SYDPATH
ST VINCENT'S PATHOLOGY

ST VINCENT'S HOSPITAL
SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Creatinine and Chronic Kidney Disease

Graham Jones
Department of Chemical Pathology
St Vincent's Hospital, Sydney

JCTLM Members and Stakeholders Meeting, Dec 4th 2013

Outline

- Kidney Function
- Kidney Disease
- Diagnosis / monitoring
  - Evidence
  - Implementation
- Role of GFR
- Role of creatinine

Functions of the Kidney

- Waste removal / homeostasis
  - Water
  - Electrolytes / hydrogen ions
  - Nitrogen
- Endocrine
  - Vitamin D 1-hydroxylation
  - Erythropoetin
  - Renin
- Drug removal
- Metabolic

Functions of the Kidney

- Waste removal / homeostasis
  - Water **– fluid overload***
  - Electrolytes / hydrogen ions **– acidosis***
  - Nitrogen **– azotaemia*, f**
- Endocrine
  - Vitamin D 1-hy **– hypocalcaemia***
  - Erythropo **mia***
  - Reni
- Drug **al – drug toxicity**
- Metabolic

Not Used For Diagnosis

*** laboratory diagnosis**

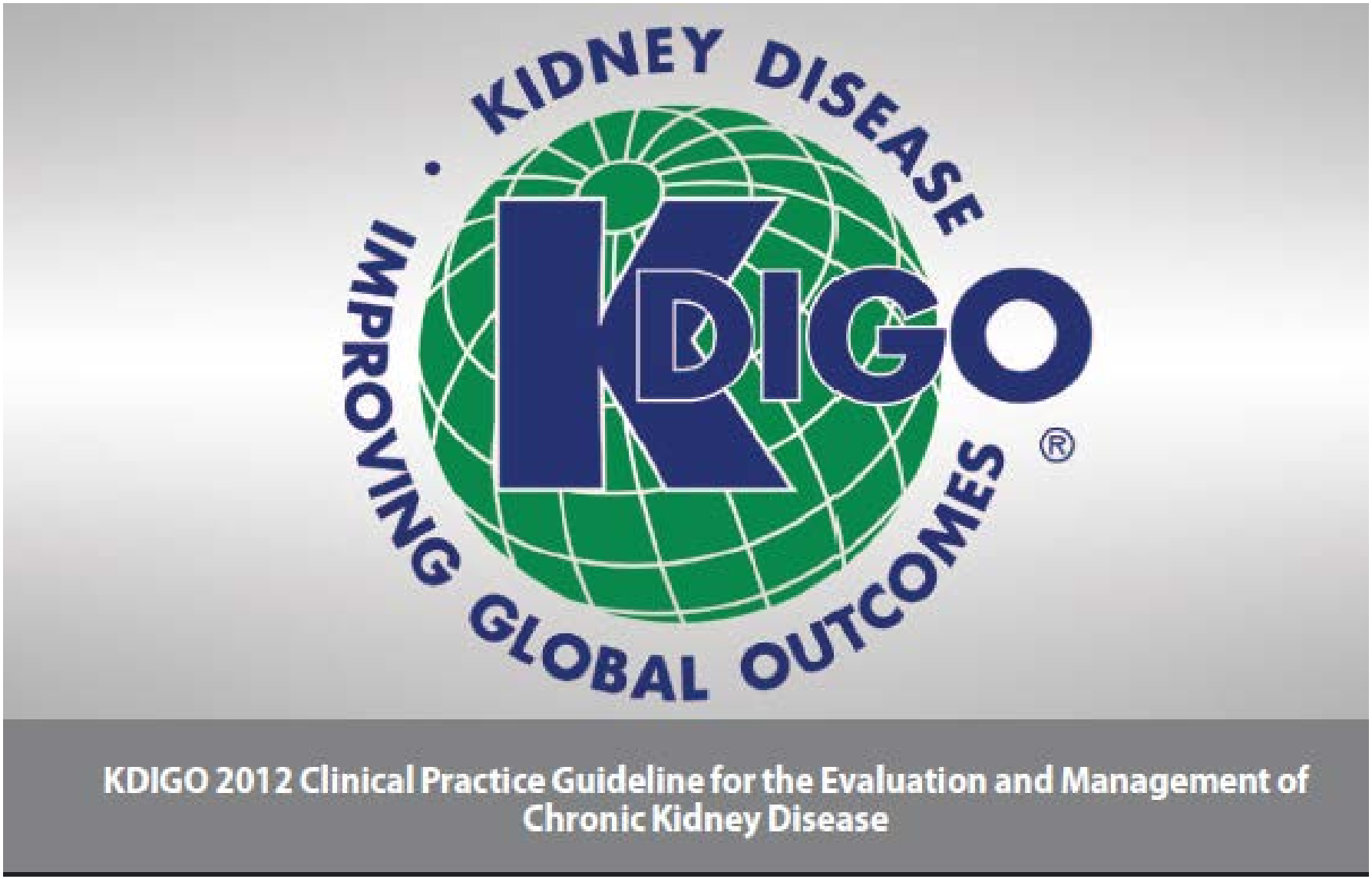
Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ 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)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months.

K/DOQI 2002 (USA)

International Guidelines



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	A2	A3
				Normal to mildly increased	Moderately increased	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			

markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

GFR Grading (mL/min/1.73m^2)

GFR categories (ml/min/ 1.73 m^2) Description and range	Code	Terminology	Definition
	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

Laboratory diagnosis

Albuminuria grading

Persistent albuminuria categories Description and range		
A1	**A2**	**A3**
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol

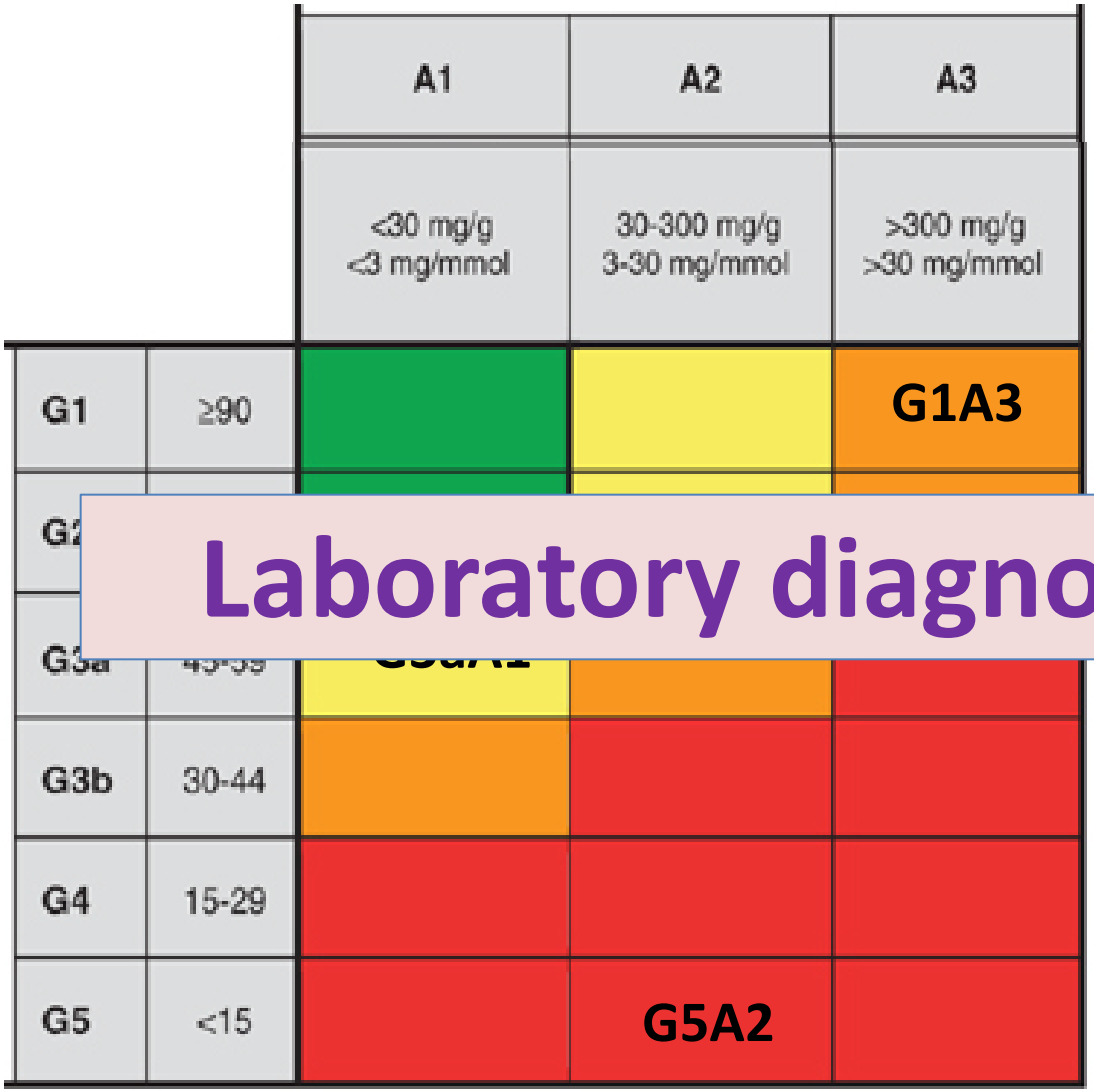
Code

Terminology

Definition

Laboratory diagnosis

“Heat Map”



Laboratory diagnosis

Diagnosis and Classification

- Global uniformity
- Clinical Trials
- Prevalence data

Risk prediction

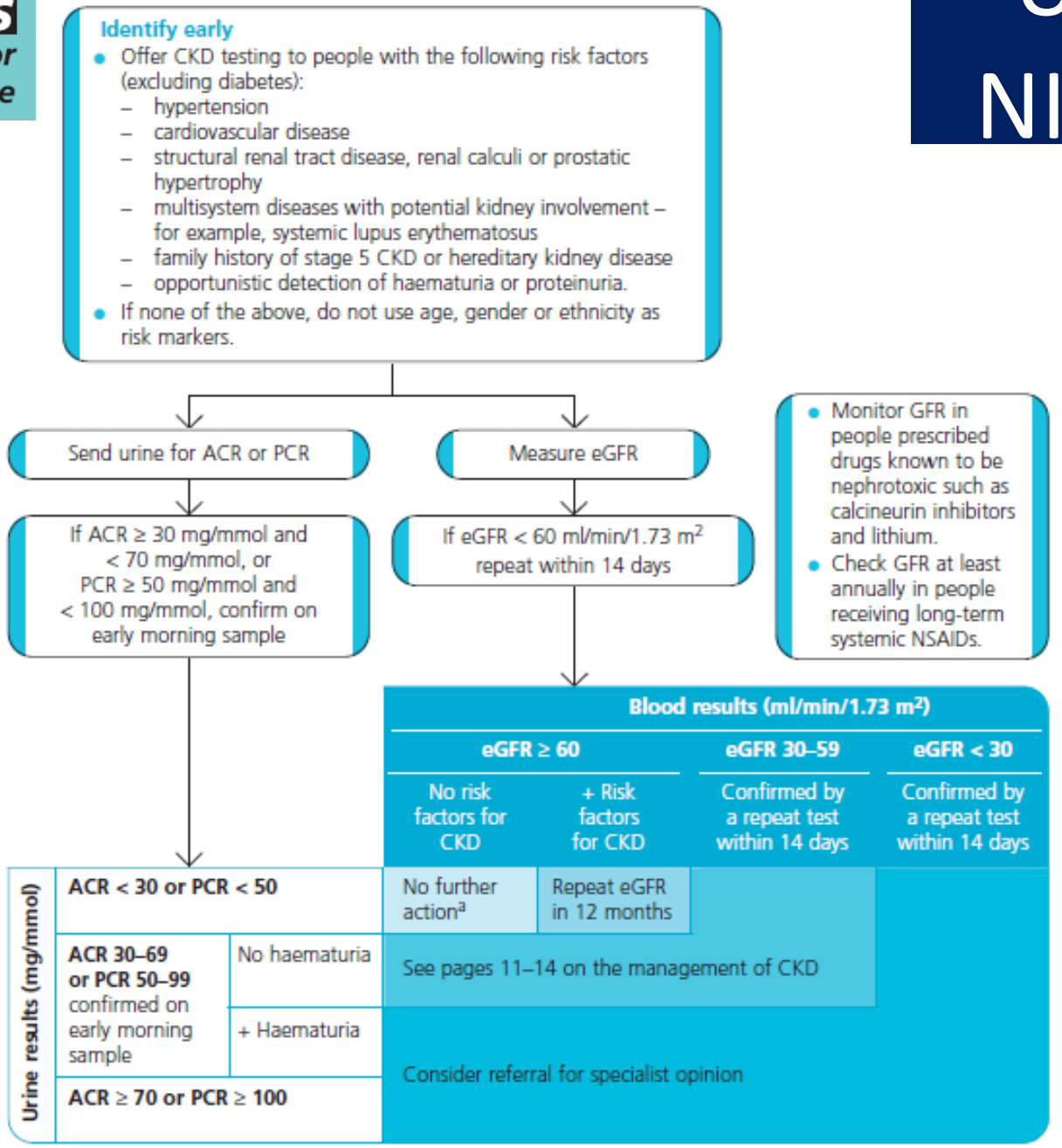
- Green: none
- Yellow: moderately increased
- Orange: high
- Red: very high

