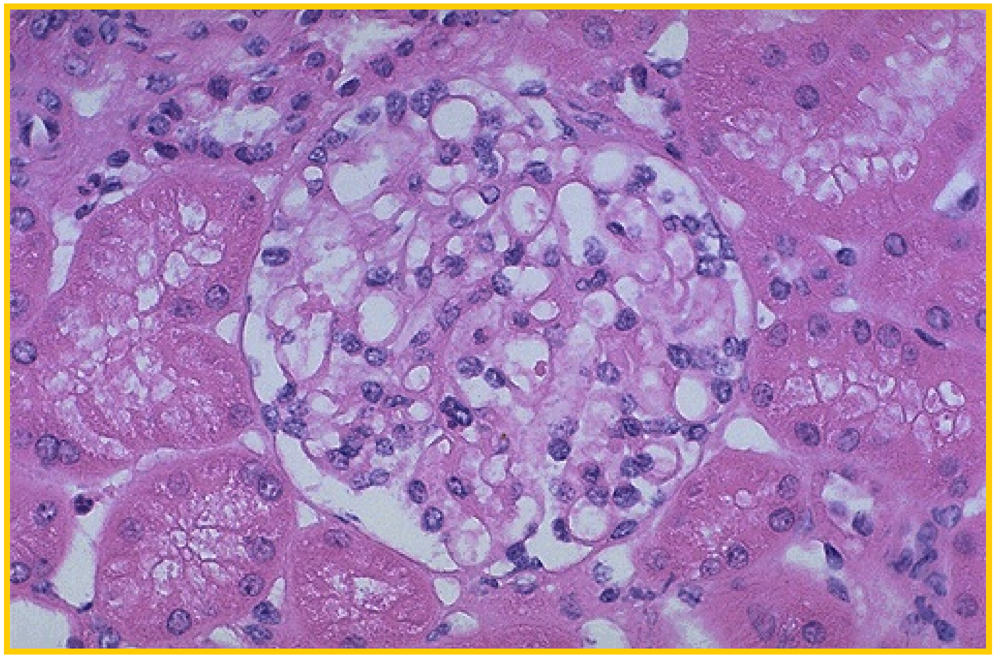
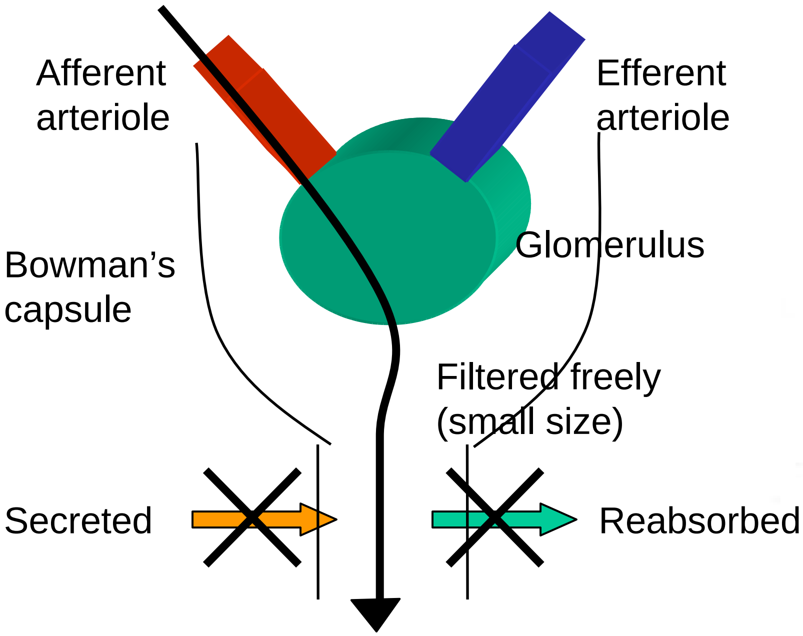
Glomerular Filtration Rate



Hui Li, PhD, FCACB, DABCC

Glomerular Filtration Rate (GFR): Amount of blood that is filtered per unit time through glomeruli. It is a measure of the function of kidneys.

The Concept of Clearance of a substance: the volume of plasma from which the substance is completely cleared by the kidneys per unit of time.



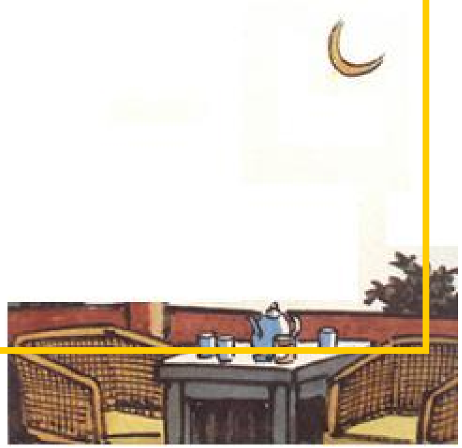
$$\text{Filtered S} = \text{Excreted S}$$

$$GFR \times Ps = Us \times V$$

$$GFR = Us \times V/Ps$$

Measurement of GFR

	Hierarchy	Marker
Exogenous Clearance	Gold Standard	Inulin continuous infusion urinary clearance
	Silver Standard	Inulin single bolus plasma clearance
		^{51}Cr-EDTA
		^{99m}Tc-DTPA
		^{125}I-iothalamate
		Iohexol
Endogenous Serum markers	Bronze standard	Creatinine
		Cystatin C
	Of uncertain clinical use	Creatinine urinary clearance*
		Urea
		Retinol-binding protein
		α1-microglobulin
		β2-microglobulin
		Prostaglandin D synthase



