

eGFR – a historical timeline and update

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AACB, Annual Scientific Meeting – Sydney 2011



Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement

MJA 2005; 183 (3): 138-141

“An e-GFR shall be automatically calculated for every request for serum creatinine concentration in people aged ≥ 18 years”

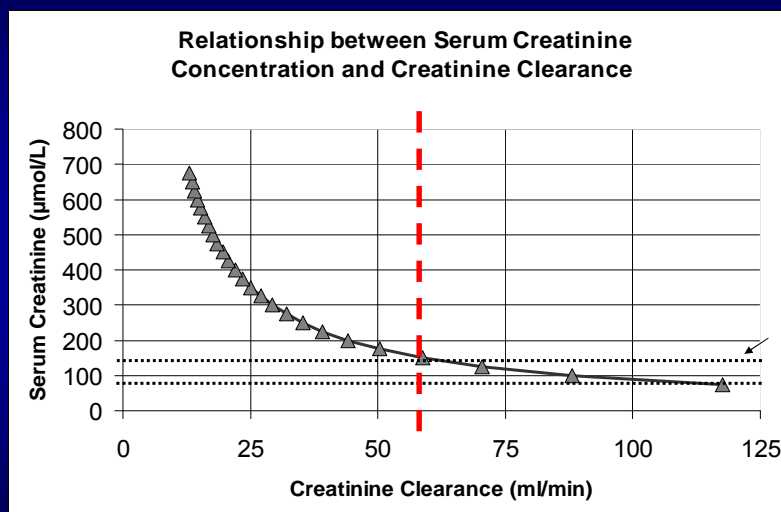


eGFR: the timeline

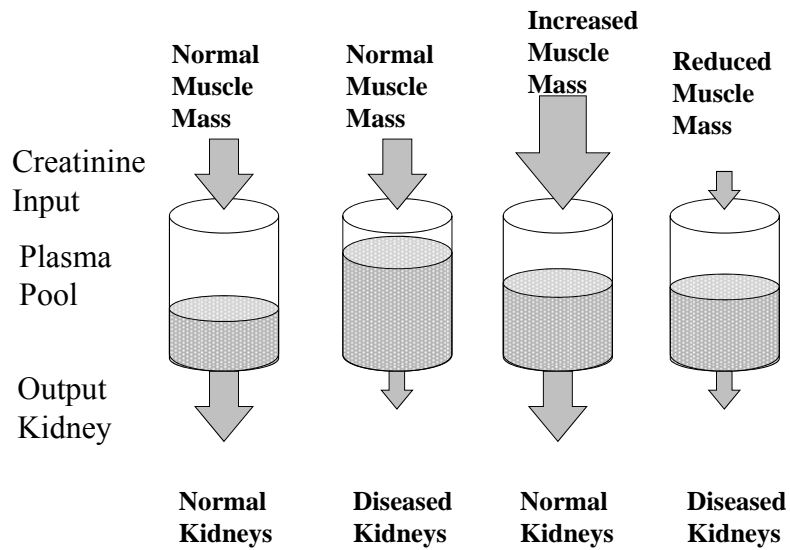
- Australasian Position Statement – Aug 2005
- Widespread uptake of MDRD equation
- Australasian Creatinine Consensus Working Group – December 2006
- Revised Recommendations – Oct 2007
– *MJA* 2007; 187(8): 459-463
- Updated consensus 2011 – new equation: CKD-EPI



The problem with serum Creatinine



Effect of Muscle Mass on Serum Creatinine:



Original Article

The influence of a cooked-meat meal on estimated glomerular filtration rate

David J Preiss¹, Ian M Godber¹, Edmund J Lamb², R Neil Dalton³ and Ian R Gunn¹

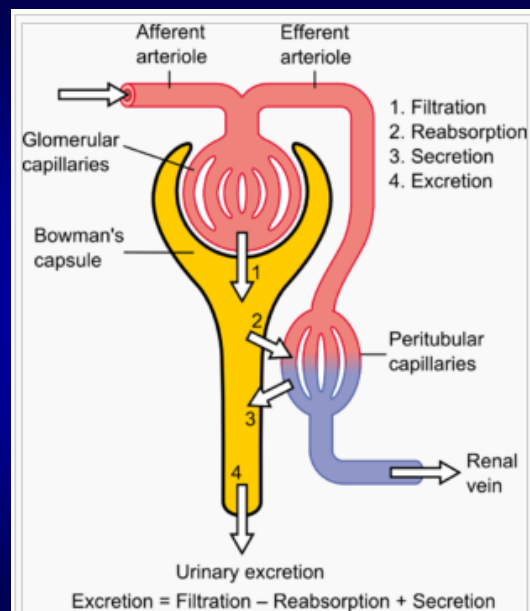
Results Following intake of cooked meat, median serum creatinine concentration (kinetic Jaffe) increased from 80.5 $\mu\text{mol/L}$ preprandially to 101.0 $\mu\text{mol/L}$ 1–2 h postprandially ($P < 0.0001$), and 99.0 $\mu\text{mol/L}$ 3–4 h postprandially ($P < 0.0001$).

Ann Clin Biochem 2007; 44: 35–42

Glomerular Filtration Rate (GFR)

Based on concept of clearance: -

"The volume of plasma from which a substance is removed (per unit time) by glomerular filtration during its passage through the kidney"

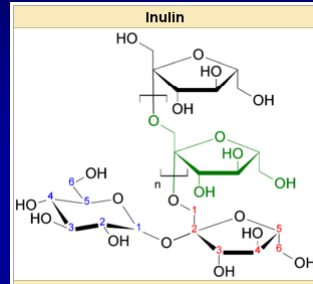


Inulin Clearance – a gold standard?

Inulin - naturally occurring plant polysaccharides belonging to class of compounds known as fructans

It is not secreted or reabsorbed at the nephron allowing GFR to be calculated

Complex protocol –rarely used



GFR (Glomerular Filtration Rate) Procedure Guidelines

Nuclear Medicine Department
Christchurch Hospital
Phone 80867
Fax 80869

Canterbury
District Health Board
Te Pahi Hāora o Waitaha

Issue Date May 2009

99Tc-DTPA clearance

TEST DATA:
Height: 167 cm
Weight: 42 kg
Mass of Injected Dose: 0.8380 g
Injection Time: 09:23

Sample	Day	Time	Elapsed Time	Counts
1	1	11:12	1:49	18445
2	1	13:00	3:27	8184
3	1	14:52	5:29	4237

Standard Mass: 0.0850 g
Standard Volume: 500.0 mL
Standard Counts: 139950
Blood Standard Mass: 0.0510 g
Blood Standard Volume: 500.0 mL
Blood Standard Counts: 82931

TEST RESULTS:
Surface Area: 1.4232 m²
Predicted Counts at T0: 37652
Extra-cellular Volume: 17.3 L
DTPA Half-life in Blood: 103.7 min

GFR: 119.45 mL/min GFR adjusted for surface area: 140.34 mL/min
1.52 mL/sec 2.34 mL/sec

Creatinine Clearance

Timed urine collection for creatinine measurement
(usually 24h)

Blood sample - within the period of collection

Problems: -

- Accurate collection and volume measurement
- Within subject variability = 11%



Creatinine Clearance - more issues:

- Tubular secretion of creatinine
- Overestimates GFR 1.1 to 1.2 x Inulin Clearance
GFR of 80 - 90 mL/min:
 - overestimate GFR greater in renal failure



National Kidney Foundation; Disease Outcomes Quality Initiative (K-DOQI)

Ann Intern Med 2003; 139: 137-147

- Serum creatinine should not be used alone
- Clinical Laboratories should report an estimate of GFR using a **prediction equation**, in addition to reporting serum creatinine
- Measurement of CrCl using timed urine collections (eg 24h) does not improve the estimate of GFR



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 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Ann Intern Med 2003; 139: 137-47



Prediction of Creatinine Clearance from Serum Creatinine¹

DONALD W. COCKCROFT and M. HENRY GAULT

Departments of Medicine, Queen Mary Veterans' Hospital, Montreal, Quebec,
and Memorial University, St. John's, Newfoundland

Key Words. Serum creatinine · Creatinine clearance · Creatinine excretion · Renal function · Age

Abstract. A formula has been developed to predict creatinine clearance (C_{cr}) from serum creatinine (S_{cr}) in adult males:

$$C_{cr} = \frac{(140 - \text{age}) (\text{wt kg})}{72 \times S_{cr} (\text{mg}/100 \text{ ml})}$$

(15% less in females). Derivation included the relationship found between age and 24-hour creatinine excretion/kg in 249 patients aged 18-92. Values for C_{cr} were predicted by this formula and four other methods and the results compared with the means of two 24-hour C_{cr} 's measured in 236 patients. The above formula gave a correlation coefficient between predicted and mean measured C_{cr} 's of 0.83; on average, the difference between predicted and mean measured values was no greater than that between paired clearances. Factors for age and body weight must be included for reasonable prediction.

It is useful to be able to quickly predict creatinine clearance (C_{cr}) without collecting urine, particularly when instituting therapy with potentially toxic drugs which are primarily excreted by the kidneys. Several formulae [1-3] and a nomogram [4, 5] have been reported to give satisfactory results. Serum creatinine (S_{cr}), body weight, age and sex are variables which have been utilized to predict C_{cr} .

