Utility of Biomarkers for Prognosis in CKD G4+

KDIGO

Lesley Inker
Tufts Medical Center

Disclosure of Interests

- Funding to Tufts Medical Center for research, consulting or contracts with the National Institutes of Health, National Kidney Foundation, Pharmalink AB, Gilead Sciences, Otsuka, Ardea
- Provisional patent [Coresh, Inker and Levey] filed 8/15/2014 –"Precise estimation of glomerular filtration rate from multiple biomarkers" PCT/US2015/044567. The technology is not licensed in whole or in part to any company. Tufts Medical Center, John Hopkins University and Metabolon Inc. have a collaboration agreement to develop a product to estimate GFR from a panel of markers

KDIGO

- Conceptual framework
- GFR and albuminuria
- Other markers
- Where to go from here?

KDIGO

Why do we need biomarkers?

Clinical care

- Inform patients of their risk for significant events (ESRD, CVD, death, etc)
- Help to identify cause, site of damage, mechanism of injury etc
- Inform clinical decisions (access, transplant, and ideally ultimately eligibility for treatments)

Public health

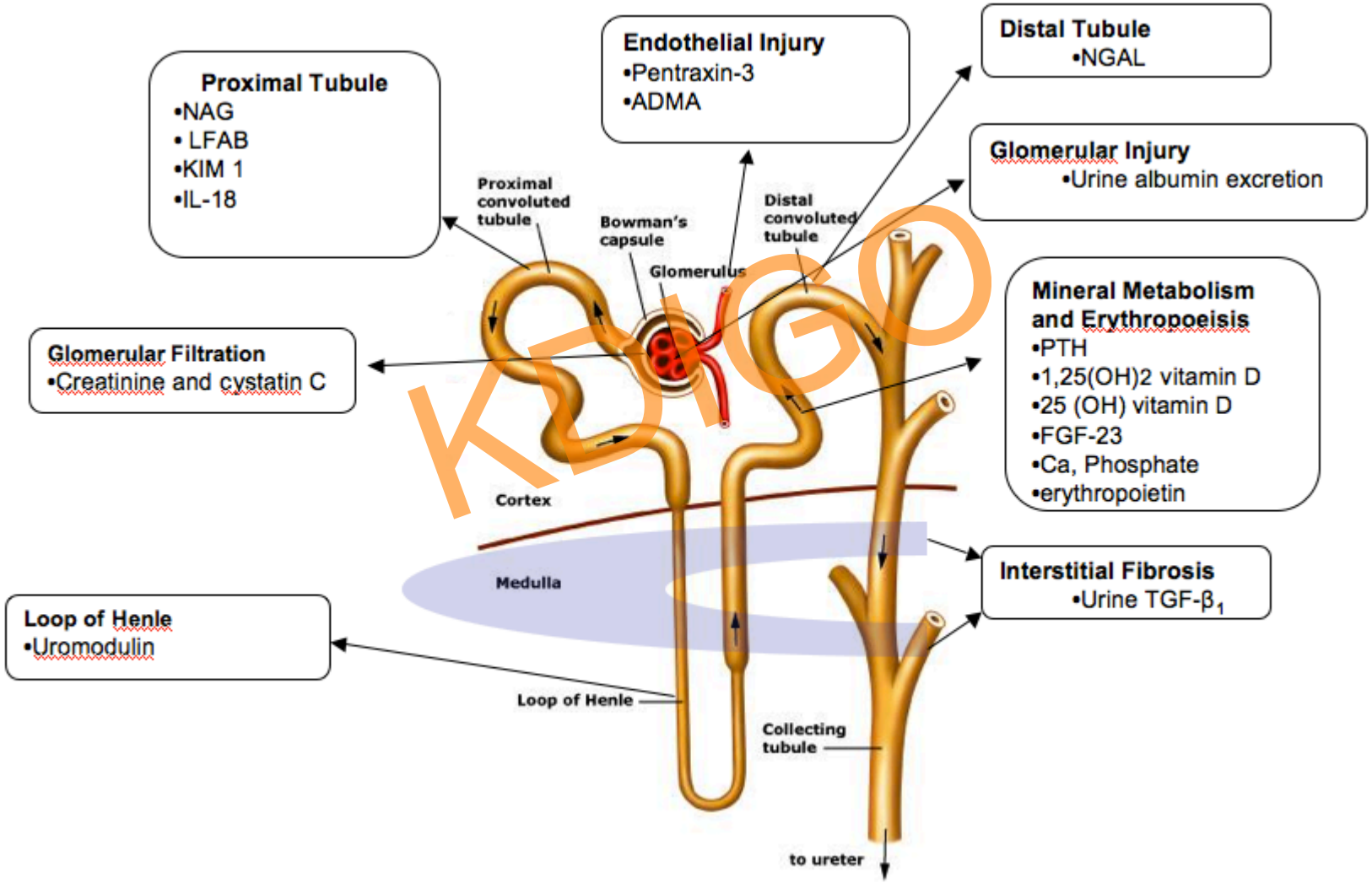
- Identify high risk patients who might benefit from intensive mgmt

Research

- Identify high risk participants for inclusion in trials
- Targets for therapy
  - Identification of pathophysiogical pathways
  - Use as alternative endpoints
- Markers of therapeutic response

KDIGO

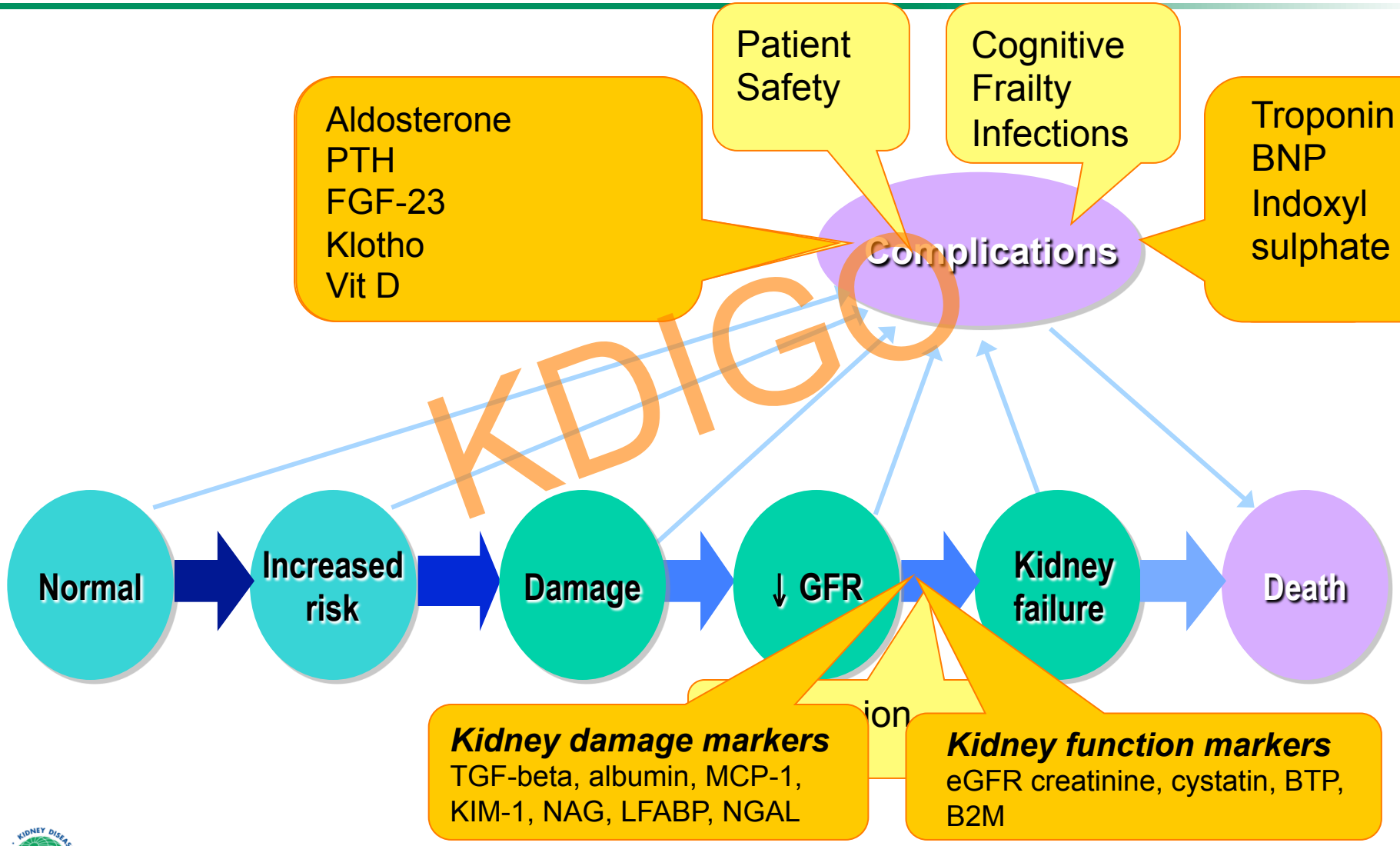
Biomarkers, the nephron, and kidney disease



