Overview of Current Biomarkers in Kidney Disease

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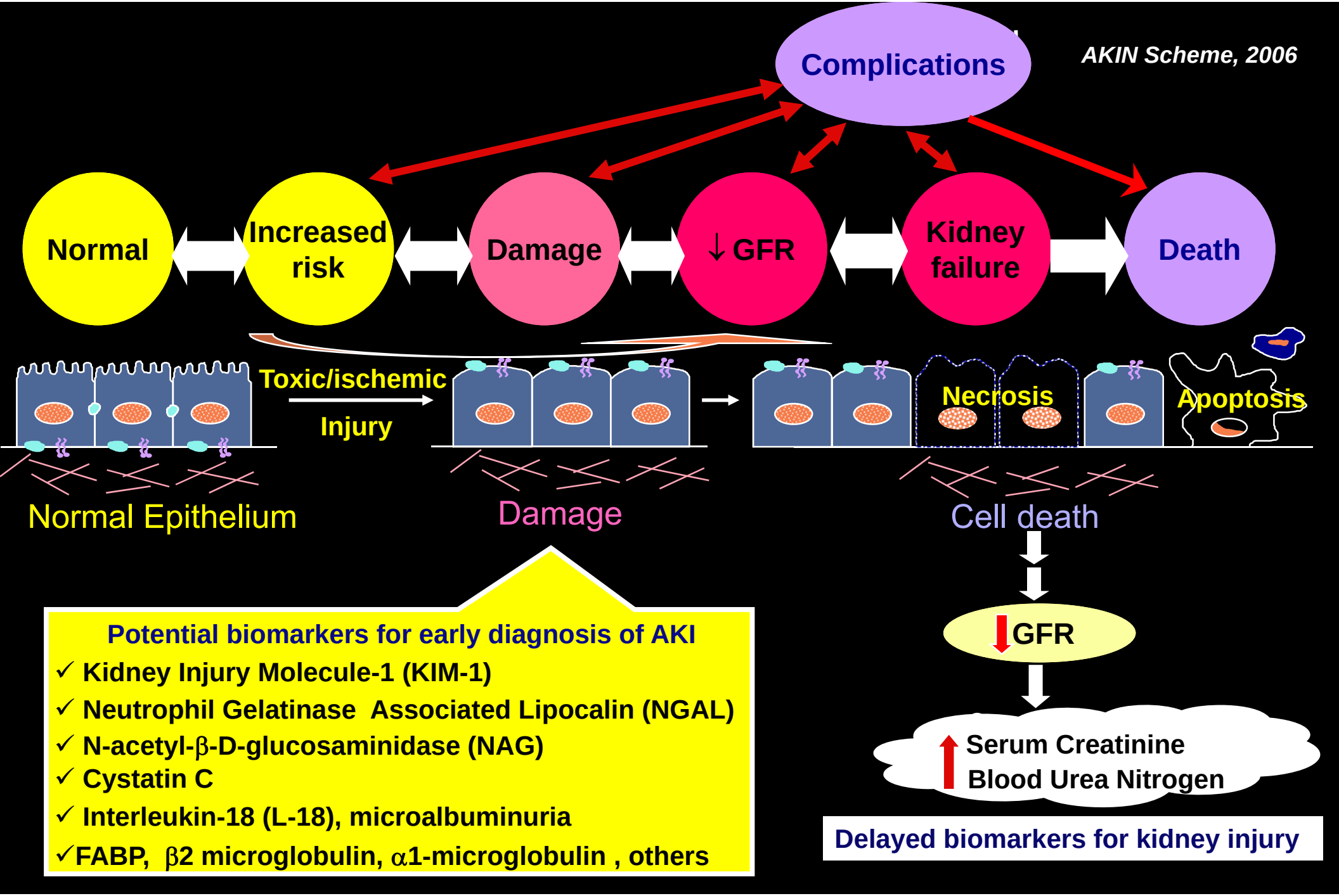
Disclosure: JVB is co-inventor on KIM-1 patents that have been licensed to a number of companies including Johnson and Johnson, Genzyme, R and D, BioAssay Works, and BiogenIdec

Outline

- AKI Biomarkers
- Lessons Learned from Success in Identification and Qualification of Kidney Biomarkers to Guide Drug Development
- The Gold Standard Problem
- Clinical studies of Biomarkers in AKI
- Challenges with CKD Biomarkers
- Biomarkers provide insight into pathophysiology

Characteristics of an Ideal Biomarker for AKI

- Easy to measure in easily obtainable fluids: urine or blood
- Sensitive enough to pick up meaningful injury prior to functional changes
- Produced by a specific segment of the kidney tubule or kidney endothelium
- Distinguishes tubular from prerenal and glomerular injury
- Stable in the blood or urine, devoid of interferences with other substances, and unaffected by chemical composition of the urine, including ionic strength and pH among others
- Increases in levels are predictive of severity of acute injury and chronic sequelae
- Decreases in levels are reflective of recovery
- Understandable function of the marker in the kidney


Complications
AKIN Scheme, 2006
Normal
Increased risk
Damage
↓GFR
Kidney failure
Death
Toxic/ischemic
Injury
Necrosis
Apoptosis
Normal Epithelium
Damage
Cell death
↓GFR
↑Serum Creatinine
↑Blood Urea Nitrogen
Delayed biomarkers for kidney injury
Potential biomarkers for early diagnosis of AKI
✓ Kidney Injury Molecule-1 (KIM-1)
✓ Neutrophil Gelatinase Associated Lipocalin (NGAL)
✓ N-acetyl-β-D-glucosaminidase (NAG)
✓ Cystatin C
✓ Interleukin-18 (L-18), microalbuminuria
✓FABP, β2 microglobulin, α1-microglobulin , others

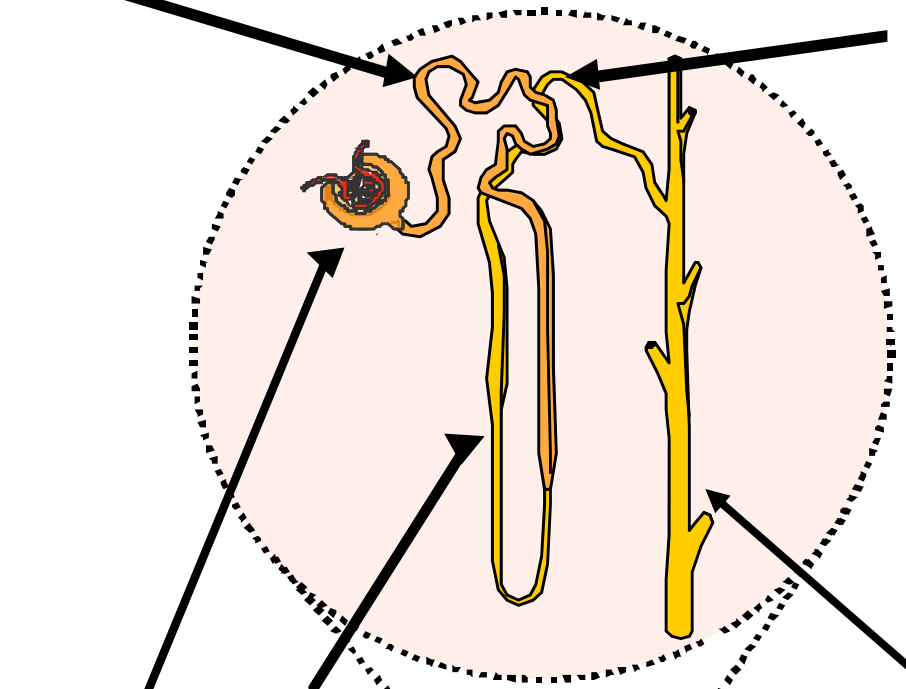
Candidate Biomarkers for Kidney Injury

Proximal Tubules

KIM-1
L-FABP
Albumin
Clusterin
Lipocalin (NGAL)
GSTα
β2-microglobulin
α1-microglobulin
NAG
Osteopontin
Cystatin C
Netrin-1
IL-18
Retinol binding prot
HGF, NHE-3
Cyr61
Exosomal Fetuin-A
TIMP2
IGFBP7

Distal Tubules

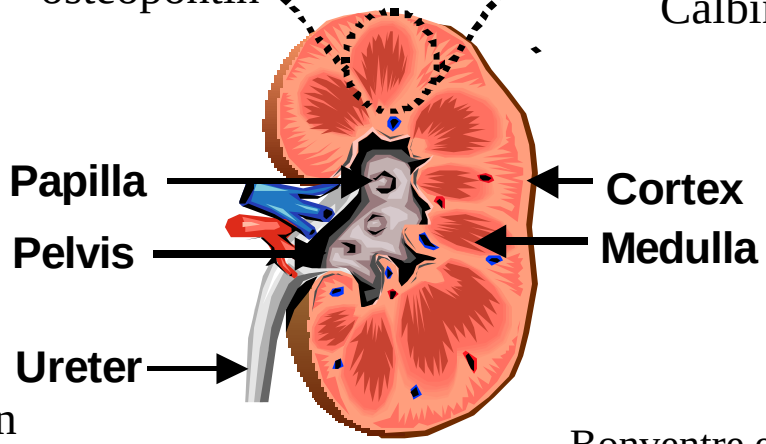
Osteopontin
Clusterin
Lipocalin (NGAL)
GST-μ/π
NAG
EGF
Osteopontin
Cystatin C
IL-18
Calbindin-D28



Loop of Henle
osteopontin

Collecting Duct
Calbindin- D28

Glomerulus
Creatinine
Cystatin C
Protein, albumin
Podocalyxin
β2-microglobulin
WT-1 in exosomes



Bonventre et al. Nature Biotech 2010

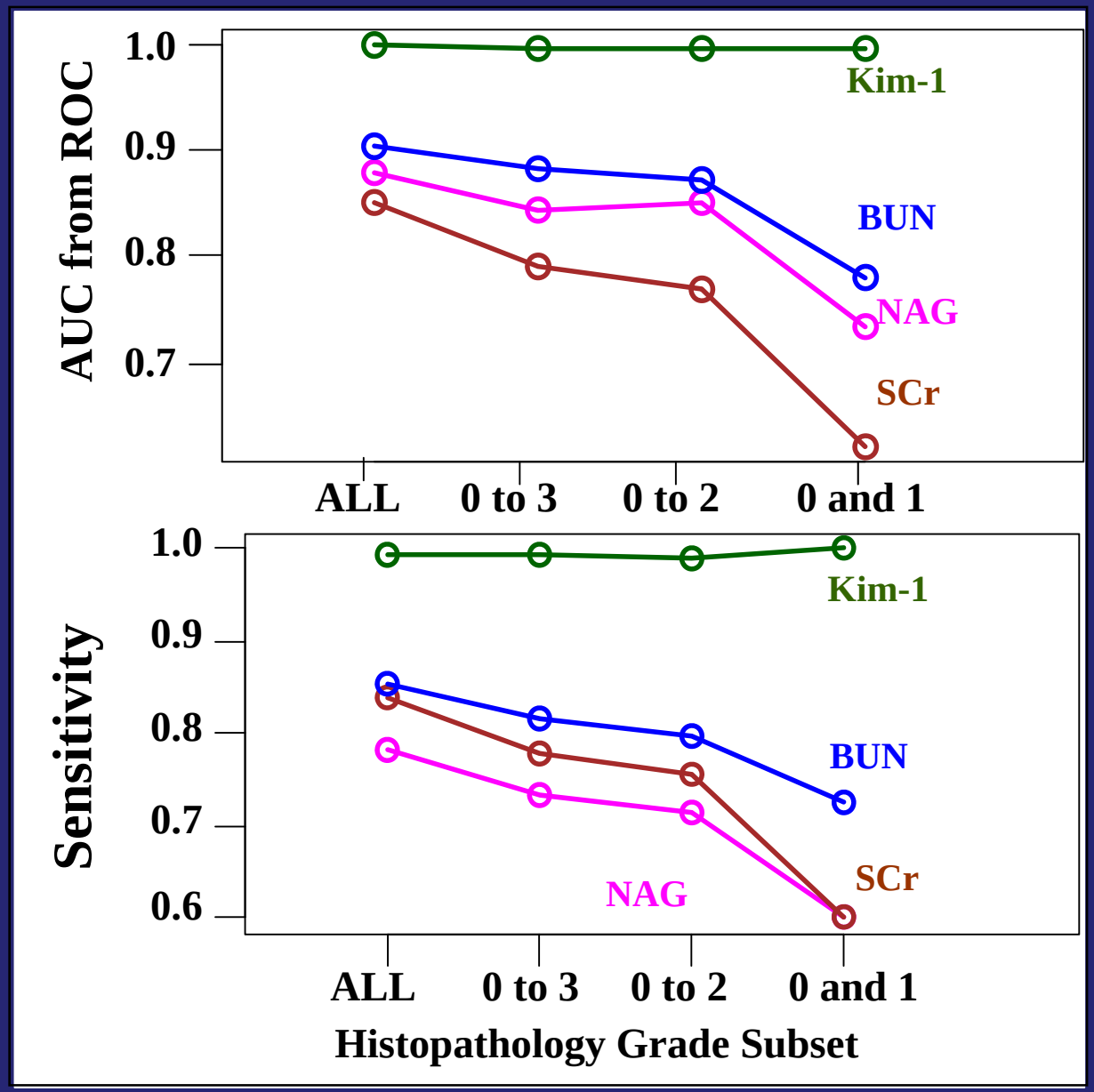
FDA's Critical Path Initiative

"Additional biomarkers (quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development."