- 249 hospitalised patients
- aged 18 - 92
- Almost all males
- Compared (CrCl) 24h urine with prediction formula based on serum creatinine
- Correlation between predicted and mean measured CrCl = 0.83

Canterbury District Health Board
To Pouri Hauora o Waiatahi

Blue Book | Management Guidelines for Common Medical Conditions

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How to adjust the dose:

1. Choose the dose-rate (DR) that you would use in this patient if renal function were normal (DR(normal)).
2. Calculate renal function. For estimated renal function, use either the estimated GFR (eGFR) as supplied by Canterbury Health Laboratories, or calculate CrCl using the Cockcroft and Gault equation as follows:

$$CrCl (\text{ml}/\text{min}) = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{plasma creatinine (mcmol/l)} \times 0.8} \quad (\times 0.85 \text{ if female})$$

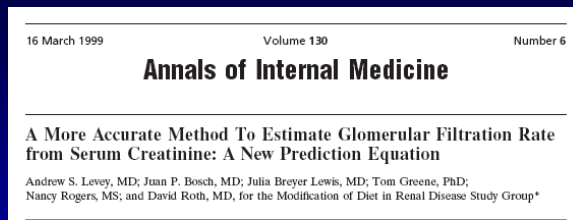
- Lean body weight (males) = 50 kg + 0.9 kg for each cm over 150 cm in height.
- Lean body weight (females) = 45 kg + 0.9 kg for each cm over 150 cm in height.

Guidance given to RMOs
Needs height for calculation (*of lean body weight*)
NB – advice says can use eGFR from laboratory (MDRD)

MDRD = Modification of Diet in Renal Diseases

MDRD (mL/min/1.73m²) 1999

$$GFR = 186 \times \left(\frac{[creatinine]}{0.0884} \right)^{-1.154} \times age^{-0.203} \times 0.742 \text{ (female)}$$

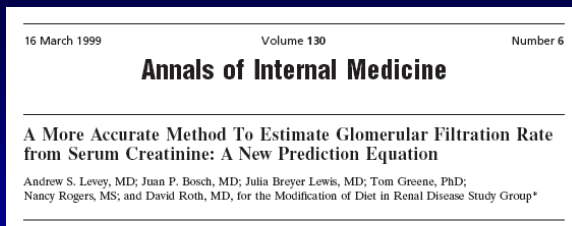


“MDRD” study

A multicenter trial, evaluated the effect of dietary protein restriction and BP control on progression of renal disease

At baseline, GFR, serum creatinine and other variables were measured in patients with chronic renal disease

The purpose was to develop an equation that could improve the prediction of GFR from serum creatinine



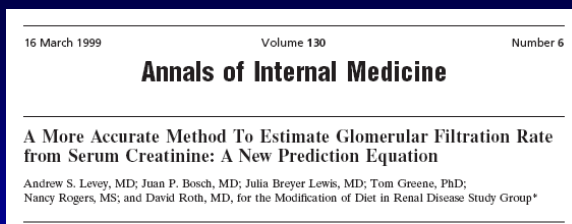
“MDRD” study

1628 patients enrolled in the baseline period;

- 1070 were selected as the training sample
- remaining 558 were the validation sample

MDRD Equation was developed by stepwise regression analysis applied to the training sample

It was then tested and compared with other equations in the validation sample



“MDRD” study

GFR measured as renal clearance of ^{125}I -iothalamate

Creatinine clearance computed from creatinine excretion in 24-h urine collection and single measure of serum creatinine

16 March 1999

Volume 130

Number 6

Annals of Internal Medicine

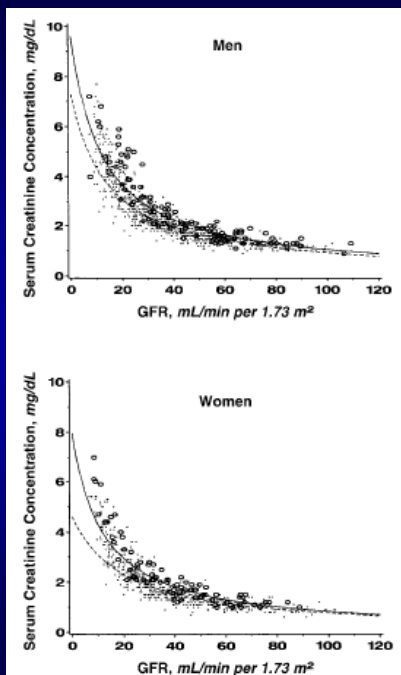
A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation

Andrew S. Levey, MD; Juan P. Bosch, MD; Julia Breyer Lewis, MD; Tom Greene, PhD; Nancy Rogers, MS; and David Roth, MD, for the Modification of Diet in Renal Disease Study Group*

“MDRD” study

Serum and urine creatinine measured by kinetic alkaline picrate assay

GFR and creatinine clearance were expressed per 1.73 m² of body surface area by multiplying values by 1.73/body surface area



“MDRD” study

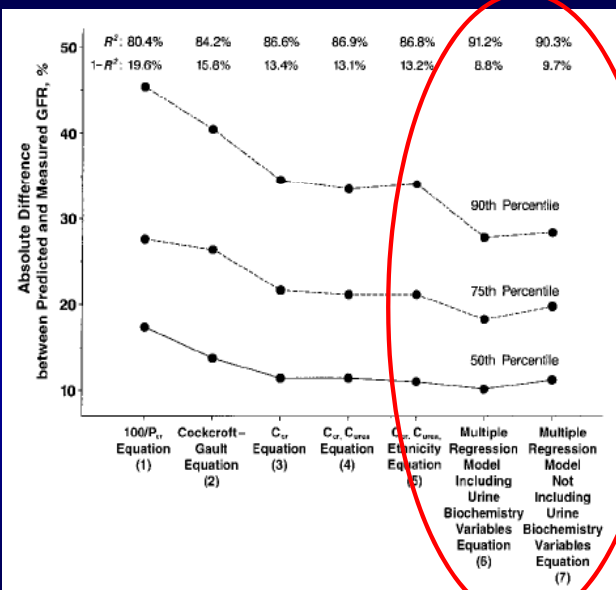
Each point represents the baseline measurement for one patient during the MDRD Study

GFR was measured as the renal clearance of ¹²⁵I-iothalamate

“MDRD” study

Table 3. Comparison of Equations To Predict Glomerular Filtration Rate (mL/min per 1.73 m²) from Serum Creatinine Concentration*

Equation 1: Serum creatinine GFR = 0.69 × [100/P _{cr}]
Equation 2: Cockcroft-Gault formula GFR = 0.84 × [Cockcroft-Gault formula]
Equation 3: Creatinine clearance GFR = 0.81 × [C _{cr}]
Equation 4: Average of creatinine and urea clearance GFR = 1.11 × [(C _{cr} + C _{urea})/2]
Equation 5: Creatinine clearance, urea clearance, and demographic variables GFR = 1.04 × [C _{cr}] ^{+0.751} × [C _{urea}] ^{+0.226} × [1.109 if patient is black]
Equation 6: Demographic, serum, and urine variables GFR = 198 × [P _{cr}] ^{-0.858} × [Age] ^{-0.167} × [0.822 if patient is female] × [1.178 if patient is black] × [SUN] ^{-0.293} × [UUN] ^{+0.249}
Equation 7: Demographic and serum variables only GFR = 170 × [P _{cr}] ^{-0.999} × [Age] ^{-0.176} × [0.762 if patient is female] × [1.180 if patient is black] × [SUN] ^{-0.170} × [Alb] ^{+0.319}



“MDRD” study

Modification of Diet in Renal Diseases

(MDRD) equation; *Ann Intern Med* 1999; 130: 461-70

- $\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times [\text{creat } (\mu\text{mol/l)} \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ (if female)}$



Modification of Diet in Renal Diseases

(MDRD) equation; *Ann Intern Med* 1999; 130: 461-70

- $\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times [\text{creat } (\mu\text{mol/l)} \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ (if female)}$
- Does not require height or weight
- Recommended by the National Kidney Foundation and American Society of Nephrology
- www.kidney.org/kls/professionals/gfr_calculator.cfm



Modification of Diet in Renal Diseases

(MDRD) equation; *Ann Intern Med 1999; 130: 461-70*

- $\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times [\text{creat } (\mu\text{mol/l)} \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ (if female)}$
- **Validated** in patients with CKD (GFR 40ml/min/1.73m²) and predominantly Caucasian (>500 subjects)
- Also validated in diabetic kidney disease, renal transplants, African-Americans with non-diabetic kidney disease



Modification of Diet in Renal Diseases

(MDRD) equation; *Ann Intern Med 1999; 130: 461-70*

- $\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times [\text{creat } (\mu\text{mol/l)} \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ (if female)}$
- **Not validated** in children (age<18 years), pregnant women, the elderly (age >70 years)
- Ethnic groups other than Caucasians and African Americans
- In normal individuals



Modification of Diet in Renal Diseases

(MDRD) equation; *Ann Intern Med* 1999; 130: 461-70

- $\text{GFR (ml/min/1.73m}^2) = 186 \times [\text{creat } (\mu\text{mol/l)} \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ (if female)}$
- Note "186" equation reflecting non-IDMS aligned creatinine
- Beckman Coulter CX3 used in MDRD study: +ve bias
- Latterly "175" equation with IDMS aligned methods



MDRD versus C&G - which is better ?