KDIGO

Courtesy of Mark Sarnak

CKD Outcomes



Can biomarkers improve prognostication in CKD Stage G4+?

Yes (pro)	No (con)
• Higher likelihood of extreme levels of biomarkers	• End stage kidneys act in similar ways and biomarkers wont be able to differentiate future events
• High risk population. Greater number of events within shorter time frames	• High use of medications may effect biomarkers
	• For patients at end stage, age will outweigh any other factors to predict death vs other outcomes

KDIGO

Statistical evaluation of biomarkers

Parameter	Metric	Description
1. Association		
	Odds ratio, relative risk, hazard ratio	Quantifies association between biomarker and outcome
2. Prediction (static and dynamic)		
Discrimination	Sensitivity and specificity	Good separation in risk scores between individuals who will vs will not develop outcomes
	ROC curve, AUC, C-statistic	
Calibration	Homer-Lemeshow	Predicted probabilities match the observed rates of the outcome
Incremental value	NRI	Better or worse reclassification to risk categories
	IDI	Improvement in difference in risk for cases vs risk for controls
3. Clinical use and decision analytics		

KDIGO

Evaluation of biomarkers at Stage G4+

- Populations that are restricted primary to this range of GFR
- Subgroup within larger studies
- Interactions by GFR level

KDIGO

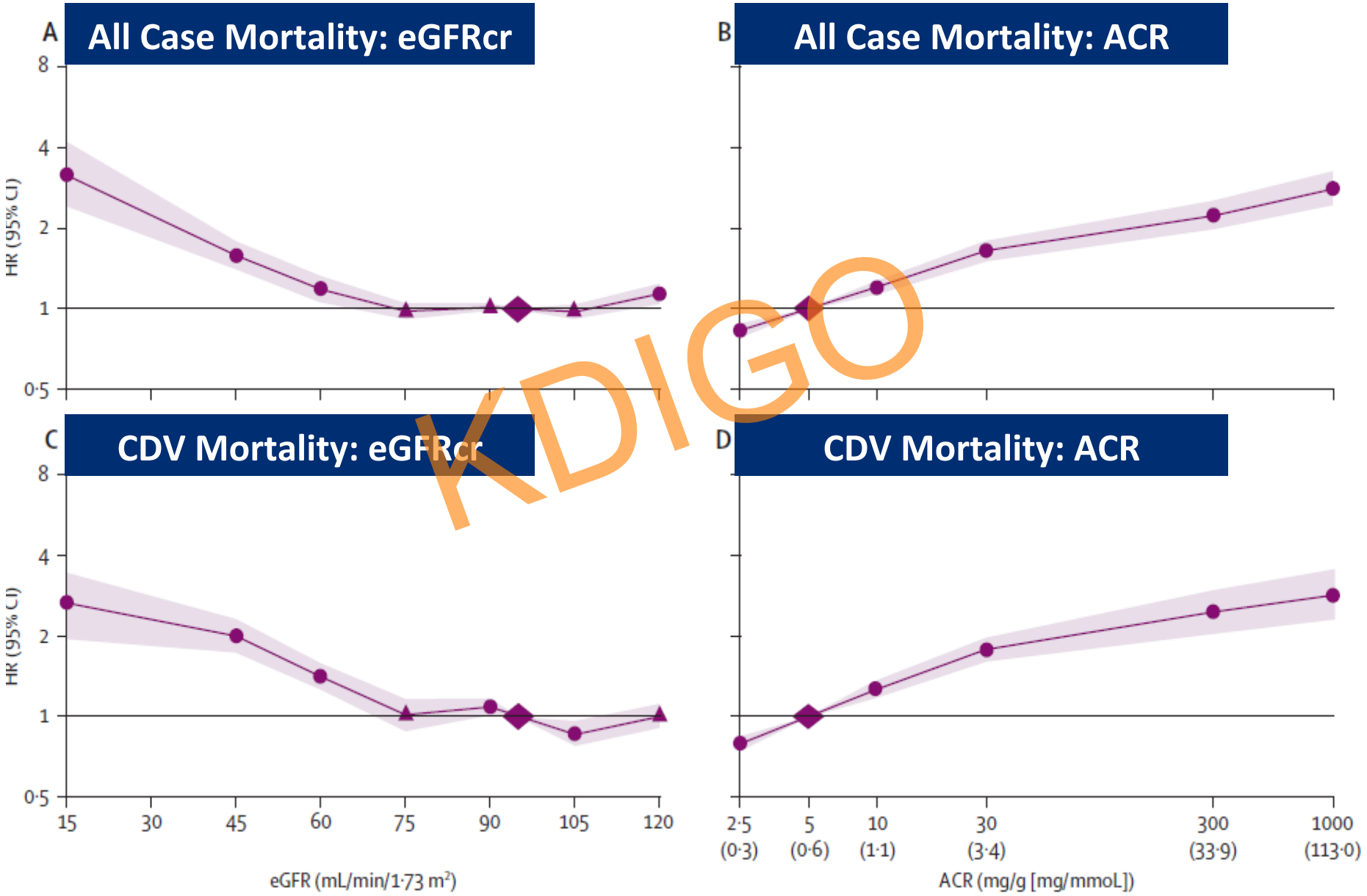
GFR and Albuminuria: Associations and Predictions with ESRD

KDIGO

- Static measurements of GFR and ACR
- Dynamic measurements of GFR
- Novel filtration markers

Risk of all-cause and CVD mortality according to level of eGFR & ACR.

Matsushita K. Lancet. 2010 Jun 12;375(9731):2073-81.