Sensitivity and Specificity of Kim-1, NAG, BUN, SCr

Predictive Safety Testing Consortium Rat Toxicity Studies

Vaidya et al.
Nature Biotechnology, May, 2010

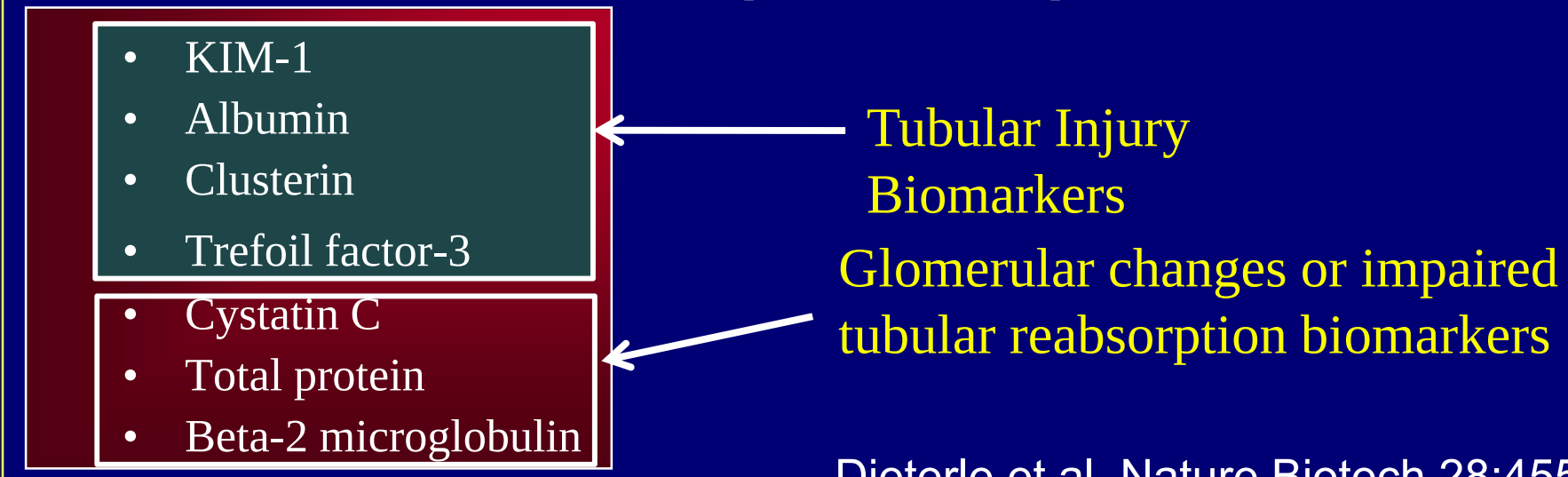


FDA and European Medicines Agency Will Consider New Biomarker Test Results When Assessing Kidney Toxicity of Experimental Drugs

In the first use of a framework allowing submission of a single application to the 2 agencies, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) will allow drug companies to submit the results of 7 new tests that evaluate kidney toxicity…,(FDA news release, 6/17/2008).

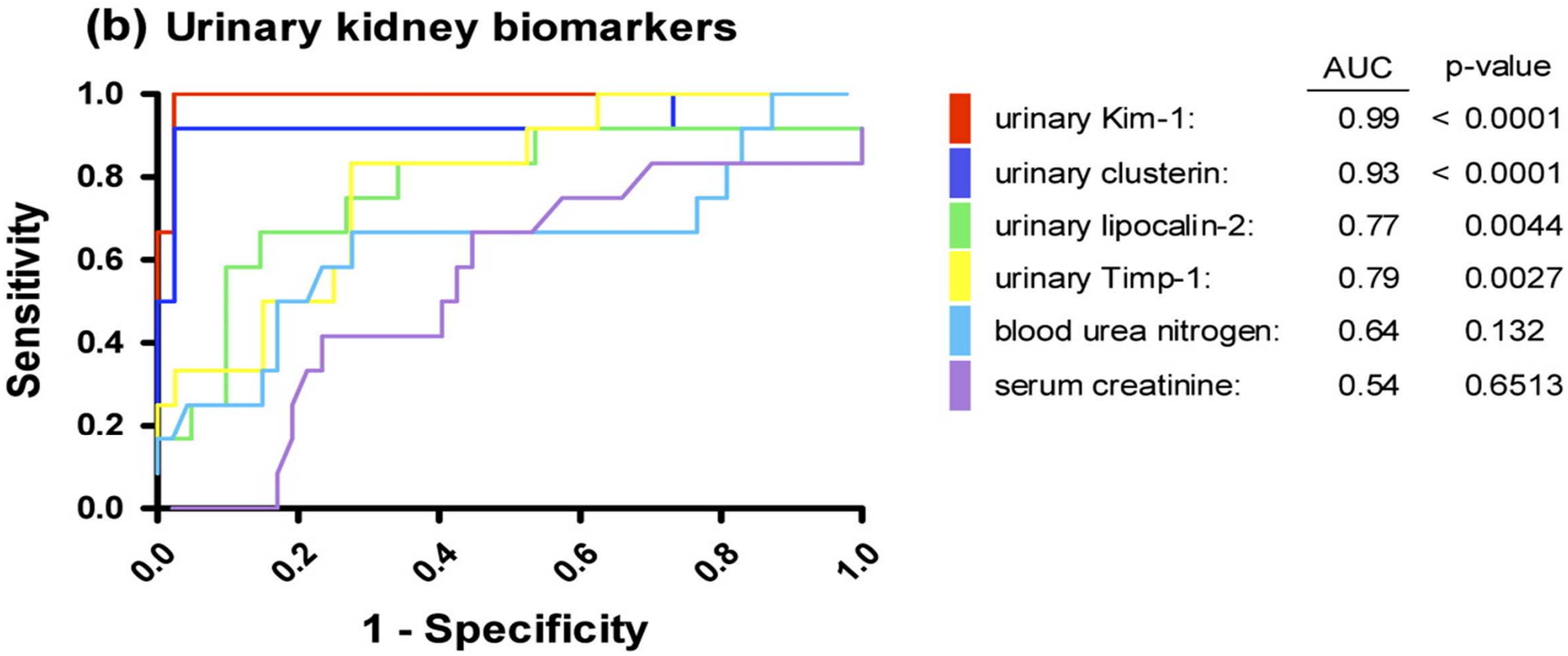
The tests measure levels of 7 key biomarker proteins found in urine that can provide information about drug-induced damage to kidney cells (renal toxicity). The new biomarkers are:

http://www.hivandhepatitis.com/recent/2008/061708_e.html



Dieterle et al. Nature Biotech 28:455-62, 2010

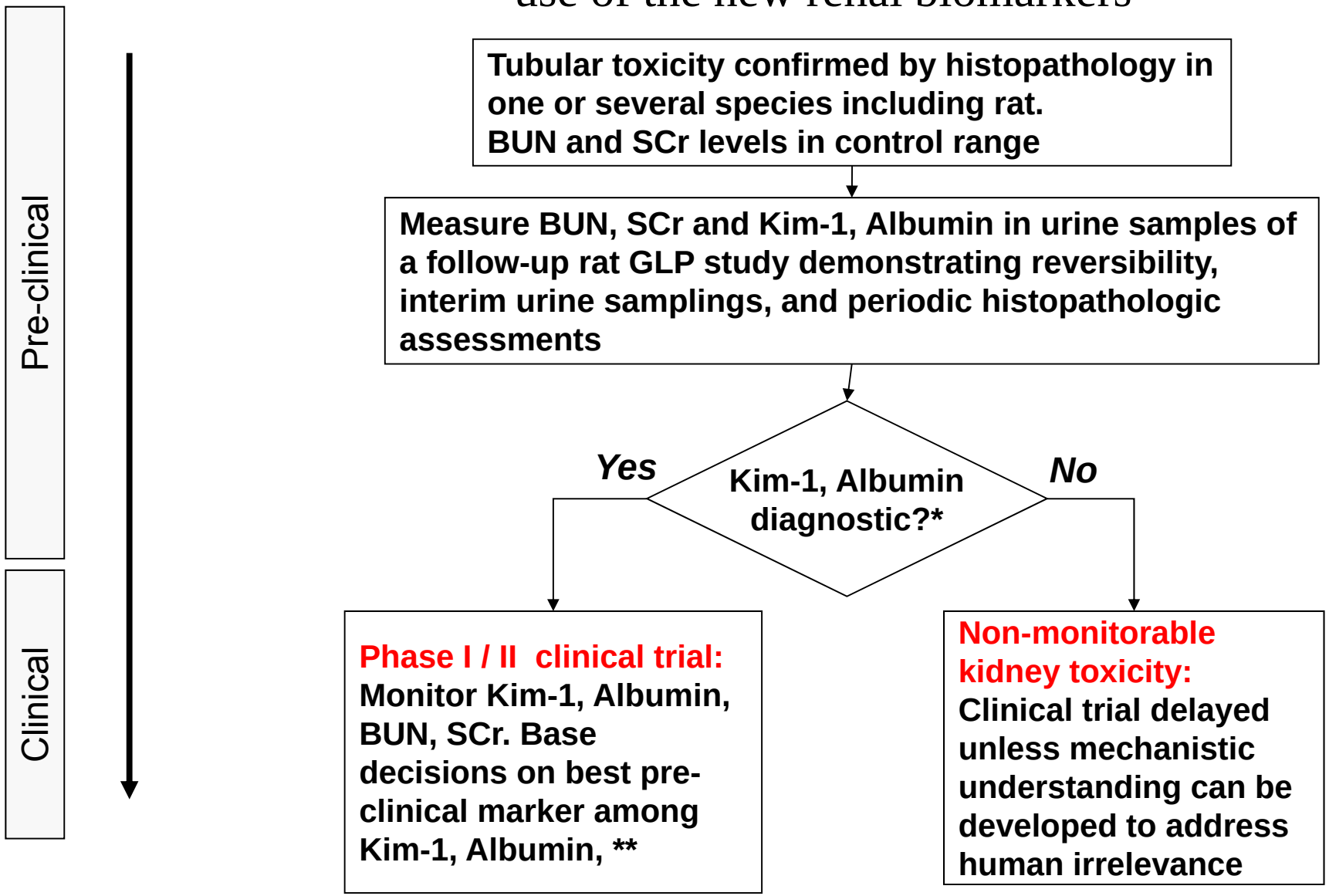
European InnoMed Predictive Toxicology Consortium ROC curves for urinary biomarkers compared to traditional clinical chemistry parameters.



