine should rival or surpass GFR for indicating early changes in renal function.
  - Standard for AKI and monitoring kidney transplant rejection.
- Three reports in ***Clin Chem*** support clinical value of serum creatinine: *Clin Chem* 2010; 56: (pages 687, 740, and 799)
- Age and sex specific reference ranges for creatinine are at least as good as the eGFR values for diagnosing kidney disease (*Scand J Clin Lab Invest* 2009; 69(5): 550-561).



# ***What Was the Purpose of the eGFR Equations?***

- Because of the population variation in serum creatinine, increased creatinine in some individuals might go unnoticed by physicians.
- The “experts” then tried to develop an equation to calculate an eGFR from the creatinine result that would numerically mimic the measured GFR determined by iothalamate clearance.
- Believing that measure GFR was the “gold standard”, they used the eGFR to categorize individuals into various stages of kidney disease.
- For several reasons, numerical MDRD eGFR reported only when less than 60 mL/min/1.73m<sup>2</sup>.
- The more recent CKD-EPI equation would allow all values of eGFR to be reported.

# ***Old and New eGFR Equations for Predicting GFR In Adults***

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

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

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

$$\text{eGFR} = 186 \times (S_{\text{Cr}})^{-1.15} \times (\text{Age})^{-0.20} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

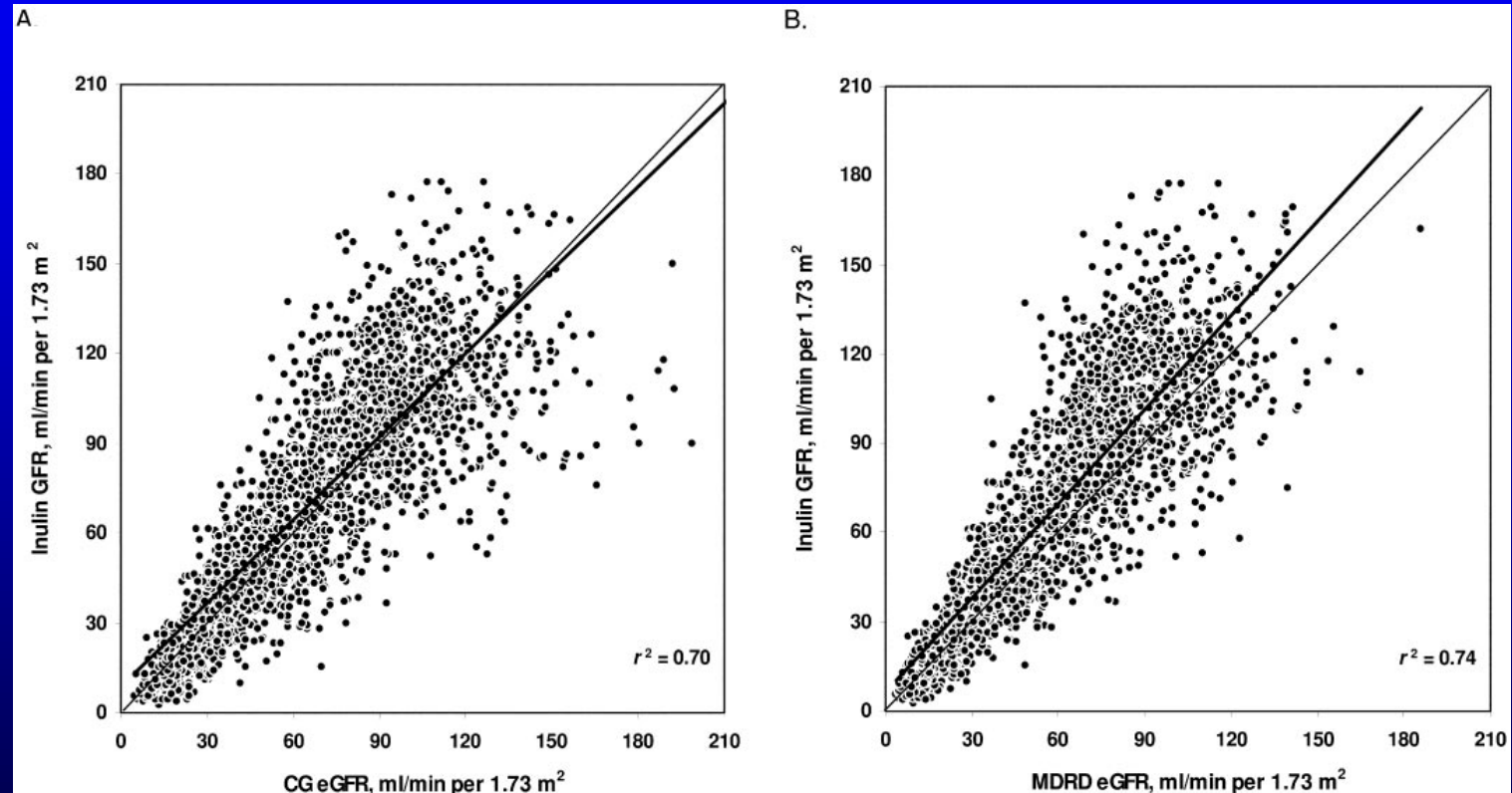
$$\text{eGFR (IDMS)} = 175 \times (S_{\text{Cr}})^{-1.15} \times (\text{Age})^{-0.20} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