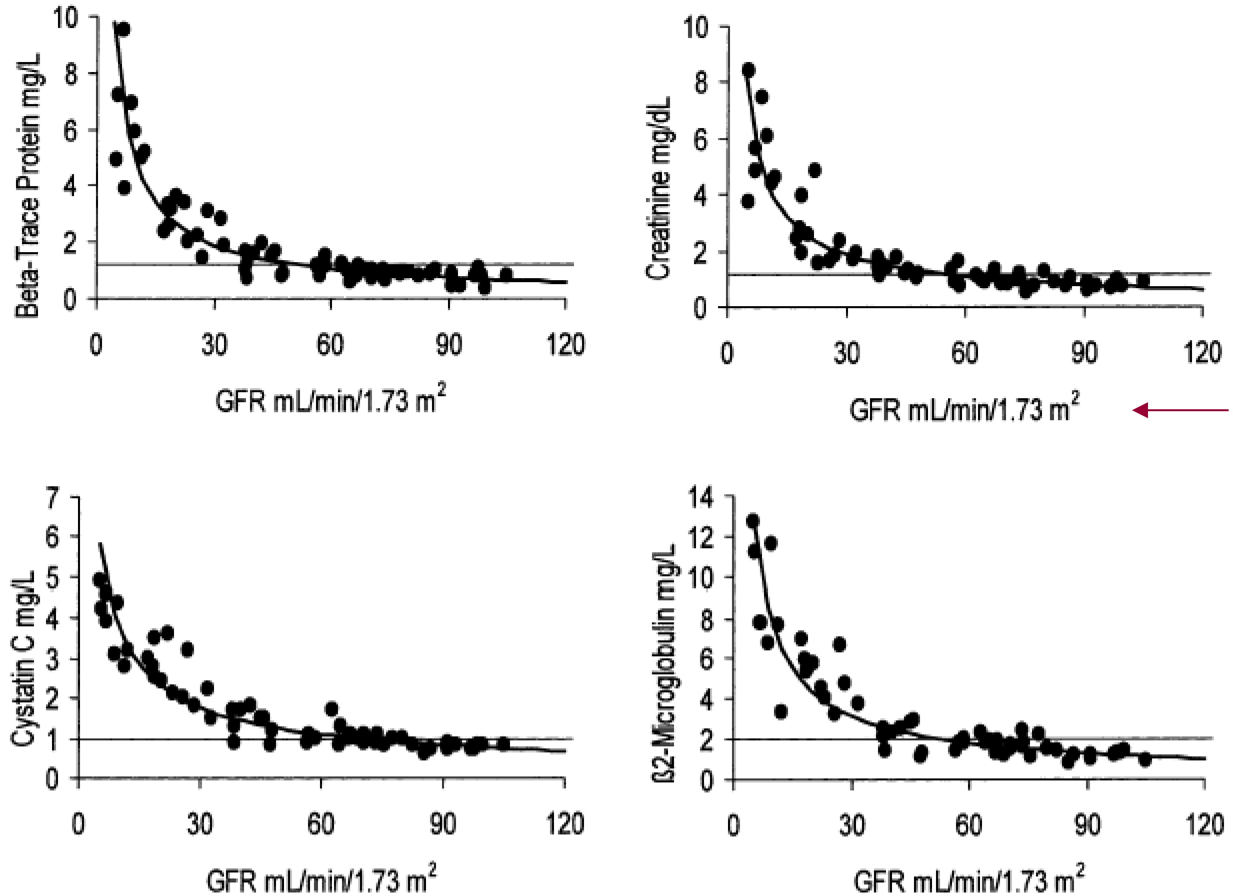
Exogenous urinary/plasma clearance

Advantages	Disadvantages

Designed to closely satisfy the criteria of an ideal marker of GFR	Exogenous
	Time consuming
	Requires a timed urine/plasma collection
	Overestimation (plasma clearance)
	    extrarenal clearance
	    ignored distribution phase
	Radioisotopic

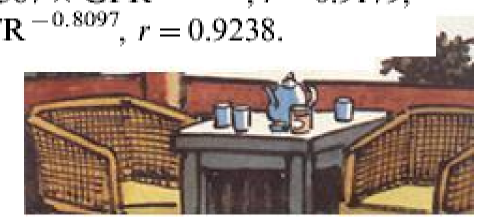
Endogenous Serum Markers

Advantages	Disadvantages
Endogenous More convenient Less expensive Converted to GFR using formula	Nonrenal influences on production rate Secretion/ Reabsorption in renal tubular cells.



^{99m}Tc-DTPA urinary clearance

Fig. 2. Serum concentrations of BTP, Creat, Cys, and β2M plotted vs. GFR. The straight lines represent the upper limit of values found in the group of 15 patients with GFR > 75 ml/min per 1.73 m^2 (mean + 2S.D.): 1.2 mg/l for BTP, 1.2 mg/dl for Creat, 1.0 mg/l for Cys, and 2.0 mg/l for ß2M. The curve lines represent the logarithmic correlation with GFR. $BTP = 33.367 \times GFR^{-0.8445}$, $r = 0.9179$; $Creat = 27.320 \times GFR^{-0.7915}$, $r = 0.9323$; $Cys = 18.255 \times GFR^{-0.6868}$, $r = 0.9371$; $\beta 2M = 49.406 \times GFR^{-0.8097}$, $r = 0.9238$.



Donadio et al., J Pharm Biomed Anal 2003;32:1099-104.

Renal transplantation patients

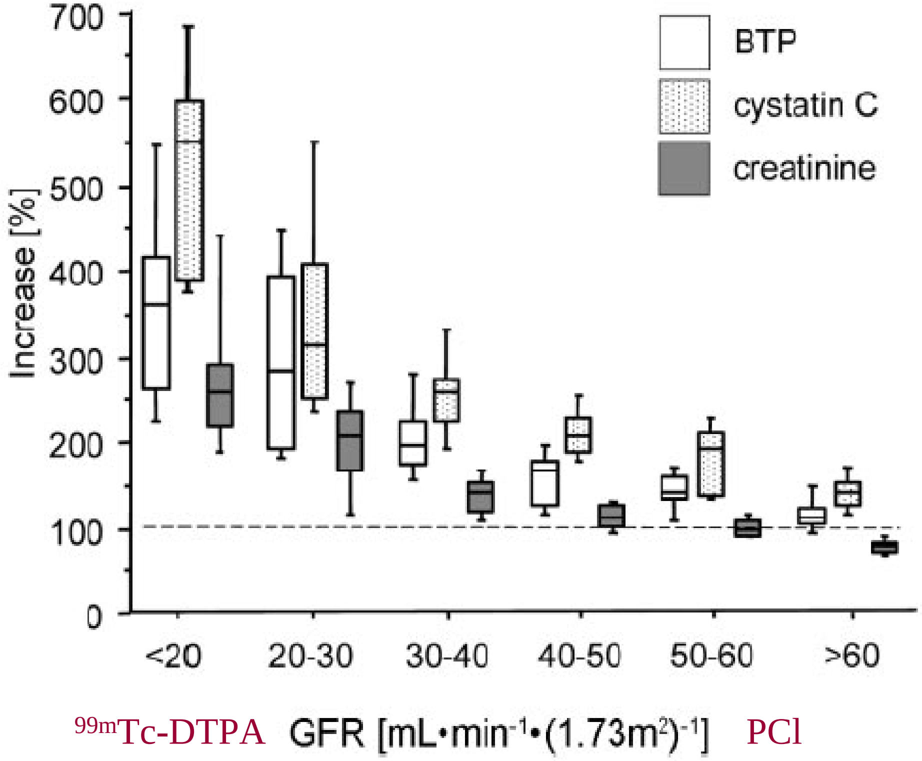


Fig. 1. Cys C, BTP, and creatinine concentrations at different stages of renal impairment.

Patients were stratified into 6 renal impairment groups according to the GFR measured as ^{99m}TC-DTPA clearance: <20 (n = 9), 20–30 (n = 18), 30–40 (n = 24), 40–50 (n = 14), 50–60 (n = 10), and >60 (n = 10) mL · min^{-1} · (1.73 m^2)$^{-1}$. Data are given as box plots, where the *limits* of the *boxes* indicate the 25th and 75th percentiles and the *lines* inside the *boxes* indicate the 50th (median) percentile. The *whiskers* indicate the 10th and 90th percentiles. Relative increases in Cys C and BTP were significantly higher than increases in creatinine (*P* <0.003 for each); however, the increases in Cys C were significantly more prominent than the increases in BTP for all groups (*P* <0.012 for each), except for the subgroup of patients with GFR = 20–30 mL · min^{-1} · (1.73 m^2)$^{-1}$.

Poge et al., Clin Chem 2005;51:1531-33.