Management plans

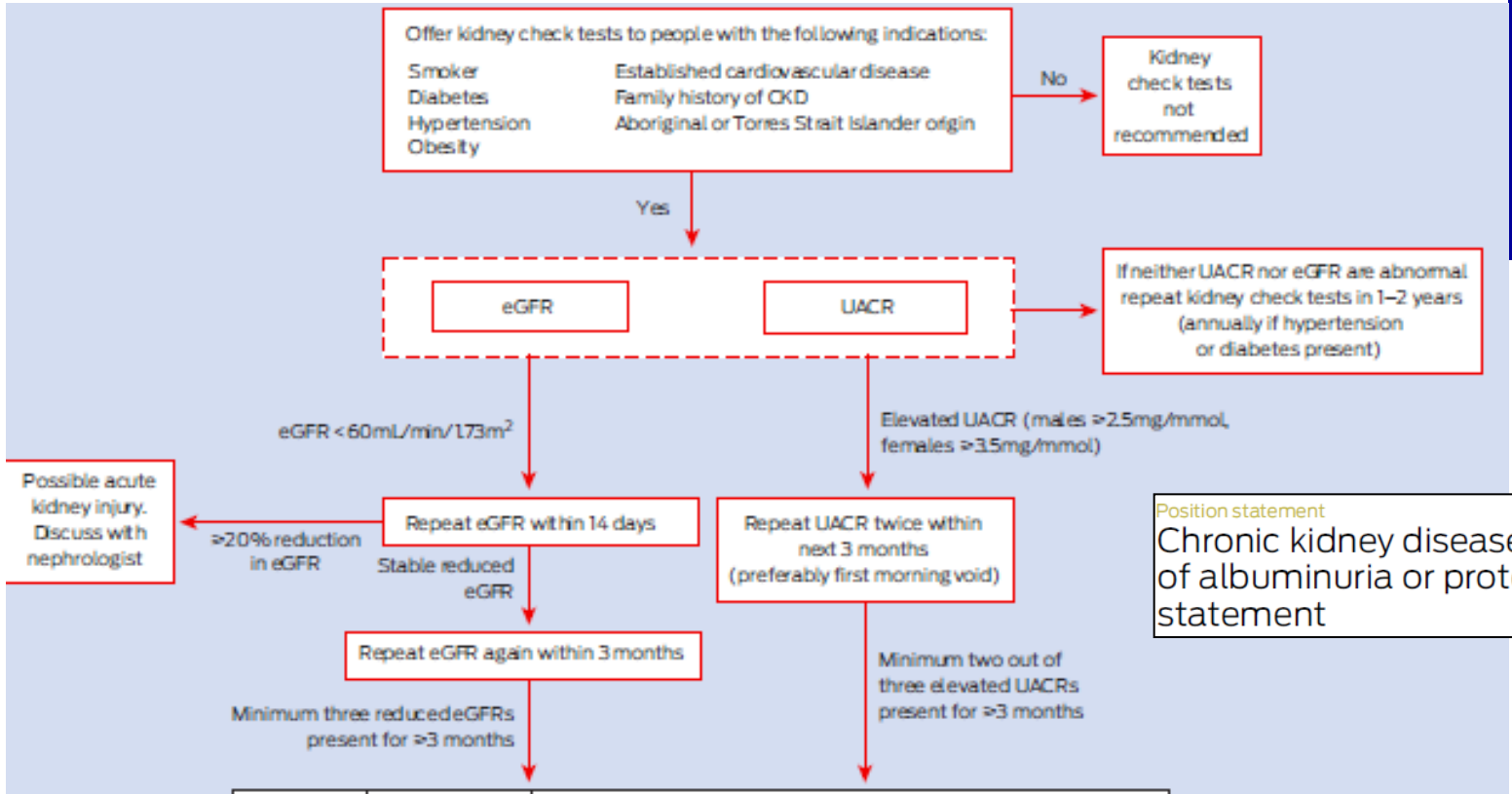
People with CKD without diabetes

NHS
National Institute for Health and Clinical Excellence

UK NICE



Aust 2012



		Albuminuria stage		
Kidney function stage	GFR (mL/min/1.73m²)	Normal (UACR, mg/mmol male: <2.5 female: <3.5)	Microalbuminuria (UACR, mg/mmol male: 2.5–25 female: 3.5–35)	Macroalbuminuria (UACR, mg/mmol male: >25 female: >35)
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60–89			
3a	45–59			
3b	30–44			
4	15–29			
5	<15 or on dialysis			

Combine eGFR stage (1–5), albuminuria stage and underlying diagnosis to fully specify CKD stage (eg, stage 2 CKD with microalbuminuria secondary to diabetic kidney disease).

Refer to colour-coded action plans in *Chronic kidney disease (CKD) management in general practice*. 2nd ed. Kidney Health Australia, 2012

Position statement

Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement

KHA

KIDNEY HEALTH AUSTRALIA

Yellow Clinical Action Plan

eGFR ≥60 mL/min/1.73m² with mikroalb
or eGFR 45-59 mL/min/1.73m² with no

Goals of management

- Investigations to exclude treatable
- assessment of absolute cardiovasc
- reduce CVD risk
- avoidance of nephrotoxic medica

Monitoring

- 12 monthly clinical review
- clinical assessment
  - blood pressure
  - weight
- laboratory assessment
  - urine ACR
  - biochemical profile inclu
  - eGFR
  - HbA1c (for people wit
  - fasting lipids

Absolute cardiovascula

- The presence of CKD
- Perform absolute ca
  all adults aged 45-
  Islander peoples)
  factor (see NVDP
- Provide lifestyle
  on the patient'
  intensive inter

Lifestyle modif

- Lifestyle mo
  physical ac
  overall CV
- Refer to s

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KIDNEY HEALTH AUSTRALIA

Orange Clinical Action Plan

eGFR 30-59 mL/min/1.73m² with microalbuminuria
or eGFR 30-44 mL/min/1.73m² with normoalbumin

Goals of management

- Investigations to exclude treatable disease (se
- reduce progression of kidney disease
- reduce CVD risk
- early detection and management of comp
- avoidance of nephrotoxic medications (se
- adjustment of medication doses to leve
  (see Page 19)
- appropriate referral to a Nephrologist

Monitoring

- 3-6 monthly clinical review
- clinical assessment
  - blood pressure
  - weight
- laboratory assessment
  - urine ACR
  - biochemical profile incl
  - eGFR
  - HbA1c (for people w
  - fasting lipids
  - full blood count
  - calcium and phos
  - parathyroid hor

Absolute cardiov

- People with
  >25 mg/m
  are considered
  to be assessed by the
- For these groups, identifying
  enable intensive management by
  pharmacological interventions (where in

See also lifestyle modification, blood pressure reduction, lipid-lowering treatm
per Yellow Action Plan.

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KIDNEY HEALTH AUSTRALIA

Red Clinical Action Plan

Macroalbuminuria irrespective of eGFR or
eGFR <30 mL/min/1.73m² irrespective of albuminuria

Goals of management

- appropriate referral to a Nephrologist when indicated (see Page 18)
- prepare for dialysis or pre-emptive transplant if eGFR <30 mL/min/1.73m²
- discuss advanced care directive if dialysis inappropriate
- reduce progression of kidney disease
- reduce CVD risk
- early detection and management of complications (see Page 25-33)
- avoidance of nephrotoxic medications (see Page 19)
- adjustment of medication doses to levels appropriate for kidney function (see Page 19)
- multidisciplinary team involvement (see Page 34)

Monitoring

- 1-3 monthly clinical review
- clinical assessment
  - blood pressure
  - weight
  - oedema
- laboratory assessment
  - urine ACR
  - biochemical profile including urea, creatinine and electrolytes
  - eGFR
  - HbA1c (for people with diabetes)
  - fasting lipids
  - full blood count (if anaemic see Page 30)
  - calcium and phosphate
  - parathyroid hormone (6-12 monthly if eGFR < 45 mL/min/1.73m²)
  - advanced care planning

Absolute cardiovascular risk assessment

- People with moderate or severe CKD (defined as persistently having a urine ACR >25 mg/mmol (males) or >35 mg/mmol (females) or eGFR <45mL/min/1.73m² are considered to be at the highest risk of a cardiovascular event and do not need to be assessed by the cardiovascular risk tool.
- For these groups, identifying all cardiovascular risk factors present will enable intensive management by lifestyle interventions (for all patients) and pharmacological interventions (where indicated).

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API
The Association of Physicians of India

Chronic K
Challeng

Ilangovan Veerappan,

Chronic diseases have becon
Chronic diseases are a leading
India and other low- and mi
diseases account for 60% of all
of chronic disease deaths wo
income countries.[1] In India, th
chronic disease was around 5.
rise to 7.63 million in 2020 (66.

CHRONIC KIDNEY DISEA
HEALTH PROBLEM

Chronic kidney disease (CKD) i

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)

GFR stages, description and range (mL/min Per 1.73 m^2)				Albuminuria stages, description and range (mg/g)				
				A1		A2	A3	
				Optimal and high-normal		High	Very high and nephrotic	
				< 10	10–29	30–299	300–1999	≥ 2000
	G1	High and optimal	> 105					
			90–104					
	G2	Mild	75–89					
			60–74					
	G3a	Mid-moderate	45–59					
	G3b	Moderate-severe	30–44					
	G4	Severe	15–29					
	G5	Kidney failure	< 15					

Medicine Update, 2013, section 17, chapter 130

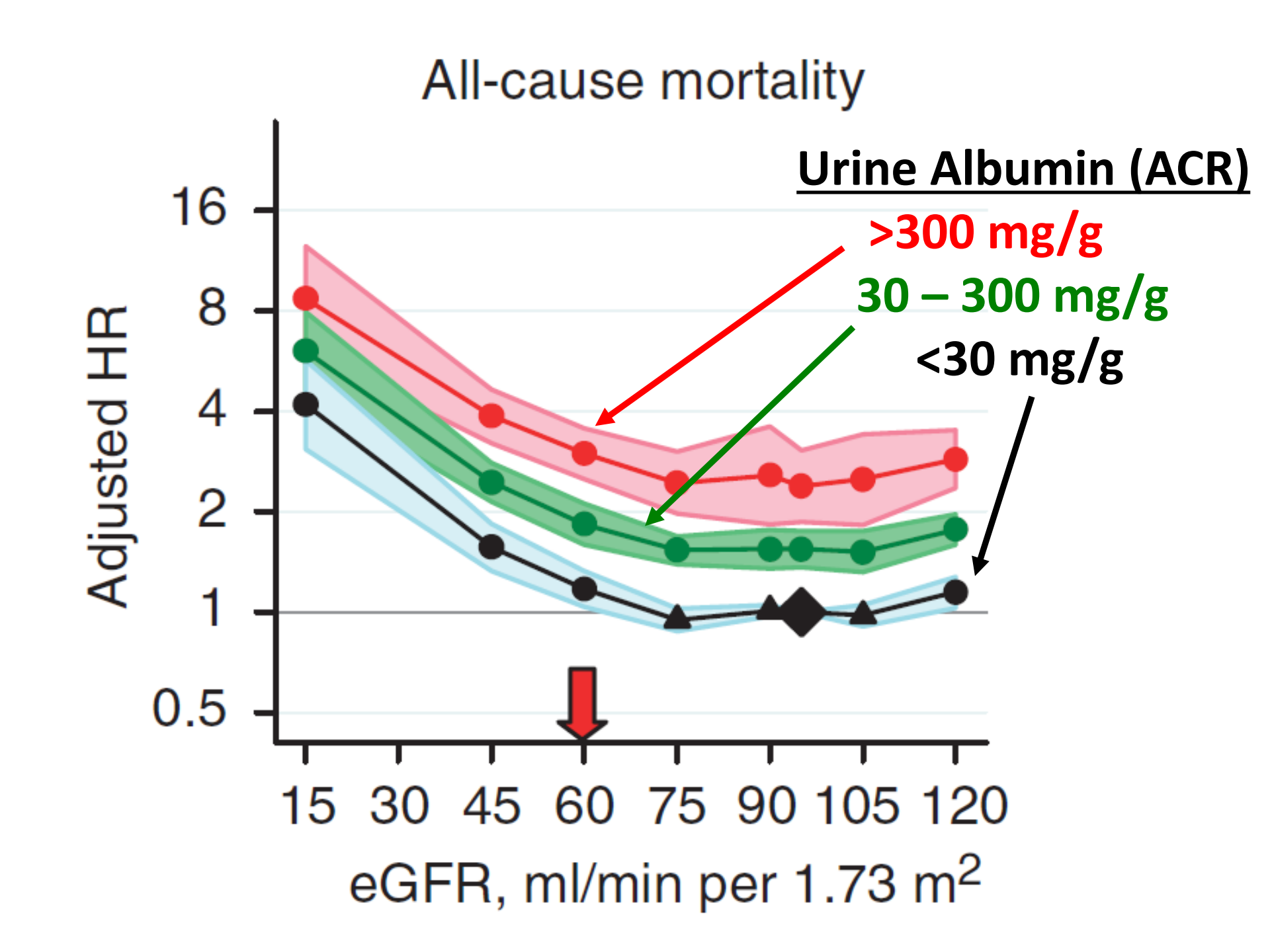
The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report