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

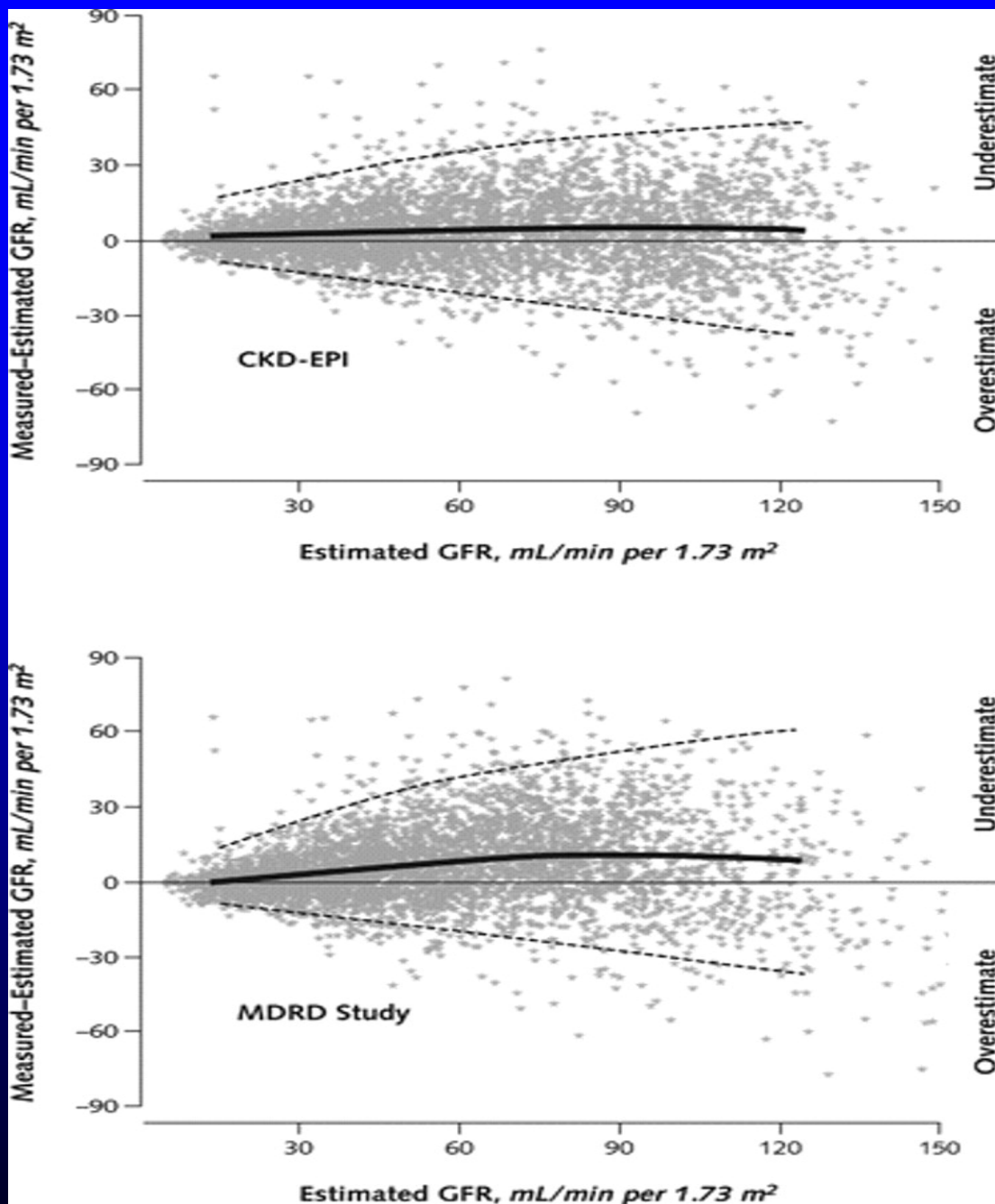
$$\text{eGFR} = 141 \times \min(S_{\text{Cr}}/k, 1)^a \times \max(S_{\text{Cr}}/k, 1)^{-1.21} \times (0.99)^{\text{Age}} \times (1.018 \text{ if female}) \times (1.16 \text{ if black})$$