Children

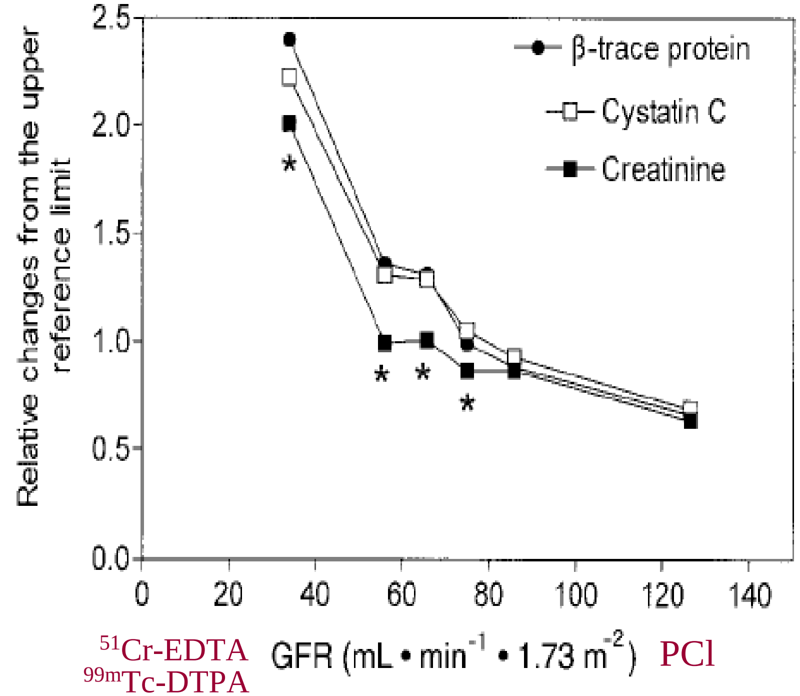
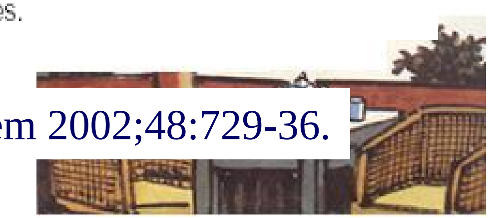


Fig. 3. Relative changes of BTP (●), Cys-C (□), and creatinine (■) from their upper reference limits in different degrees of renal failure.

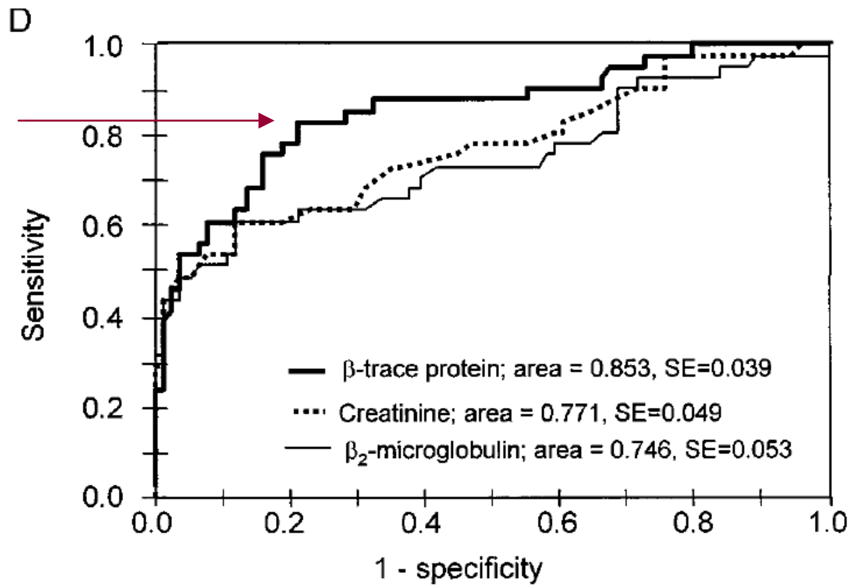
The analyte concentrations were divided by the the upper reference limit value of the respective analyte (for BTP, 1.01 mg/L; for Cys-C, 1.20 mg/L; and for creatinine in the age groups 1–6, 6–12, and 12–18 years, 51, 75, and 91 µmol/L, respectively). The data represent mean values of the resulting multiples calculated in the GFR ranges <50, 50–60, 60–70, 70–80, 80–90, and >90 mL · min^{-1} · 1.73 m^{-2}. *, significant differences of both BTP and Cys-C vs creatinine (*P* values at least <0.05; *t*-test of paired data). No differences (*P* values between 0.141 and 0.575) were found between the relative changes of BTP and Cys-C in various GFR ranges.



Filler et al., Clin Chem 2002;48:729-36.

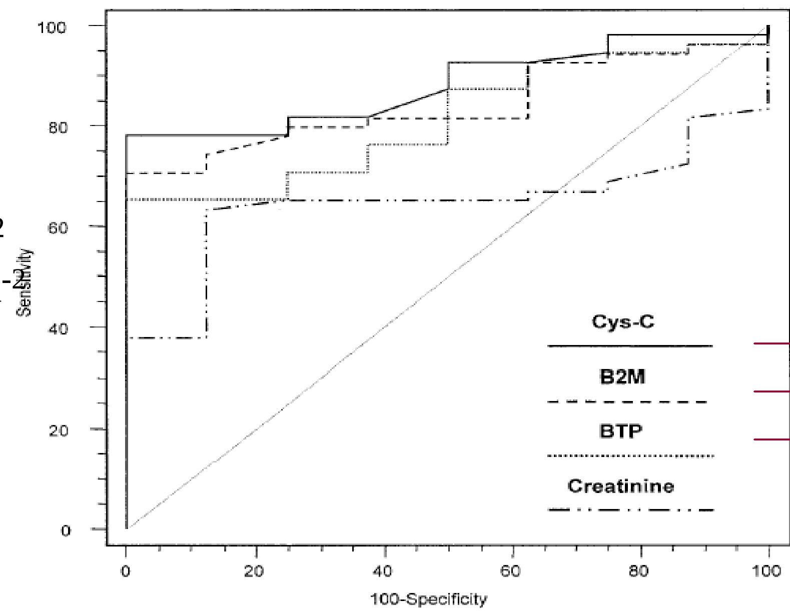
Significantly higher than the other two

115 diabetic patients
n=74, GFR>80ml·min^{-1}
n=41, GFR<80ml·min^{-1}



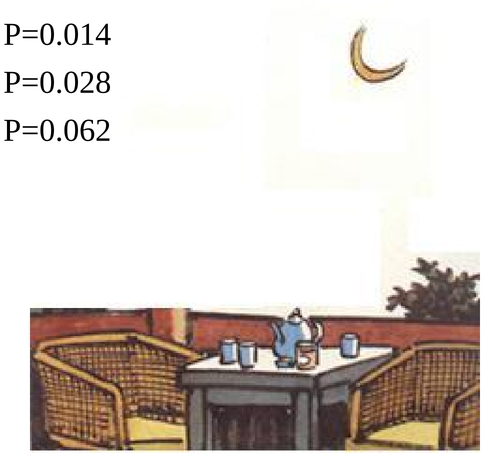
Inulin continuous infusion urinary clearance

n=8, GFR>70ml·min^{-1}·1.73m^{-2}
n=54, GFR<70ml·min^{-1}·1.73m^{-2}



Inulin continuous infusion urinary clearance

P=0.014
P=0.028
P=0.062



Priem et al., Clin Chem 1999;45:567-8

Woitas et al., Clin Chem 2001;47:2179-80

Table 2. Diagnostic accuracy (areas under the ROC curves, sensitivity, and specificity) of BTP, Cys-C, β_2-MG, creatinine, and the Schwartz GFR estimate to detect reduced GFR (<90 mL · min^{-1} · 1.73 m^{-2}) in children.[a]