- Consider *bias* - ie how close the predicted GFR is to the true GFR
- Consider *precision* - ie the variability or dispersion of prediction equation estimates around the gold standard GFR



Evaluation of e-GFR vs radionuclide GFR (N-GFR) Christchurch Hospital Study - 2005

Number of patients = 601

Age range (yrs) = 16-85

Sex (M/F) = 174/426

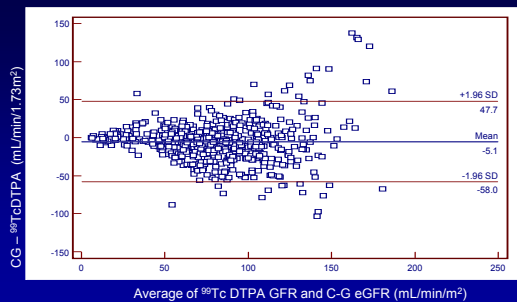
Corrected N-GFR range (mL/min/1.73m²) = 3.91- 213

Plasma Cr within 24hrs of GFR

Ann Clin Biochem 2006; 43: 309-13

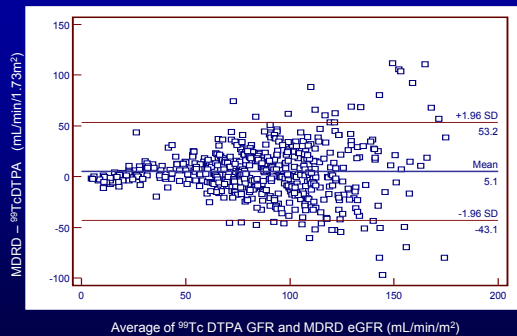


Cockcroft - Gault eGFR



Mean difference(95%CI)
- 5.1 (-7.0 to -3.1)

MDRD eGFR



Mean difference (95%CI)
+ 5.1 (3.0 to 7.3)

Ann Clin Biochem 2006; 43: 309-13

Overall accuracy of e-GFR; MDRD vs C&G

Accuracy	MDRD (%)	CG (%)
Within 30% of N-GFR	75	73
Within 50% of N-GFR	91	92

Ann Clin Biochem 2006; 43: 309-13



“Both equations perform acceptably well for most clinical purposes. The abbreviated MDRD equation, however, has operational advantages in not requiring height or weight and can easily be adapted to laboratory computer systems”.

Ann Clin Biochem 2006; 43: 309-13



So, what effect has eGFR introduction had?

- Unification of units of measurement
- Promoted standardisation of assays
- Increased referrals to Nephrology

Australasian Position Statement

MJA 2005; 183 (3): 138-141

Creatinine - preferred units are $\mu\text{mol/L}$

Creatinine to be reported to nearest $\mu\text{mol/L}$ (up to 300 $\mu\text{mol/L}$)

e-GFR to be reported in mL/min or $\text{mL/min}/1.73\text{m}^2$

e-GFR to be reported with every request for creatinine

Preferred equation for e-GFR is abbreviated MDRD

Reporting restricted to subjects >18 years

Values to be reported as $>60\text{mL/min}$, rather than exact figure

Age-adjusted reference intervals may be used



Australasian Position Statement

MJA 2005; 183 (3): 138-141

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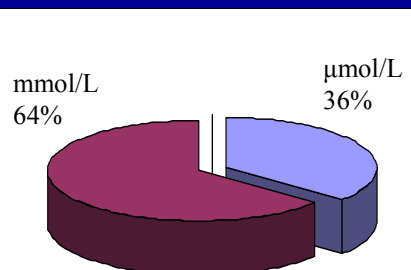
THE NEW ZEALAND MEDICAL JOURNAL

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Reporting of estimated glomerular filtration rate (eGFR) in New Zealand—what are the clinical laboratories doing?

Mohamed Saleem, Christopher Florkowski; for the Australasian Creatinine
Consensus Working Group



NZ Laboratories in 2006
units for reporting creatinine

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

Timothy H Mathew, David W Johnson, Graham RD Jones on behalf of the Australasian Creatinine Consensus Working Group

1. Measurement of serum creatinine concentration and consideration of the revised (MDRD "175") eGFR formula

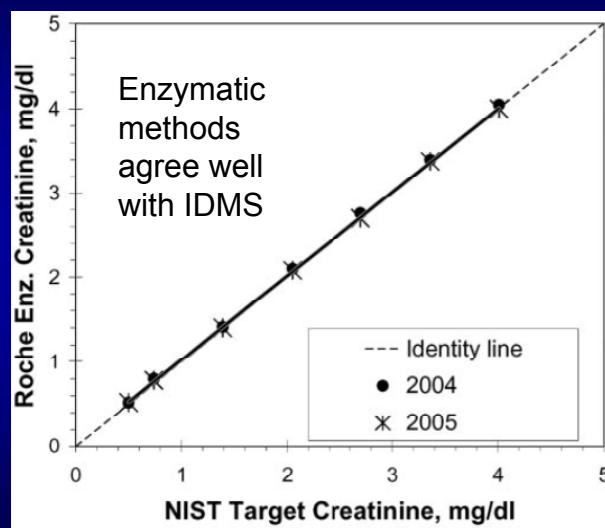
Recommendation: The calculation of eGFR should be changed to use the MDRD "175" formula for assays aligned to the international reference method.

The revised MDRD formula (the "175" formula)⁶

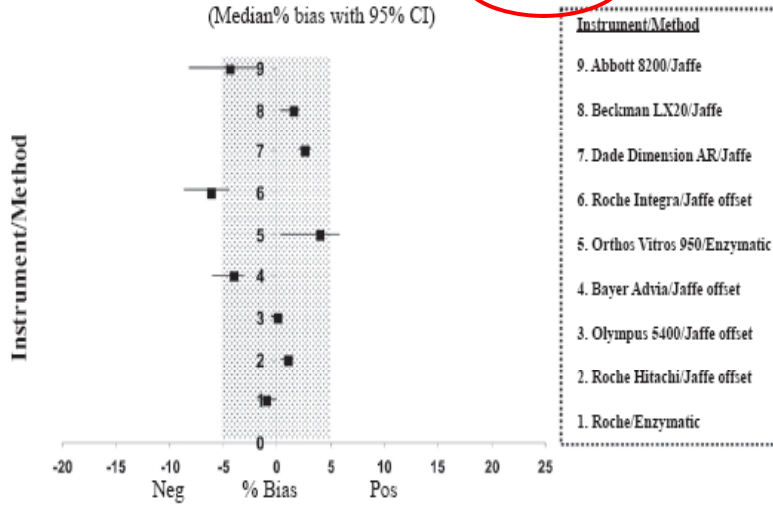
$$eGFR = 175 \times (S_{CR} \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ [if female]})$$

where MDRD = Modification of Diet in Renal Disease,² eGFR = estimated glomerular filtration rate (mL/min/1.73 m²), S_{CR} = serum creatinine concentration (μmol/L), and age is expressed in years.

Clin Chem 2006; 52(1): 5-18

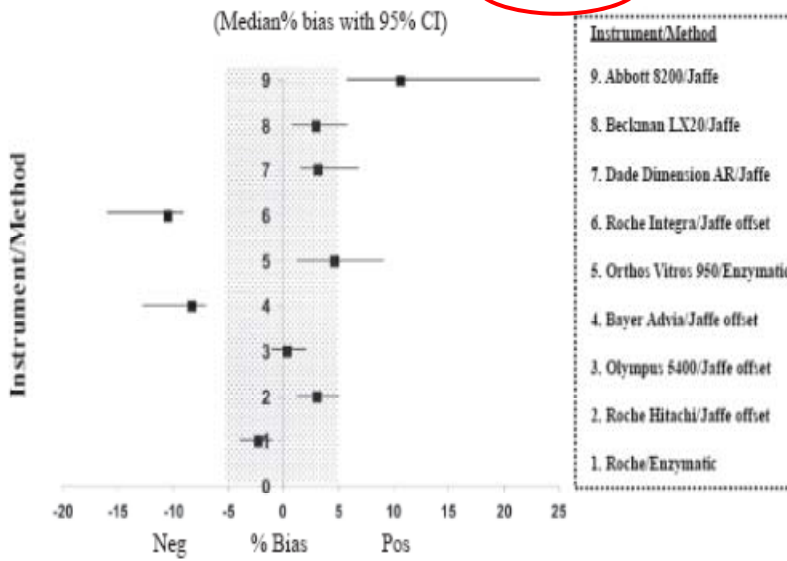


b. Creatinine Method Bias vs IDMS (Serum creat $> 150 \mu\text{mol/L}$)