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

# Plots of Inulin GFR vs C-G eGFR and MDRD eGFR



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



**84.1% agree within 30%**

**Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.**

**Both panels show the difference between measured and estimated versus estimated GFR**

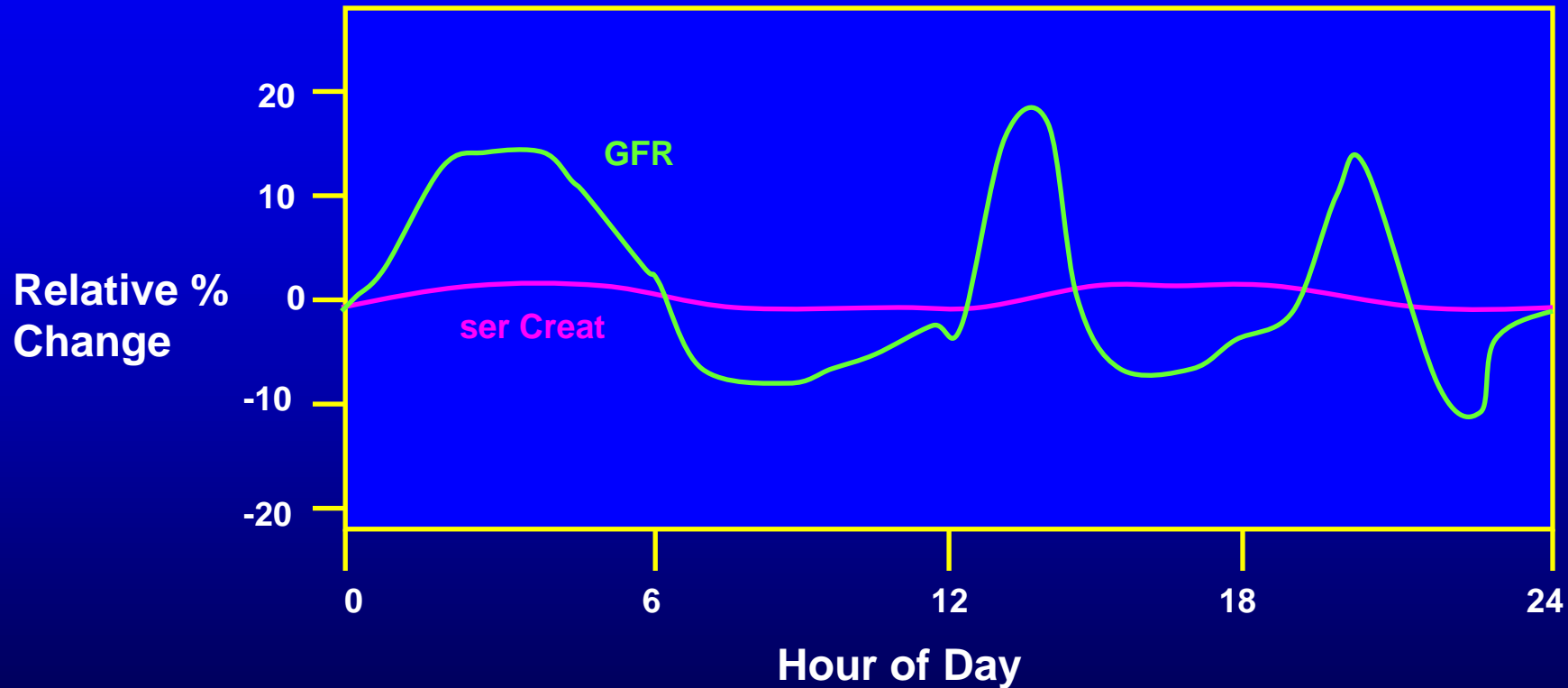
**80.6% agree within 30%**

Levey A S et al. Ann Intern Med  
2009;150:604-612