	Area under the ROC curve, mean ± SE	Sensitivity, %	Specificity, %
BTP, mg/L	0.912 ± 0.024		
1.01[b]		61 (51–71)	97 (94–99)
0.68[c]		95 (88–98)	52 (45–59)
0.94[d]		68 (58–77)	95 (91–97)
Cys-C, mg/L	0.943 ± 0.019		
1.20[b]		61 (50–72)	98 (94–100)
0.87[c]		95 (87–99)	63 (55–71)
1.11[d]		80 (69–88)	95 (91–98)
β_2-MG, mg/L	0.899 ± 0.025		
3.09[b]		38 (25–54)	94 (86–98)
1.66[c]		95 (85–99)	54 (44–63)
3.30[d]		32 (21–45)	95 (89–98)
Creatinine, µmol/L	0.840 ± 0.031		
85.9[b]		29 (21–39)	97 (93–99)
47.7[c]		95 (88–98)	47 (40–54)
83.0[d]		35 (26–45)	95 (91–98)
Schwartz formula, mL/min	0.917 ± 0.018		
56.0[b]		31 (21–39)	99 (96–100)
93.6[c]		95 (88–98)	65 (58–71)
70.8[d]		68 (56–78)	95 (91–98)

[a] Data (with 95% confidence intervals in parentheses) result from ROC curve analysis performed with 150 children with a GFR >90 mL · min^{-1} · 1.73 m^{-2} and 75 children with GFR <90 mL · min^{-1} · 1.73 m^{-2}.

[b] Upper cutoff limit (97.5% percentile); lower cutoff limit (2.5% percentile) in the case of the Schwartz GFR (see Table 1).

[c] Threshold with diagnostic sensitivity of 95%.

[d] Threshold with diagnostic specificity of 95%.

Significantly lower than the others → Creatinine

^{99m}Tc-DTPA PCl in Ottawa

^{51}Cr-EDTA PCl in Berlin

Filler et al., Clin Chem 2002;48:729-36.

Table 1. Diagnostic performance of creatinine, Cys C, and BTP.

GFR cutoff, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	Creatinine			Cys C			BTP		
	AUC	Sensitivity, %	Specificity, %	AUC	Sensitivity, %	Specificity, %	AUC	Sensitivity, %	Specificity, %
30	0.931	85.2	96.6	0.912	81.5	87.2	0.917	77.8	89.1
95% CI	(0.855–0.974)	(66.2–95.7)	(88.1–99.5)	(0.831–0.963)	(61.9–93.6)	(76.7–95.0)	(0.837–0.966)	(53.7–91.3)	(78.8–96.1)
40	0.942	72.5	100	0.926	78.4	97.1	0.934	84.3	94.1
95% CI	(0.869–0.981)	(58.3–84.1)	(100–100)	(0.848–0.971)	(64.7–88.7)	(84.6–99.5)	(0.859–0.976)	(71.4–93.0)	(80.3–99.1)
50	0.956	93.8	85.0	0.939	76.9	95.0	0.932	84.6	90.0
95% CI	(0.888–0.988)	(85.0–98.3)	(62.1–96.6)	(0.865–0.979)	(64.8–86.5)	(75.1–99.2)	(0.855–0.975)	(73.5–92.4)	(68.3–98.5)
60	0.970	93.2	90	0.966	93.8	100	0.932	83.8	90.0
95% CI	(0.908–0.994)	(84.9–97.7)	(58.7–98.5)	(0.902–0.993)	(83.2–96.6)	(100–100)	(0.856–0.975)	(73.4–91.3)	(58.7–98.5)

[a] Sensitivity and specificity were obtained from the following analyte concentrations: for GFR cutoffs of 30, 40, 50, and 60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, the optimum creatinine concentrations were 172, 142, 106, and 96.9 μmol/L, respectively; the optimum Cys C concentrations were 2.18, 1.99, 1.75, and 1.41 mg/L, respectively; and the optimum BTP concentrations were 1.62, 1.29, 1.17, and 1.12 mg/L, respectively.

83 Renal transplantation patients

^{99m}Tc-DTPA plasma clearance

No difference in AUC

Poge et al., Clin Chem 2005;51:1531-33.

Estimated glomerular filtration rate (eGFR): an estimate of the GFR calculated from concentration of serum markers.

GFR prediction equations using plasma creatinine concentration

Cockroft-Gault ml/min	$(140 - \text{age}) \times \text{weight}/72 \times S_{cr}$ ($\times$ 0.85 if female)
MDRD 1 ml/min/1.73m^2	$170 \times (S_{cr}/88.4)^{-0.999} \times \text{age}^{-0.176} \times$ (0.762 if female) $\times$ (1.180 if black) $\times (S_c \times 2.801)^{-0.170} \times \text{Alb}^{+0.318}$
MDRD 2 ml/min/1.73m^2	$186 \times (S_{cr}/88.4)^{-1.154} \times \text{age}^{-0.203} \times$(1.212 if black) $\times$ (0.742 if female)
Schwartz ml/min	$0.55 \times \text{height} \times (S_{cr}/88.4)^{-1}$
Counahan-Barratt ml/min/1.73m^2	$0.43 \times \text{height} \times (S_{cr}/88.4)^{-1}$

Height(cm), Weight(Kg), Scr(μmol/L)

Table 2 *Comparison of the patient characteristics and methodology used in deriving the Cockcroft and Gault and MDRD study formulae*

	Cockcroft and Gault[32]	MDRD[33,34]
Source population	Canada 1976	USA 1999
Mean GFR (SD)	73 mL/min	40 (21) mL/min/1.73 m^2
Reference procedure	Creatinine clearance (duplicate)	^{125}I-iothalamate
Creatinine assay	Jaffe (Technicon Autoanalyser method N-11B)	Kinetic Jaffe (Beckman Astra CX3)
Demographic/anthropomorphic data required	Weight, gender, age	Ethnicity, gender, age
BSA-adjusted	No	Yes
% female	4%	40%
% black	Not stated	12%
Mean weight (SD), kg	72	79.6 (16.8)
Mean age (SD), year	Not given (range 18–92)	51 (13)
Mean BSA (SD), m^2	Not given	1.91 (0.23)
R^2 against reference procedure	0.69	0.89*
Accuracy estimate	Estimated GFR was within 20% of reference procedure in 67% of patients	Estimated GFR was within 30% of reference procedure in 90% of patients

BSA, body surface area; GFR, glomerular filtration rate; SD, standard deviation.
* For 4-v MDRD formula[34].

Cystatin C-based GFR prediction equation

536 patients: 0.3-96 years, 262 females and 274 males

GFR: plasma iohexol clearance

Without gender factor:
GFR [ml·min^{-1}·(1.73m^{2})$^{-1}$]
=84.69×cystatin C (mg/L)$^{-1.680}$[×1.384 if child<14 years]

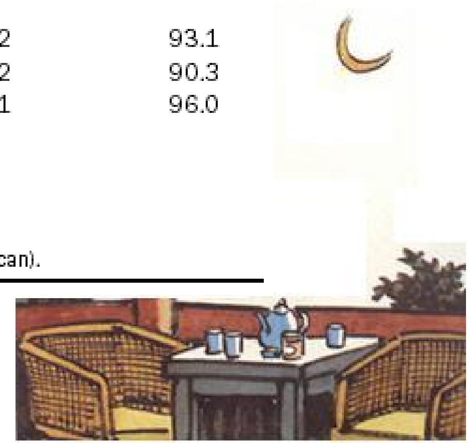
With gender factor:
GFR [ml·min^{-1}·(1.73m^{2})$^{-1}$]
=87.62×cystatin C (mg/L)$^{-1.693}$ [×1.376 if child<14 years]
[×0.940 if female]

Clin Chem 2005;51:1420-31.