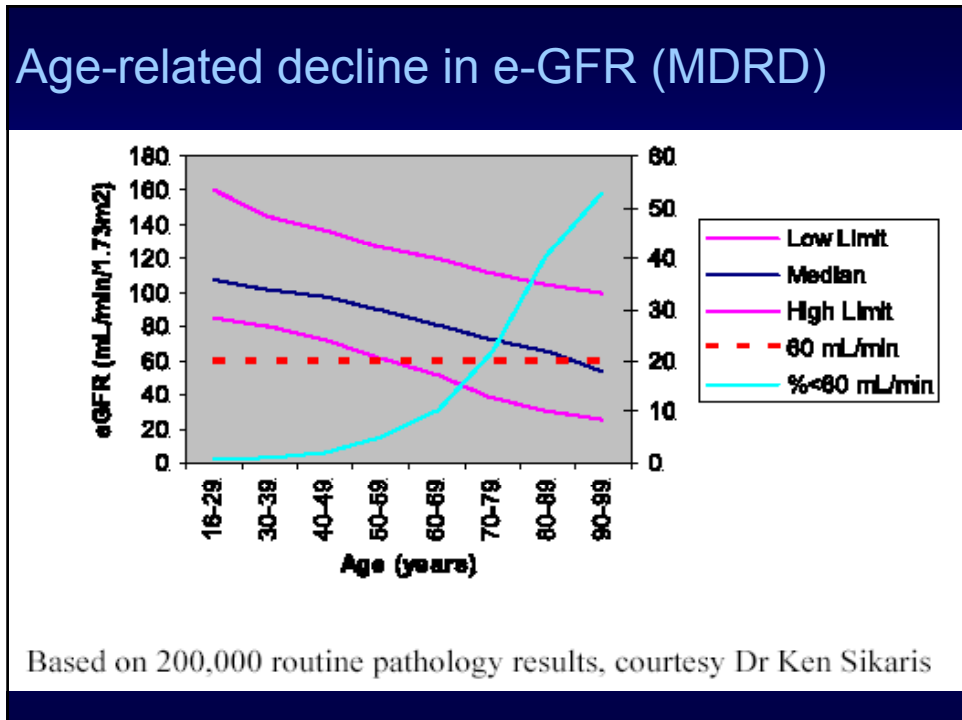
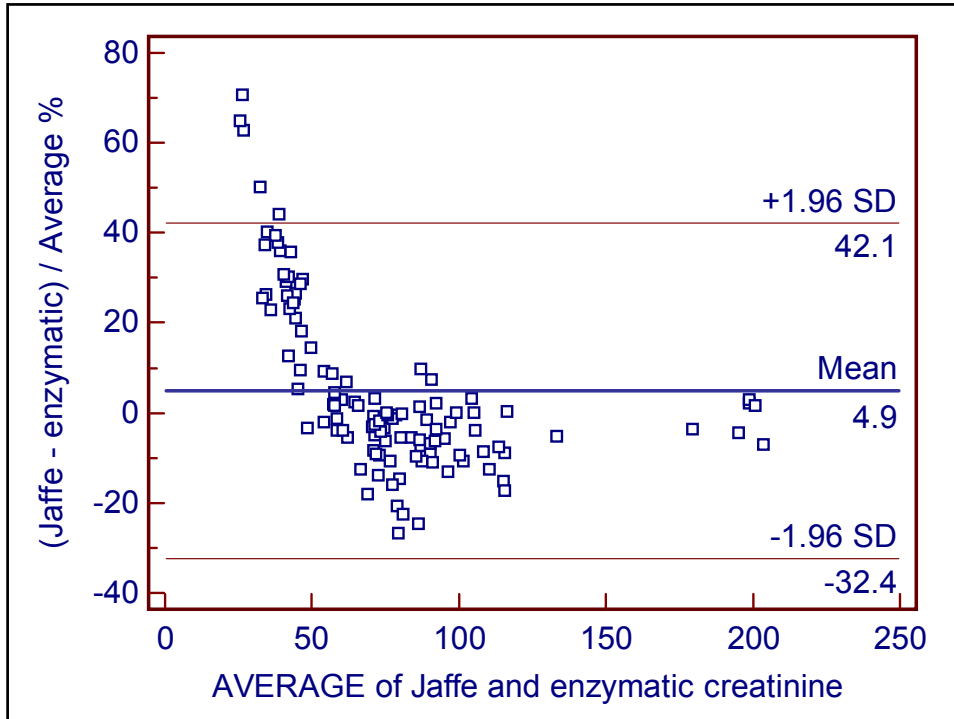


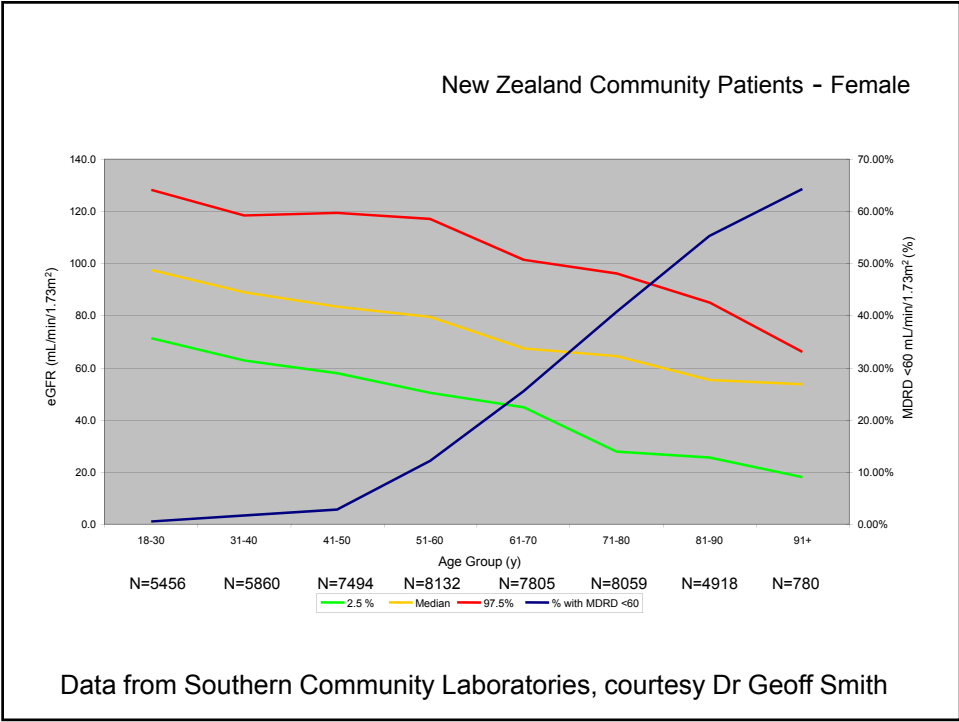
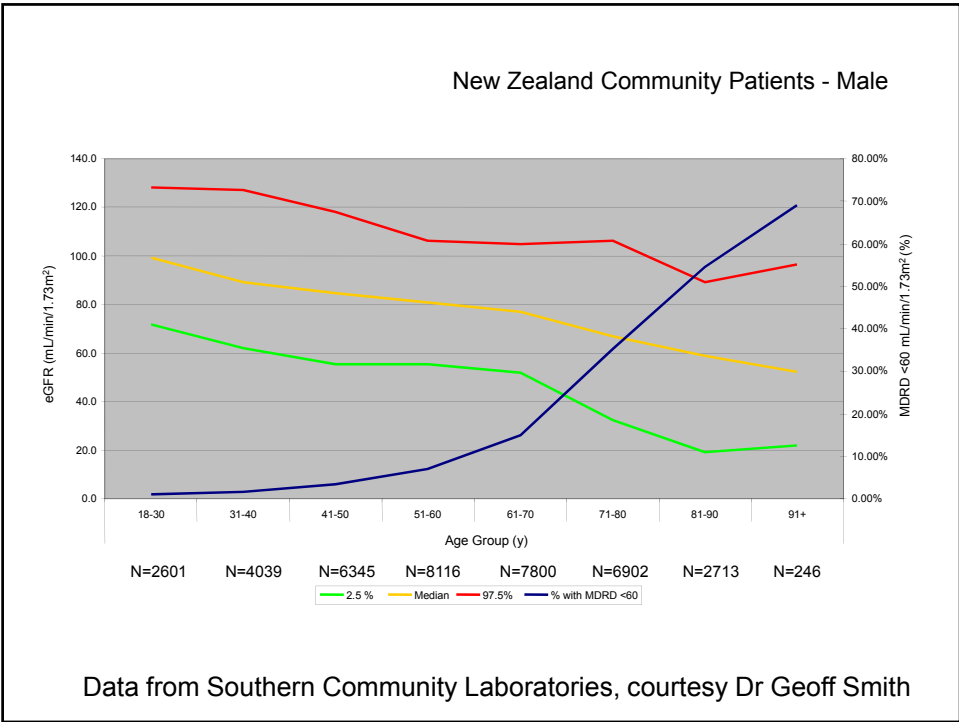
Clin Biochem Rev Vol 27 November 2006 | 173

a. Creatinine Method Bias vs IDMS (Serum creat $\leq 150 \mu\text{mol/L}$)



Clin Biochem Rev Vol 27 November 2006 | 173





Age-related decline in GFR: Physiology or Disease ?

Kidney International 1984; 26: 861-8.

- Baltimore Longitudinal Study of Ageing - 446 community-dwelling people over 24 years
- Fall in GFR with age largely attributable to hypertension (HT)
- One third, in absence of HT or other causes of renal disease had stable GFR



Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis



Chronic Kidney Disease Prognosis Consortium*

105 872 subjects from 14 studies with urine albumin to creatinine ratio (ACR) and 1,128,310 from 7 studies with protein dipstick measurements

Relationship between eGFR, proteinuria and mortality

Lancet 2010; 375: 2073-81

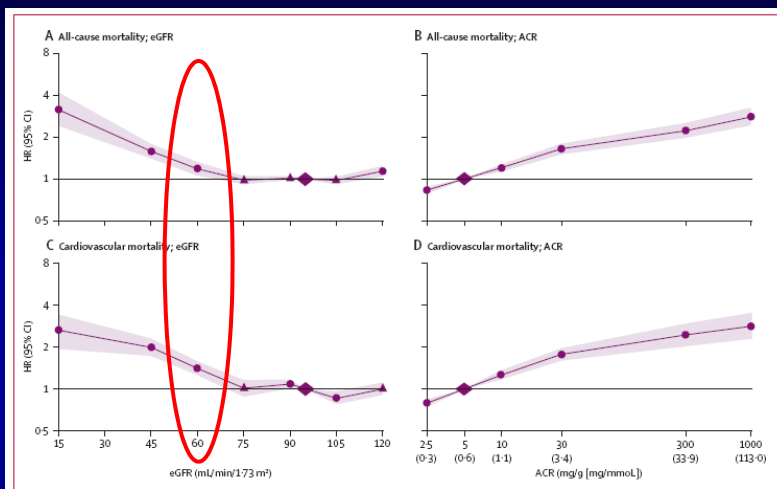


Figure 2: Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR)
 Hazard ratios and 95% CIs (shaded areas) according to eGFR (A, C) and ACR (B, D) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1.73 m² and ACR 5 mg/g (0.6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g to mg/mmol multiply by 0.113. Approximate conversions to mg/mmol are shown in parentheses.