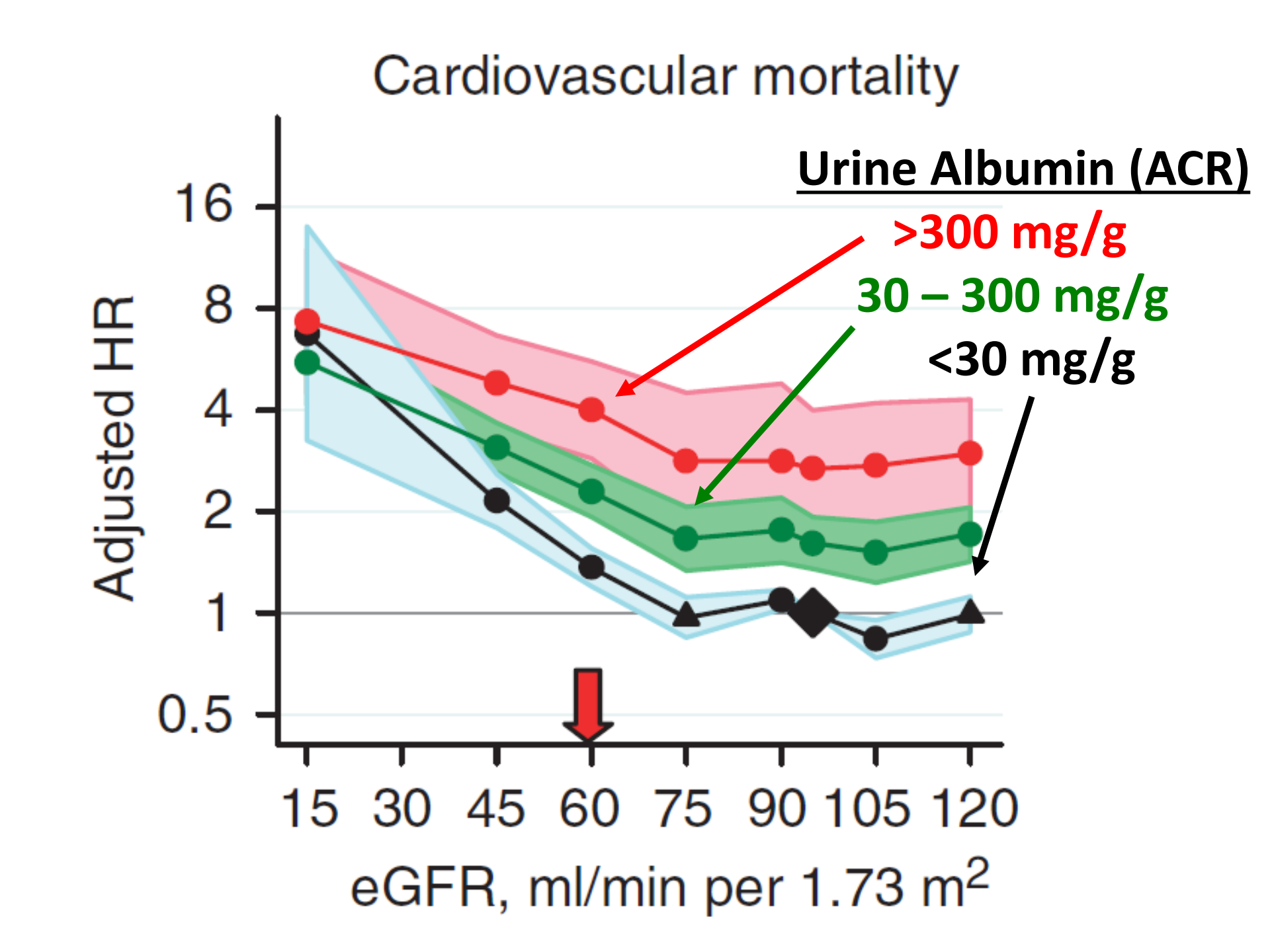
Andrew S. Levey[1], Paul E. de Jong[2], Josef Coresh[3], Meguid El Nahas[4], Brad C. Astor[3], Kunihiro Matsushita[3], Ron T. Gansevoort[2], Bertram L. Kasiske[5] and Kai-Uwe Eckardt[6]

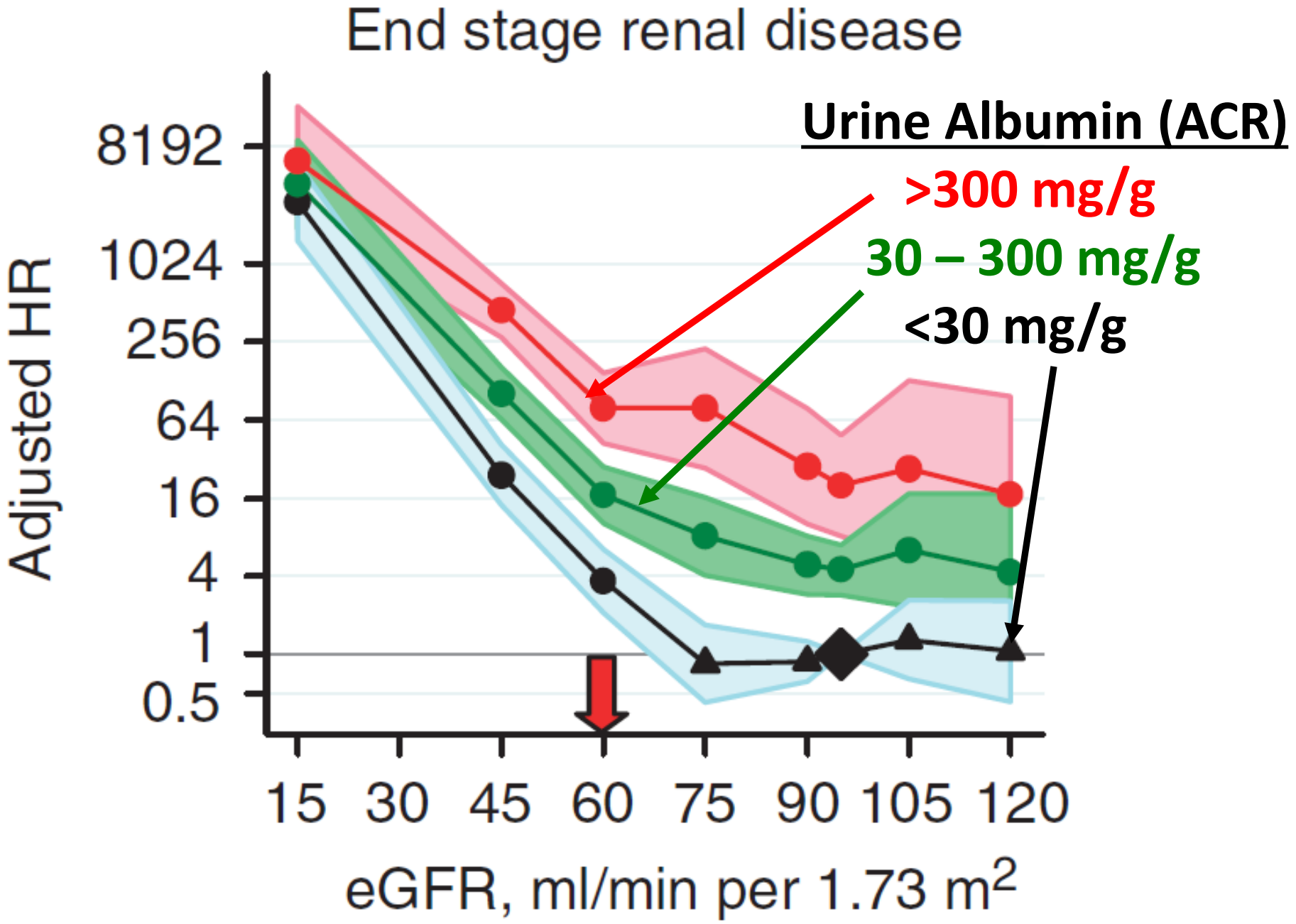
- Collaborative meta-analysis and Controversies Conference in October 2009.

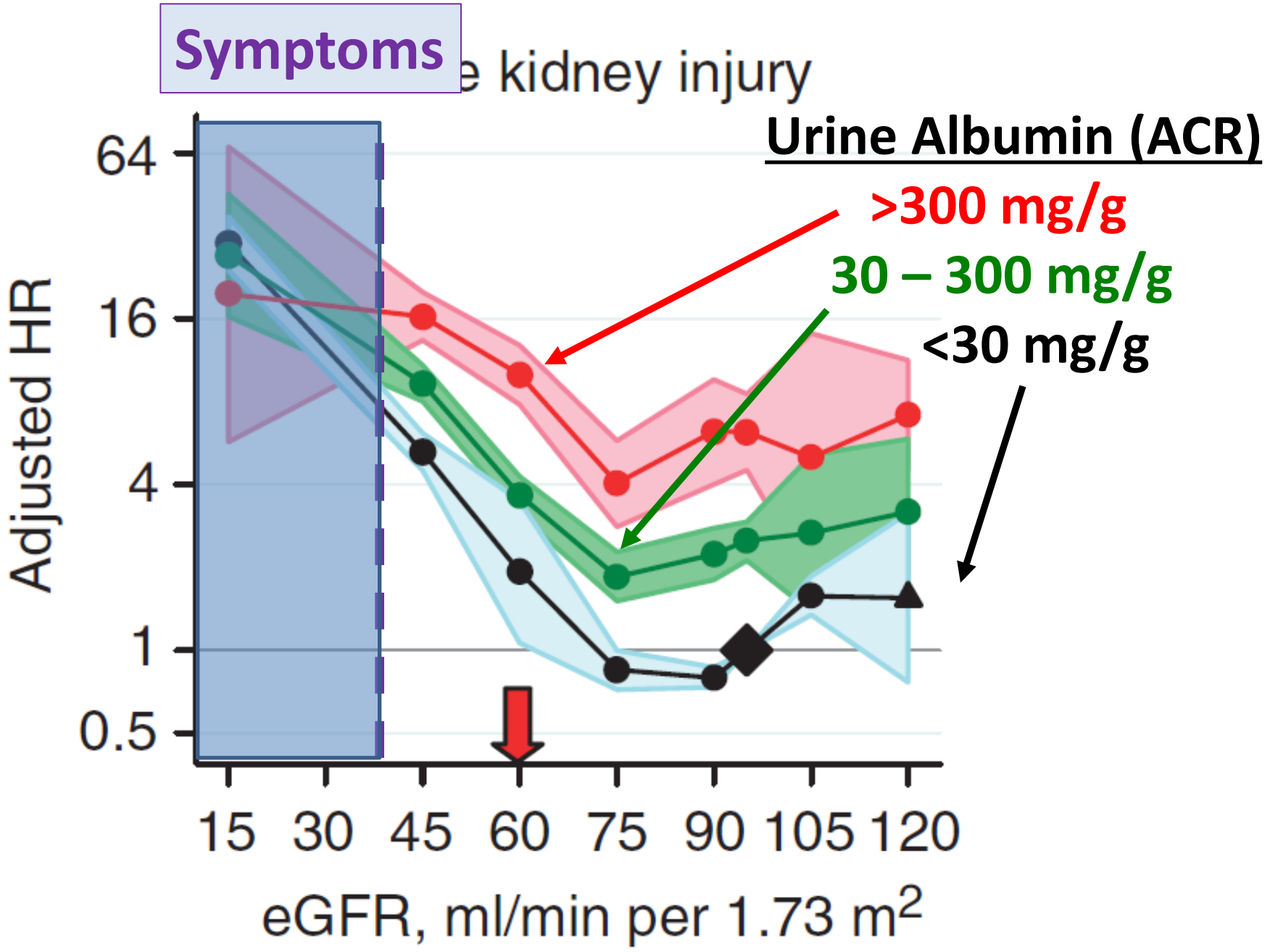
- 45 cohorts that included 1,555,332 participants from general, high-risk, and kidney disease populations.

Kidney International 2011


All-cause mortality
Urine Albumin (ACR)
>300 mg/g
30 – 300 mg/g
<30 mg/g
Adjusted HR
16
8
4
2
1
0.5
15 30 45 60 75 90 105 120
eGFR, ml/min per 1.73 m2


Cardiovascular mortality
Urine Albumin (ACR)
>300 mg/g
30 – 300 mg/g
<30 mg/g
Adjusted HR
16
8
4
2
1
0.5
15 30 45 60 75 90 105 120
eGFR, ml/min per 1.73 m2


End stage renal disease
Urine Albumin (ACR)
>300 mg/g
30 – 300 mg/g
<30 mg/g
Adjusted HR
8192
1024
256
64
16
4
1
0.5
15
30
45
60
75
90
105
120
eGFR, ml/min per 1.73 m2

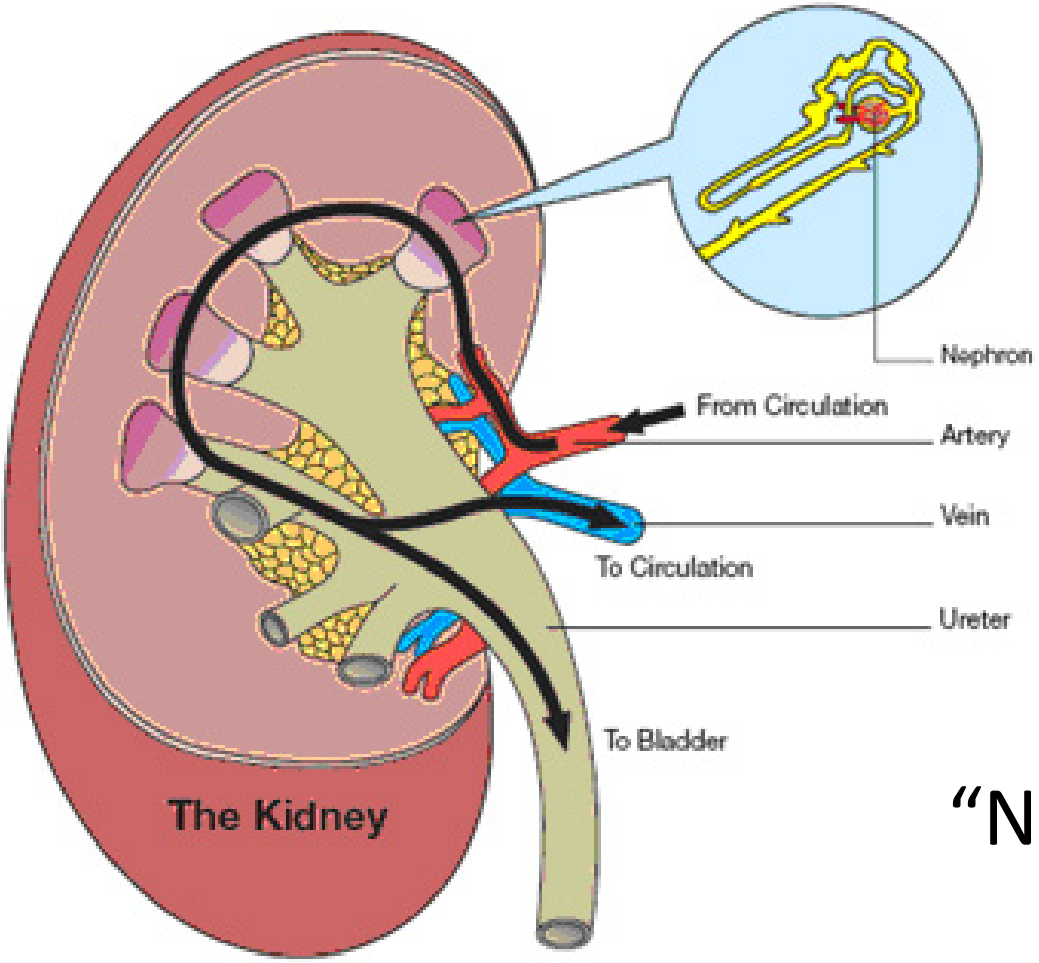

Symptoms
e kidney injury
Urine Albumin (ACR)
>300 mg/g
30 – 300 mg/g
<30 mg/g
Adjusted HR
64
16
4
1
0.5
15 30 45 60 75 90 105 120
eGFR, ml/min per 1.73 m2