Table 2. Bias, correlation, and percentage error of prediction equations to estimate relative GFR [mL · min^{-1} · (1.73 m^2)$^{-1}$] in adults (≥ 18 years).

Prediction equations to estimate relative GFR in mL · min^{-1} · (1.73 m^2)$^{-1}$	Bias, median percentage error	Correlation (adjusted R^2), %	Percentages of estimates	
			Within 30% of measured GFR	Within 50% of measured GFR
Cystatin C equations using				
Patients ≥18 years and				
GFR = 83.93 × cystatin C$^{-1.676}$				
All adults (n = 451)	1.95[a]	86.7	80.0	96.0
Males (n = 226)	−0.90		81.9	96.0
Females (n = 225)	4.35		78.2	96.0
GFR = 86.49 × cystatin C$^{-1.686}$ × 0.948 (if female)				
All adults (n = 451)	1.91[a]	86.8	82.3	96.7
Males (n = 226)	1.82		81.9	96.0
Females (n = 225)	1.97		82.7	97.3
All patients 0.3–93 years and juvenile factor[b]				
All adults (n = 451)	2.85	86.7	80.0	95.3
Males (n = 226)	−0.19		81.9	96.0
Females (n = 225)	5.25		78.2	94.7
All patients 0.3–93 years and gender and juvenile factors[c]				
All adults (n = 451)	2.57	86.8	81.8	96.5
Males (n = 226)	2.99		81.0	95.6
Females (n = 225)	2.48		82.7	97.3
Simplified MDRD[d]				
All adults (n = 451)	11.8	84.6	70.7	88.0
Males (n = 226)	13.3		69.5	86.7
Females (n = 225)	11.3		72.0	89.3
Simplified MDRD using mathematical bias correction[e]				
All adults (n = 451)	0.02[a]	84.6	79.2	93.1
Males (n = 226)	1.33		79.2	90.3
Females (n = 225)	−0.45		79.1	96.0

[a] Zero median percentage error expected for this regression model because it was fitted based on all adults.
[b] GFR = 84.69 × cystatin C$^{-1.680}$ × 1.384 (if child <14 years).
[c] GFR = 87.62 × cystatin C$^{-1.693}$ × 1.376 (if child <14 years) × 0.940 (if female).
[d] GFR = 186.3 × [creatinine (μmol/L)/88.4]$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if African American).
[e] GFR = (1/1.118) × 186.3 × [creatinine (μmol/L)/88.4]$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if African American).



Clin Chem 2005;51:1420-31.

Table 3. Bias, correlation, and percentage error of prediction equations to estimate relative GFR [$mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$] in children (<18 years).

Prediction equations to estimate relative GFR in $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	Bias, median percentage error	Correlation (adjusted R^2), %	Percentages of estimates: Within 30% of measured GFR	Percentages of estimates: Within 50% of measured GFR
Cystatin C equations using				
All patients, juvenile factor[a]				
All children (n = 85)	−1.95	80.5	77.6	96.5
Males (n = 48)	−5.17		72.9	97.9
Females (n = 37)	9.22		83.8	94.6
All patients, juvenile and gender factors[b]				
All children (n = 85)	−0.60	81.1	82.4	96.5
Males (n = 48)	−1.82		79.2	97.9
Females (n = 37)	5.83		86.5	94.6
Schwartz equation[c]				
All children (n = 85)	50.9	76.1	24.7	49.4
Males (n = 48)	46.0		31.3	58.3
Females (n = 37)	59.2		16.2	37.8
Counahan–Barratt equation[d]				
All children (n = 85)	18.0	76.1	62.4	80.0
Males (n = 48)	14.1		66.7	83.3
Females (n = 37)	24.4		56.8	75.7

[a] $GFR = 84.69 \times \text{cystatin C}^{-1.680} \times 1.384$ (if child <14 years).
[b] $GFR = 87.62 \times \text{cystatin C}^{-1.693} \times 1.376$ (if child <14 years) $\times 0.940$ (if female).
[c] $GFR = 0.55 \times \text{height (cm)} \times [\text{plasma creatinine } (\mu mol/L)/88.4]^{-1}$.
[d] $GFR = 0.43 \times \text{height (cm)} \times [\text{plasma creatinine } (\mu mol/L)/88.4]^{-1}$.

Clin Chem 2005;51:1420-31.

GFR measured in MSH

Data Information

For specimens received Jan 2004 to Oct 2005
Includes inpatients and outpatients
Female (n=808), Male (n=317)
Includes pregnant subjects

Exclusions
Urine Collected for <20 or >25.5 Hours
Urine Creatinine <3 or >25 mmol/Day
Weight <34 or >146 Kg
Height <110 or >193 cm

Analytical method for serum, plasma and urine creatinine: Creatininase, creatinase, and sarcosine oxidase, with the liberated hydrogen peroxide tied to a colorimetric reaction.

Blood Creatinine / Creatinine Clearance (Non-normalized vs. Normalized to BSA)

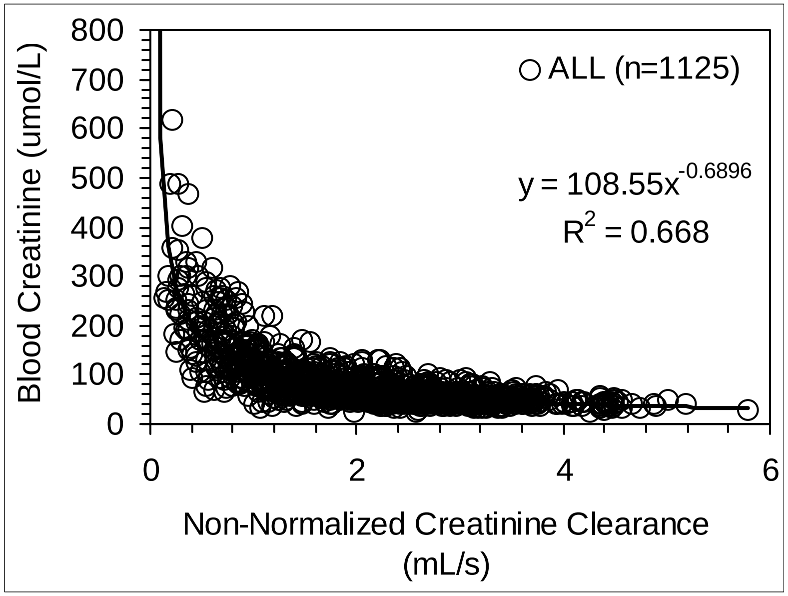
Body Surface Area
Du Bois vs. Gehan George