Increased mortality below 60 ml/min/1.73m²
 No consistent age interaction

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate:

New developments and revised recommendations

Australasian Creatinine Consensus Working Group

4a. Age-related reference intervals for serum creatinine concentration in adults

Recommendation: Age-related reference intervals for serum creatinine concentration are not recommended in adults.

4b. Age-related reference intervals for eGFR in adults

Recommendation: Age-related decision points for eGFR are not recommended in adults.

Updated 2011 recommendations – in press

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

Timothy H Mathew, David W Johnson, Graham RD Jones on behalf of the Australasian Creatinine Consensus Working Group

3. Age-related decision points for eGFR

Recommendation: eGFR values in the range 45–59 mL/min/1.73 m² in people aged ≥ 70 years should be interpreted with caution. If there are no other signs of kidney damage (eg, proteinuria, haematuria), a stable eGFR in this range may be consistent with typical GFRs for this age group and an absence of chronic kidney disease (CKD)-related complications.

The screenshot shows a laboratory information system (LIS) interface. The window title is 'Latte - [WE]'. The menu bar includes 'Format', 'Edit', 'View', 'Options', 'Lists', 'Window', 'Help', and 'Browse'. The toolbar contains various icons for file operations and editing. The main display area shows patient information and lab results.

Page 01 MORE TO COME Next WE

Lab No Name Causal Prt
 Test Doctor Date Sex Birthdate

Prof. P M George PMGEO Arr 10Jun05 12:18
 Chch Hospital Outpatient CGN Col 10Jun05 11:30
 Fax destination : CGN No fax available

HIGHLIGHTED OR FLASHING RESULTS HAVE NOT BEEN RELEASED BY THE LAB FOR REPORTING

Sodium	142	mmol/L	136-146
Potassium	4.2	mmol/L	3.5-5.0
Creatinine	0.10	mmol/L	0.05-0.11
Est GFR	70*	mL/min/1.73m2	80-120

Estimated GFR is only reliable under steady state conditions (stable creatinine >4 days). Caution should be used in interpretation in non-Caucasians, extremes of body weight, pregnancy, anaemalous subjects, low creatinine (<0.05mmol/L) and other complex cases. **GFR declines by 1mL/min/year over age 40 years.**

Lipid Screen

			Desirable Range
Cholesterol	5.9*	mmol/L	3.2-5.2
Triglyceride	4.1*	mmol/L	0.3-1.5

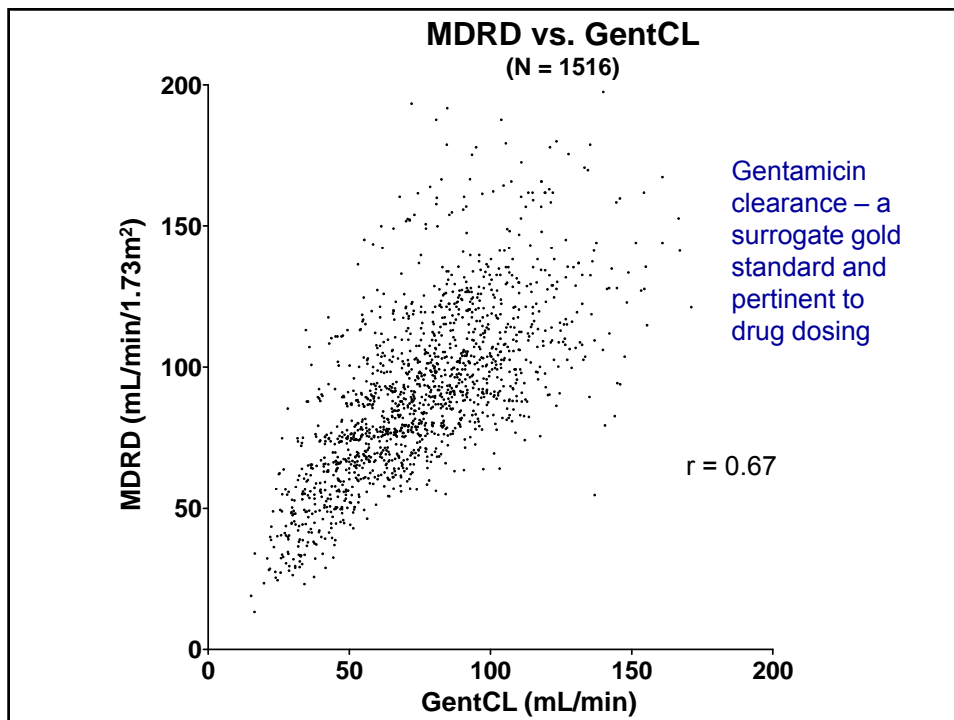
User: WOLF CANTERBURY HEALTH LABORATORIES Printer: 52 CLIP OVR NUM

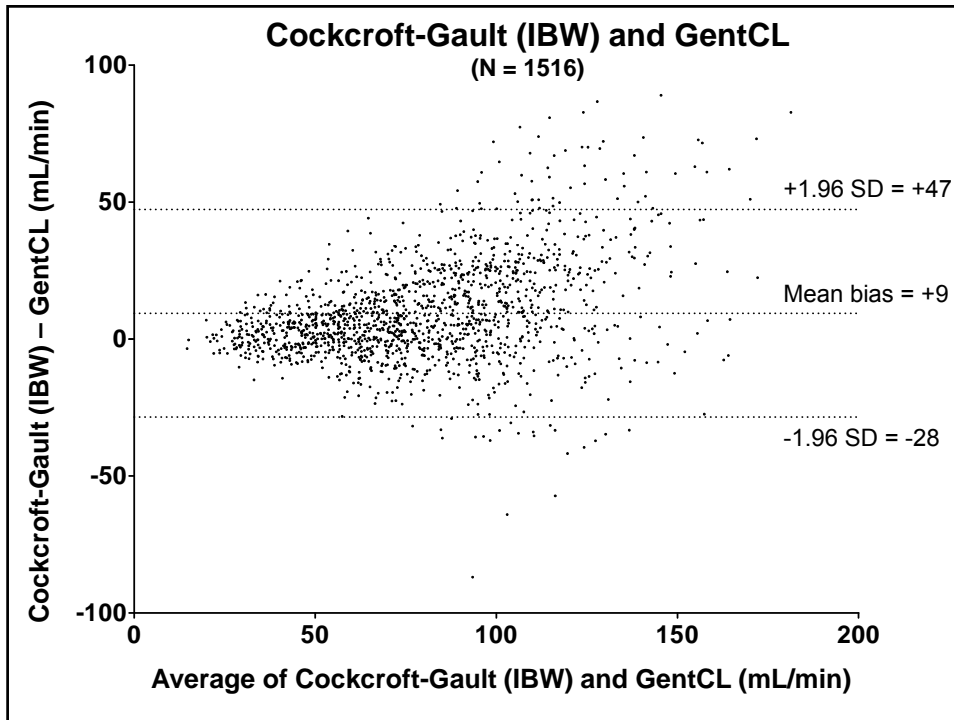
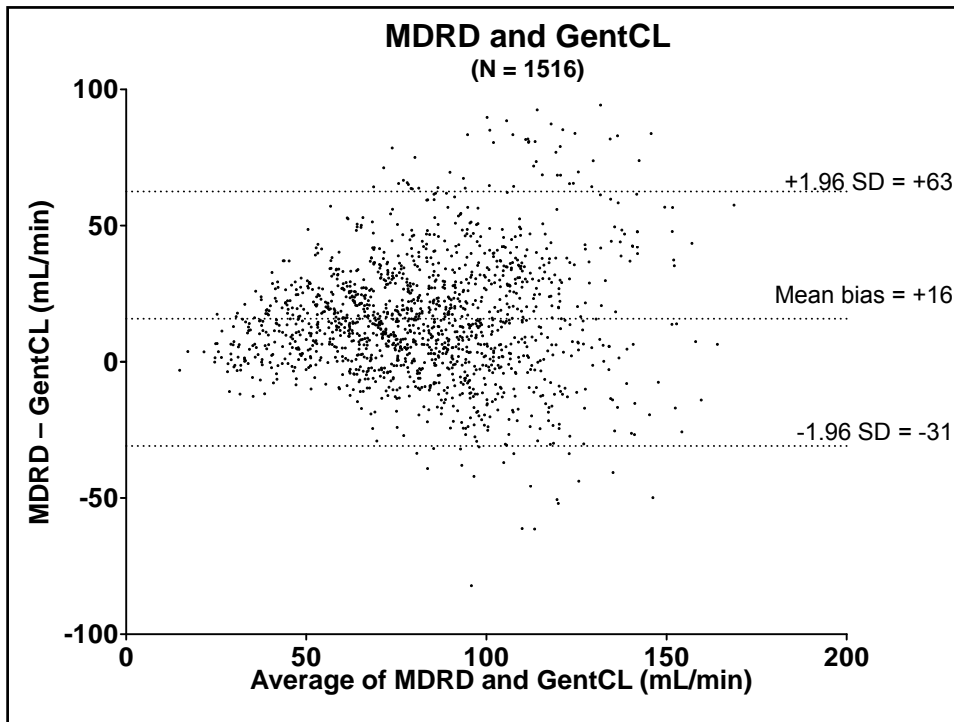
Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