Glomerular Filtration Rate

GFR

- Methods
- Creatinine
- eGFR equations (estimated GFR)
- Other factors

Glomerular Filtration Rate



Amount of fluid passing through the 2 million glomeruli in a fixed period of time

"Normal" >90 mL/min (130 L/day)

Measuring GFR

- Formal GFR measurement
- Creatinine alone
- Creatinine Clearance
- Cockcroft and Gault formula
- eGFR (MDRD, CKD-EPI)
- Other Markers (eg Cystatin C)

Formal Measurement of GFR

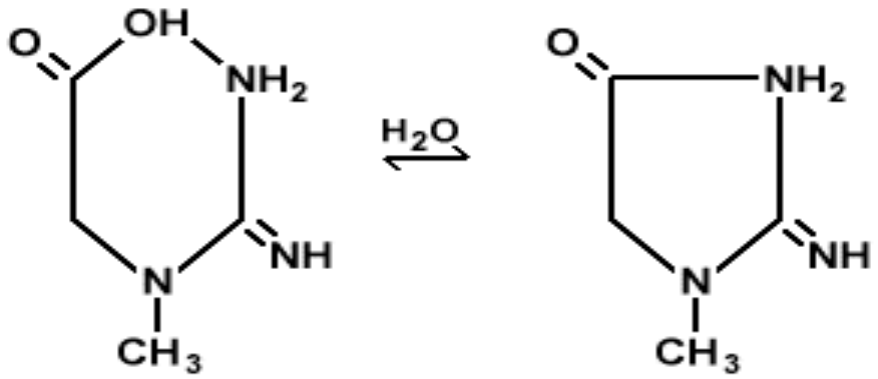
- Inulin
- Cr^{51}-EDTA, I^{125}-iothalamate, Tc^{99}-DTPA, iohexol
- Intravenous injection of substrate
- Measure in blood and or urine at various times
- Calculate clearance as estimate of GFR
- *Basis for assessing all other methods*
- **But:**
  - time consuming, expensive, radiolabels
  - Less commonly available
  - ***Variable quality!!!***

Tools for GFR estimation

- Creatinine alone
  - **S creatinine**
- Creatinine Clearance
  - **S creatinine**, 24 hour urine creatinine
- Cockcroft and Gault formula
  - **S creatinine**, age, sex, weight
- MDRD, CKD-EPI (eGFR)
  - **S creatinine**, age, sex, (race)

Creatinine

- Small nitrogen-containing compound (MW 113)
- Formed spontaneously from creatine in muscle at a (fairly) constant rate
- Largely removed from the blood by renal filtration



Creatine Creatinine

Creatinine Measurements

Creatinine Measurement

- Jaffe Method**s**
  - Chemistry described in 1896!
  - Non-specific
    - Interferences (non-creatinine chromogens)
  - Multiple formats
    - Reagent concentrations, pH
    - Read frame, temperature, detergents
    - End-point, rate, rate-blanked, protein precipitation
  - Standardisation issues
    - Need commutable calibrators or “adjustment”
- Cheap, very widely used

Creatinine Measurement

- Enzymatic assay**s**
  - More specific, easier to standardise
  - Different enzymes and formats
  - Readilly commercially available
  - More expensive
- HPLC (research)
- Fullers earth (historical)
- IDMS (JCTLM-listed)

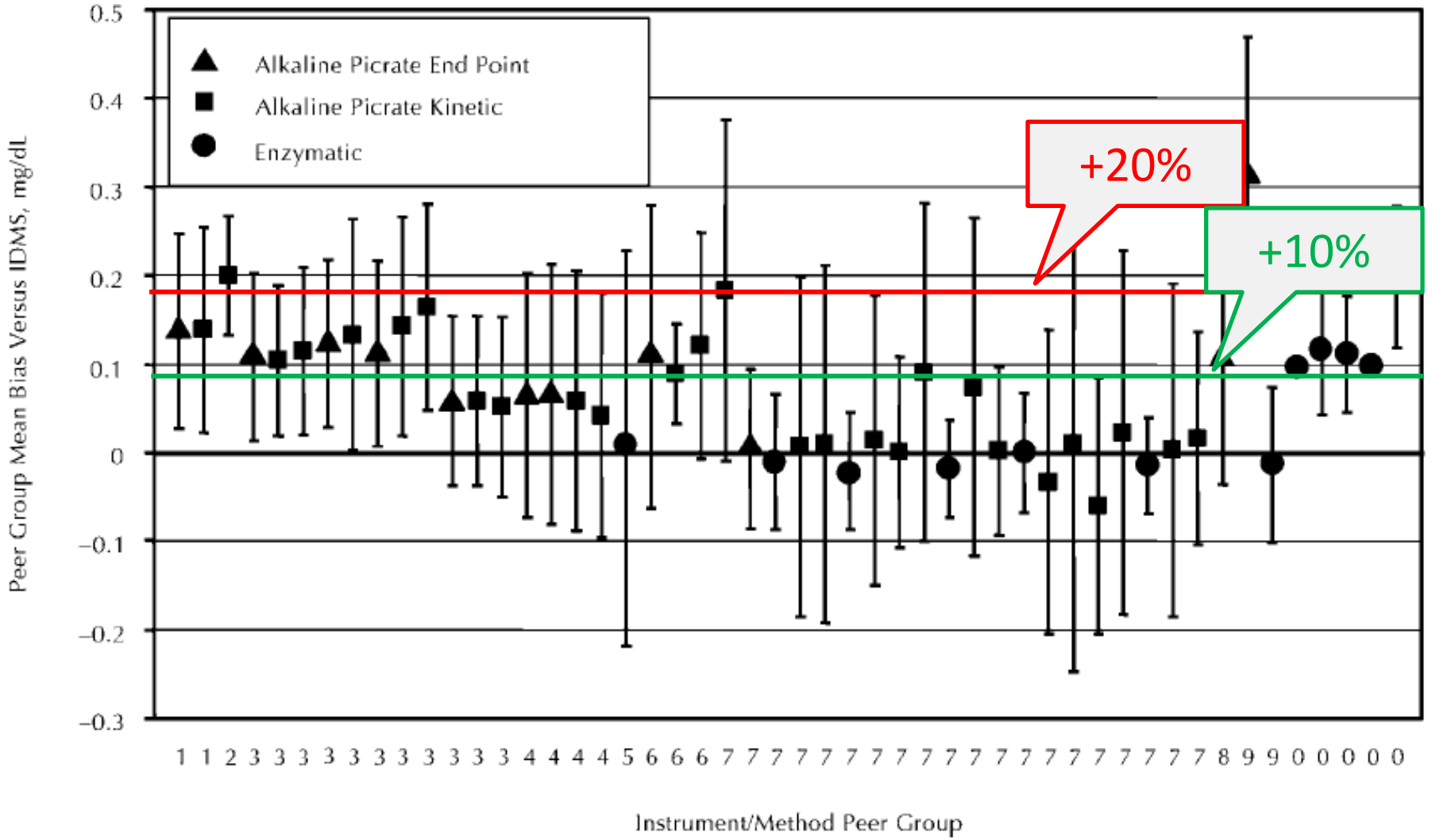
- **Mid 2000's – results highly variable!**

Creatinine Measurement

State of the Art in Accuracy and Interlaboratory Harmonization

W. Greg Miller, PhD; Gary L. Myers, PhD; Edward R. Ashwood, MD; Anthony A. Killeen, MD, PhD; Edward Wang, PhD; Linda M. Thienpont, PhD; Lothar Siekmann, PhD

Arch Pathol Lab Med. 2005;129:297–304



1, is Abbott; 2, Bayer; 3, Beckman Coulter; 4, Dade Behring; 5, Nova; 6, Olympus; 7, Roche; 8, Schiapparelli; 9, Toshiba; and 0, Vitros.

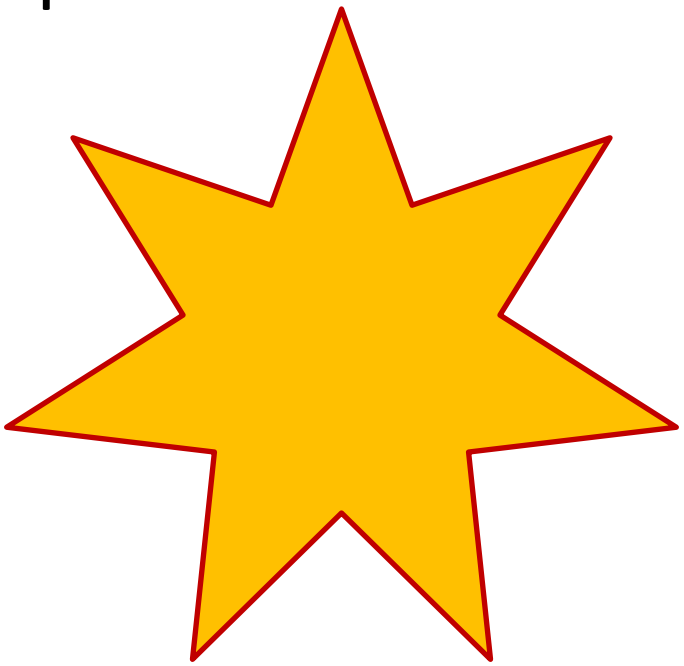
0.9 mg/dL (80 umol/L)

Creatinine Standardisation

- **Without standardisation:**
- **Cannot** reliably compare results from:
  - Different labs
  - With clinical guidelines
  - With literature references
  - Or get the same results from GFR formulae

NKDEP

- National Kidney Disease Education Program
- Laboratory Working Group
  - Clinicans
  - Laboratorians
  - Metrologists
  - Manufacturers



NKDEP National Kidney Disease Education Program

Clinicians

- Confirmed clinical need
- Provided motivation (customers)
  - Laboratories
  - Manufacturers
- Contributed to analytical requirements
- Linked testing to interpretation

NKDEP National Kidney Disease Education Program

Clinical Chemistry 52:1
5–18 (2006)

Special Report

Recommendations for Improving Serum Creatinine Measurement: A Report from the Laboratory Working Group of the National Kidney Disease Education Program

Gary L. Myers,[1*] W. Greg Miller,[2] Josef Coresh,[3] James Fleming,[4] Neil Greenberg,[5] Tom Greene,[6] Thomas Hostetter,[7] Andrew S. Levey,[8] Mauro Panteghini,[9] Michael Welch,[10] and John H. Eckfeldt[11] for the National Kidney Disease Education Program Laboratory Working Group

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NKDEP National Kidney Disease Education Program

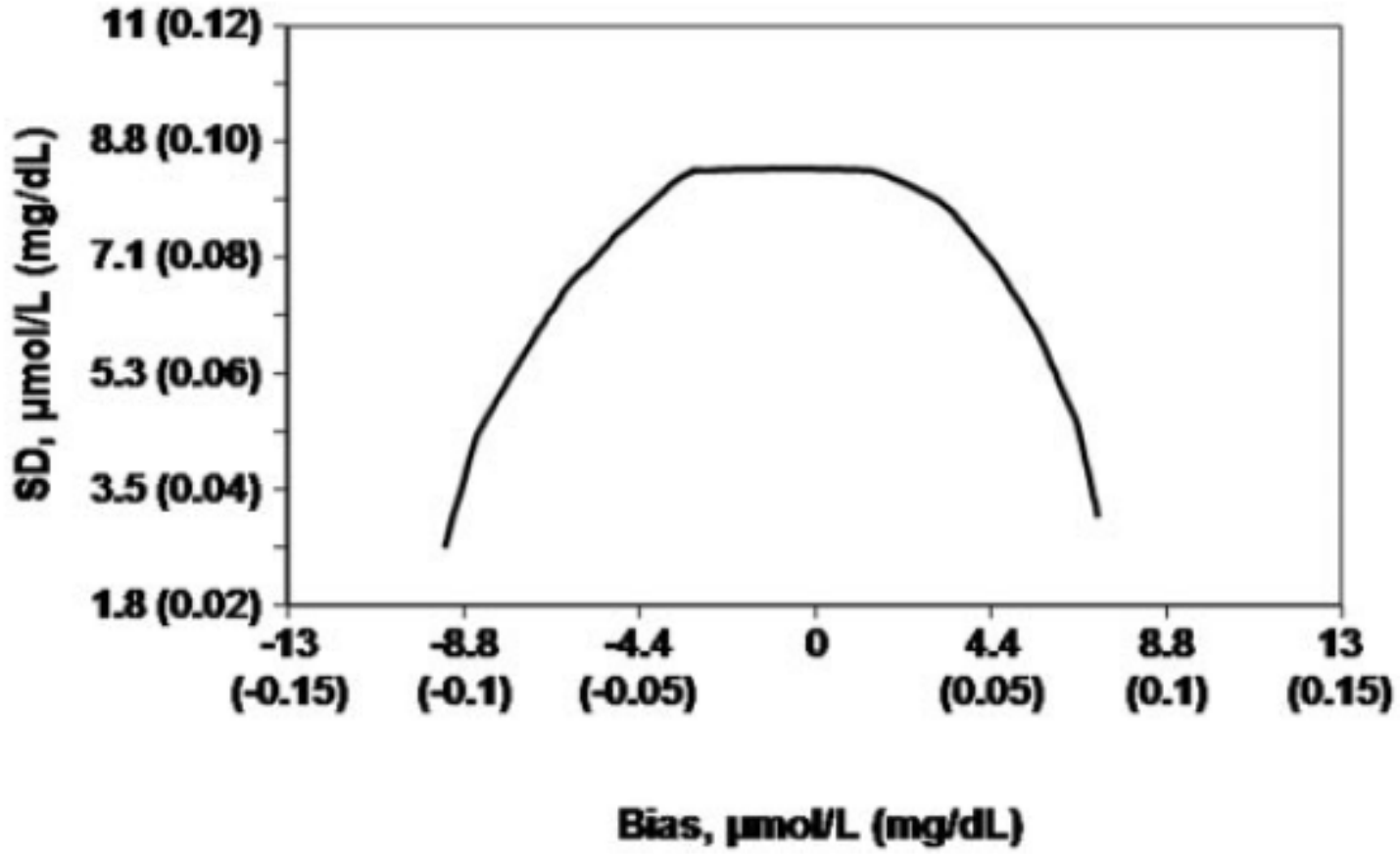


Fig. 3. Total error budget for creatinine measurements in the range 88.4–133 µmol/L (1.00–1.50 mg/dL).