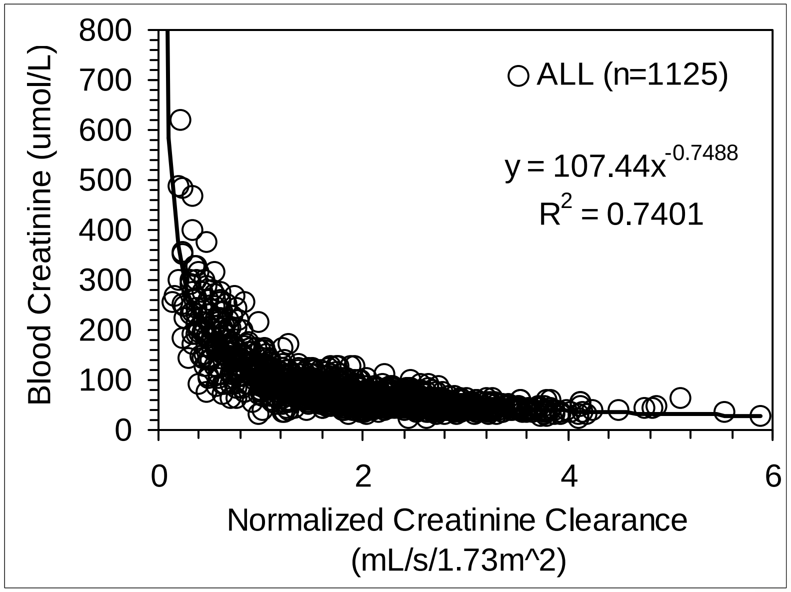
Blood Creatinine / Creatinine Clearance
Female vs. Male

Inverse Creatinine vs. eGFR / Creatinine Clearance

Inverse Creatinine vs. eGFR / Creatinine Clearance
$GFR < 90 ml \cdot min^{-1} \cdot 1.73 m^{-2}$

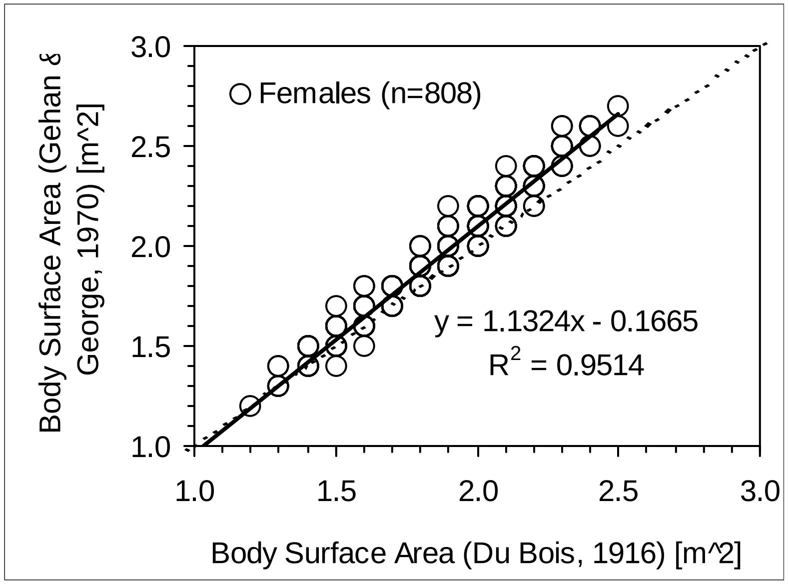
Blood Creatinine / Creatinine Clearance
Non-normalized vs. Normalized