Hoffmann D et al. Toxicol. Sci. 2010;116:8-22

TOXICOLOGICAL SCIENCES

Flow chart explaining the proposed limited clinical translational use of the new renal biomarkers



* Sponsor can voluntary measure Albumin or Kim-1 alone or both markers together

** Pre-clinical best marker means marker with the best diagnostic performance compared to histopathology

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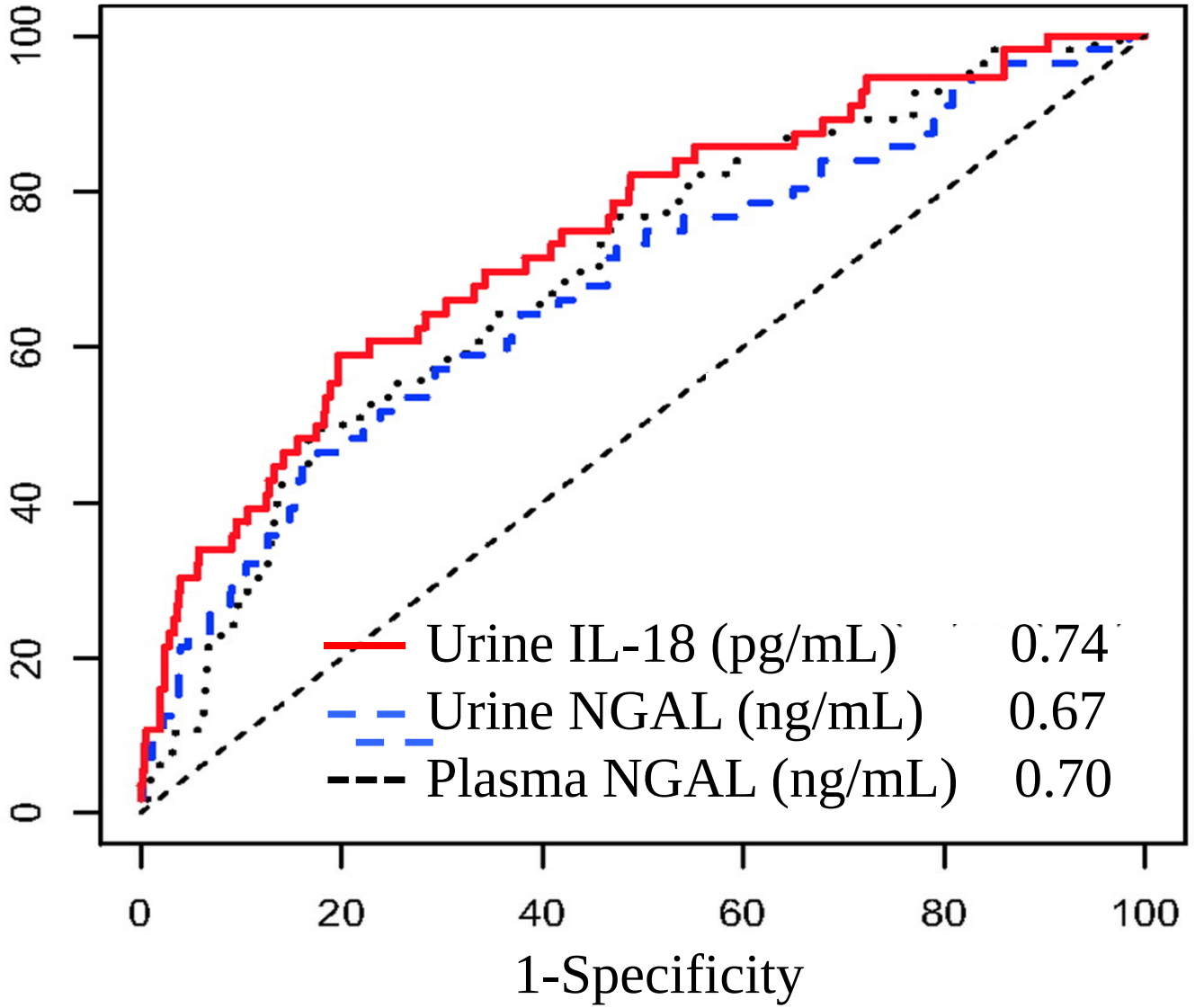
Diagnostic performance of the first postoperative value of urine IL-18, urine NGAL, and plasma NGAL for the detection of AKI.



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Parikh C R et al. JASN 2011;22:1748-1757

JASN

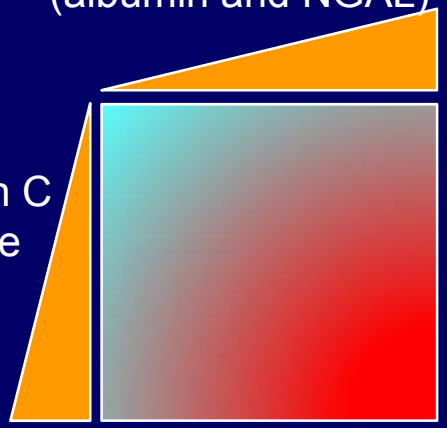
Potential Context of Interpretation of AKI Markers

Tubular Damage

KIM-1, L-FABP, α-GST
(albumin and NGAL)

↓GFR

Creat, Cystatin C
KDIGO Stage

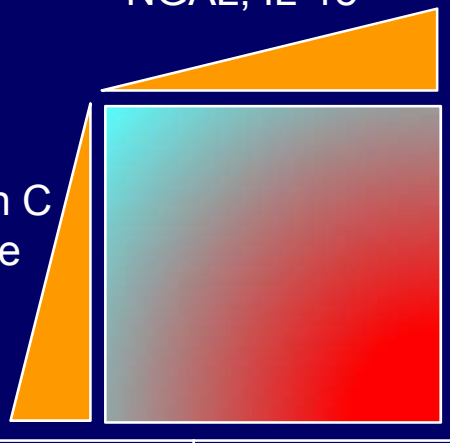


Inflammation

NGAL, IL-18

↓GFR

Creat, Cystatin C
KDIGO Stage

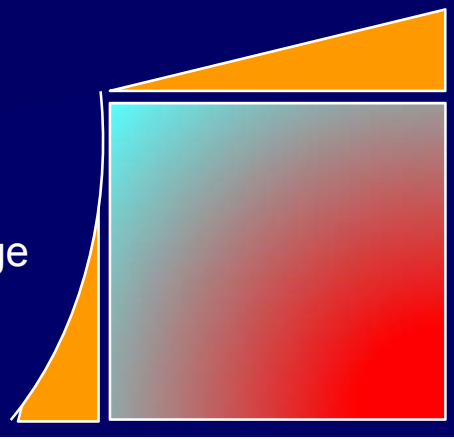


Difficulty with Creatinine

Tubular Damage
+/- Inflammation

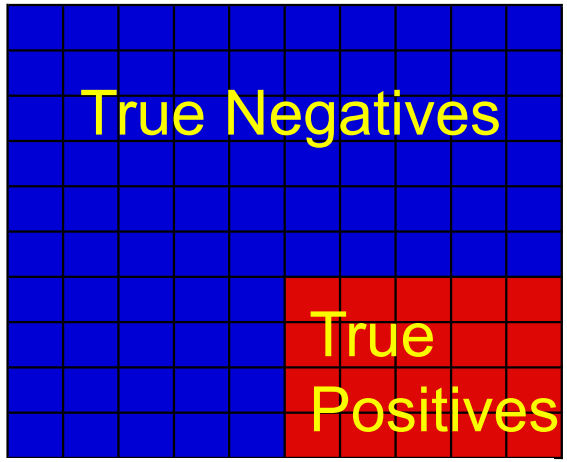
↓GFR

Creatinine,
KDIGO Stage

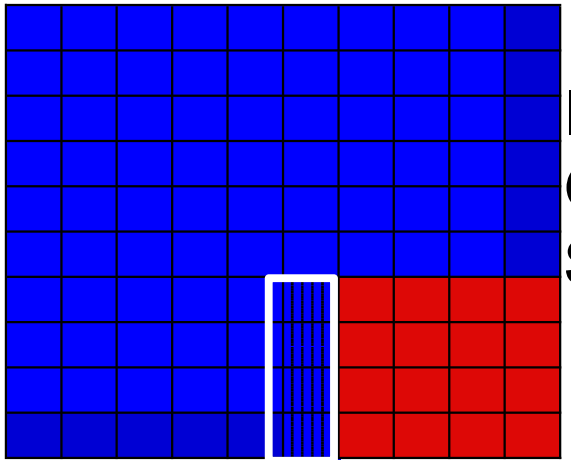


Injury Marker	Inflammation Marker	GFR Marker	? Kidney Injury
+	+/-	+	+
+	+	+	++
+	+/-	-	+
-	+/-	+	- (prerenal)
+	+	-	+
-	+	-	+/-
-	-	-	-

Perfect Biomarker Performance in Setting of Imperfect Gold Standard



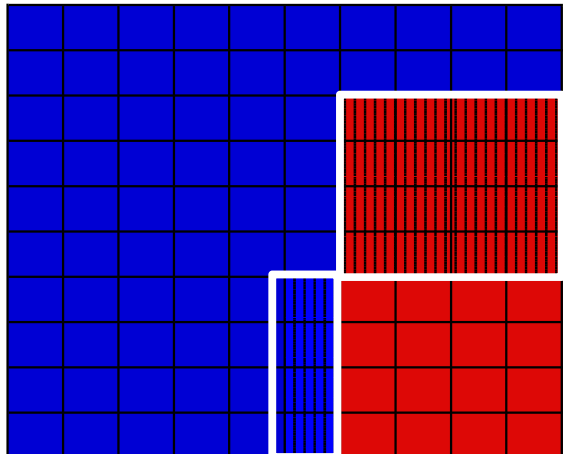
Prevalence = 20 %
(20/100)



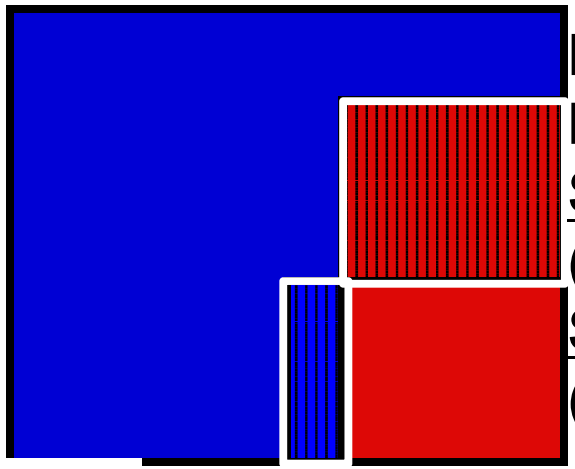
Imperfect
Gold Standard
Sensitivity=80%

Imperfect gold standard picks up
16 of 20 true positives

Imperfect
Gold Standard
Specificity=80%

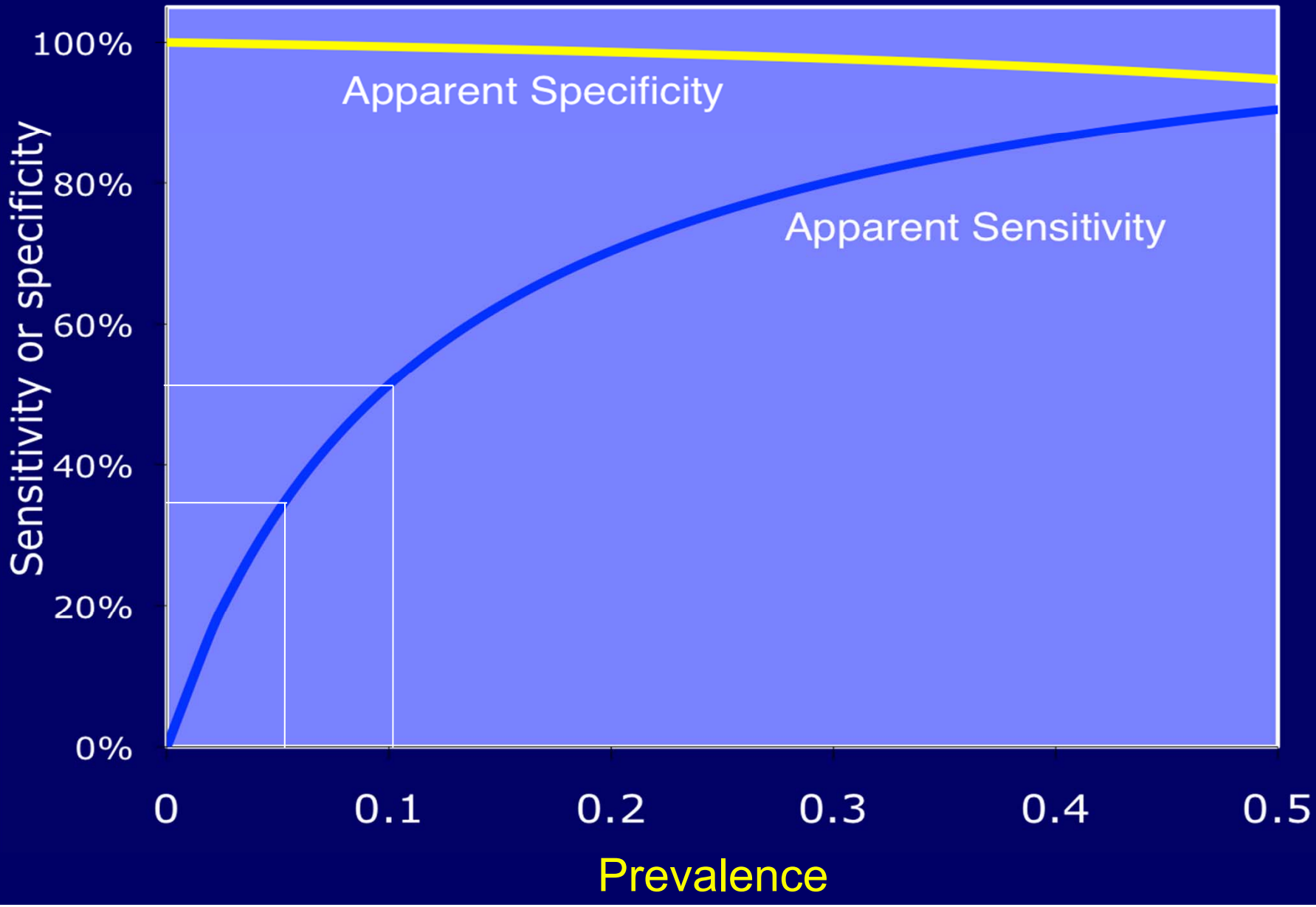


Imperfect gold standard picks up
64 of 80 true negatives



Perfect
Biomarker
Sensitivity=50%
(16 of 32)
Specificity = 94%
(64 of 68)