BIPM
Bureau International des Poids et Mesures

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
JCTLM Database
Laboratory medicine and *in vitro* diagnostics

Results of the search for higher-order reference materials

JCTLM Database

- **SURVEY FORM**
- List of reference materials no longer listed in the JCTLM Database
- List of reference measurement methods no longer listed in the JCTLM database
- Contact us
- Back to Search Form

CALL FOR NOMINATIONS

- JCTLM reference materials, measurement methods and laboratory services - Submission deadline extended to 31 May 2013

JCTLM

- Overview
- Joint Committee for Traceability in Laboratory Medicine (JCTLM)

Your search criteria: Higher-order reference materials; Analyte: creatinine; Analyte category: -; Matrix category: -

Results of the search

Your search criteria produced 7 summary results.
Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

Select all items from the list

Sort by : (•) Analyte ( ) Matrix/Material ( ) Organization

Select	Analyte	Analyte category	Matrix/Material	Organization
☐	creatinine	metabolites and substrates	creatinine crystalline material	NIST
☐	creatinine	metabolites and substrates	creatinine crystalline material	NMIJ
☐	creatinine	metabolites and substrates	frozen human serum	CENAM
☐	creatinine	metabolites and substrates	frozen human serum	NIST
☐	creatinine	metabolites and substrates	human serum	IRMM
☐	creatinine	metabolites and substrates	human serum	LGC
☐	creatinine	metabolites and substrates	human serum	NIST

RMs: Pure – 3, matrix matched - 4

BIPM
Bureau International des Poids et Mesures

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
JCTLM Database
Laboratory medicine and *in vitro* diagnostics

Result of the search for reference measurement methods/procedures

JCTLM Database

- **SURVEY FORM**
- List of reference materials no longer listed in the JCTLM Database
- List of reference measurement methods no longer listed in the JCTLM database
- Contact us
- Back to Search Form

CALL FOR NOMINATIONS

- JCTLM reference materials, measurement methods and laboratory services - Submission deadline extended to 31 May 2013

Your search criteria: Reference measurement methods/procedures; Analyte: creatinine; Analyte category: -; Matrix category: -

Results of the search

Your search criteria produced 4 results.
For more information on a reference measurement method/procedure for a given Analyte/Matrix (or Material)/Measurement principle (or technique) combination, select one or more of the options below.

Select all items from the list

Sort by : (•) Analyte ( ) Measurement principle/technique ( ) Matrix/Material

Select	Analyte	Measurement principle/technique	Matrix/Material
☐	creatinine	Isotope dilution mass spectrometry	blood plasma
☐	creatinine	Isotope dilution mass spectrometry	blood serum
☐	creatinine	Isotope dilution mass spectrometry	urine
☐	creatinine	Isotope dilution surface enhanced raman scattering	blood serum

RMP: 3 serum methods

JCTLM Database

- **SURVEY FORM**
- List of reference materials no longer listed in the JCTLM Database
- List of reference measurement methods no longer listed in the JCTLM database
- Contact us
- Back to Search Form

CALL FOR NOMINATIONS

- JCTLM reference materials, measurement methods and laboratory services - Submission deadline extended to 31 May 2013

JCTLM

- Overview
- Joint Committee for Traceability in Laboratory Medicine (JCTLM)
- Leaflet

Your search criteria: Reference measurement services; Analyte: creatinine; Analyte category: -; Matrix category: -

Results of the search

Your search criteria produced 12 summary results.
Select one or several reference measurement service summary descriptions amongst the following list and click on 'View' to access more information.

Select all items from the list

Sort by : (•) Analyte ( ) Matrix or Material ( ) Service provider

Select	Analyte	Matrix or Material	Country	Service provider
☐	creatinine	blood plasma	Germany	DGKL
☐	creatinine	blood plasma	Germany	Instand e.V.
☐	creatinine	blood plasma	Belgium	UGent
☐	creatinine	blood serum	Germany	DGKL
☐	creatinine	blood serum	Germany	Instand e.V.
☐	creatinine	blood serum	France	LNE
☐	creatinine	blood serum	Belgium	UGent
☐	creatinine	blood serum	United Kingdom	WEQAS
☐	creatinine	calibration solution	Germany	DGKL
☐	creatinine	calibration solution	France	LNE
☐	creatinine	urine	Germany	DGKL
☐	creatinine	urine	Belgium	UGent

RMS: 5 laboratories

RELA - Homepage

External quality control for Reference Laboratories

RELA Home

Welcome

login

Registration/ Account

RELA in progress

order RELA 2013

enter RELA 2013 results

former RELA results

Choose year...

RELA 2012

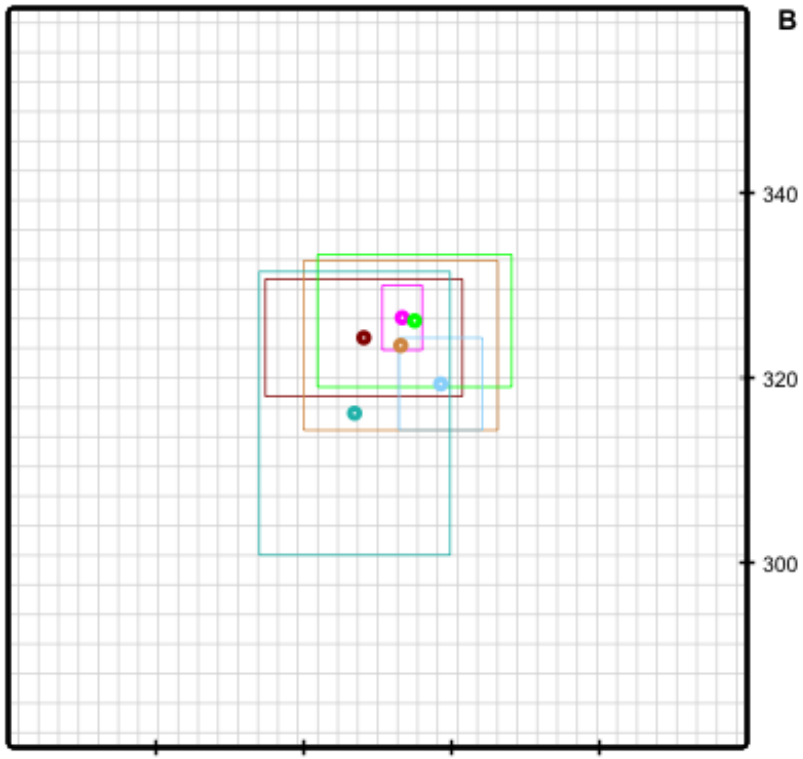
All or choose Lab ...

select lab analytes | full address

Creatinine | show result plot

with limits of equivalence

Creatinine



For highlighting a specific result please click on the corresponding result line.

Labcode	A	e.u. A	B	e.u. B	Method
1	136,7	1,4	326,5	3,5	ID/LC/MS
12	134	6,66	324,3	6,31	enzymatic kinetic spectrophotometry
51	136,6	6,6	323,5	9,2	spectrophotometry
54	137,5	6,6	326,2	7,2	ID/LC/MS/MS
87	139,3	2,77	319,4	4,96	spectrophotometry
121	133,5	6,453	316,2	15,29	ID/LC/MS

2012

Lab 1: e.u. = 1.0%

Lab 54: e.u. = 4.8%

Lab 121: e.u. = 4.8%

Manufacturers

- Participated in LWG meetings
- Restandardised assays
  - Science – assay, reference intervals
  - Manufacturing
  - Regulatory requirements
  - Change management
  - End-user education
- Costs >$10 million per company
- Delivered by end 2008!

Instructions for Use (IFU)

Calibration

The serum calibrator creatinine value is traceable to the Isotope Dilution Mass Spectroscopy (IDMS) method via National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 967.

BECKMAN COULTER®

CREATININE (ENZYMATIC)		
OSR61204	4 x 45 mL 4 x 15 mL	R1 R2

eGFR: MDRD Equations

Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461-470.

For "IDMS aligned" creatinine assays

The abbreviated MDRD equation[13]

eGFR = ~~186~~ **175** x ($[S_{CR}/88.4]^{-1.154}$) x $(age)^{-0.203}$ x (0.742 if female)
x (1.210 if African-American)

where eGFR = estimated glomerular filtration rate (mL/min/1.73m^2), S_{CR} = serum creatinine concentration (µmol/L), and age is expressed in years.

An automated calculator for MDRD-based eGFR can be found at <http://www.kidney.org.au>.

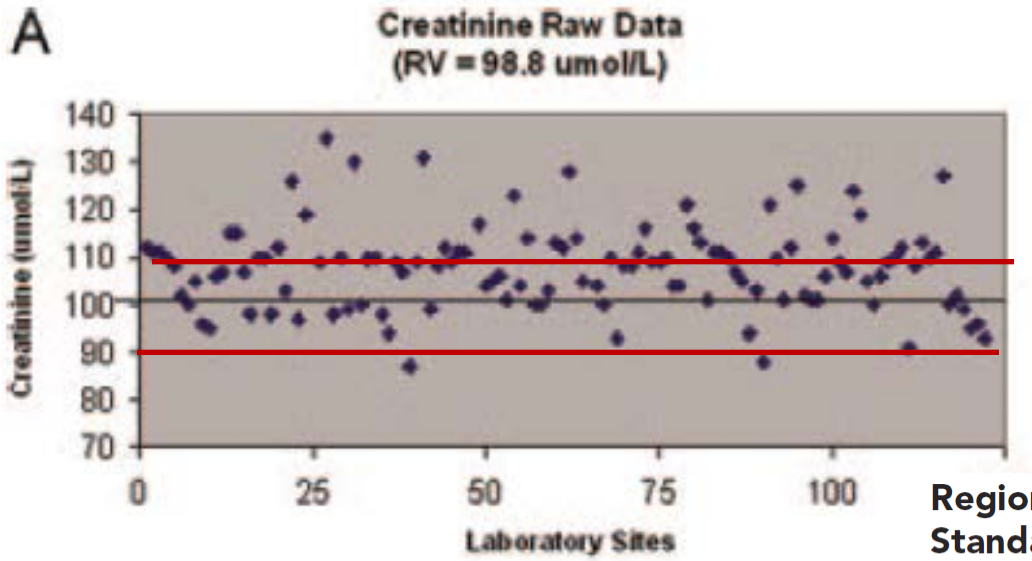
MDRD = Modification of Diet in Renal Disease.[5]

MJA 2007

~~MJA 2005~~

Interim Processes

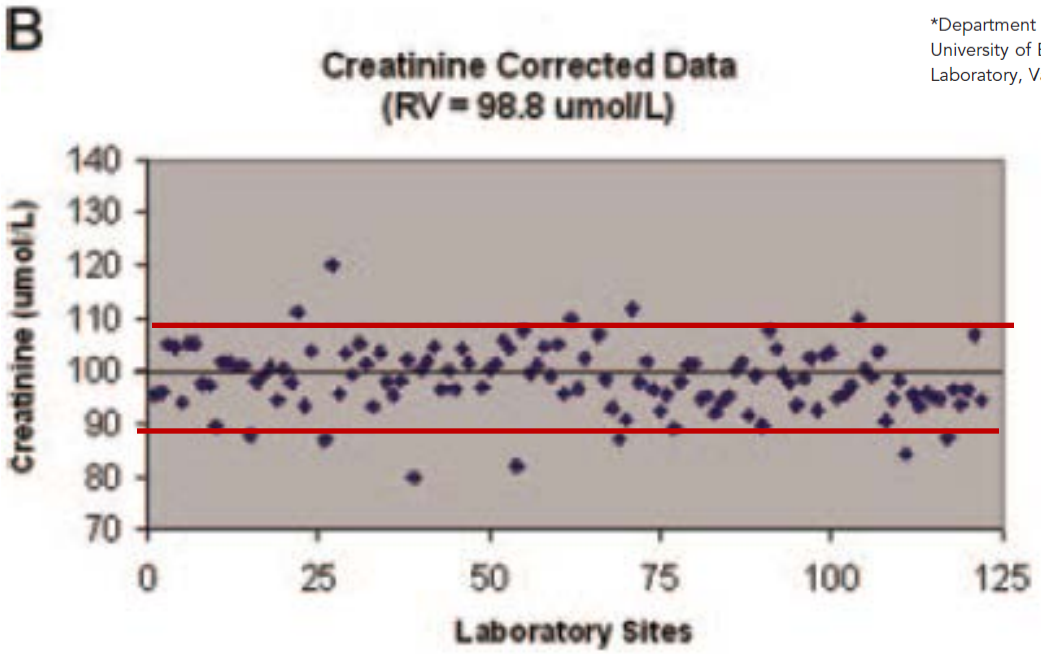
- Laboratory-specific Factors for creatinine assays
- UKNEQAS – Sausages – Finlay McKenzie
  - **S**uccessfully **A**dopting **U**K NEQAS **S**lope **A**djuster **G**FR **E**stimate **S**ystems
- British Columbia, Canada