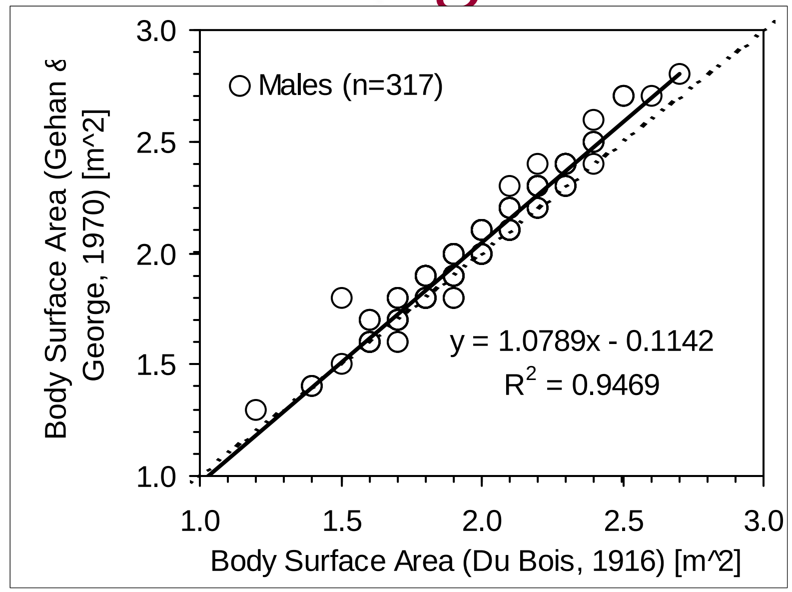


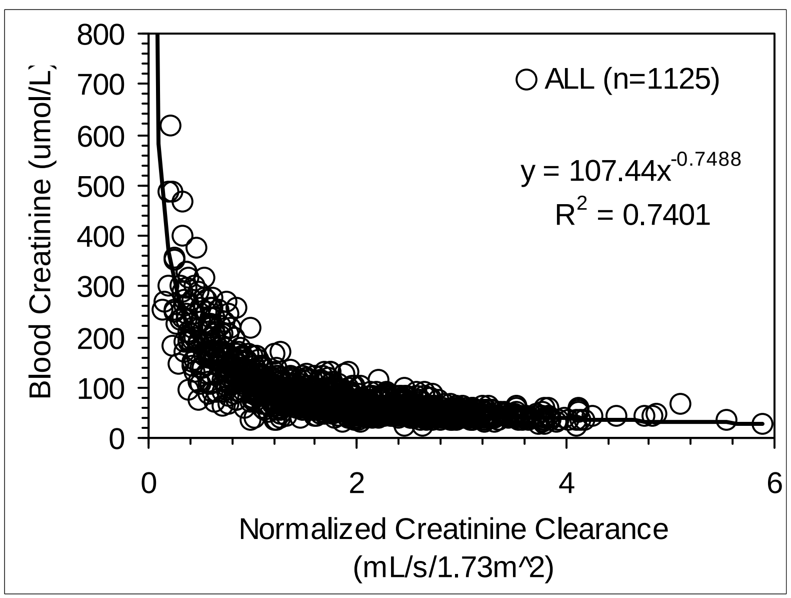


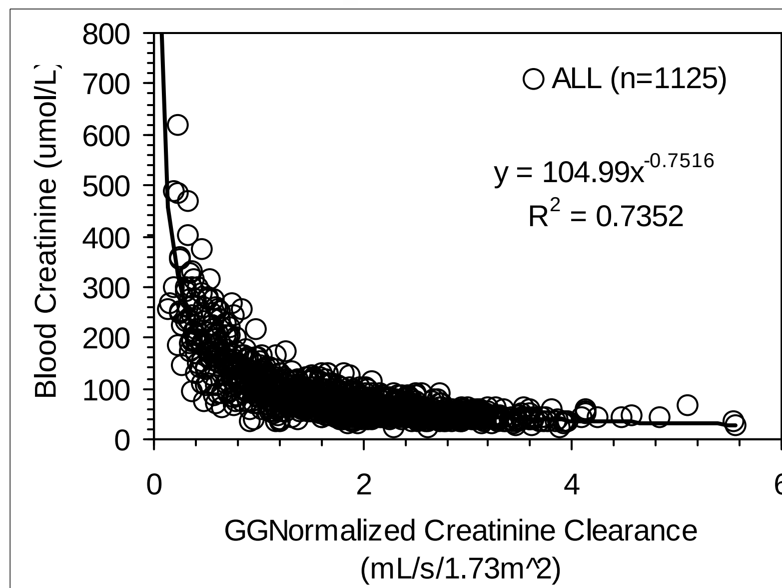
Body Surface Area

Du Bois vs. Gehan George

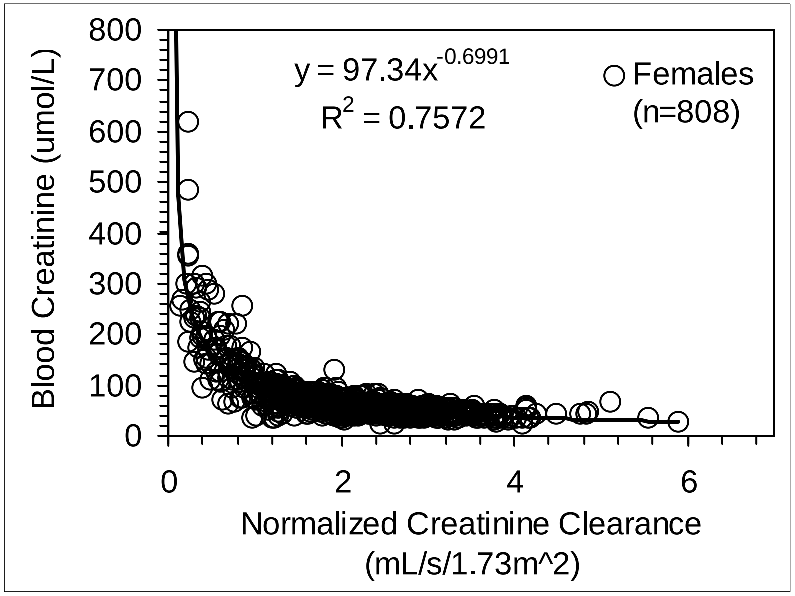


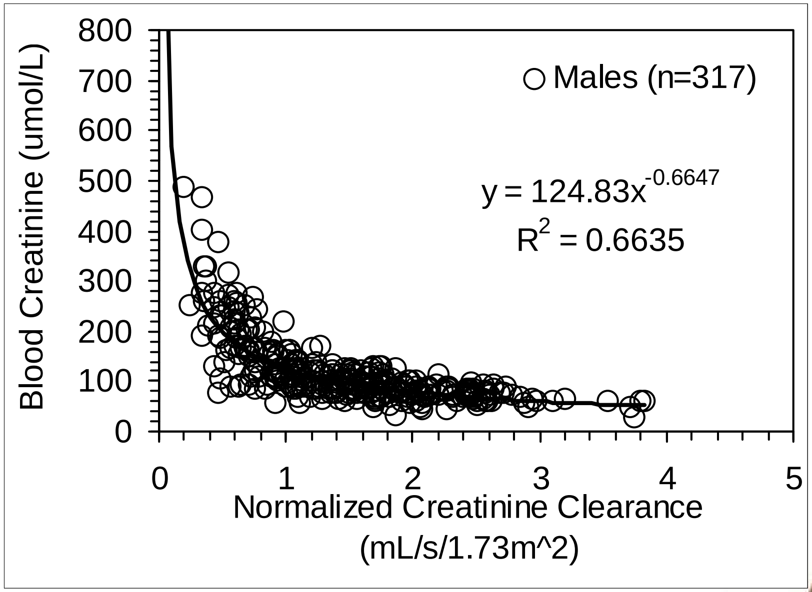




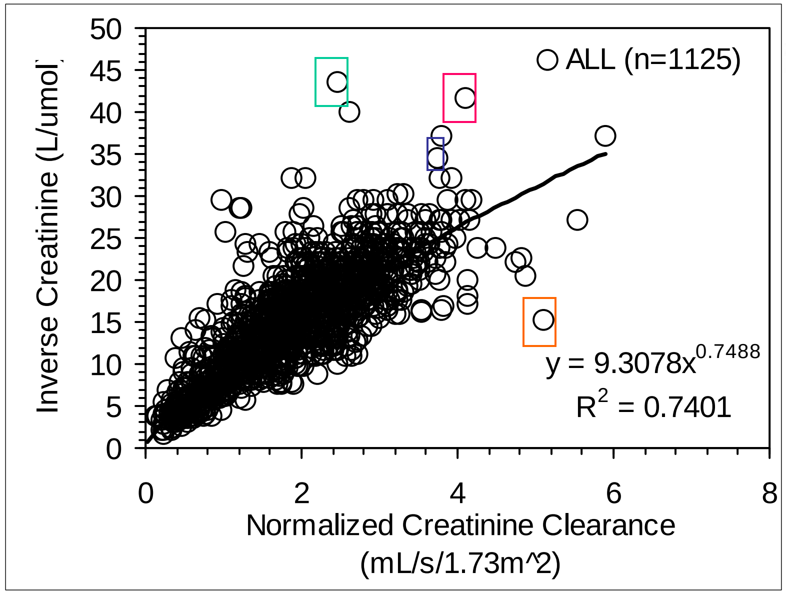


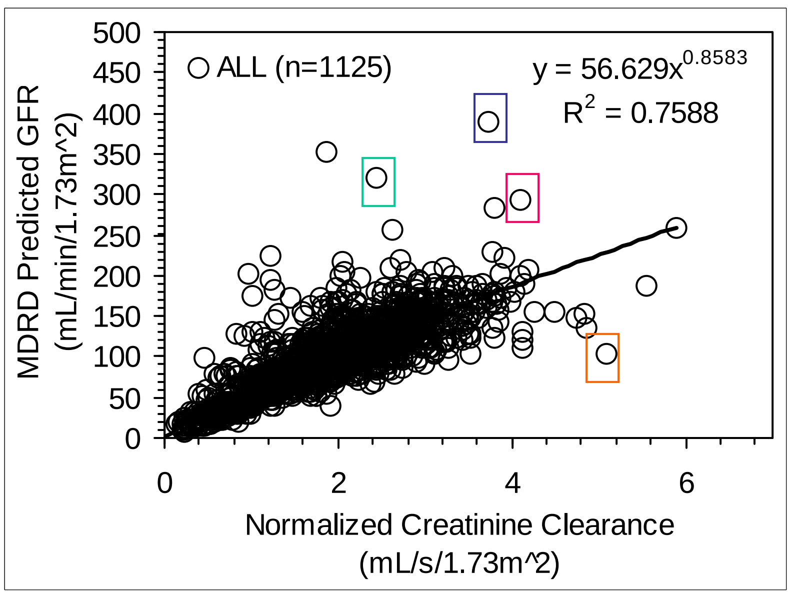
Blood Creatinine / Creatinine Clearance
Female vs. Male