Effect of Prevalence of AKI on Apparent Specificity and Sensitivity of a Perfect Biomarker when AKI Definition is Assumed 95% Sensitive and 90% Specific



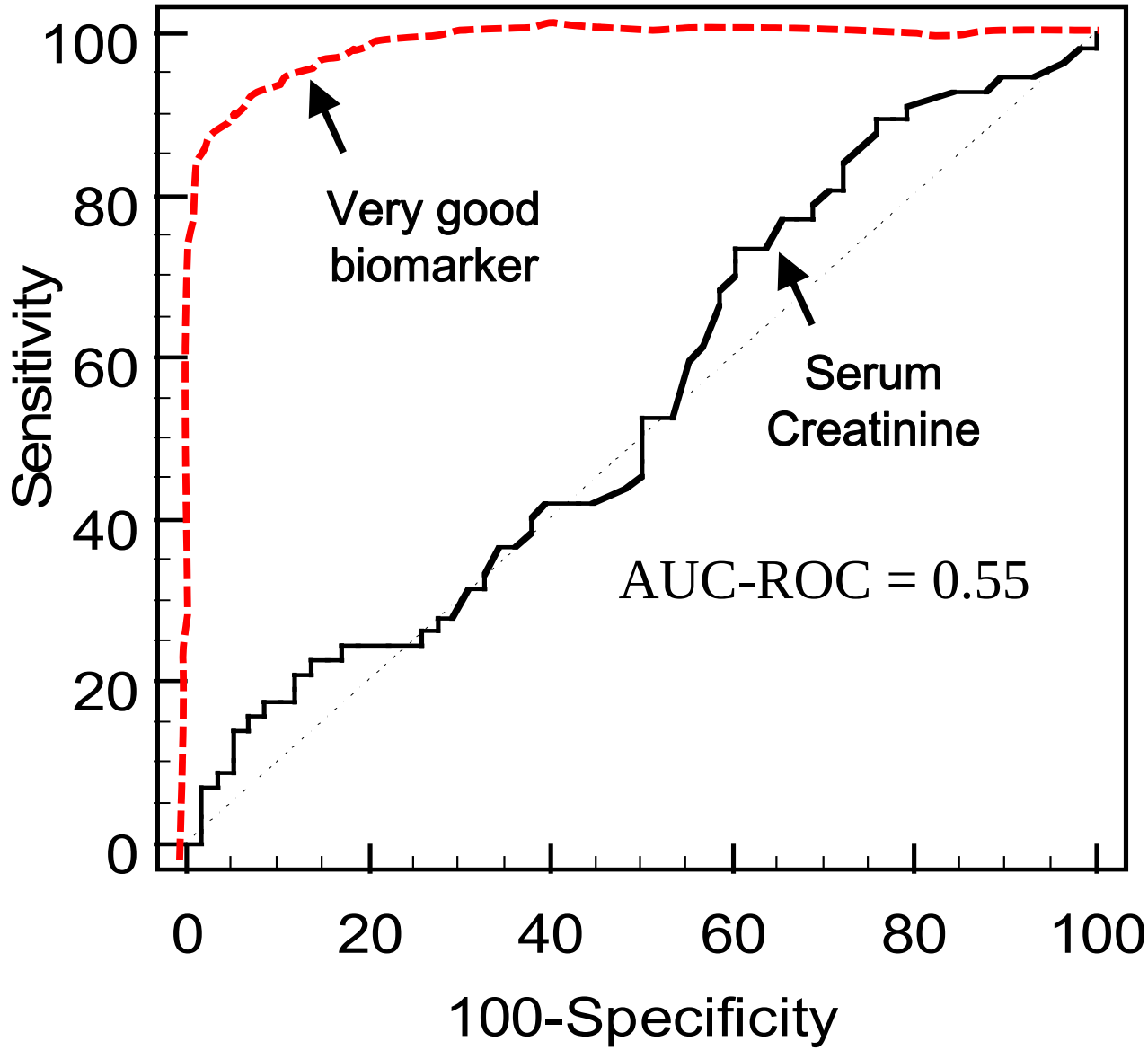
Plasma NGAL as a Predictor of AKI and Clinical Outcomes

	ROC analysis	At cutoff of 150 ng/ml			
	AuC ROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
AKI within 48 h	0.78 (0.65–0.90)	0.73 (0.45–0.92)	0.81 (0.75–0.86)	0.24 (0.13–0.39)	0.97 (0.93–0.99)
AKI within 5 days	0.67 (0.55–0.79)	0.46 (0.27–0.67)	0.80 (0.74–0.86)	0.26 (0.14–0.4)	0.91 (0.85–0.95)
RRT within ICU stay	0.82 (0.70–0.95)	0.87 (0.60–0.98)	0.65 (0.60–0.71)	0.12 (0.06–0.19)	0.99 (0.96–1.00)
ICU mortality	0.67 (0.58–0.77)	0.60 (0.45–0.73)	0.68 (0.61–0.73)	0.28 (0.20–0.37)	0.89 (0.84–0.93)
RRT + ICU mortality	0.68 (0.59–0.77)	0.60 (0.47–0.73)	0.68 (0.62–0.74)	0.31 (0.23–0.41)	0.88 (0.82–0.92)

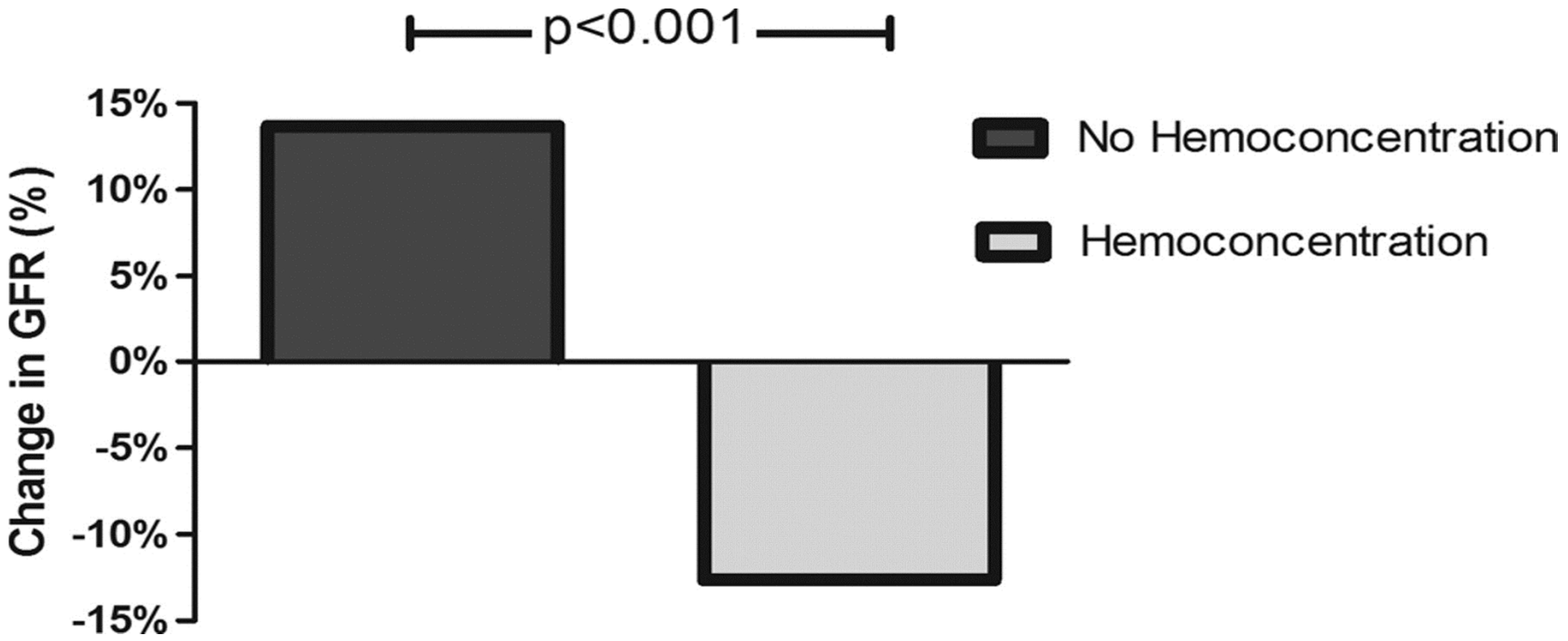
301 ICU patients; 133 (44%) developed AKI during ICU stay

Cruz…Ronco Intensive Care Med.36:444-451, 2010

ROC curve for peak post-operative SCr after cisplatin therapy for mesothelioma (using 24h KIM-1 ≥ 2 ng/mg Ucr as gold standard)



Admission-to-discharge percentage change in GFR grouped by presence or absence of hemoconcentration.



Testani J M et al. Circulation 2010;122:265-272

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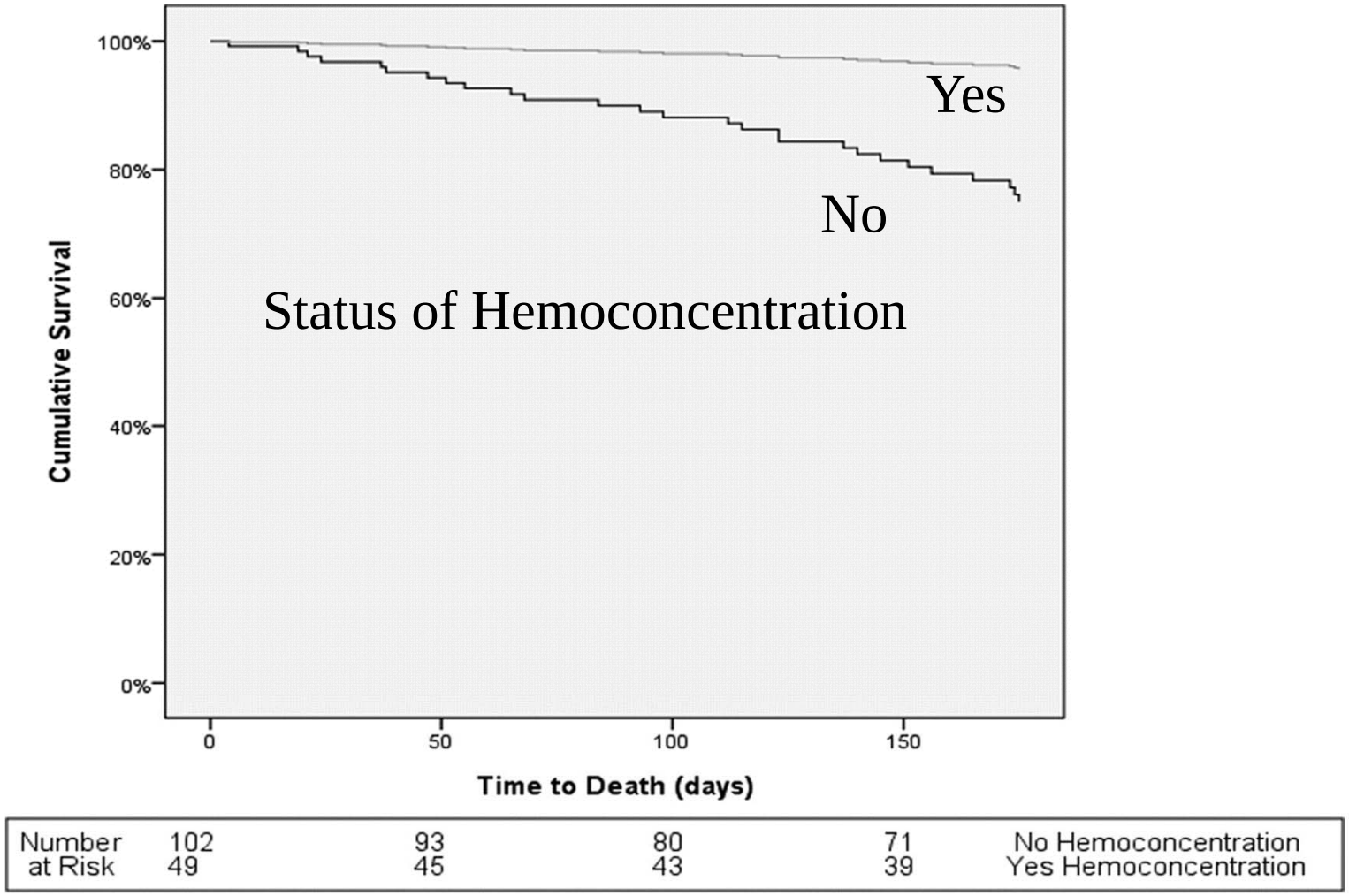
Learn and Live

Survival curves grouped by presence or absence of hemoconcentration after adjustment for baseline characteristics.