Regional Implementation of Creatinine Measurement Standardization

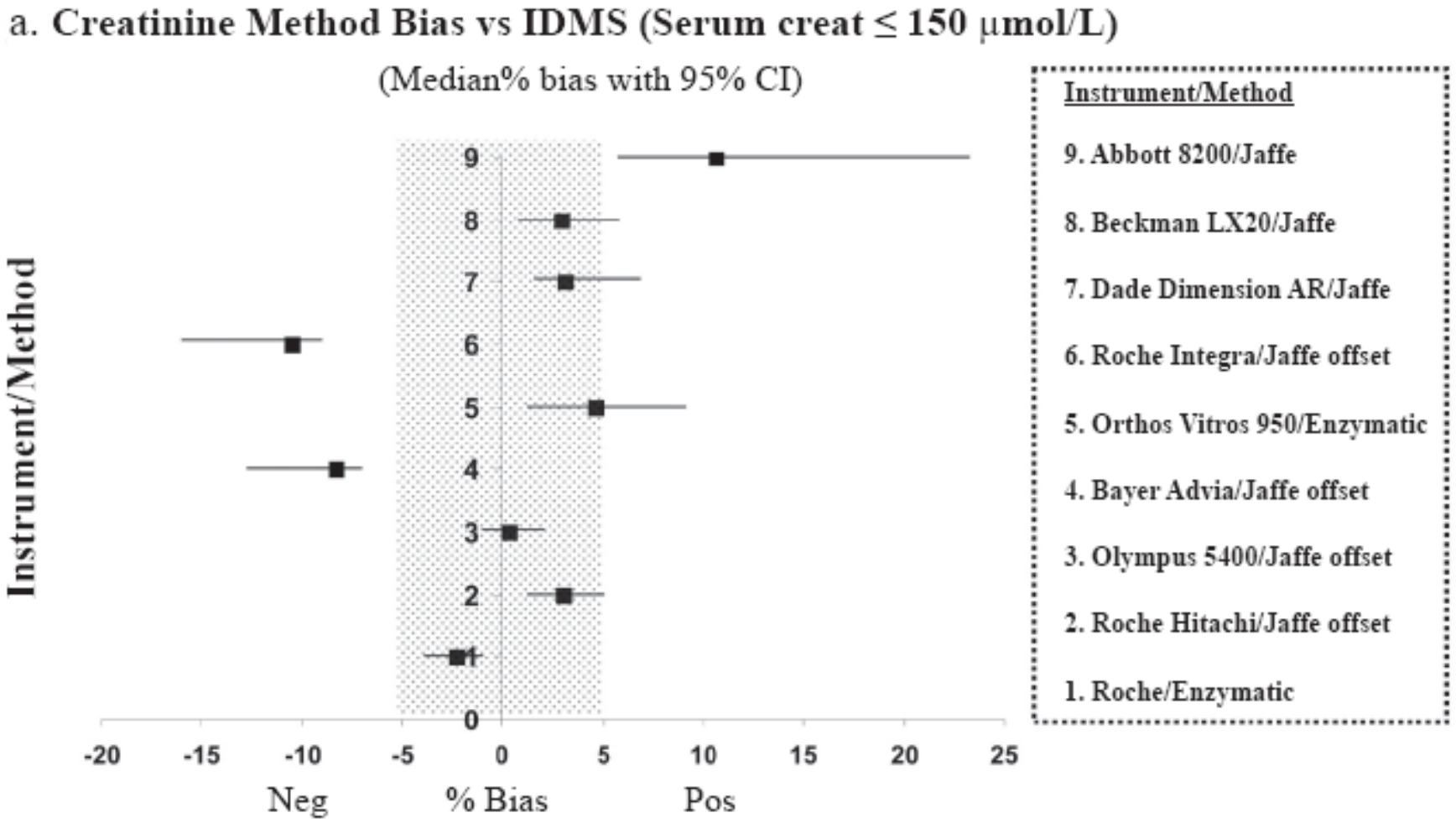
Paul Komenda,*† Monica Beaulieu,*† David Seccombe,‡§ and Adeera Levin*†

*Department of Medicine, Division of Nephrology, and ‡Department of Pathology and Laboratory Medicine, University of British Columbia, †British Columbia Renal Agency, and §Canadian External Quality Assessment Laboratory, Vancouver, British Columbia, Canada

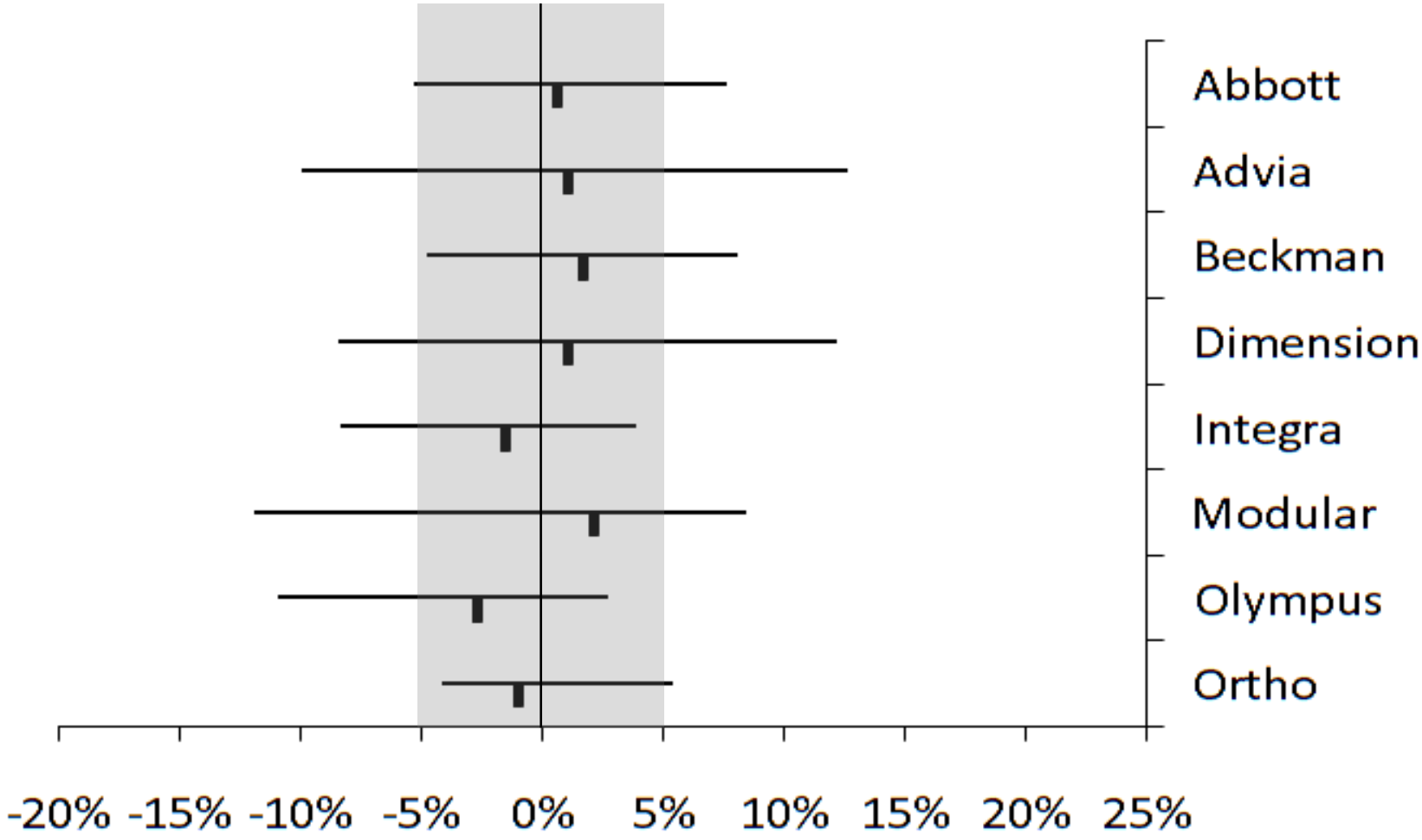


J Am Soc Nephrol 19: 164–169, 2008

2006 Data Peake et al, Clin Biochem Revs



2011 Data Thanks to Gus Coerbin and AACB



Creatinine bias – 20 samples, 8 methods, 22 laboratories

Clinical Chemistry 54:3
559–566 (2008)

Reference Intervals for Serum Creatinine Concentrations: Assessment of Available Data for Global Application

Ferruccio Ceriotti,[1*] James C. Boyd,[2] Gerhard Klein,[3] Joseph Henny,[4] Josep Queraltó,[5] Veli Kairisto,[6] and Mauro Panteghini,[7] on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL)

Table 1. Published studies on serum creatinine reference intervals in adults using enzymatic assays traceable to the reference method.

	Mazzachi et al. *(20)*	Rustad et al. *(21)* and Mårtensson et al. *(23)*	Junge et al. *(19)*
Year	2000	2004	2004
Method	Roche	Various	Roche
Analytical system	Hitachi 917		Hitachi 717
Subjects			
Race	White	White	White
Source	Blood donors	Volunteers	Volunteers
Number and sex	293 M, 269 F	113 M, 137 F[a]	120 M, 120 F
Age, years	18–70	18–90	18–74
Fasting	Not reported	No	No
Statistical calculation	Nonparametric	Nonparametric	Non parametric
Reference intervals, μmol/L			
Men	59–104	60–105	64–104
Women	45–84	46–92	49–90
Reference intervals, mg/dL			
Men	0.67–1.18	0.68–1.19	0.72–1.18
Women	0.51–0.95	0.51–1.02	0.55–1.02
Influence of age	Not reported	No	No

[a] Result obtained with enzymatic methods only. On the complete group of patients (1243 M, 1391 F), the application of the method correction factors as proposed by Mårtensson et al. *(23)* yielded the same reference intervals for men and 45–90 μmol/L (0.51–1.02 mg/dL) for women.

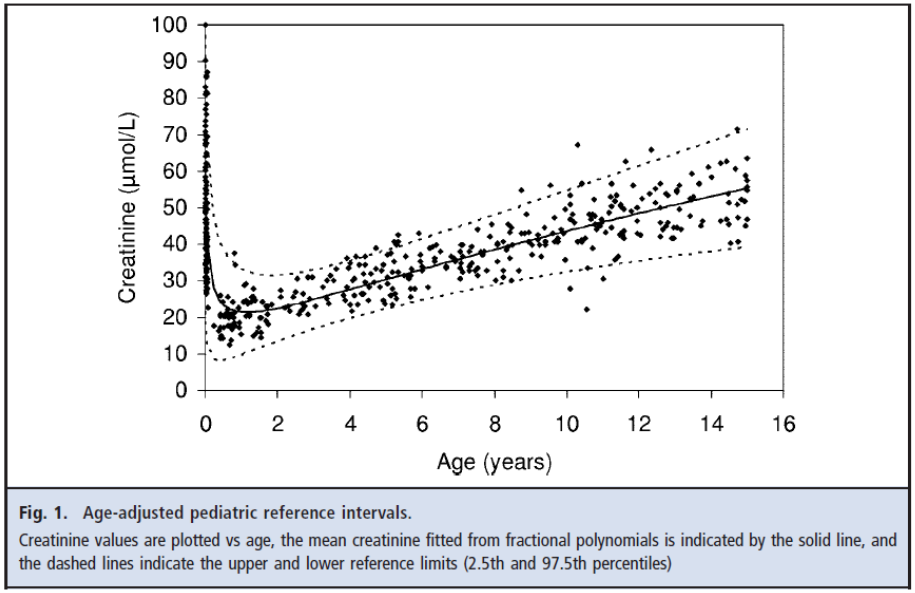


Fig. 1. Age-adjusted pediatric reference intervals.
Creatinine values are plotted vs age, the mean creatinine fitted from fractional polynomials is indicated by the solid line, and the dashed lines indicate the upper and lower reference limits (2.5th and 97.5th percentiles)

CKD-EPI Equation

- Chronic Kidney Disease Epidemiology Collaboration
- Collaboration of all major players
- Over 8000 subjects
- Wider range of ages, renal function ect