KDIGO

Summary of Hazard ratios from Categorical Meta-Analysis

All-Cause Mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Cardiovascular Mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Kidney Failure (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

Acute Kidney Injury (AKI)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	5.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6.4
eGFR 45-60	2.2	4.9	6.4	5.9
eGFR 30-45	7.3	10	12	20
eGFR 15-30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

KDIGO

A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure

Navdeep Tangri, MD, FRCPC
Lesley A. Stevens, MD, MS, FRCPC
John Griffith, PhD
Hocine Tighiouart, MS
Ognjenka Djurdjev, MSc
David Naimark, MD, FRCPC
Adeera Levin, MD, FRCPC
Andrew S. Levey, MD

Context Chronic kidney disease (CKD) is common. Kidney disease severity can be classified by estimated glomerular filtration rate (GFR) and albuminuria, but more accurate information regarding risk for progression to kidney failure is required for clinical decisions about testing, treatment, and referral.

Objective To develop and validate predictive models for progression of CKD.

Design, Setting, and Participants Development and validation of prediction models using demographic, clinical, and laboratory data from 2 independent Canadian cohorts of patients with CKD stages 3 to 5 (estimated GFR, 10-59 mL/min/1.73 m^2) who were referred to nephrologists between April 1, 2001, and December 31, 2008. Models were developed using Cox proportional hazards regression methods and evaluated using C statistics and integrated discrimination improvement for discrimination, calibration plots and Akaike Information Criterion for goodness of fit, and net reclassification improvement (NRI) at 1, 3, and 5 years.

Main Outcome Measure Kidney failure, defined as need for dialysis or preemptive kidney transplantation.

Results The development and validation cohorts included 3449 patients (386 with kidney failure [11%]) and 4942 patients (1177 with kidney failure [24%]), respectively. The most accurate model included age, sex, estimated GFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin (C statistic, 0.917; 95% confidence interval [CI], 0.901-0.933 in the development cohort and 0.841; 95% CI, 0.825-0.857 in the validation cohort). In the validation cohort, this model was more accurate than a simpler model that included age, sex, estimated GFR, and albuminuria (integrated discrimination improvement, 3.2%; 95% CI, 2.4%-4.2%; calibration [Nam and

KDIGO

An estimated 23 million people in the United States (11.5% of the adult population) have chronic kidney disease (CKD) and are at increased risk for cardiovascular events and progression to kidney failure.[1-5] Similar estimates of burden of disease have been reported around the world.[6] Although there are proven therapies to improve outcomes in patients with progressive kidney disease, these therapies may also

Original Investigation

Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure
A Meta-analysis

Navdeep Tangri, MD, PhD, FRCPC; Morgan E. Grams, MD, PhD; Andrew S. Levey, MD; Josef Coresh, MD, PhD; Lawrence J. Appel, MD; Brad C. Astor, PhD, MPH; Gabriel Chodick, PhD; Allan J. Collins, MD; Ognjenka Djurdjev, MSc; C. Raina Elley, MBCHB, PhD; Marie Evans, MD, PhD; Amit X. Garg, MD, PhD; Stein I. Hallan, MD, PhD; Lesley A. Inker, MD, MS; Sadayoshi Ito, MD, PhD; Sun Ha Jee, PhD; Csaba P. Kovesdy, MD; Florian Kronenberg, MD; Hiddo J. Lambers Heerspink, PharmD, PhD; Angharad Marks, MBBCh, MRCP, MSc, PhD; Girish N. Nadkarni, MD, MPH; Sankar D. Navaneethan, MD, MPH; Robert G. Nelson, MD, PhD; Stephanie Titze, MD, MSc; Mark J. Sarnak, MD, MS; Benedicte Stengel, MD, PhD; Mark Woodward, PhD; Kunitoshi Iseki, MD, PhD; for the CKD Prognosis Consortium

KDIGO

Supplemental content at

Thirty one cohorts, including 721,357 participants with CKD Stages 3 to 5 in more than 30 countries spanning 4 continents, and showed that "The original KFREs accurately predict the risk of progression from CKD Stages 3-5 to kidney failure in a diverse group of patients with CKD"

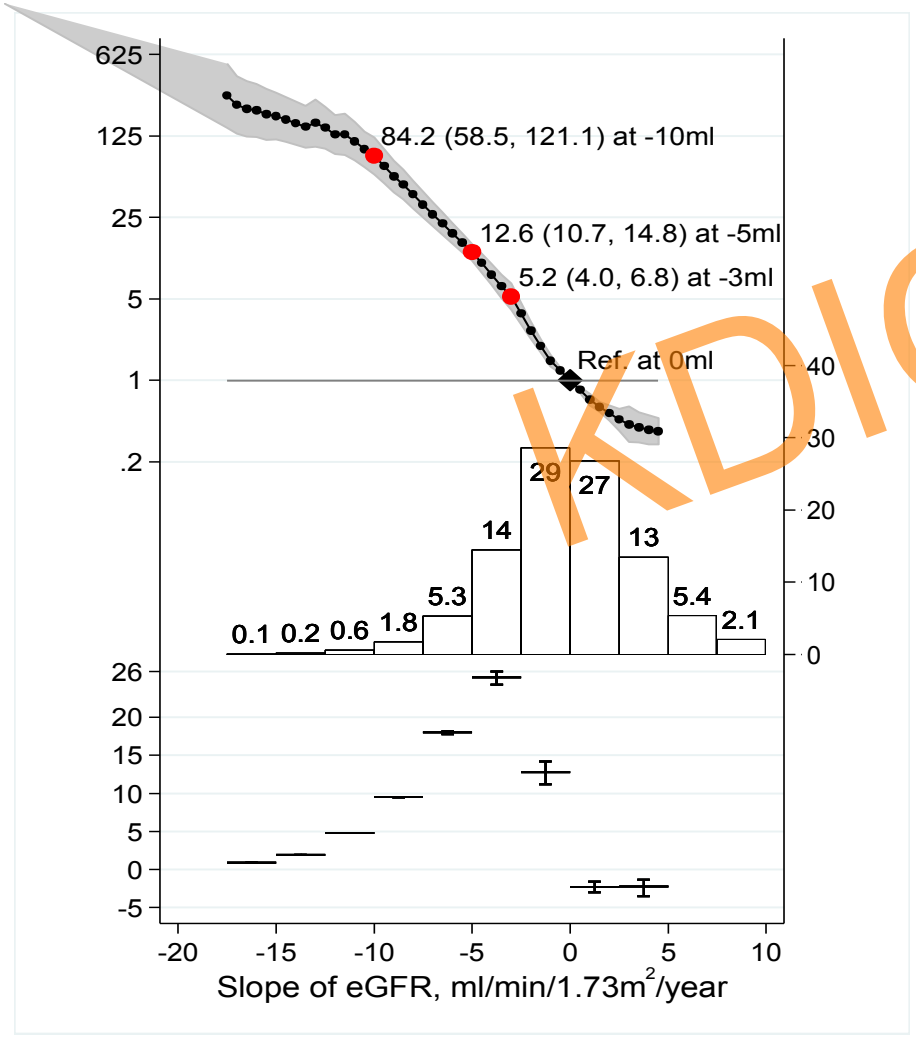
STUDY SELECTION Cohorts participating in the CKD Prognosis Consortium with data on end-stage renal disease.