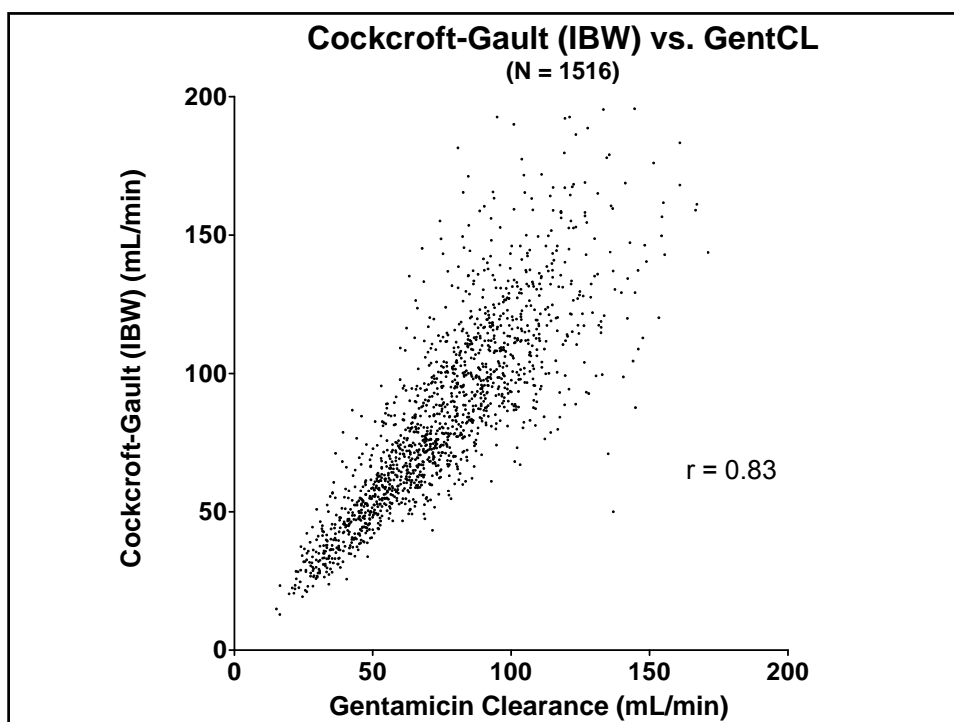
Timothy H Mathew, David W Johnson, Graham RD Jones on behalf of the Australasian Creatinine Consensus Working Group

In most out-of-hospital settings, where eGFR (MDRD) is on hand and no other measure of GFR is known, it is clinically appropriate to use eGFR to assist drug dosing decision making.

For critical dose drugs, particularly in hospital setting, it remains important to adhere to recommendations that usually involve use of the Cockcroft-Gault equation, or to measure creatinine clearance in order to amend dosing for renal function.







Chronic kidney disease and automatic reporting of estimated glomerular filtration rate:

New developments and revised recommendations

Australasian Creatinine Consensus Working Group

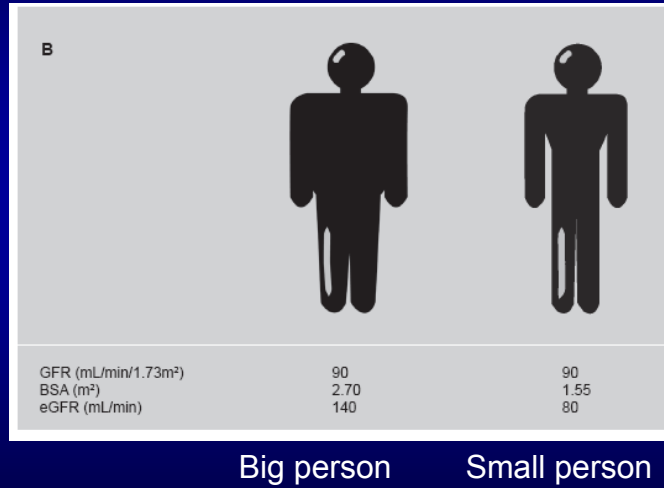
5. The use of eGFR for adjusting drug dosing in patients with reduced kidney function

Recommendation: Dose reduction of some drugs is recommended for patients with reduced kidney function. Both eGFR (mL/min/1.73m²) and estimated CrCl (mL/min) provide an estimate of relative renal drug clearance. If using eGFR for drug dosing body size should be considered, in addition to referring to the approved Product Information.

For drugs with a narrow therapeutic index therapeutic drug monitoring or a valid marker of drug effect should be used to individualise dosing.

Updated 2011 recommendations – in press

In drug dosing, body size should be considered
May need to adjust eGFR for actual BSA



JONAH
LOMU

Weight: 118 kg; Height 1.96 m

Waist 69cm

BMI: 30.7 kg/m²

Ethnicity (and e-GFR): more than just BMI ?

How do we define ethnicity ?

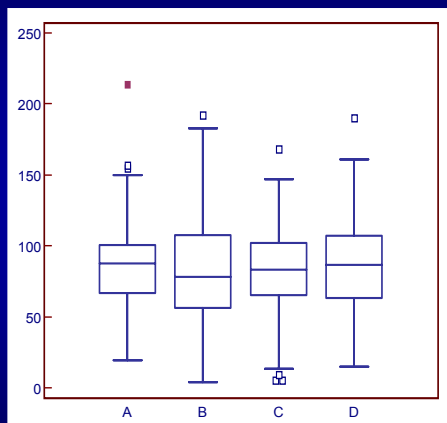
Ethnic correction factors for MDRD ?

At higher BMI levels, Polynesians significantly leaner than Europeans

Int J Obes Relat Metab Disord 1999; 23(11): 1178-83



^{99}Tc -DTPA GFR by BMI Group



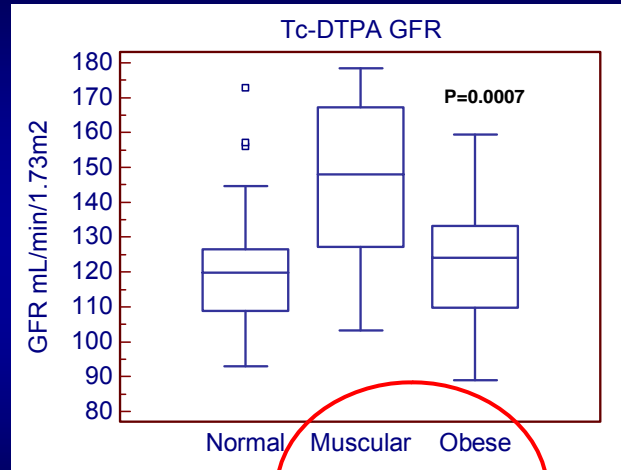
	BMI (kg/m ²)	Number	Median GFR (inter-quartile range) mL/min/1.73m ²
A	<20	74	88 (67 – 101)
B	20-25	250	78 (56 – 107)
C	25-30	177	83 (65 – 102)
D	>30	100	87 (63 – 107)

Ann Clin Biochem 2006; 43: 309-13



Healthy age-matched young males; n=23 per group

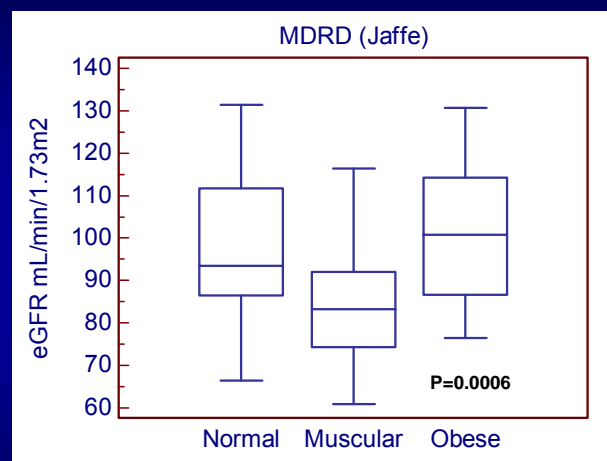
AACB – Sydney 2011; see Poster 4



BMI kg/m ²	23.6	32.1	34.2
% body fat	17.0	22.2	37.0

Healthy age-matched young males; n=23 per group

AACB – Sydney 2011; see Poster 4



GFR under-estimated most markedly in muscular group

BMI kg/m ²	23.6	32.1	34.2
% body fat	17.0	22.2	37.0

6. The use of eGFR in various ethnic populations

Recommendation 6a: The CKD-EPI formula is a useful tool to estimate GFR in all people, including various ethnic populations.

Recommendation 6b: The CKD-EPI formula has been validated as a tool to estimate GFR in some non-Caucasian populations, including South-East Asian, African, Indian and Chinese individuals living in Western countries.

Recommendation 6c: The different methods to estimate GFR from serum creatinine concentration have not been validated in Indigenous Australians, although these studies are currently underway.

Updated 2011 recommendations – in press

Aboriginal study – Paul Lawton

- 150 participants X 4 centres
- Iohexol clearance for measured GFR
- eGFR
- Bioelectrical impedance and DEXA (urban sites)
- Cystatin C

- 400+ recruited so far

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate:

New developments and revised recommendations

Australasian Creatinine Consensus Working Group

1. Adoption of CKD-EPI formula for calculating eGFR

Recommendation: The calculation of eGFR should be changed to use the CKD-EPI formula.