Testani J M et al. Circulation 2010;122:265-272

American Heart Association
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Kidney Safety Project

Site Initiation – Cisplatin Study

University of Texas

MD Anderson Cancer Center

October 17, 2012

Brigham & Women's Hospital

Dana-Farber Cancer Institute

November 2012

FNIH

Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Study Team – BWH Harvard Partners DFCI

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- **Robert Haddad, MD**
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  Dana-Farber Cancer Institute
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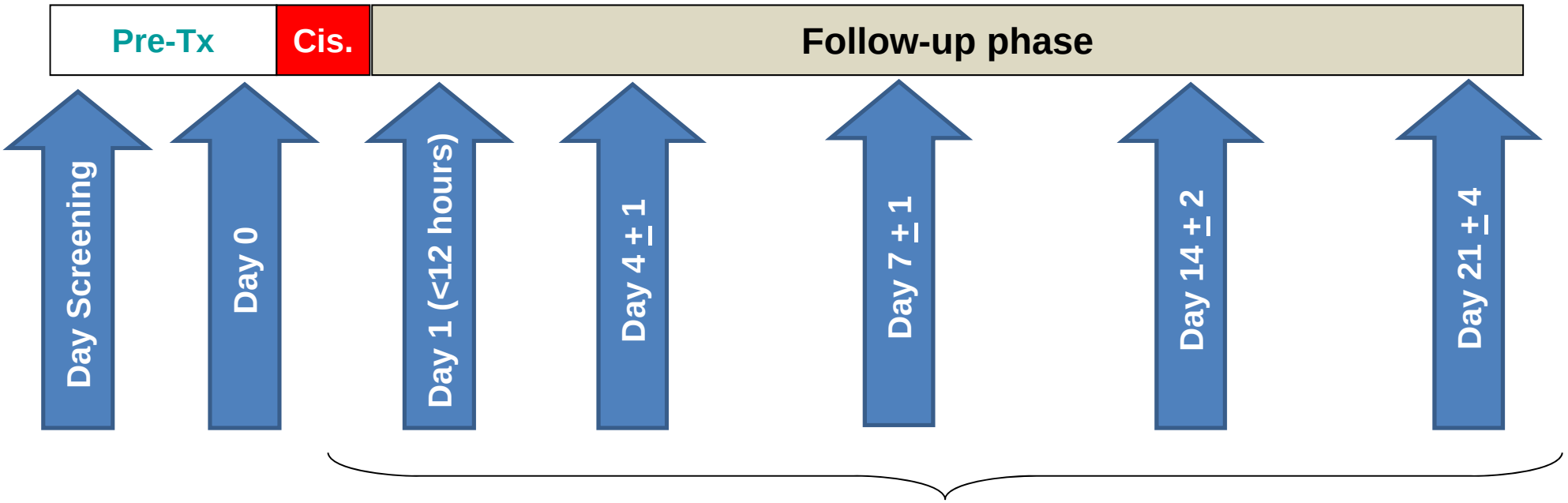
Cisplatin Study

- **A Prospective Observational Study of Urinary Biomarkers of Nephrotoxicity in Cancer Patients Receiving Cisplatin Chemotherapy**

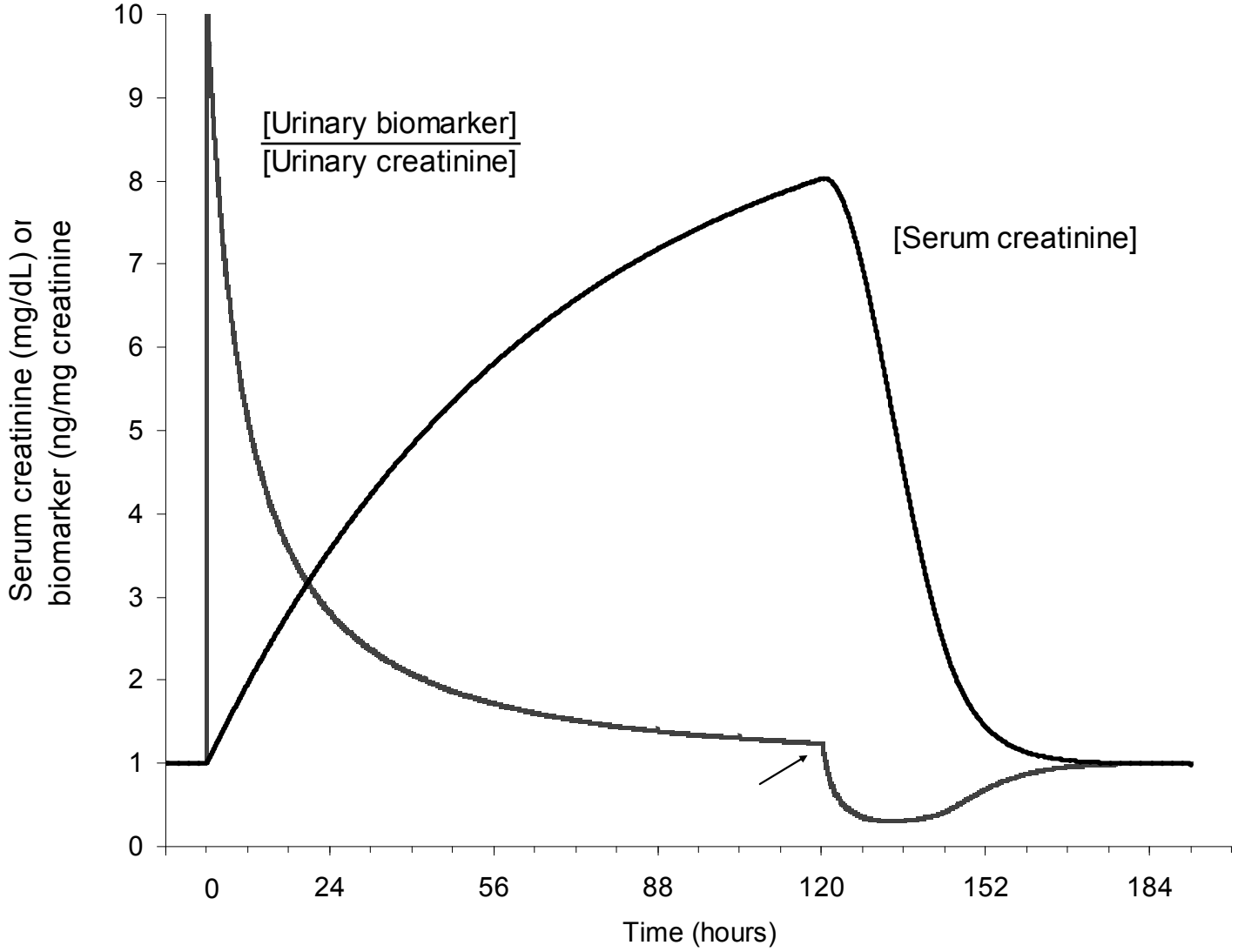
They will assess the performance of a large panel of kidney biomarkers in patients with various cancers who are scheduled to receive high-dose cisplatin chemotherapy and compare these with cancer control patients. Results from this study will be used to support the clinical qualification of biomarkers for drug-induced kidney injury.

Scheduled Visits & Sample Collection Time-Points



Urine & Blood samples
(serum BUN, creatinine, cystatin C, sodium, and spot urine samples for novel biomarkers)

The Creatinine Normalization Issue



Waikar et al. Kidney Int. 2010

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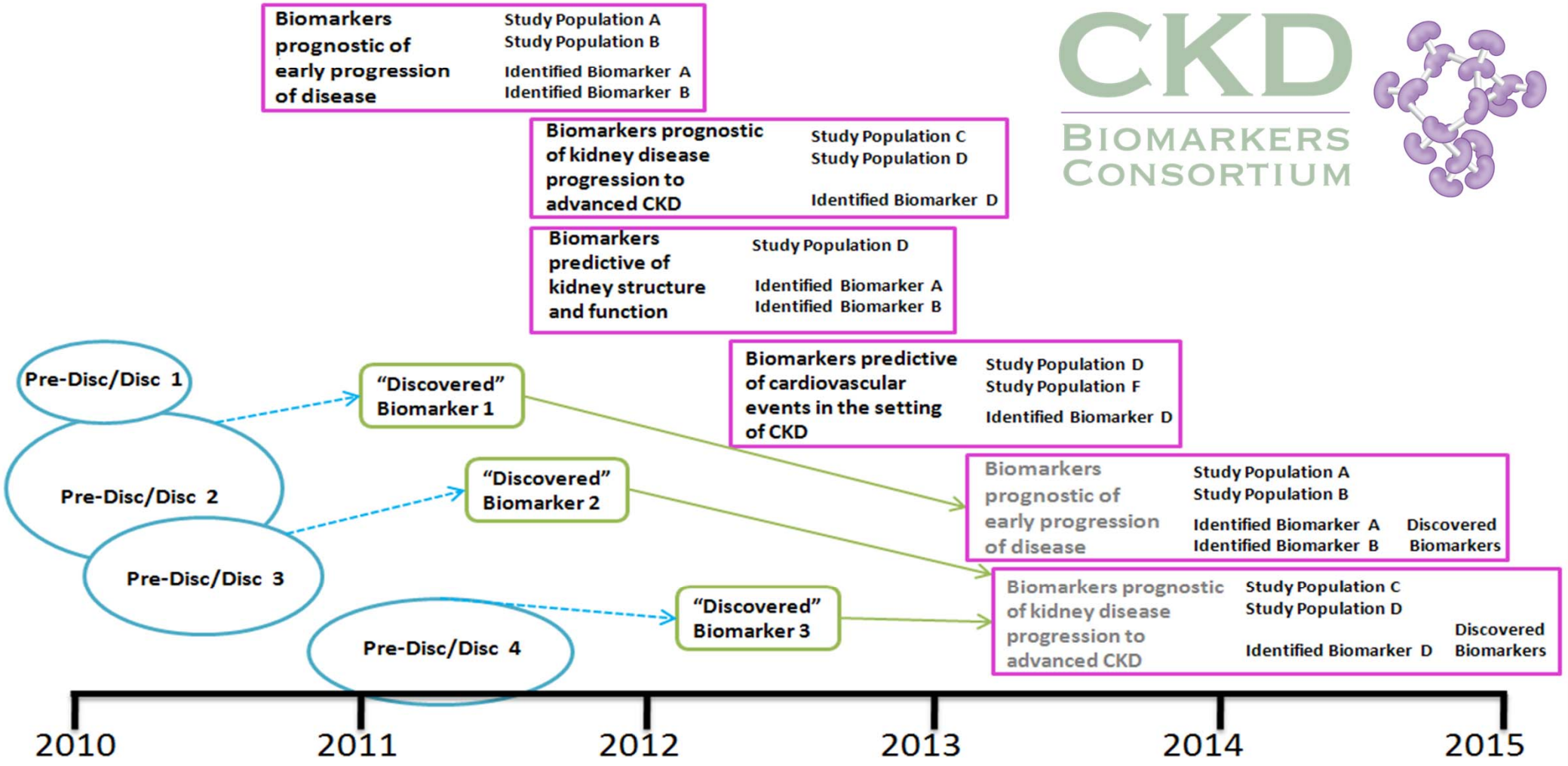
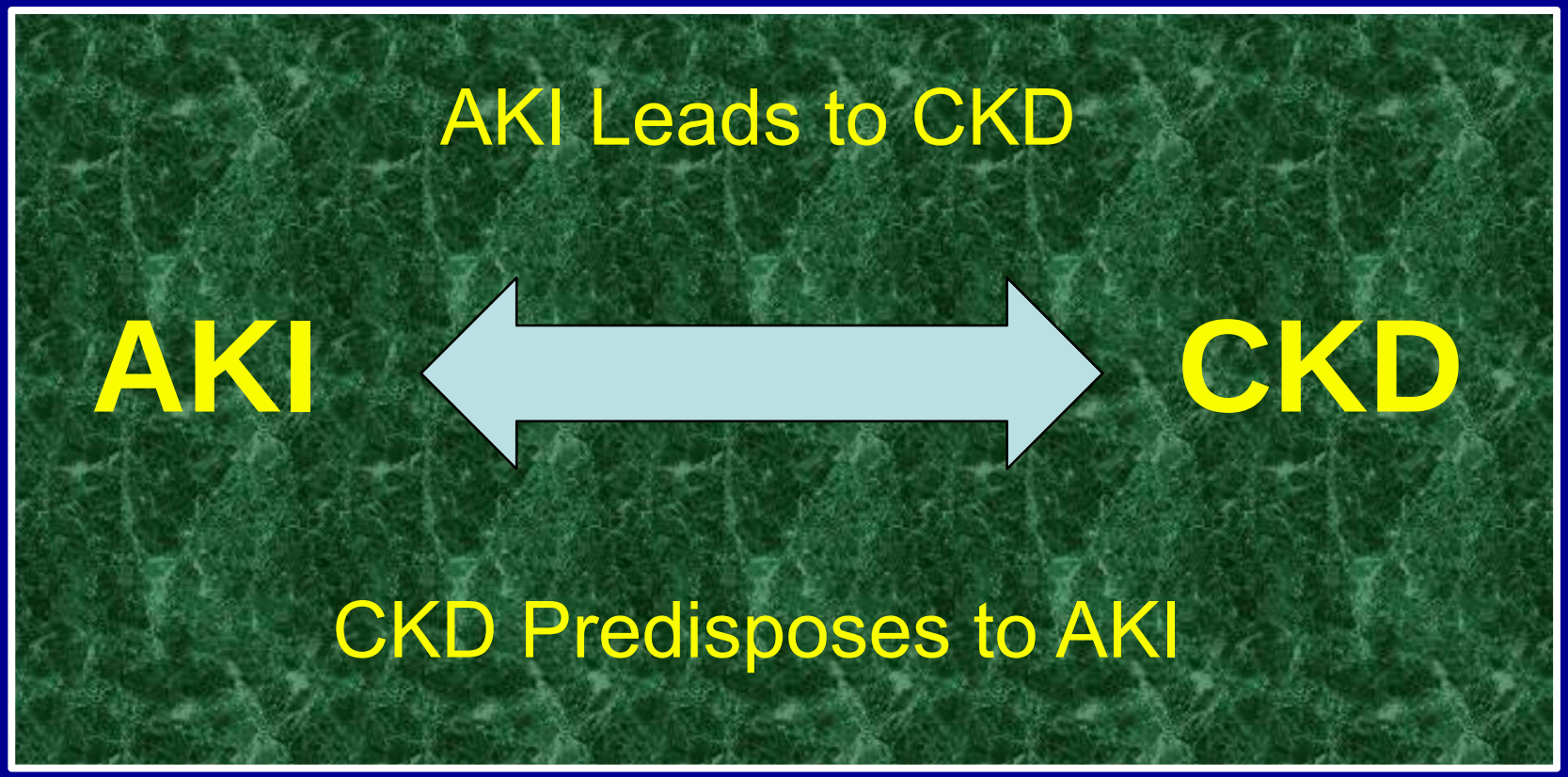
Criteria for an Ideal Biomarker for CKD