DATA EXTRACTION AND SYNTHESIS Data were obtained and statistical analyses were

Effect of time of adjusted GFR on associations of change in GFR over 3 years with subsequent development of ESRD

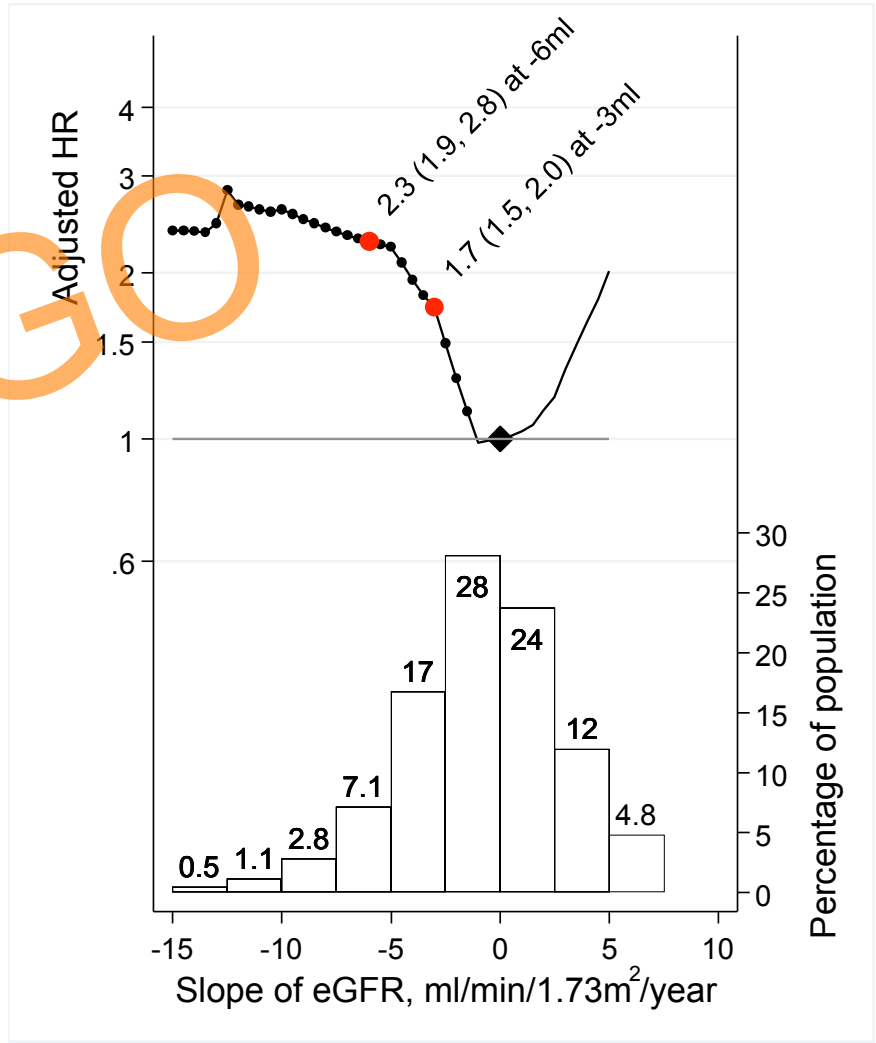
Adjustment for FIRST GFR
GFR < 60

Coresh et al. JAMA. 2014



Adjustment for LAST GFR
CKD cohorts

Kovesdy et al. JASN. 2015



KDIGO

A Dynamic Predictive Model for Progression of CKD

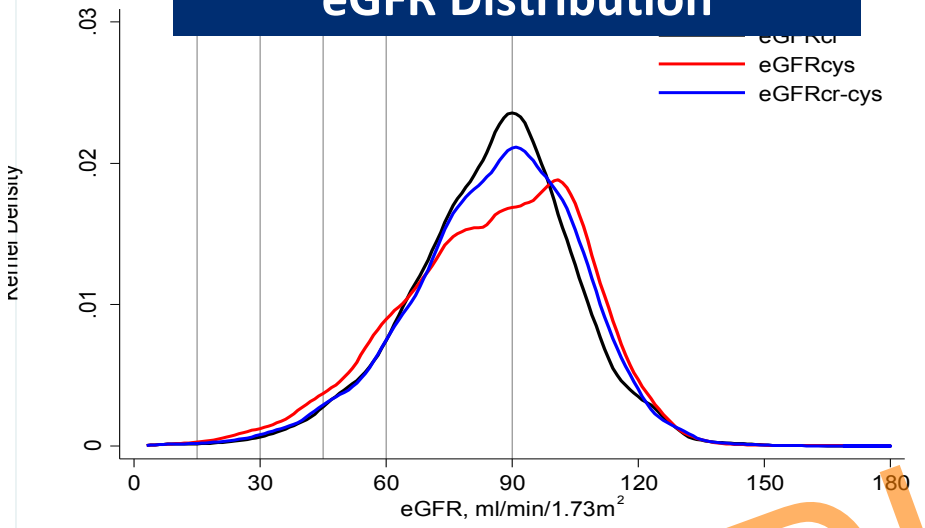
Variable	Baseline Static Model Hazard ratio (95% CI)	All Visits Dynamic Model Hazard ratio (95% CI)
eGFR	0.65(0.62 - 0.69)	0.44(0.41 - 0.48)
Log Urine ACR	1.45(1.32 - 1.58)	1.30(1.19 - 1.43)
Age (per 10 yrs)	0.86(0.80 - 0.92)	0.86(0.80 - 0.93)
Male sex	1.29(1.03 - 1.61)	1.09(0.87 - 1.36)
Albumin (per 5 g/L)	0.87(0.78 - 0.98)	0.98(0.87 - 1.10)
Phosphate (per 1.0 mg/dL)	2.03(1.52 - 2.72)	1.05(0.78 - 1.42)
Bicarbonate (per 1.0 mEq/L)	0.95(0.92 - 0.98)	0.98(0.95 - 1.01)
Calcium (per 1.0 mg/dL)	0.86(0.76 - 0.97)	0.88(0.77 - 1.00)
C Statistic	0.90 (0.88, 0.92)	0.91 (0.89, 0.93)
AIC*	4092	3795
IDI (95% CI)*	N/A	1.39% (1.23%, 1.56%)
NRI (95% CI)*	N/A	18.29% (12.64%, 23.93%)