Updated 2011 recommendations – in press



NIH Public Access

Author Manuscript

Ann Intern Med. Author manuscript; available in PMC 2009 October 19.

Published in final edited form as:

Ann Intern Med. 2009 May 5; 150(9): 604–612.

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD¹, Lesley A. Stevens, MD, MS, FRCP(C)¹, Christopher H. Schmid, PhD¹, Yaping (Lucy) Zhang, MS¹, Alejandro F. Castro III, MPH², Harold I. Feldman, MD, MSCE³, John W. Kusek, PhD⁴, Paul Eggers, PhD⁴, Frederick Van Lente, PhD⁵, Tom Greene, PhD⁶, and Josef Coresh, MD, PhD, MHS² for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)⁷

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“CKD-EPI”

CKD-EPI; *Ann Intern Med 2009; 150(9): 604-12*

The MDRD equation was developed in people with CKD; major limitations are imprecision and systematic underestimation of measured GFR (bias) at higher levels

Objective was to develop a new equation based on serum creatinine that would be as accurate as MDRD at GFR <60 ml/min/1.73 m² and more accurate at higher GFR

CKD-EPI; *Ann Intern Med 2009; 150(9): 604-12*

CKD-EPI collaborators provided data from 8,254 participants from 6 studies and 4 clinical populations, divided randomly into separate datasets for development (n=5,504) and internal validation (n=2,750)

For all studies, serum creatinine values were recalibrated to the the Roche enzymatic method

CKD-EPI; *Ann Intern Med* 2009; 150(9): 604-12

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

Race and Sex	Serum Creatinine $\mu\text{mol/L}$ (mg/ dL)	Equation	
Black	Female	$\leq 62 (<0.7)$	$\text{GFR} = 166 \times (\text{Scr}/\kappa)^{-0.329} \times (0.993)^{\text{Age}}$
	Female	$>62 (>0.7)$	$\text{GFR} = 166 \times (\text{Scr}/\kappa)^{-1.209} \times (0.993)^{\text{Age}}$
	Male	$\leq 80 (<0.9)$	$\text{GFR} = 163 \times (\text{Scr}/\kappa)^{-0.411} \times (0.993)^{\text{Age}}$
Male	$>80 (>0.9)$	$\text{GFR} = 163 \times (\text{Scr}/\kappa)^{-1.209} \times (0.993)^{\text{Age}}$	
White or other	Female	$\leq 62 (<0.7)$	$\text{GFR} = 144 \times (\text{Scr}/\kappa)^{-0.329} \times (0.993)^{\text{Age}}$
	Female	$>62 (>0.7)$	$\text{GFR} = 144 \times (\text{Scr}/\kappa)^{-1.209} \times (0.993)^{\text{Age}}$
	Male	$\leq 80 (<0.9)$	$\text{GFR} = 141 \times (\text{Scr}/\kappa)^{-0.411} \times (0.993)^{\text{Age}}$
Male	$>80 (>0.9)$	$\text{GFR} = 141 \times (\text{Scr}/\kappa)^{-1.209} \times (0.993)^{\text{Age}}$	

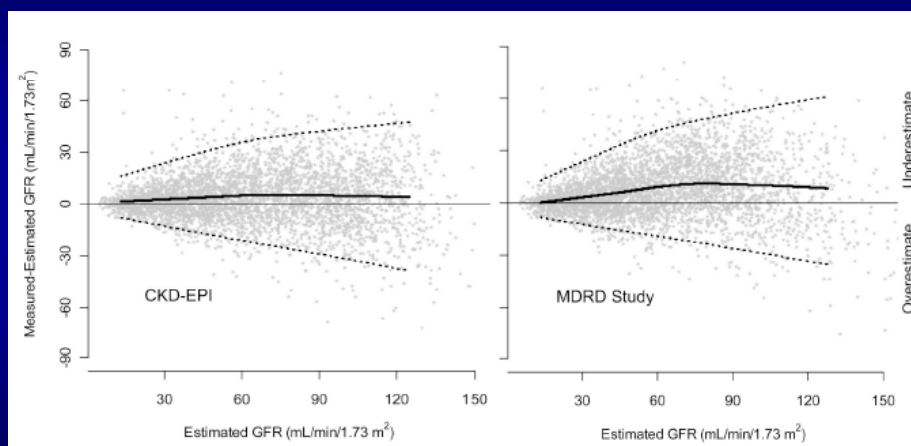
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

* Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m² to mL/s per 1.73 m², multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets.

The CKD-EPI equation, expressed as a single equation, is $\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

In the CKD-EPI equation, the spline for log serum creatinine allows for steeper and identical slopes of GFR vs creatinine for men and women above the knots and less steep and different slopes below the knots, leading to higher estimated GFR at lower creatinine values.

Less under-estimation of eGFR in normals with CKD-EPI



CKD-EPI; *Ann Intern Med 2009; 150(9): 604-12*

Median difference (bias), Inter-quartile ranges for differences (precision) and root mean square error, were all improved with the CKD-EPI equation ($p < 0.001$)

The CKD-EPI equation was as accurate as MDRD in the subgroup with $eGFR < 60 \text{ ml/min/1.73 m}^2$ and substantially more accurate in the subgroup with $eGFR > 60 \text{ ml/min/1.73 m}^2$

CKD-EPI; *Ann Intern Med 2009; 150(9): 604-12*

Improved accuracy of the CKD-EPI equation could have important implications for public health and clinical practice. We suggest that the CKD-EPI equation could replace the MDRD Study equation for estimated GFR reporting for general clinical use

AUSDIAB – subjects re-classified

Am J Kid Dis 2010; 55(4): 660-70

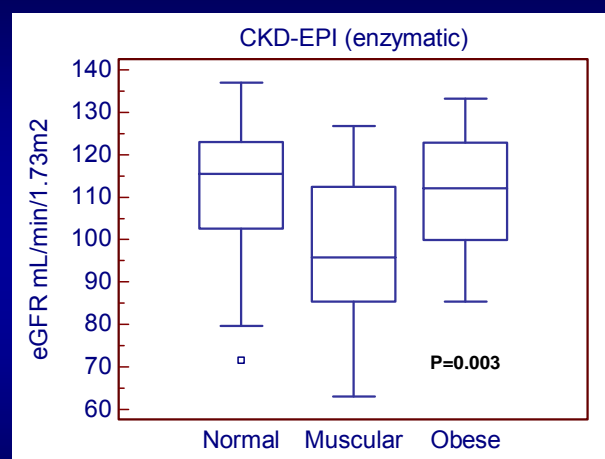
11,247 Australians aged ≥ 25 years

Using MDRD, prevalence of CKD was 13.4%
and using CKD-EPI was 11.5%

266 participants were reclassified to no CKD

Reclassified individuals - predominantly women
with favourable cardiovascular risk profile

AACB – Sydney 2011; see Poster 4



BMI kg/m ²	23.6	32.1	34.2
% body fat	17.0	22.2	37.0

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations

Timothy H Mathew, David W Johnson, Graham RD Jones on behalf of the Australasian Creatinine Consensus Working Group

2. Extension of upper reporting limit of eGFR to 90 mL/min/1.73m²

Recommendation: eGFR values over 90 mL/min/1.73 m² should be reported as ">90 mL/min/1.73 m²" rather than as a precise figure.

Consistent with UK and what some Labs were doing at the time
With CKD-EPI, could report up to 120 or all values?

7. The use of eGFR in pregnancy

Recommendation: The validity of eGFR in pregnancy is not known. Serum creatinine concentration should be maintained as the standard test for kidney function in pregnant women.

Updated 2011 recommendations – in press

8. Measurement of serum creatinine concentration and calculation of GFR in paediatric populations

Recommendation: The use of an enzymatic assay is recommended for the measurement of serum creatinine concentration in children and youth (individuals aged less than 18 years). Routine calculation of eGFR is not recommended in children and youth. Age-appropriate reference values for serum creatinine concentration should be reported for individuals up to 18 years of age.