# ***Why the Variability in GFR by Clearance Measurements (Creatinine, Iothalamate, etc)?***

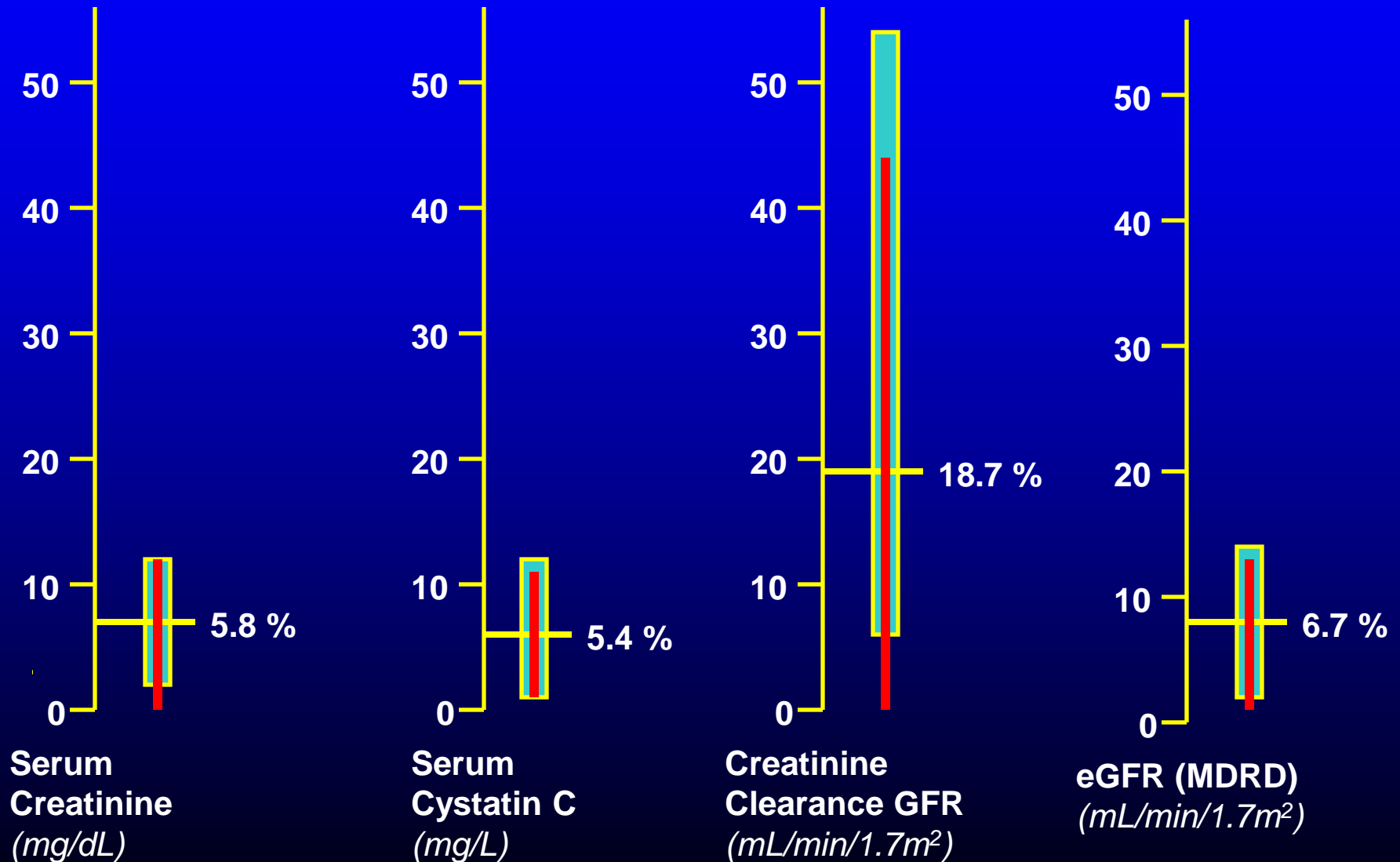
- **Incomplete voiding.**
  - That's why ultrasound and catheters are sometimes used to ensure bladder is "empty".
- **Variation or interference to urine (creatinine, iothalamate) measurement:**
  - 20 fold dilution for urine creatinine.
- **GFR is physiologically much more variable than serum creatinine!**