KDIGO

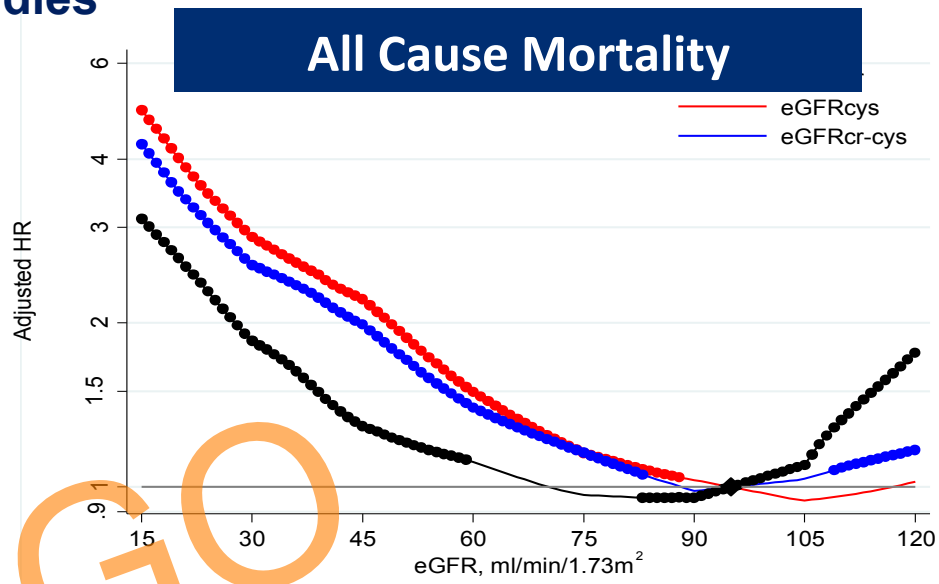
Tangri N, Inker LA, Heibert B, et al. (2016). A Dynamic Predictive Model for Progression of Chronic Kidney Disease. AJKD in press

Risk Relationships for eGFRcr, eGFRcys and eGFRcrcys in General Population Studies

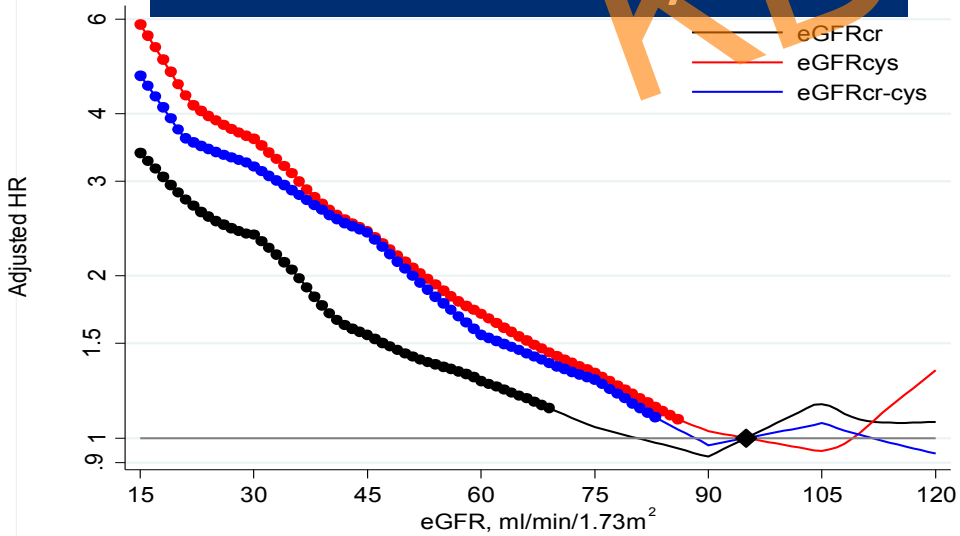
eGFR Distribution



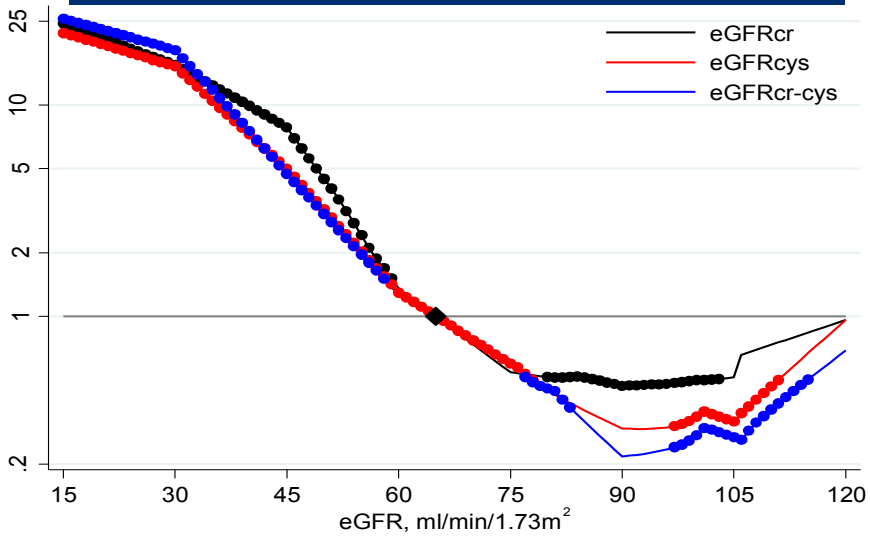
All Cause Mortality



CVD Mortality



ESRD



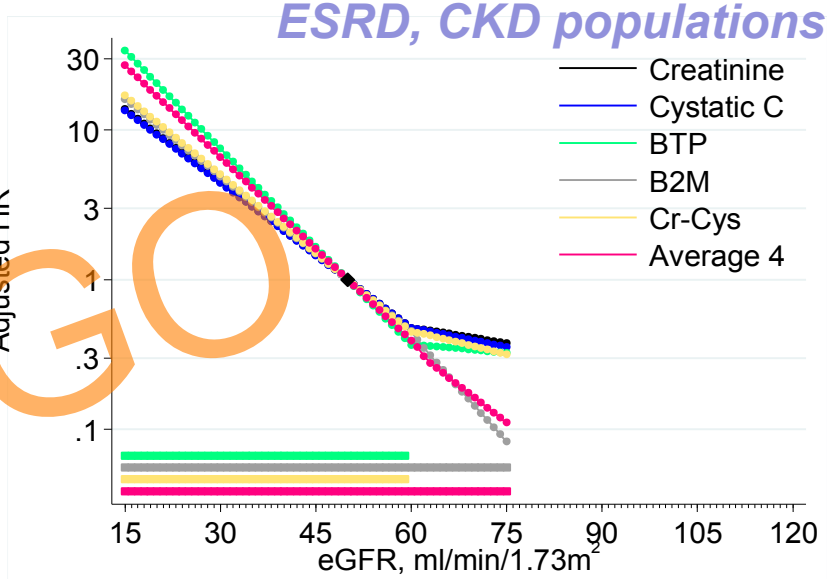
KDIGO

N = 90,750 participants in 11 cohorts, Shlipak NEJM 2013

Filtration markers as predictors of end-stage renal disease and mortality – meta-analysis

Lesley Inker, Josef Coresh, Yingying Sang et al for the CKD Biomarkers Consortium. CJASN in press

- Individual patient meta-analysis of 3 general population or high risk cohorts (**N=17903,** *ARIC, NHANES, Pima*) and 3 CKD studies (**N=5415**,*MDRD, AASK and CRIC)*
- Compared associations and risk prediction for eGFR from BTP, B2M, Cys and combinations compared to creatinine for ESRD and death