ARTICLE | Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*

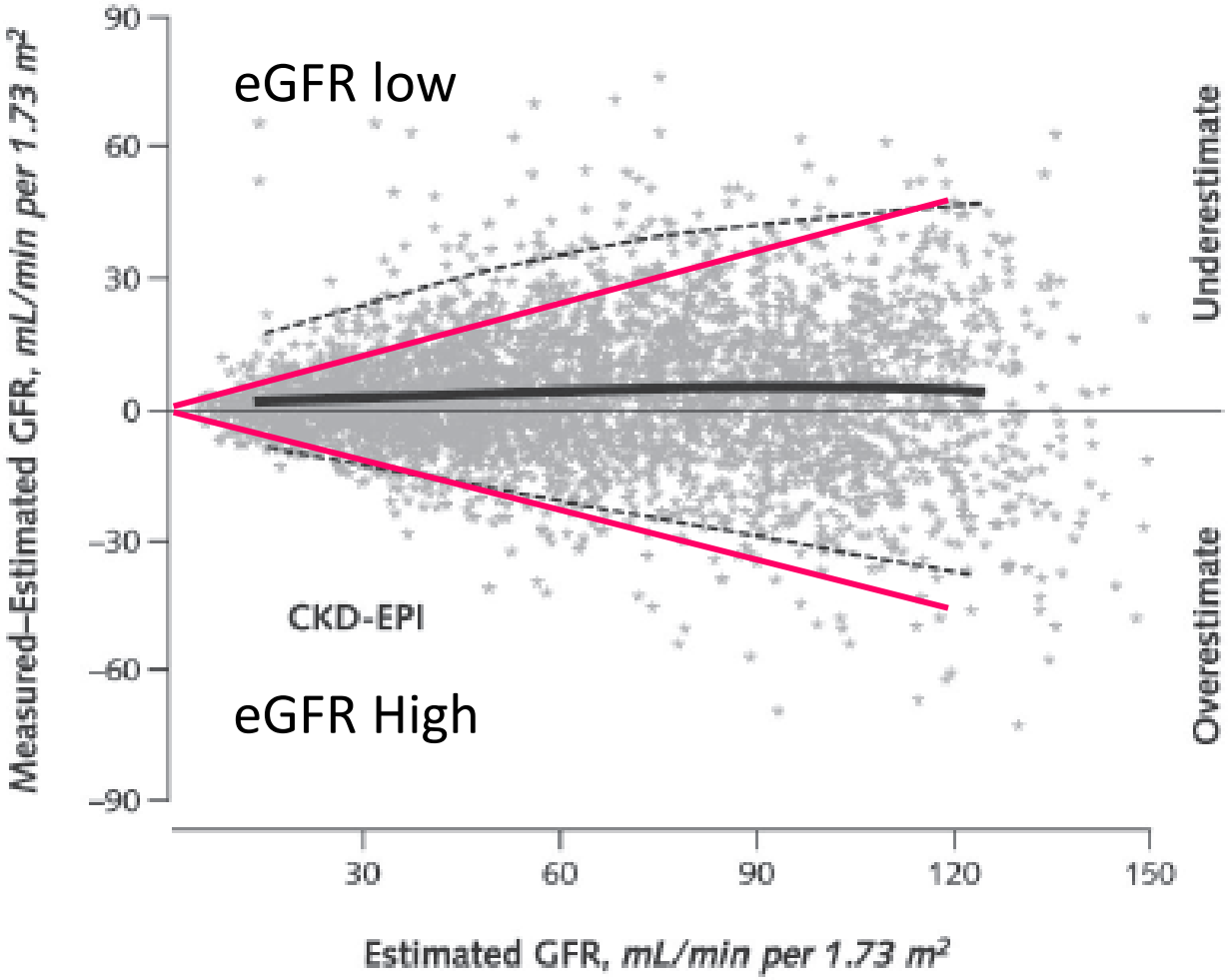
Ann Intern Med. 2009;150:604-612.

Table 2. **The CKD-EPI Equation for Estimating GFR on the Natural Scale***

Race and Sex	Serum Creatinine Level, *μmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Ann Intern Med. 2009;150:604-612.

CKD-EPI

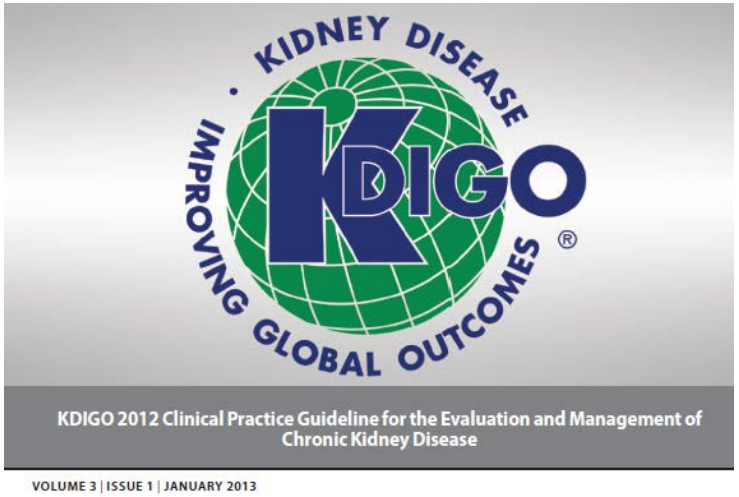


Ann Intern Med. 2009;150:604-612.

CKD-EPI

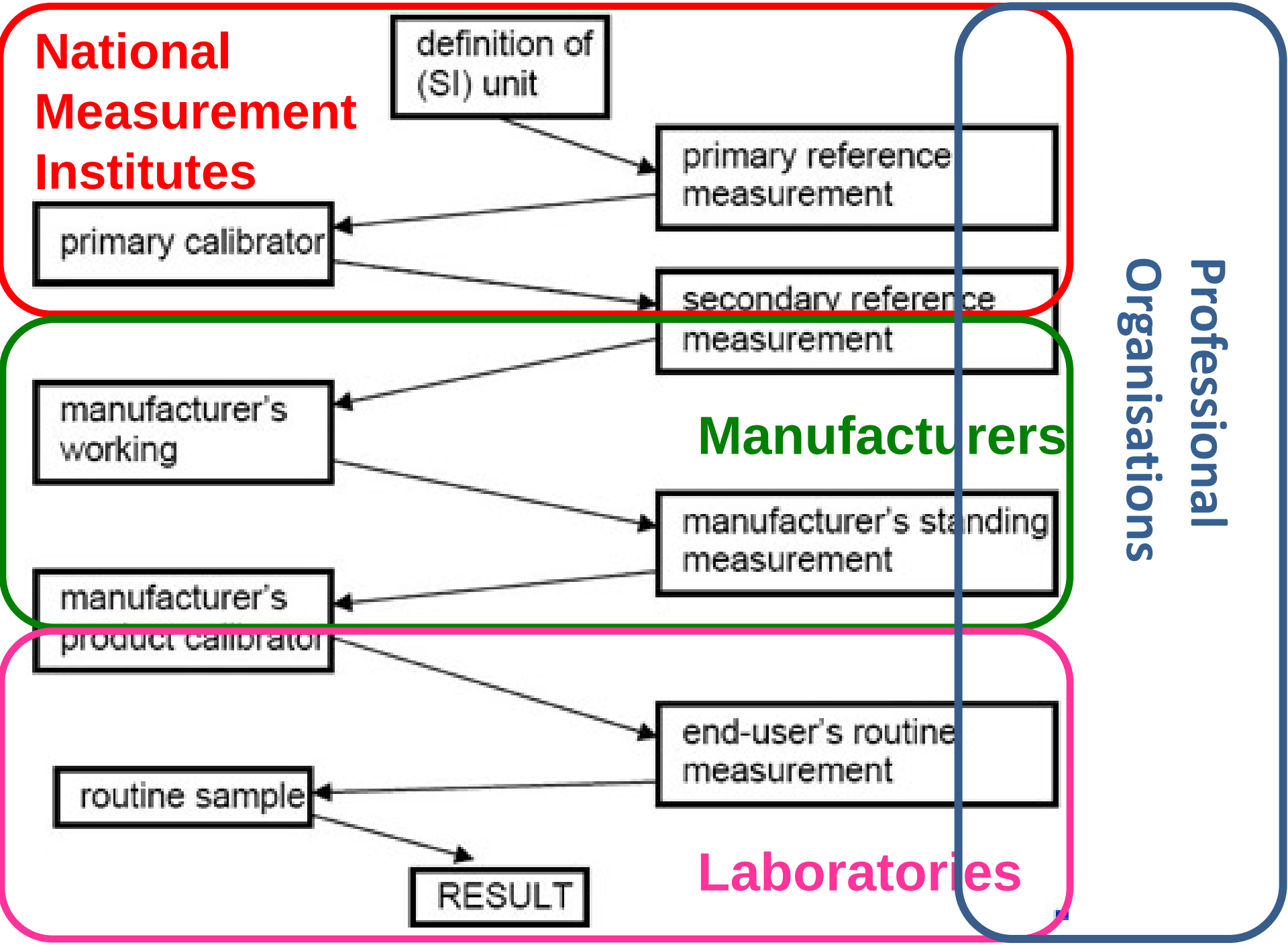
KDIGO - 2012

- **Recommends adoption of CKD-EPI formula for calculating eGFR**
- **Unless there is evidence of a superior equation**
- **Requires IDMS aligned creatinine assays**



5 Pillars of Traceability

- Reference Materials
- Reference Methods
- Reference Laboratories
- Reference intervals / decision points
- Traceable External Quality Assurance
  - (Mauro Panteghini)


National Measurement Institutes
definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference measurement
Manufacturers
manufacturer's working
manufacturer's standing measurement
manufacturer's product calibrator
Laboratories
end-user's routine measurement
routine sample
RESULT
Professional Organisations

2010

- Victory declared!

or was it……

Clinical Chemistry 55:3
549–558 (2009)

Prime Time for Enzymatic Creatinine Methods in Pediatrics

Problem: Interferences

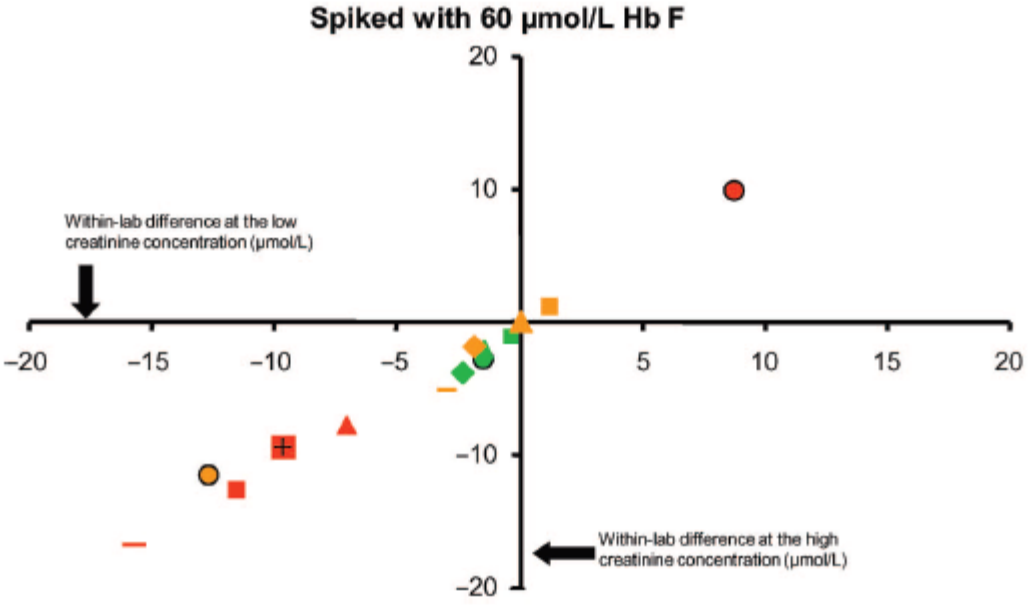
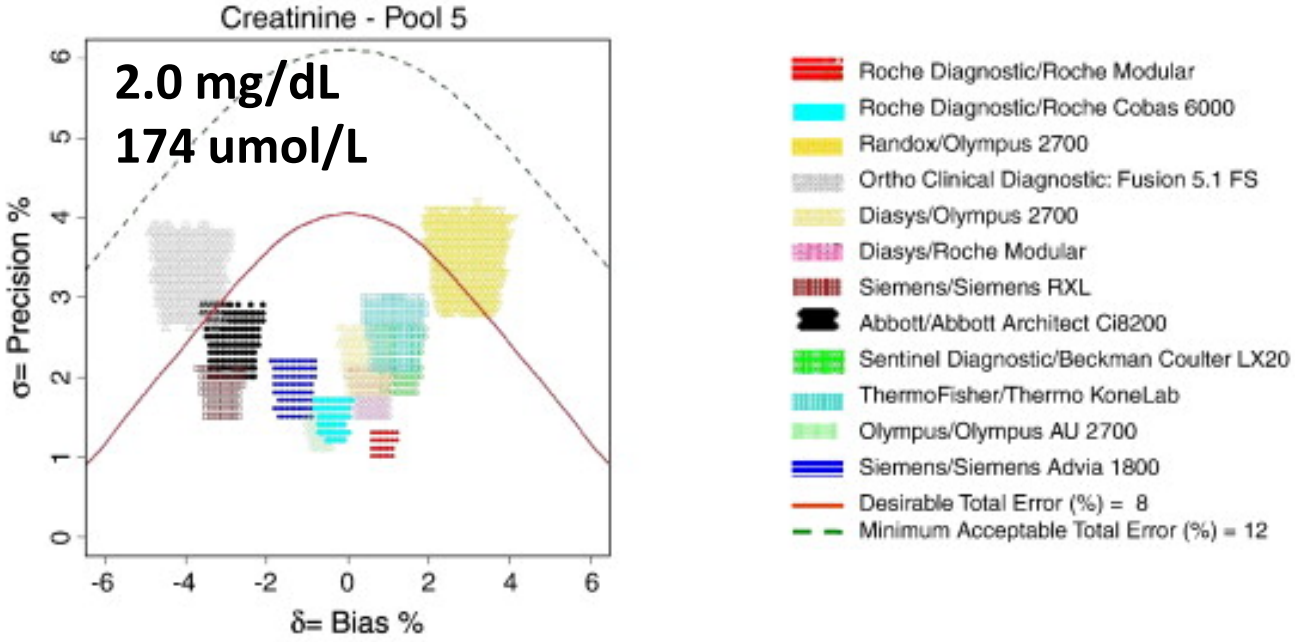