# ***My Conclusion: GFR and Serum Creatinine Have Inherently Different Regulation Patterns***



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

Mean W-I variation = — Range of W-I variations = ± 2SD of W-I variations =





*The IRB Did Not Approve Our Method of  
Ensuring Complete Voiding of Urine*



***Plasma Creatinine is Frequently Criticized  
for Having a Large Population Variation.***

***However:***

***GFR Also Has a Large Population Variation  
(in addition to a large within-individual variation).***

## ***GFR Varies by Age***

<b>Age (years)</b>	<b>Average GFR (mL/min/1.73 m<sup>2</sup>)</b>
<b>20-29</b>	<b>116</b>
<b>30-39</b>	<b>107</b>
<b>40-49</b>	<b>99</b>
<b>50-59</b>	<b>93</b>
<b>60-69</b>	<b>85</b>
<b>70+</b>	<b>75</b>

## ***GFR Also Varies in Health***

Parameter	Healthy Persons ( <i>n</i> = 501)	
	<i>Mean + 2 SD</i>	<i>Range</i>
<b>Serum creatinine</b> (mg/dL)	<b>0.73 – 1.37</b>	<b>0.6 – 1.6</b>
<b>Iothalamate GFR</b> (mL/min/1.73 m <sup>2</sup> )	<b>67 - 135</b>	<b>63 – 177</b>

# GFR vs Stage of Chronic Kidney Disease:

## Some Recent Changes

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

### New Albuminuria Categories:

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

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

Normal Range for GFR is 67-135

Reportable Range for MDRD eGFR

# Newer Chronic Kidney Disease Stages: Assessed by GFR and Albuminuria

**Table 2. Risk Assessment for CVD in CKD**

CKD Stages	GFR	Urine Albumin/Creatinine Ratio (mg/g)		
		10-29	30-299	>300
1	90+			
2	89-60			
3A	59-45			
3B	44-30			
4	29-15			
5	< 15			

CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate.  
Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group<sup>9</sup>

# *If eGFR is Here to Stay, What is It's Future?*

- Should all values be reported?
  - The CKD-EPI may allow this.
  - Duke nephrologists said “no”, continue with  $< 60$ .
- The use of both eGFR and urine albumin should improve diagnostic usefulness:
  - Minimize false positives.
- We should emphasize value of serial measurements:
  - Both of creatinine and eGFR!

# ***Summary of Conclusions***

- AKI and CKD are interconnected diseases.
- Optimal tests for AKI = cell injury marker (cys C, NGAL, KIM, etc); for CKD = functional marker for glomerular loss (creatinine (eGFR), cys C)
- The time course of cys C, NGAL, IGFBP7, creatinine may have added diagnostic value.
- Creatinine is still a very good renal function test:
  - More sensitive than often believed.
  - More precise than measured GFR.
  - Serial measurements have added clinical value.
- Actual GFR is a fairly mediocre renal function test:
  - A very cumbersome test, and has large population and individual variations.
- Cystatin C:
  - Can be a useful when creatinine/eGFR are equivocal
  - Has clinical value in both AKI and CKD (but not going to replace creatinine)
- New CKD classification system with both eGFR and urine albumin may have much improved clinical use.



***Thank You For Your  
Attendance and Attention!***