KDIGO

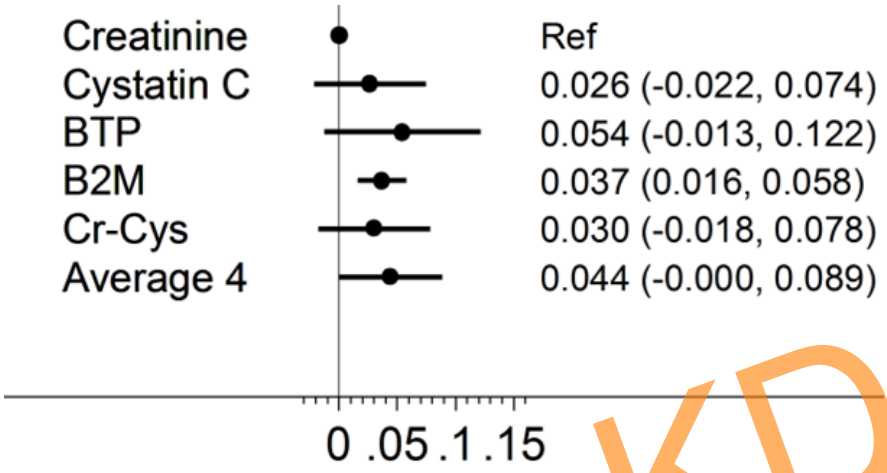
	Creatinine	Cystatin C	BTP	B2M	All 4 markers
45-59	Ref	Ref	Ref	Ref	Ref
30-44	2.12 (1.80, 2.50)	1.94 (1.30, 2.90)	1.92 (1.17, 3.13)	2.26 (1.66, 3.08)	2.36 (1.44, 3.88)
15-29	4.67 (3.37, 6.48)	5.18 (3.37, 7.97)	5.22 (2.89, 9.45)	5.47 (3.38, 8.86)	6.83 (3.83, 12.18)
<15	14.62 (6.99, 30.55)	9.84 (4.25, 22.78)	49.82 (6.34, 391.36)	14.00 (8.37, 23.43)	18.69 (3.59, 97.25)

Incremental predication of novel filtration markers

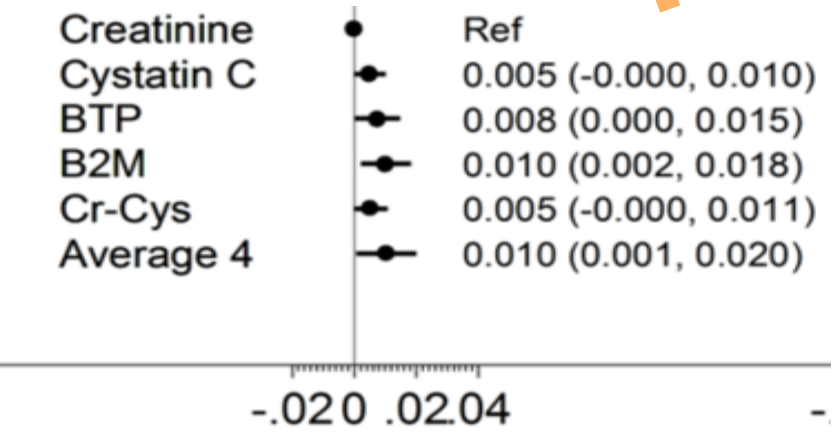
eGFRcr alone

Change in c-statistic

Base model c-statistic 0.824

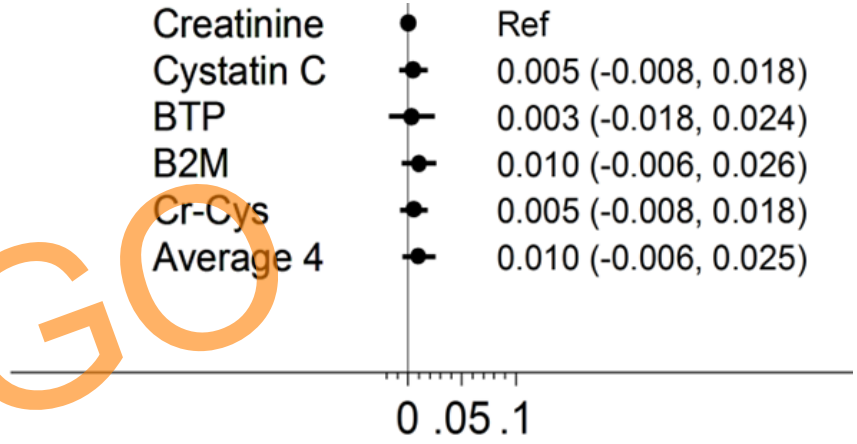


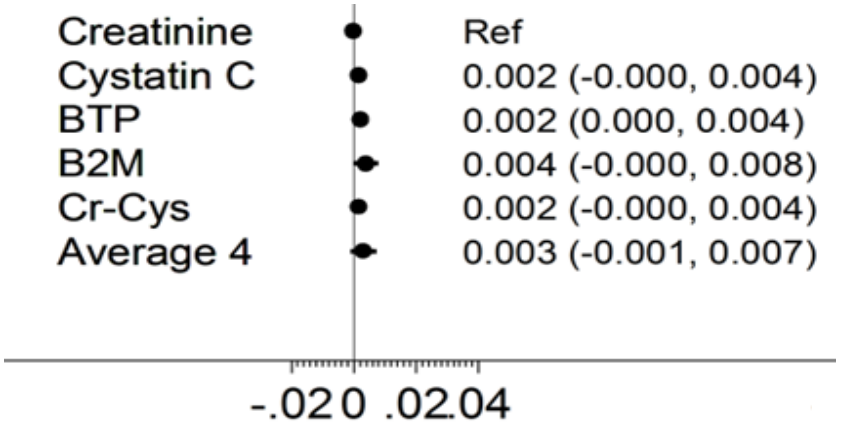
Net reclassification index



eGFRcr and Albuminuria

Base model c-statistic 0.856





KDIGO

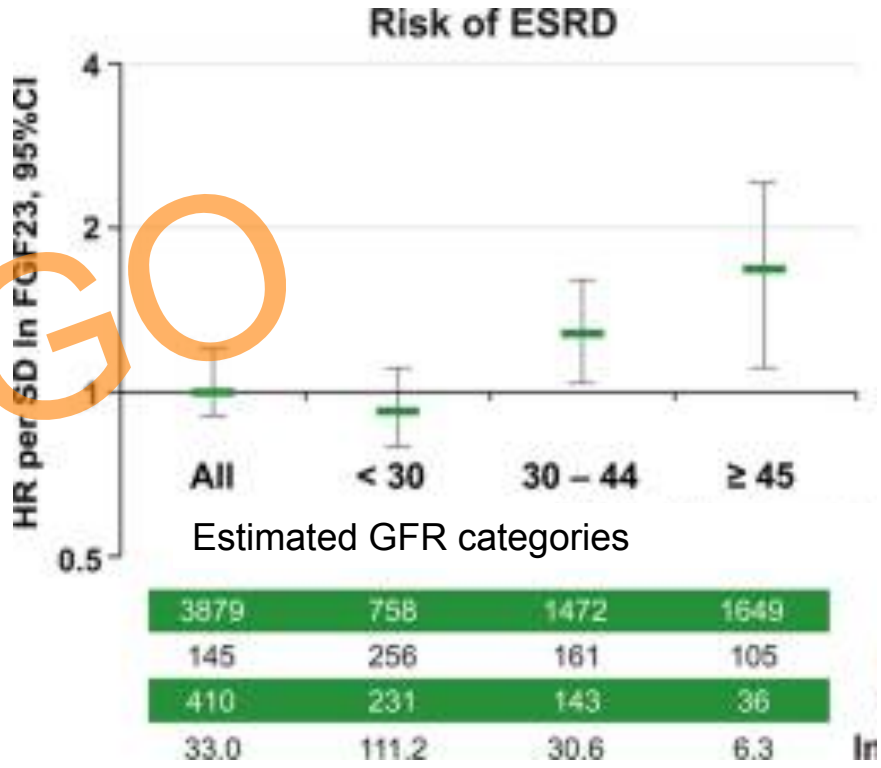
Base model includes eGFRcr, age, sex, race, SBP, diabetes, CRP, smoking, CVD, For NRI, risk cutoffs at 1 year of 1% and 10% and 5% and 40% at 5 years