- Easy to measure in easily obtainable fluids: urine or blood
- Produced by a specific segment of the kidney tubule or kidney endothelium
- Stable in the blood or urine, devoid of interferences with other substances, and unaffected by chemical composition of the urine, including ionic strength and pH among others
- Levels are predictive of clinically significant outcome
- Prognostic: Levels predict rapid progressors from others so that aggressive therapies can be personalized and clinical trials of new therapeutics can be facilitated.
- Progression: Levels reflect change in disease state over time. Usually require repeated measurements.
- Understandable function of the marker in the kidney

Conceptual Framework for the CKD Biomarker (CKDBiocon) Consortium

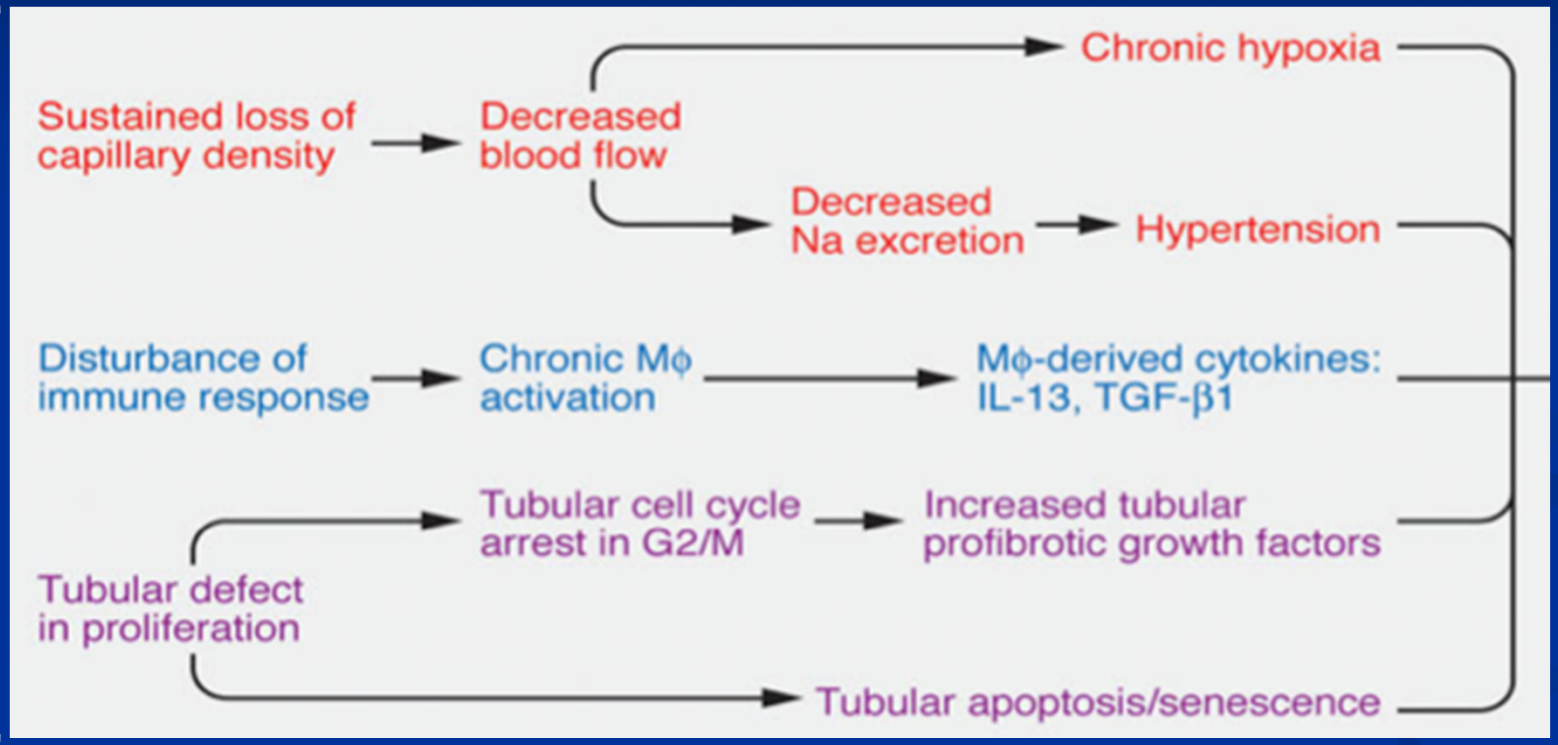



AKI Leads to CKD
AKI
CKD
CKD Predisposes to AKI

Many Factors contribute to the Progression of Kidney Disease

Tubular Injury, Oxidative Stress, Endothelial Injury, Fibrosis,
Metabolic Dysfunction, Systemic Inflammation, Glomerular Injury

AKI



CKD

The more biomarkers we have for these pathways the more likely we are to be able to predict rates of progression and intervene effectively to alter the outcome.

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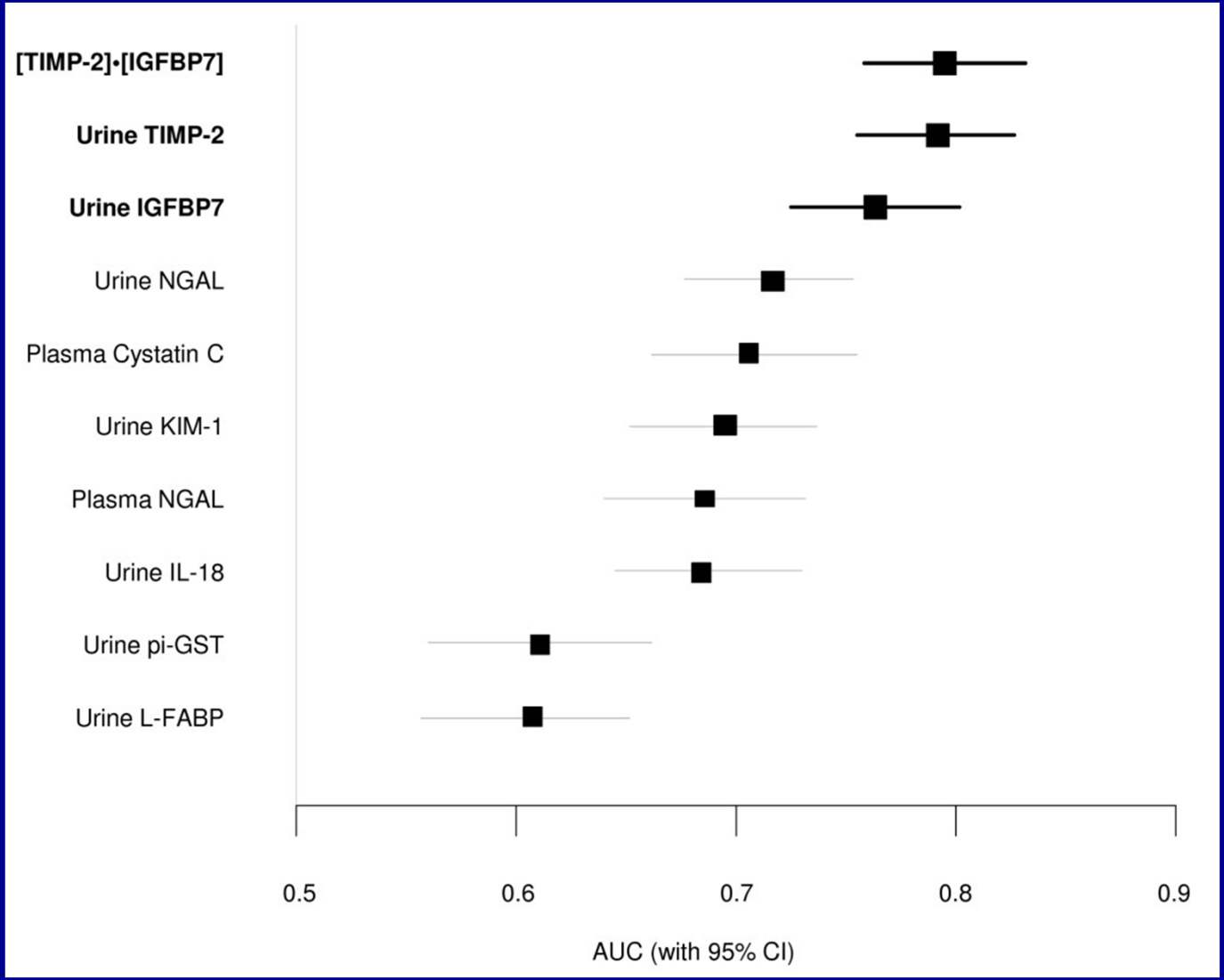
Biomarkers Reveal Important Aspects of Underlying Pathophysiological Disease Processes