Updated 2011 recommendations – in press

Address <http://www.labnet.co.nz/testmanager/index.php?fuseaction=main.DisplayTest&testid=72>

ACCREDITATION

HELP ON TESTS

USEFUL LINKS

Specimen Collection

Patient Specimen 4.5 ml heparinised PST or plain tube
Paediatric Specimen Heparin microtainer tube 600 µL

Instructions for Referral to CHLabs

Aliquot Instructions 100 uL plasma or serum Fridge
Aliquot Transport to CHL On ice or ambient

CHLabs Laboratory

Department **Biochemistry - Core**
Contact Details [Lesney Stuart](#)
Contact Phone Number (03) 364 0397 | x80397
Test Availability Mon - Sun, 24 hrs
Turnaround Time 2-3 hrs
Reference Interval

Creatinine		µmol/L
0 - 30 days	20	60
1 mth - 1 yr	20	50
2 yrs - 3 yrs	20	60
4 yrs - 5 yrs	25	65
6 yrs - 9 yrs	25	70
10 yrs - 14 yrs	40	80
Male 15yr + Adult	50	110
Female 15 yr + Adult	45	90

Delphic Number Test Number

5422

Prediction equations for use in children

TABLE 1: PREDICTION EQUATIONS FOR CYSTATIN C AND CREATININE

Cystatin C - based formula

Filler *et al* $91.62 [1/\text{cystatin C (mg/L)}]^{1.123}$

Creatinine - based formulae

Counahan - Barratt $43.00 [\text{Height (m)} / \text{Creatinine } (\mu\text{mol/L)}] \times 0.011312$

Schwartz $55.00 [\text{Height (m)} / \text{Creatinine } (\mu\text{mol/L)}] \times 0.011312$

Lager *et al* $0.641[\text{weight (kg)} / \text{Creatinine } (\mu\text{mol/L)}] \times 0.011312$
 $+ 16.063 [\text{height}^2 \text{ (m)} / \text{Creatinine } (\mu\text{mol/L)}] \times 0.011312$

Cystatin C and Creatinine combined formulae

Bouvet *et al* $63.2 \{ [1.2 / \text{cystatin C (mg/L)}]^{0.56} \times [96 / \text{Creatinine } (\mu\text{mol/L)}]^{0.25}$
 $\times [\text{weight (kg)} / 45]^{0.20} \times [\text{age (years)} / 14]^{0.40} \}$

Zapitelli *et al* $43.82 [1 / \text{cystatin C (mg/L)}]^{0.535} \times [1 / \text{Creatinine } (\mu\text{mol/L)}] \times 0.011312]^{0.547} \times [1.35]^{height}$

Considerations for the Future

Measurement of serum cystatin C concentration to estimate GFR

There is no convincing evidence yet that serum cystatin C measurement or its incorporation into GFR estimating equations offers any clinical advantage over eGFR. Nevertheless, the future potential of cystatin C for measurement of kidney function is promising.

Updated 2011 recommendations – in press

Steady state is the single most important factor for interpretation and is frequently not fulfilled in acute care settings

If delta check failed (variation of >17% in creatinine over four days) - RCV with 95% probability

"Steady state conditions are not fulfilled due to recent variation in plasma creatinine. Caution should be exercised in interpretation of estimated GFR."



Latte - [WE]

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Page 01 MORE TO COME Next WE

Lab No Name Doctor Date Sex Birthdate Causal Prt

Prof. P M George PMGEO Arr 10Jun05 12:18
Chch Hospital Outpatient CGN Col 10Jun05 11:30
Fax destination : CGN No fax available

HIGHLIGHTED OR FLASHING RESULTS HAVE NOT BEEN RELEASED BY THE LAB FOR REPORTING

Sodium	142	mmol/L	136-146
Potassium	4.2	mmol/L	3.5-5.0
Creatinine	0.10	mmol/L	0.05-0.11
Est GFR	70*	mL/min/1.73m ²	90-120

Estimated GFR is only reliable under steady state conditions (stable creatinine 7 days). Caution should be used in interpretation in non-caucasians, extremes of body weight, pregnancy, ~~edematous~~ subjects, low creatinine (<0.06mmol/L) and other complex cases. GFR declines by 1mL/min/year over age 40 years.

Lipid Screen

			Desirable Range
Cholesterol	5.9*	mmol/L	3.2-5.2
Triglyceride	4.1*	mmol/L	0.3-1.5

User: WOLF CANTERBURY HEALTH LABORATORIES Printer: 52 CLIP OVR INUM

When to refer to a Nephrologist ?

<http://www.kidney.org.au>



- e-GFR <30 mL/min/1.73m²
- Rapidly declining renal function (>15% increase in e-GFR over 3 months)
- Proteinuria > 1g in 24 hrs
- Glomerular haematuria
- Kidney disease and hypertension that proves difficult to control
- Diabetes and e-GFR < 60 mL/min/1.73m²

Nephrol Dial Transplant (2008) 23: 3845–3850
doi: 10.1093/ndt/gfn385
Advance Access publication 16 July 2008

NDT
Nephrology Dialysis Transplantation

Original Article

The impact of automated eGFR reporting and education on nephrology service referrals

Euan Noble¹, David W. Johnson¹, Nicholas Gray², Peter Hollett², Carmel M. Hawley¹, Scott B. Campbell¹, David W. Mudge¹ and Nicole M. Isbel¹

¹Department of Renal Medicine, University of Queensland at Princess Alexandra Hospital, Brisbane and ²Department of Renal Medicine, Nambour General Hospital, Nambour, Australia

Referrals have increased:

Nephrol Dial Transplant 2008;23: 3845- 50

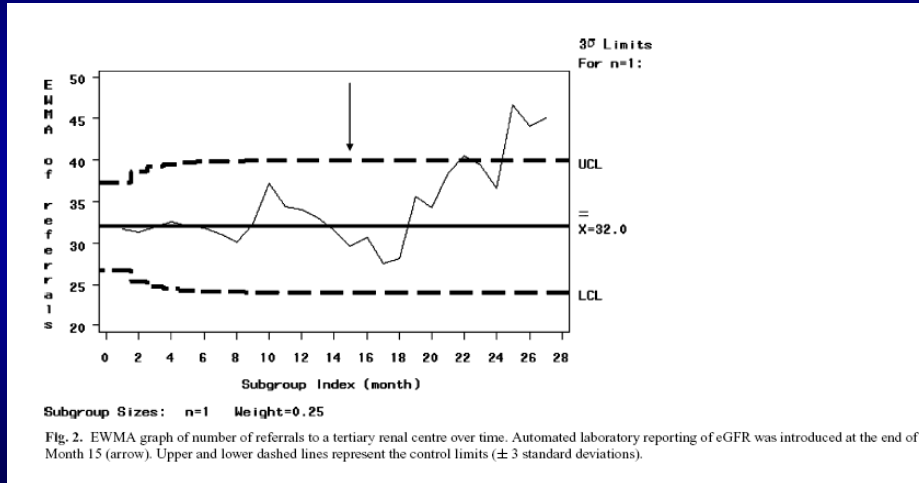


Table 3. Reasons for referral of CKD patients to nephrologists prior to and following the introduction of automated laboratory reporting of eGFR. The differences in reasons for referral between the two time periods were statistically significant ($P < 0.001$)

KCAT criteria met	Referral reason	Pre-eGFR (n = 171)	Post-eGFR (n = 831)
Yes	eGFR <30 mL/min/1.73 m ²	43 (25%)	203 (24%)
	Rapidly declining kidney function (15% in eGFR over 3 months irrespective of baseline level)	0 (0%)	2 (0%)
	Proteinuria $>1g/24$ h	18 (11%)	38 (5%)
	Glomerular haematuria	19 (11%)	48 (6%)
	Kidney disease and hypertension that proves difficult to control	7 (4%)	41 (5%)
No	Diabetes and eGFR <60 mL/min/1.73 m ²	24 (14%)	107 (13%)
	As deemed appropriate by nephrologist (e.g. ADPKD)	16 (9%)	95 (11%)
	CKD but eGFR >30 mL/min/1.73 m ²	41 (24%)	289 (35%)
	Diabetes but eGFR >60 mL/min/1.73 m ²	3 (1.8%)	0 (0%)
	Not defined	0 (0%)	8 (1%)

Appropriateness of referrals, by KCAT criteria, fell from 74.3% in the 3/12 pre-eGFR to 65.2% in the 12/12 after ($P < 0.05$)

Increase in referrals predominantly in older and diabetic patients with stage 3 CKD and appeared to result in net benefit

THE NEW ZEALAND MEDICAL JOURNAL

Vol 118 No 1225 ISSN 1175 8716



Older patients in the nephrology clinic—should they be referred?

Sarah Lynn, Richard Sainsbury, Martin Searle

Abstract

Aim To review the outcomes of elderly patients referred to a nephrology clinic and to develop referral guidelines.

Methods A retrospective audit of patients aged 65 years or older referred over a 24-month period to a nephrology clinic. Outcomes assessed were whether a renal diagnosis was made and if there was any change in management.

Results Sixty-one patients were referred with an average age of 74 years (range 65–88 years). The commonest reason for referral was renal impairment (69%); mean estimated creatinine clearance 32 ml/min. Diagnoses included hypertensive renal disease (30%), chronic renal failure—cause unknown (18%) and diabetic nephropathy (8%). In the majority of cases, the diagnosis was clinical. Renal biopsy was performed on four patients and declined by a further two. Management usually consisted of advice regarding clinical monitoring and drug treatment (80%). The clinic visit resulted in a change of management in 50% of cases.

Conclusions Most elderly patients with renal disease have chronic pathology for which intensive investigation is not warranted. The majority of nephrology clinic referrals resulted in advice on clinical management being given to the general practitioner. Patients with severe or acute renal impairment are more likely to be investigated and offered treatment. Referral guidelines for general practitioners may aid appropriate referral.

THE NEW ZEALAND MEDICAL JOURNAL

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Response to the article by Lynn et al: Older patients in the nephrology clinic—should they be referred?

Detailed guidelines for management of CKD stage 3 (GFR 30–60 ml/min) patients will allow primary care givers to be more effective in management. However, reduced GFR <60 ml/min remains an appropriate indication for nephrology clinic referral for diagnosis and assessment of prognosis, “even in the elderly”.

Patients with stable CKD and no requirement for intervention should be discharged or managed in partnership with the primary care giver. Late referral is simply locking the door after the horse has bolted.

Zoltan Endre
Professor and Head of Department of Medicine
Christchurch School of Medicine and Health Sciences
& Consultant Nephrologist, Christchurch Hospital
Christchurch

eGFR – *caveat emptor*

- All mathematical abstractions
- Relating patients to the populations from which the equations were derived
- There is no “one size fits all”
- (Lack of) steady state is the major confounder