- Examples of other biomarkers in CKD Stage 4+
  - FGF-23
  - KIM-1
  - suPAR

KDIGO

Associations of FGF -23 with ESRD in CRIC by Quartile

	Hazard Ratio (95% CI)	
	Unadjusted	+eGFR and ACR
1	1 [Reference]	1 [Reference]
2	**2.5 (1.6-4.0)**	1.2 (0.8-2.0)
3	**5.5 (3.6-8.4)**	1.4 (0.9-2.2)
4	**10.1 (6.7-15.2)**	1.3 (0.8-2.1)



KDIGO

Model 2 adjusts for covariates in model 1 plus estimated glomerular filtration rate, natural log-transformed urine albumin-to-creatinine ratio, serum albumin, and hemoglobin.

Isakova T et al. JAMA. Jun 2011; 305(23): 2435.

KIM-1: Marker of tubular damage

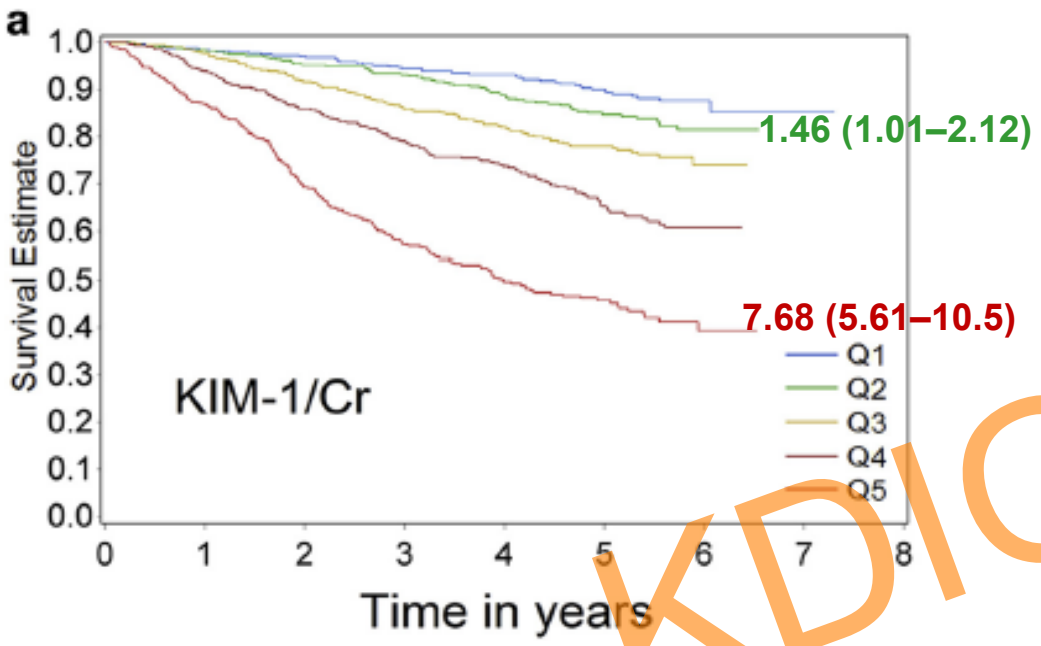
	ACR < 30	ACR 30 – 299	ACR ≥ 300
eGFR ≥ 90	615 (162 – 1701)	941 (229 – 3896)	870 (291 – 2881)
eGFR 60-89	804 (289 – 1779)	995 (357 – 2278)	1197 (442 – 2403)
eGFR 45-59	912 (305 – 2130)	1127 (398 – 2966)	1762 (689 – 3394)
eGFR 30-44	1035 (307 – 2672)	1230 (489 – 3529)	1853 (668 – 4391)
eGFR 15-29	1477 (447 – 2844)	1874 (541 – 4957)	2031 (758 – 5123)
eGFR < 15	1334 (432 – 2504)	1154 (447 – 8157)	1596 (460 – 9160)

KDIGO

Median (10^{th}-90^{th} percentiles) levels of urinary KIM-1 in the five cohorts [Atherosclerosis Risk in Communities (ARIC); Chronic Renal Insufficiency Cohort (CRIC); Pima Indian Cohort (PIMA); Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS); Uppsala Longitudinal Study of Adult Men (ULSAM)]