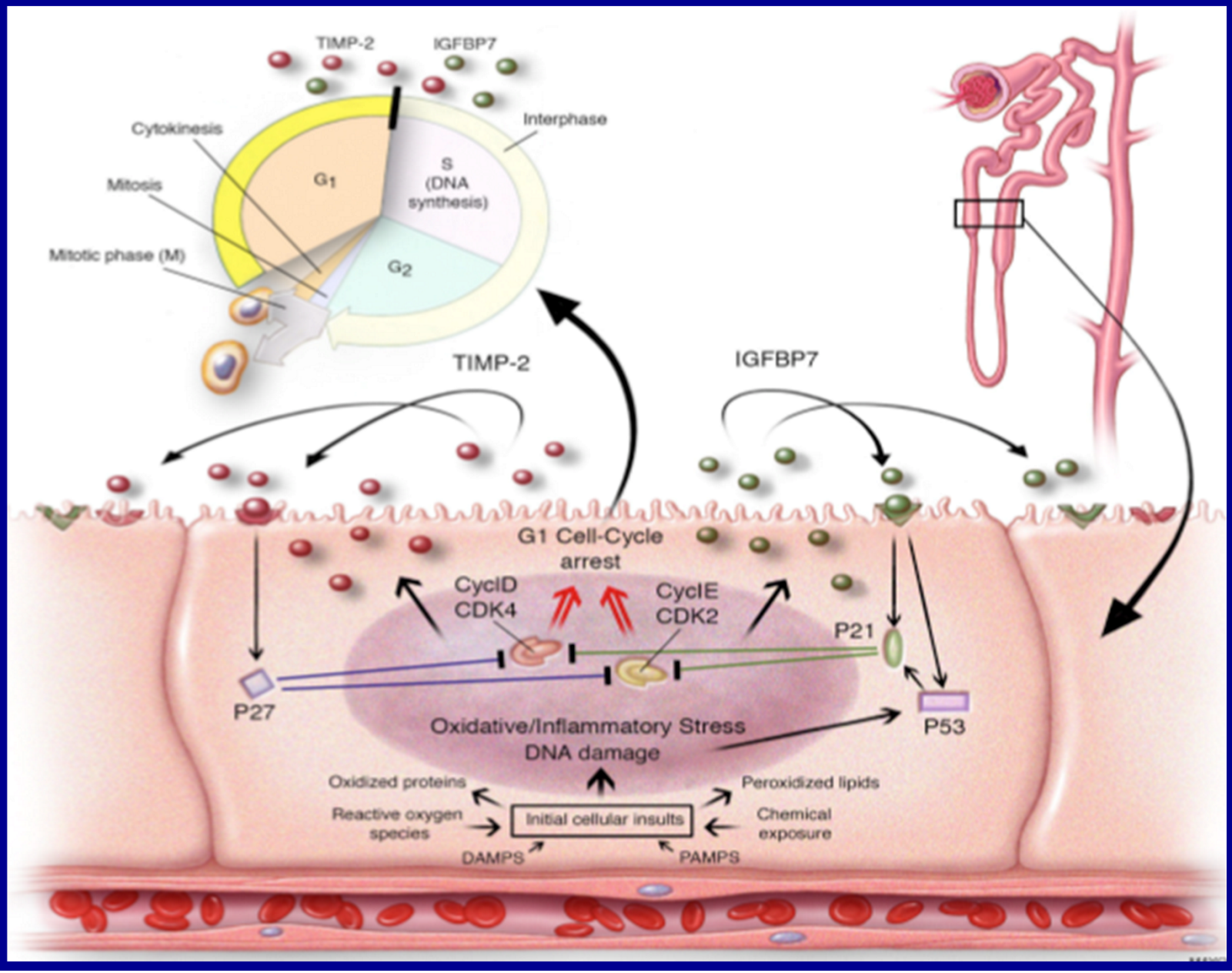
Area under Receiver Operator Curve for Several Biomarkers for Development of KDIGO stage 2 or 3 within 12 hours of Sample Collection



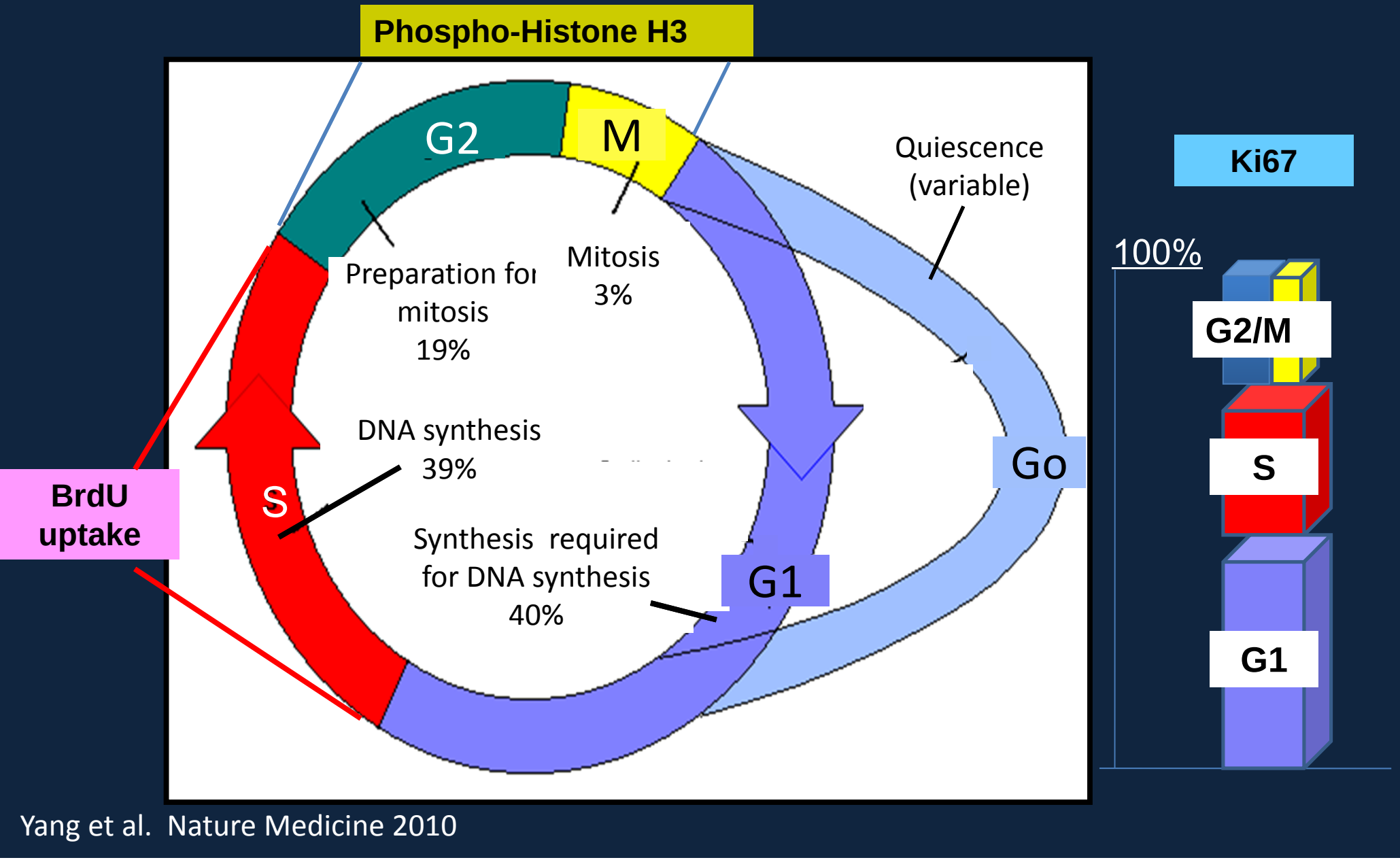
Kashani et al Critical Care 17:R25, 2013

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kashani et al. Critical Care 17:R25, 2013