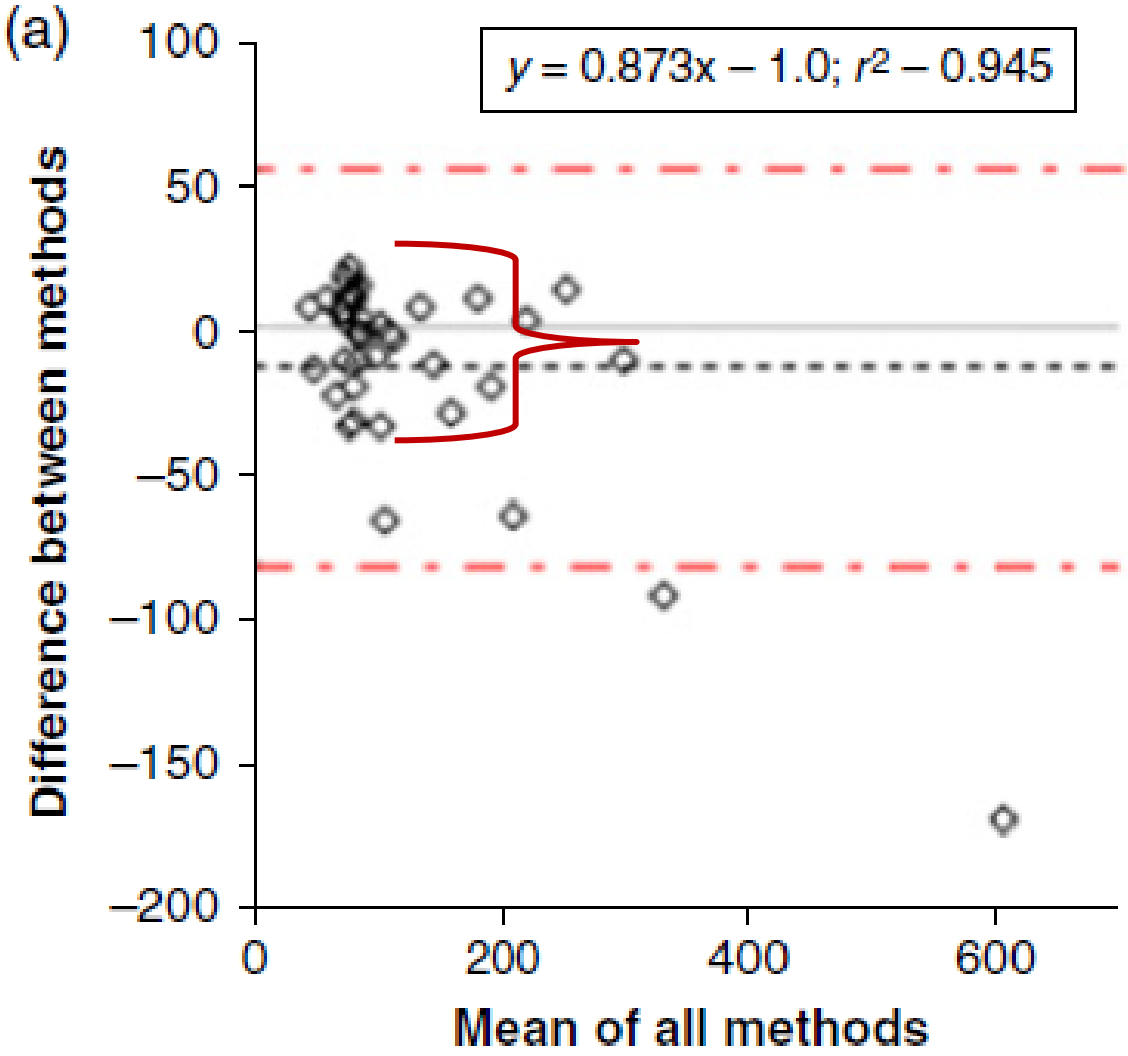
Fig. 5. Scattergram of differences in within-laboratory serum creatinine concentration between human Hb F–spiked and unspiked samples at low creatinine (*x* axis) and high creatinine (*y* axis) concentrations.

Within-laboratory differences between human Hb F–spiked and unspiked samples are grouped by method–analyzer combination (see legend to Fig. 1 for symbol definitions; green, red, and orange symbols indicate enzymatic, compensated Jaffe, and uncompensated Jaffe method–analyzer combinations, respectively). Data are presented as mean differences and are calculated from the individual laboratory data.

Problem: Low creatinine concentrations



Europe - Clin Chim Acta 2011; 412: 2070–5



-20 to + 30%
(outliers removed)

Zero bias

Nova Statstrip LH whole blood

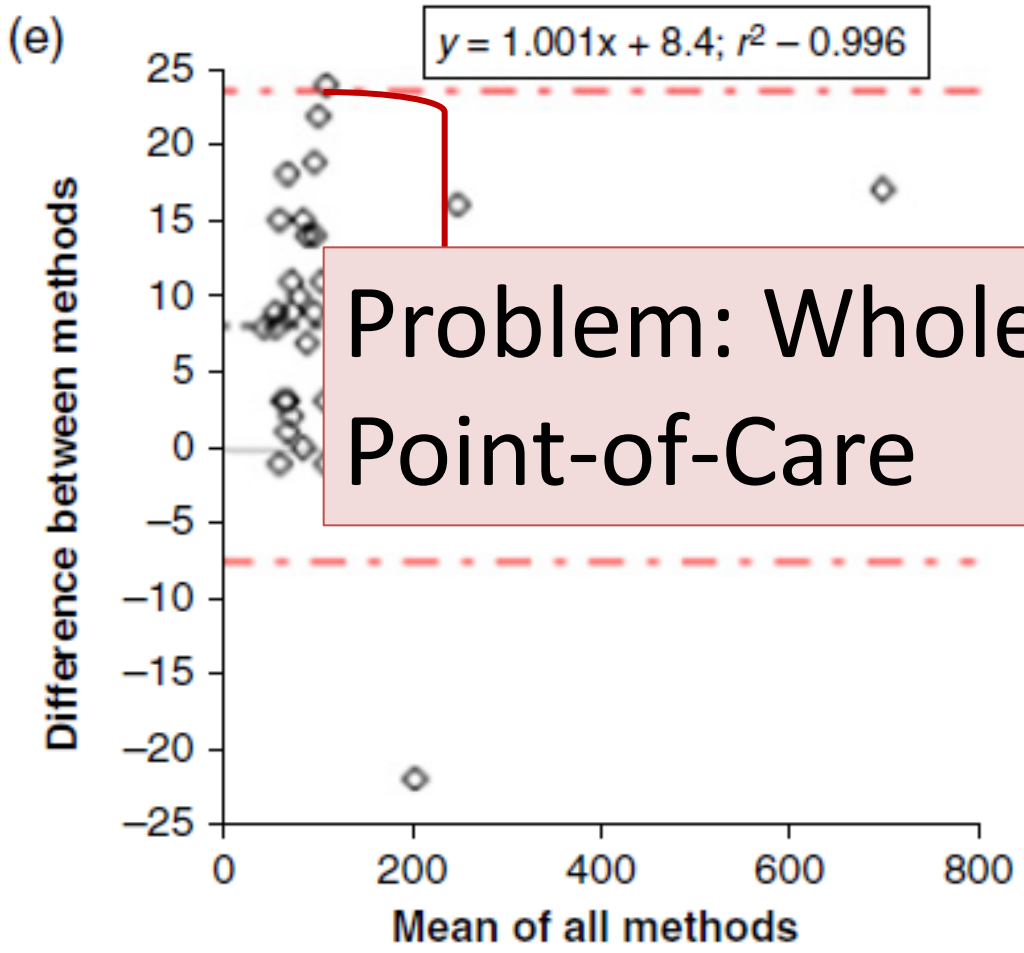
Ann Clin Biochem 2013; **50**: 47–52.

Original Article

Which point-of-care creatinine analyser for radiology: direct comparison of the i-Stat and StatStrip creatinine methods with different sample types

Goce Dimeski, Vera Tilley, Brock W Jones and Nigel N Brown

Pathology Queensland, Chemical Pathology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia
Corresponding author: Goce Dimeski. Email: goce_dimeski@health.qld.gov.au



-2 to + 24%
(outlier removed)

Problem: Whole Blood / Point-of-Care

i-STAT LH whole blood

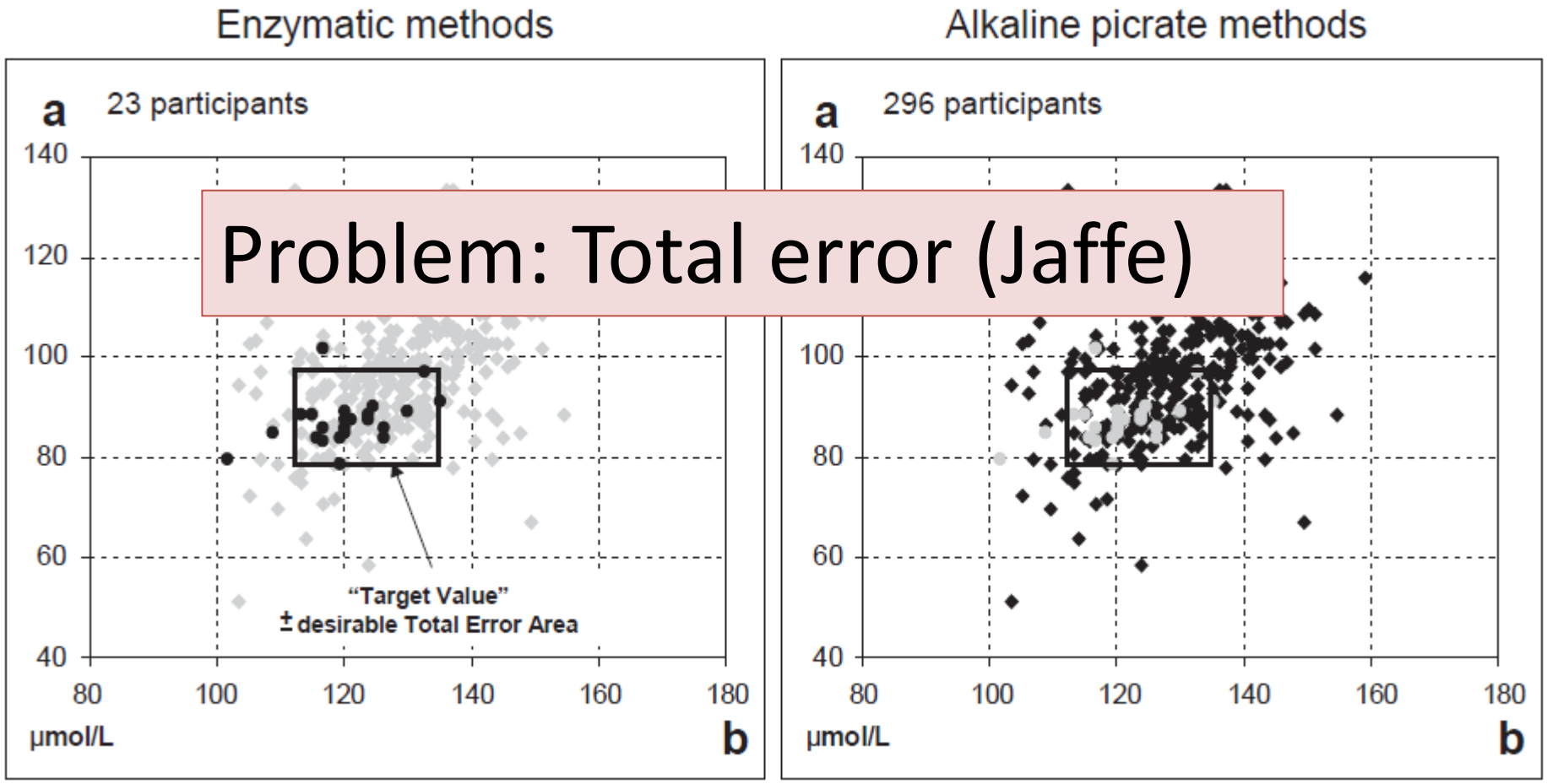
Original Article

Which point-of-care creatinine analyser for radiology: direct comparison of the i-Stat and StatStrip creatinine methods with different sample types

Goce Dimeski, Vera Tilley, Brock W Jones and Nigel N Brown

Pathology Queensland, Chemical Pathology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia
Corresponding author: Goce Dimeski. Email: goce_dimeski@health.qld.gov.au

Ann Clin Biochem 2013; **50**: 47–52.



Problem: Total error (Jaffe)

Fig. 2. Youden plots for creatinine results of control materials B 2011 (a) and D 2011 (b) by individual laboratories participating in EQAS Prolarit.

2014


Clinica Chimica Acta 427 (2014) 100–106
Contents lists available at ScienceDirect
Clinica Chimica Acta
journal homepage: www.elsevier.com/locate/clinchim

Evaluation of the impact of standardization process on the quality of serum creatinine determination in Italian laboratories

Anna Carobene [a,*], Ferruccio Ceriotti [a], Ilenia Infusino [b], Erika Frusciante [b], Mauro Panteghini [b]

IFU (Egypt)

Assay Principle

Creatinine reacts with picric acid under alkaline condition to form a yellow-red complex. The absorbance of the color produced, measured at a wavelength 492 nm, is directly proportional to creatinine concentration in the sample.

Creatinine + picrate $\xrightarrow{\textit{Alkaline pH}}$ yellow-red complex

Reagents

Standard (ST)

2 mg/dL	177 µmol/L

Reagent (R)

Picric acid	25 mmol/L
Sodium hydroxide	0.4 mol/L

Creatinine assays

- IDMS aligned: Abbott, Beckman-Coulter.

Problems: Non-standardised assays
Inadequate information

- Internet Search (2013):
- 53 manufacturers; 85 assays
  - "IDMS" traceable 13
  - Calibrator traceable 16
  - Calibrator Value 19
  - No calibrator 10
  - Uncertain 27

Most assays either not traceable or unable to tell

Ongoing Issues

- Good assays available for adults
  - Traceable enzymatic assays
  - Cost is major factor
- Reasonable assays available for adults
  - Traceable Jaffe assays
- Improvements required
  - Paediatrics (accuracy, interferences)
  - Whole blood assays
  - Developing world (assays, assay information)

Creatinine – the lessons

- Traceability for routine tests is possible
- Even for “simple” analytes, it is difficult
- It requires collaboration between:
  - Metrology
  - Clinical Laboratory Science
  - Clinical groups
  - Manufacturers
  - EQA Providers
  - Regulators business
- The people and the organisations

CKD Task Force

- International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)
- World Association of Societies of Pathology and Laboratory Medicine (WASPLM)

- Goal:
- To help national organisations implement best practice programs for CKD management