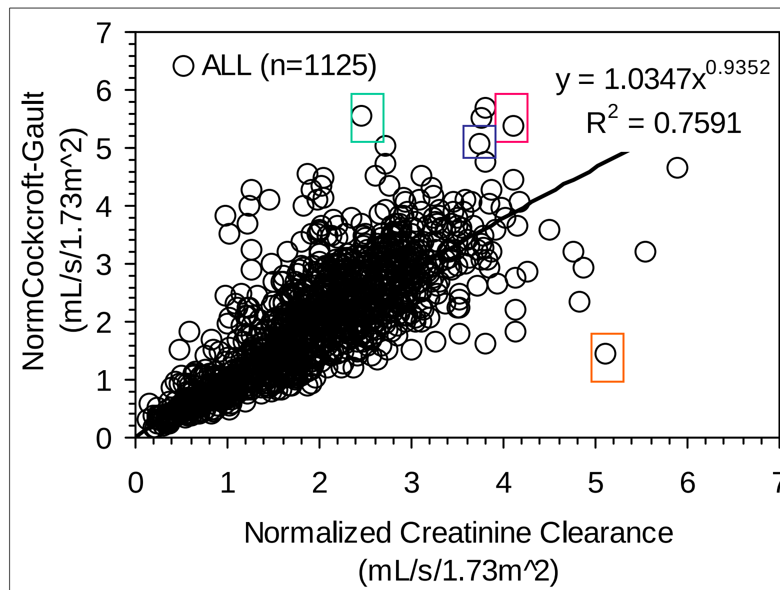


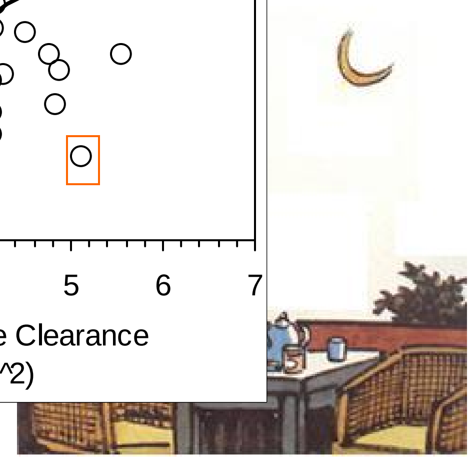


Inverse Creatinine vs. eGFR / Creatinine Clearance



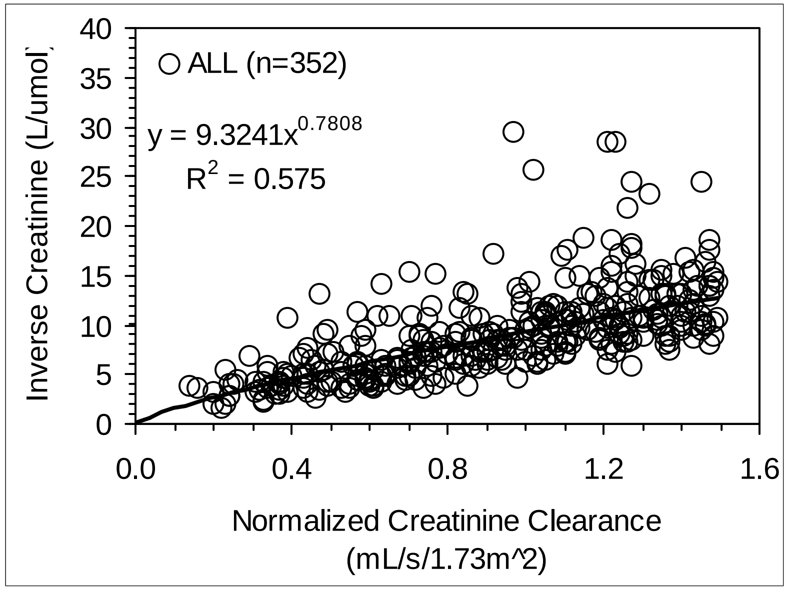


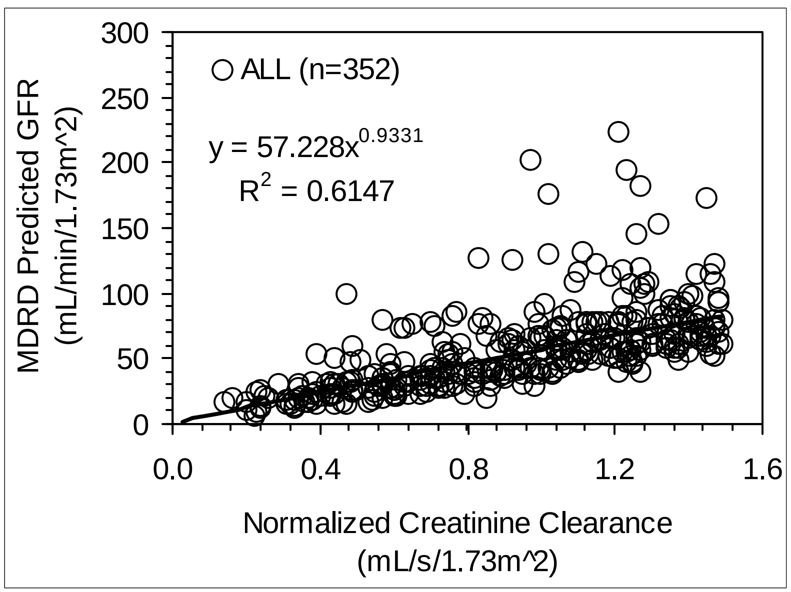


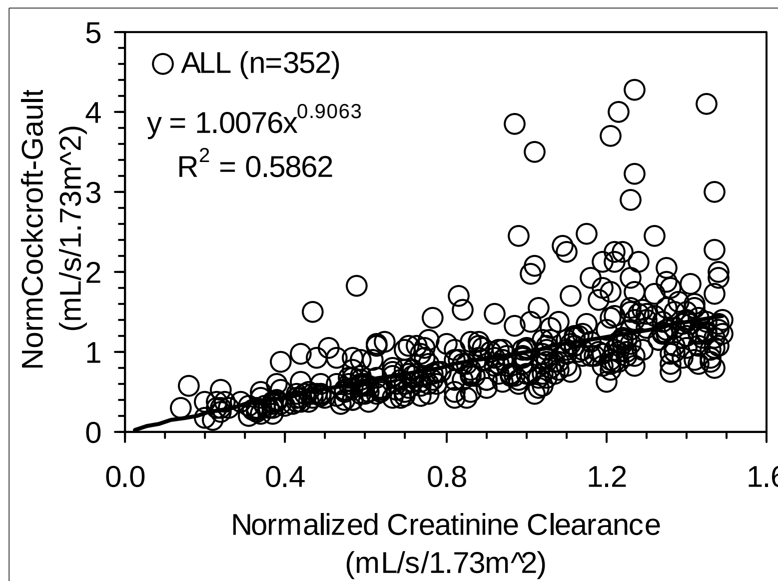


Inverse Creatinine vs. eGFR / Creatinine Clearance

GFR< 90ml·min^{-1}·1.73m^{-2}







Conclusions

Serum creatinine correlates better with BSA-normalized creatinine clearance than with unnormalized creatinine clearance

The correlation between serum creatinine and BSA-normalized creatinine clearance is not affected by different methods used to calculate BSA (Du Bois/Gehan and George).

Inverse serum creatinine, the estimated GFR using Cockcroft-Gault formula or MDRD formula yielded similar prediction of Creatinine Clearance.