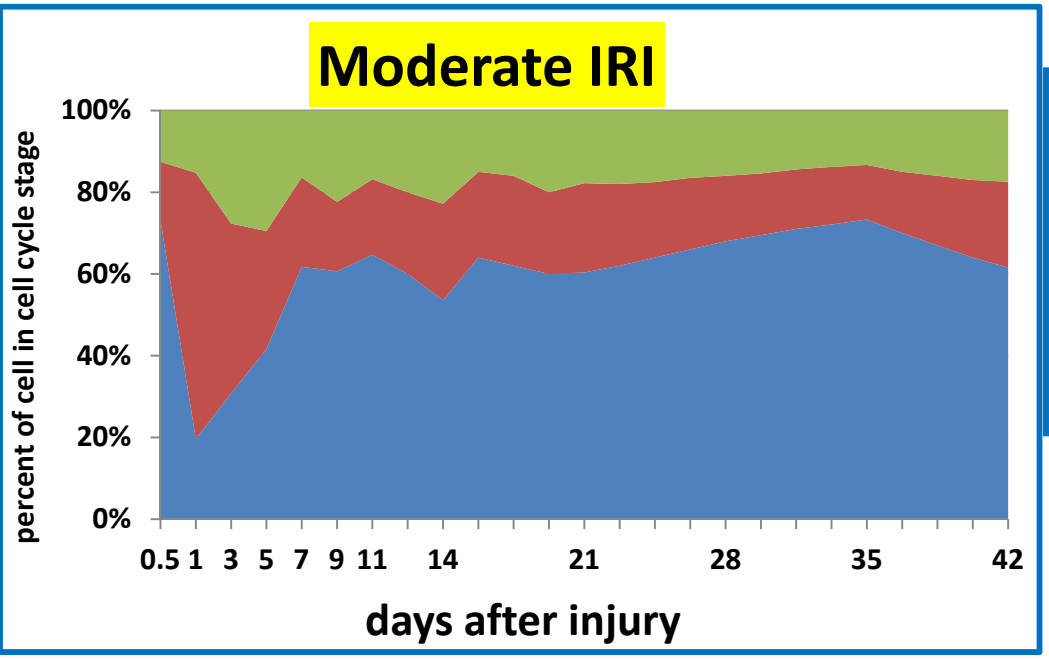


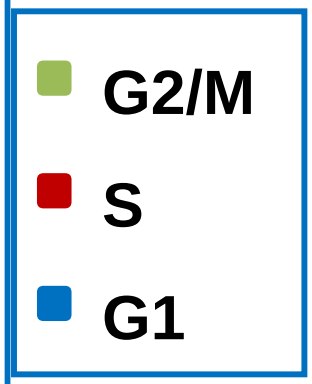
In Vivo Cell Cycle Analysis



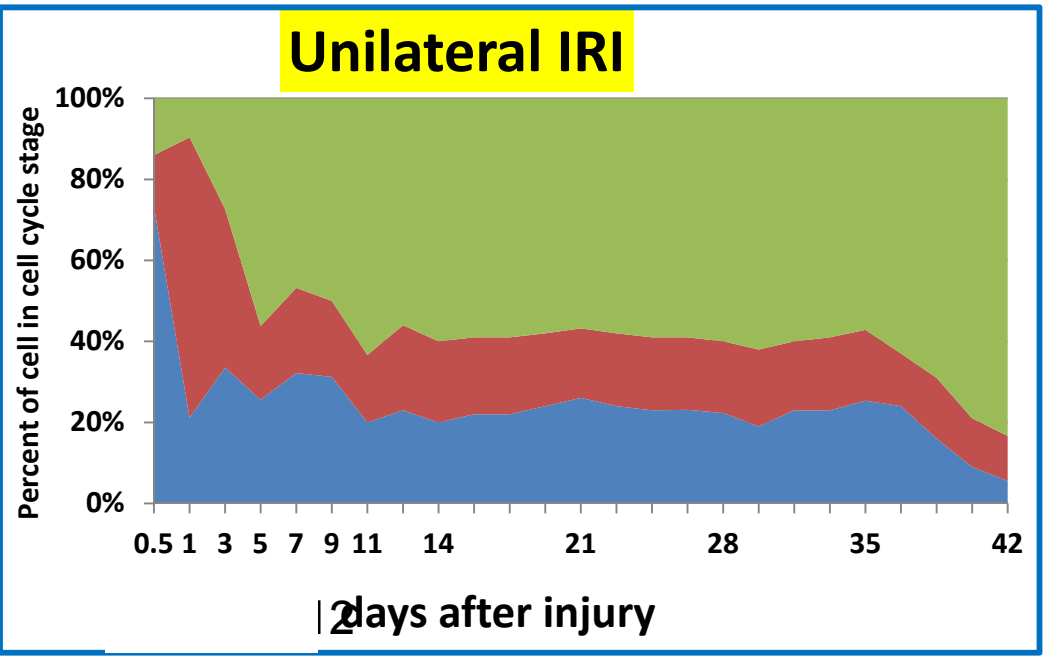
Yang et al. Nature Medicine 2010

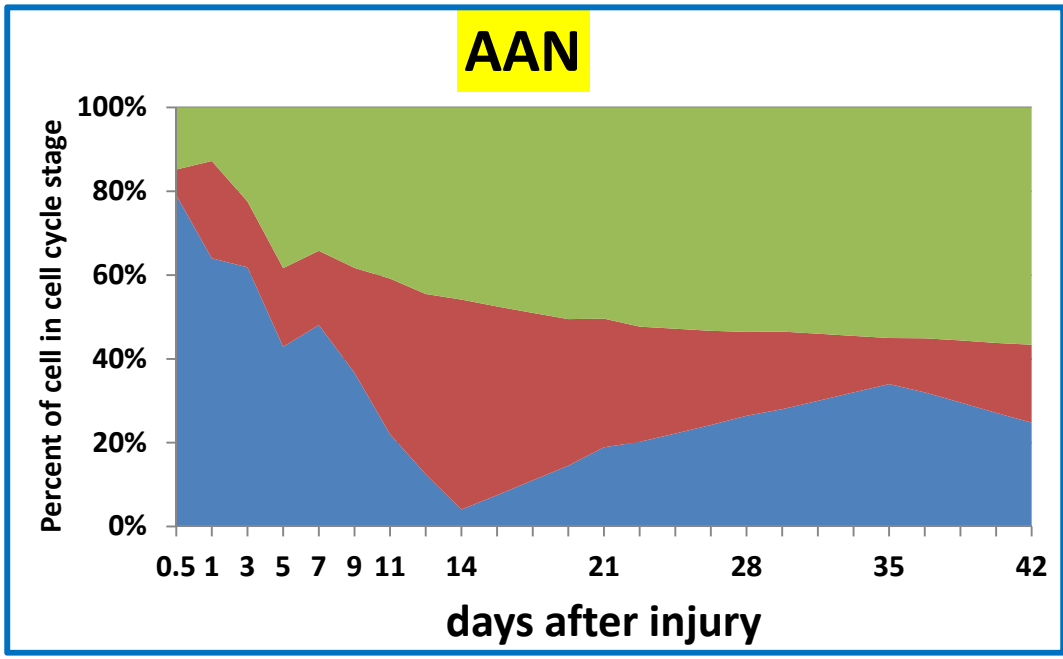
In Vivo Cell Cycle Analysis in AKI



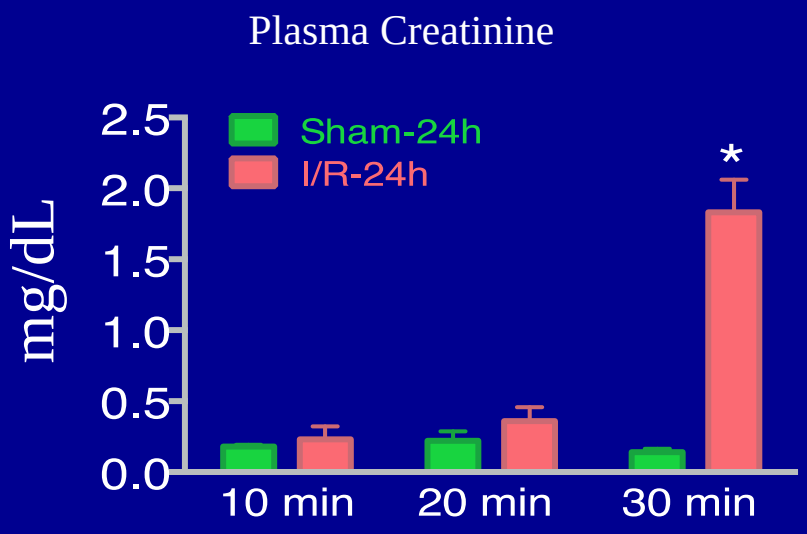


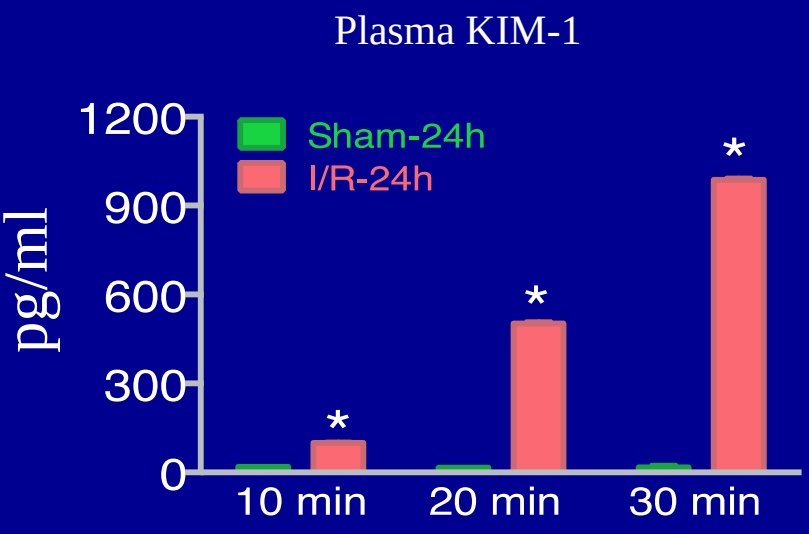
Yang et al. Nature Medicine 2010



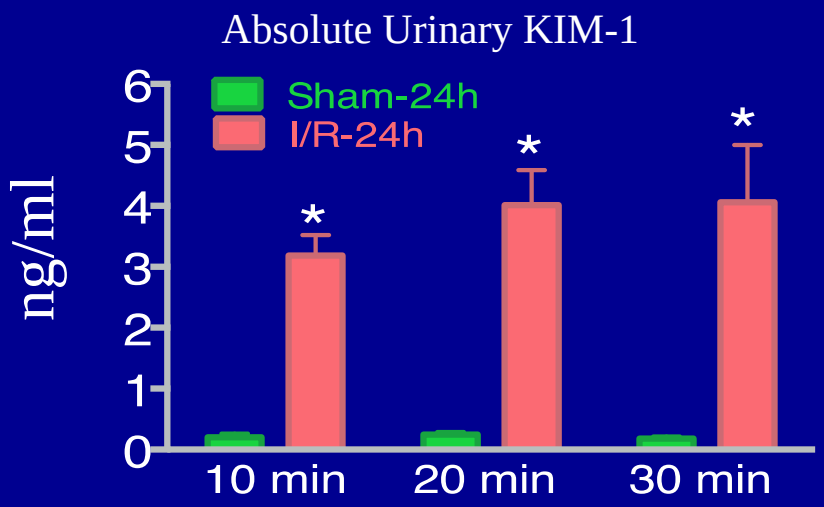


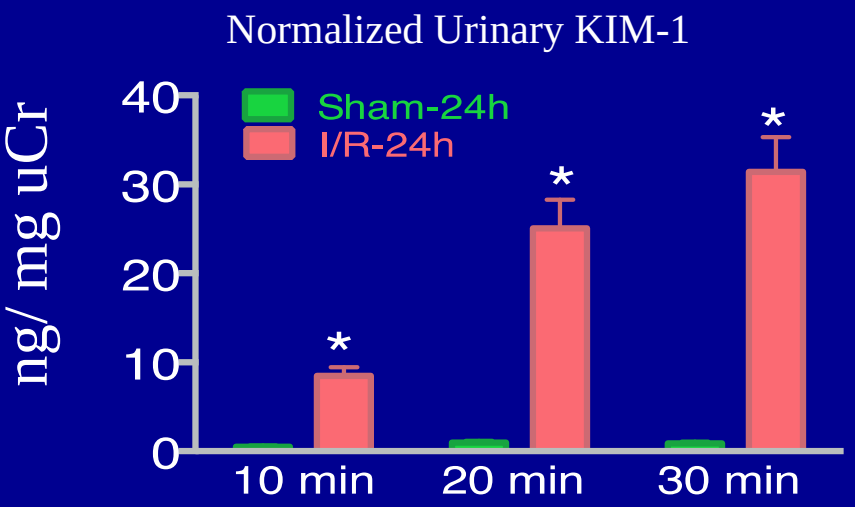
Plasma KIM-1 is elevated in I/R mice



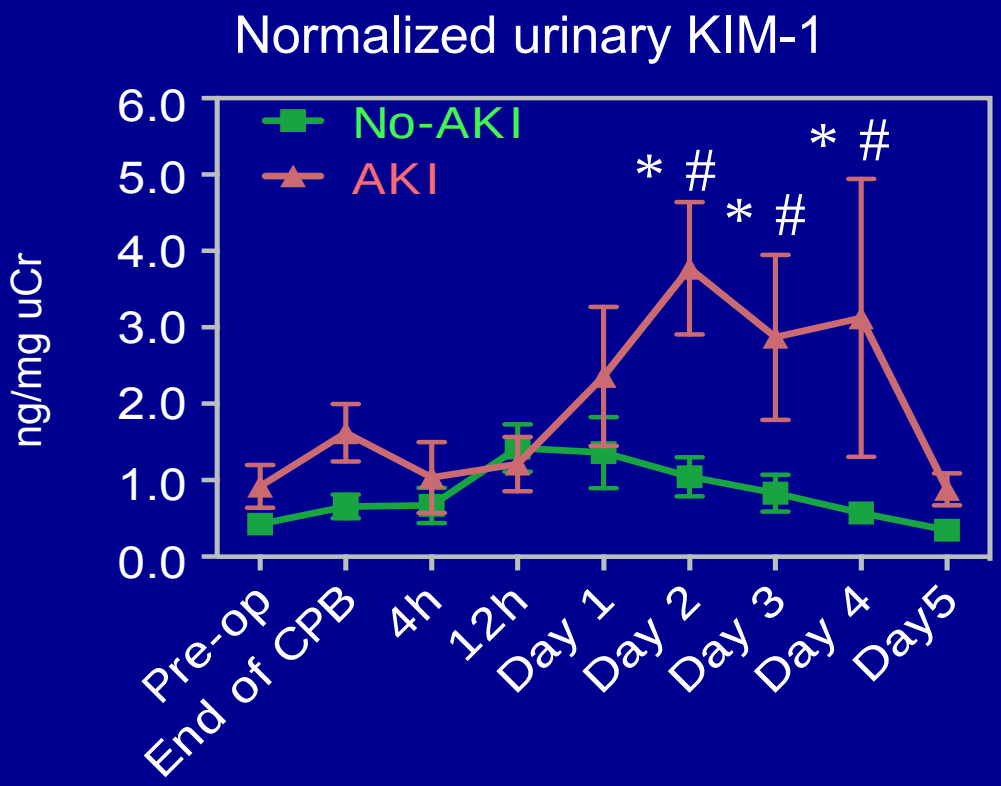


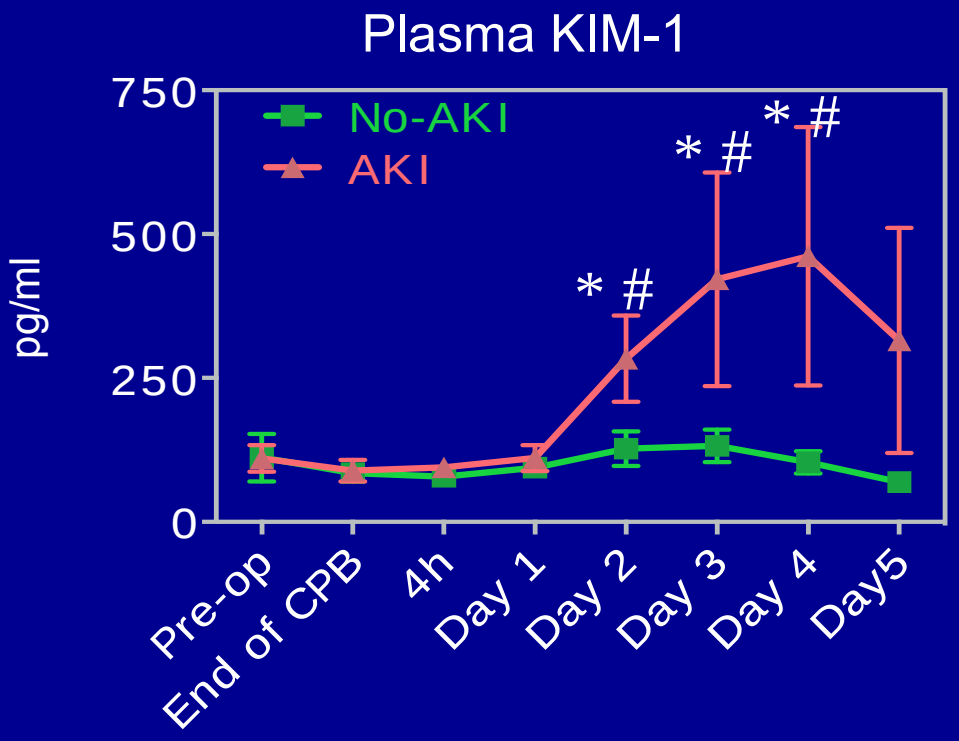
* P<0.001





Elevation of Plasma KIM-1 in patients who developed AKI after CPB





# p<0.05, significant difference from baseline

* p<0.05, significant difference between AKI and non-AKI group (N=9)

How can Novel Biomarkers, assuming they bring new information about Kidney Disease, be a "False Dawn?"

- *Their insight into pathophysiology is unappreciated and unincorporated into our approaches to therapies. How can we ignore new, easy to obtain information about pathophysiology, when we have no therapies???*
- *We do not spend enough effort understanding the origins, specificity and insight into kidney pathobiology they reveal.*
- *We rely on inadequate "gold standards" to validate the biomarker.*
- *In the case of CKD we are likely asking too much of a single biomarker given the complexity of disease process and the multiple factors that affect progression over time.*

Biomarkers Provide Much More Insight Than This

Outline

- AKI Biomarkers
- Lessons Learned from Success in Identification and Qualification of Kidney Biomarkers to Guide Drug Development
- The Gold Standard Problem
- Clinical studies of Biomarkers in AKI
- Challenges with CKD Biomarkers
- Biomarkers provide insight into pathophysiology

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