Waikar et al NDT 2016

Urine KIM-1and Risk of ESRD

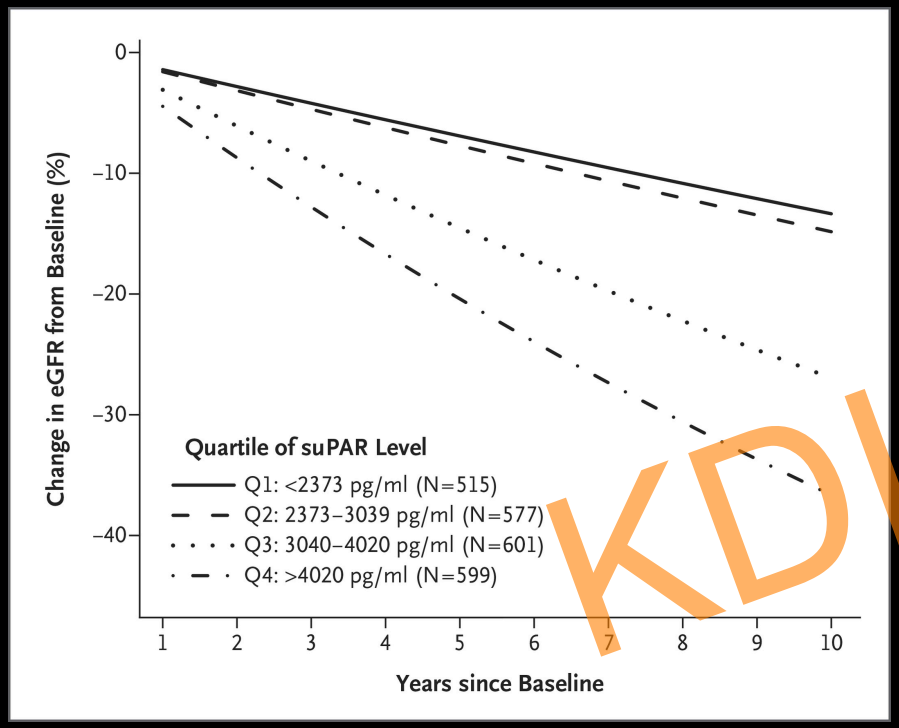


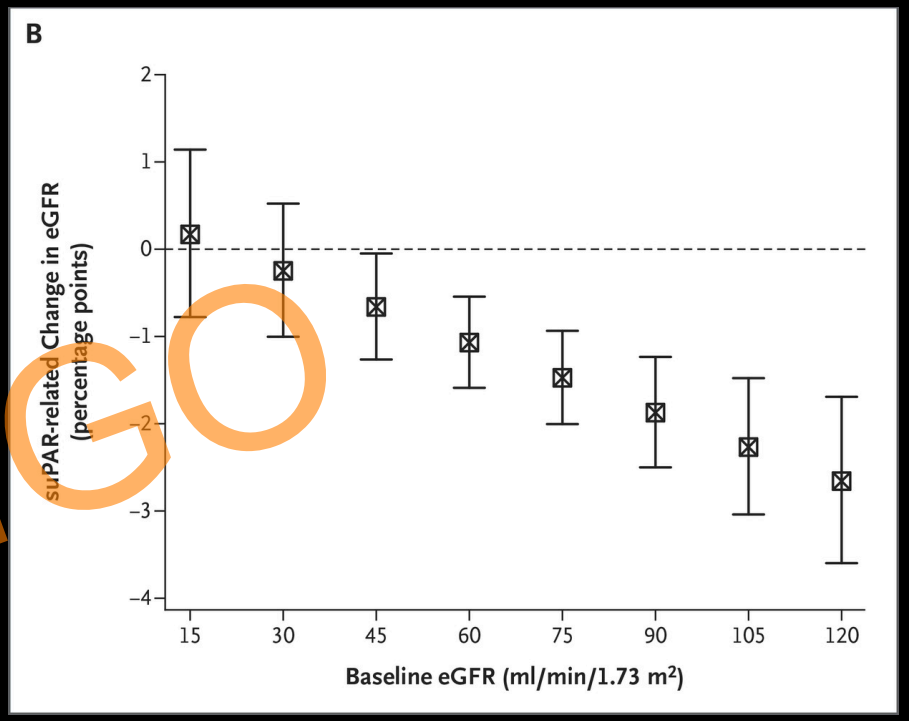
Model	C-stat
Base Clinical Model	0.890
Base Clinical + KIM-1/Cr	0.890

KDIGO

Kim/Cr (ng/g)	Unadjusted	Adjusted for ACR and eGFR
≤661	Ref	Ref
>661-1112	1.46 (1.01-2.12)	0.98 (0.67-1.43)
>1112-1831	2.24 (1.59-3.17)	1.10 (0.76-1.58)
>1831-2990	3.76 (2.72-5.21)	1.19 (0.83-1.70)
>2990	7.68 (5.61-10.5)	1.30 (0.89-1.89)

Levels of suPAR and Decline in the eGFR Emory Cardiovascular Biobank Cohort (mean GFR 73)





KDIGO

suPAR, soluble urokinase-type plasminogen activator receptor

Hayek SS et al. N Engl J Med 2015;373:1916-1925

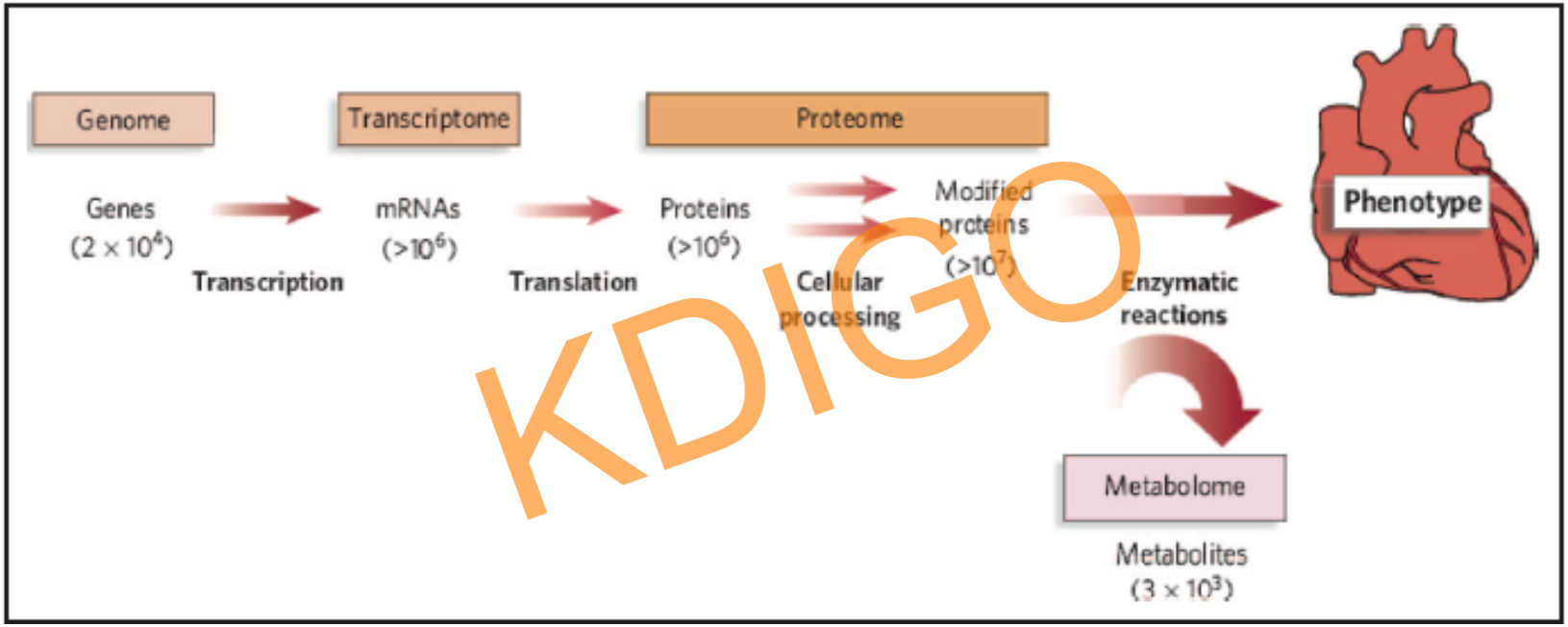
The NEW ENGLAND JOURNAL of MEDICINE

Where do we go from here?

KDIGO

1. Evaluate current markers in the right populations
2. Evaluate current markers using the right outcomes, appropriate for the biomarker
3. New biomarkers

Methods to identify new biomarkers



KDIGO

Rhee et al. Clin Chem. Jan 2012; 58(1): 140

Metabolites significantly associated with annual eGFRcr change and incident CKD in the KORA study between visits S4 and F4

Metabolite	Annual eGFRcr Change			Incident CKD (*n*=95 cases)		
	n	Direction	*P* Value	*n*	Direction	*P* Value
C-mannosyltryptophan	985	+	8.7E-06	920	+	1.1E-03
Pseudouridine	989	+	1.3E-05	924	+	3.7E-03
O-sulfo-L-tyrosine	987	+	6.8E-05	922	+	1.4E-02

KDIGO

- A positive direction in eGFRcr change denotes a decline of kidney function over time per unit increase in metabolite concentration and a positive association with incident CKD with higher odds of CKD.

Sekula Goek,Quaye et al JASN 2016

Summary

- Biomarkers can have utility in CKD, for prognosis as well as other uses
- Current biomarkers do not appear to outperform GFR and ACR for prediction of kidney failure, but might be helpful for identifying cause, mechanisms, intercurrent episodes injury or specific clinical decisions making
- For CKD Stage G4+, there have been insufficient studies for many biomarkers, perhaps due to insufficient large populations
- Future success depends upon having large cohorts, with detailed clinical and outcome data, as well as better biomarkers

KDIGO