Funzione renale

Moderatore: Luigi Biancone (*Torino*)

Presenter: Umberto Maggiore (*Parma*)

Systematic: Barbara Buscemi (*Palermo*) - Ilaria Umbro (*Roma*)

Linee guida ERBP 2013

3.6. What lower level of kidney function precludes living donation?

We recommend that all potential living kidney donors have their GFR assessed. (1C)
We recommend that in cases where more exact knowledge on GFR is needed or where is doubt regarding the accuracy of GFR from estimation methods, a direct measurement of GFR is undertaken by exogenous clearance methods. (Ungraded Statement)
We recommend that all potential donors should have a predicted GFR that is projected to remain above a satisfactory level after donation within the life-time of the donor as indicated in figure 3. (Ungraded Statement)

Linee guida KDIGO 2015

5.1: We recommend expressing kidney function as glomerular filtration rate (GFR) andNOT as serum creatinine concentration. (1A)
5.2: We recommend expressing GFR in mL/min/ 1.73 m2 rather than mL/min. (1B)
5.3: We recommend initial evaluation of GFR (screening) using estimated GFR from
serum creatinine concentration (eGFRcr). (1B)
5.3.1: We recommend that serum creatinine be measured using an assay standardized to the international reference standard. (1B)
5.3.2: We recommend that eGFRcr should be computed using the 2009 CKD-EPI
creatinine equation or other equations that are more accurate than the 2009 CKD-EPI equation. (1B)

Linee guida KDIGO 2015

5.4: We suggest confirmation of GFR using one or more of the following, if eGFRcr is out
of range of reliability, depending on the accuracy and reproducibility at the transplant center: (2B)
5.4.1: Measured GFR (mGFR) using an exogenous filtration marker: Urinary or plasma clearance of inulin, urinary or plasma clearance of iothalamate, urinary or plasma clearance of 51Cr-EDTA, urinary or plasma clearance of iohexol, and urinary clearance of 99mTc-DTPA are preferred. Other
methods, including imaging, are less accurate. (Not Graded)
5.4.2: Measured creatinine clearance (mClcr) should be used if mGFR is not available. (Not Graded)

Linee guida KDIGO 2015

5.4.3: Estimated GFR from the combination of serum creatinine and cystatin C (eGFRcr-cys) should be used if mGFR and mClcr are not available. (Not Graded)
5.4.3.1: We recommend that serum cystatin C be measured using an assay traceable to the international reference standard. (1B)
5.4.3.2: We recommend that eGFRcr-cys should be computed from the 2012 CKD-EPI equations. (1B)
32 5.4.4: Repeat estimated GFR from serum creatinine (eGFRcr) if mGFR, mClcr and eGFRcr-cys are not available. (Not Graded)
5.5: If there is evidence of greater than expected asymmetry of kidney size on medical imaging, assess individual kidney GFR by using radionuclides or contrast agents that are excreted by glomerular filtration (e.g., 99mTc-DTPA). (Not Graded)

Linee guida KDIGO 2015

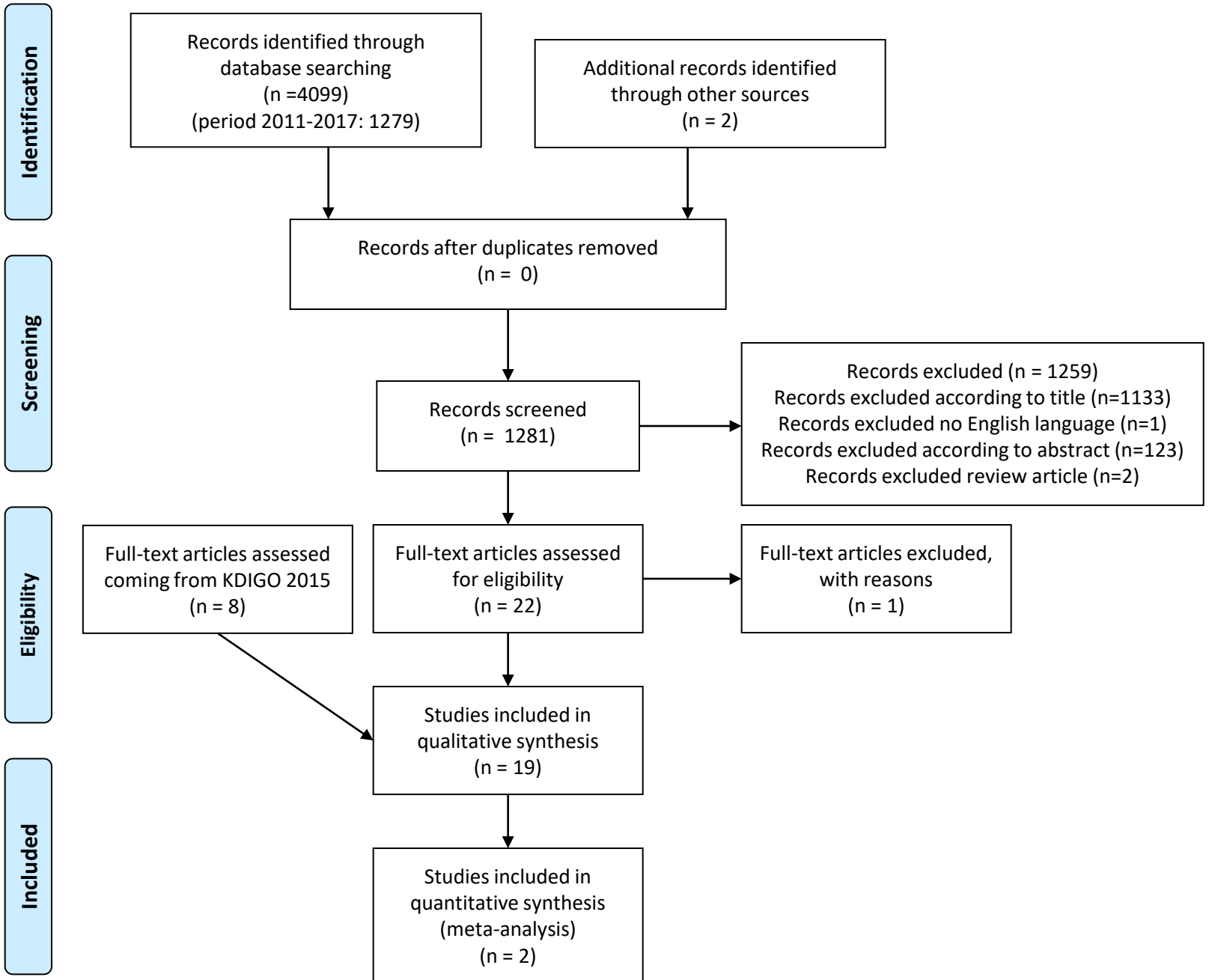
Criteria for Acceptable Pre-Donation GFR

5.6: mGFR ≥ 90 mL/min/ 1.73 m2 should be considered as an acceptable level of kidney function for kidney donation. (Not Graded)

5.7: The decision to approve donor candidates with mGFR 60-89 ml/min/1.73 m2 should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. (Not Graded)

5.8: Donor candidates with mGFR <60 ml/min/1.73 m2 should be excluded from donation. (Not Graded)

5.9: If the donor candidate's mGFR is acceptable but there is a difference in size or function between the two kidneys that is greater than expected, the transplant center should consider procuring the kidney with smaller size or lower function and leaving the donor with the kidney with larger size or higher function. (Not Graded)

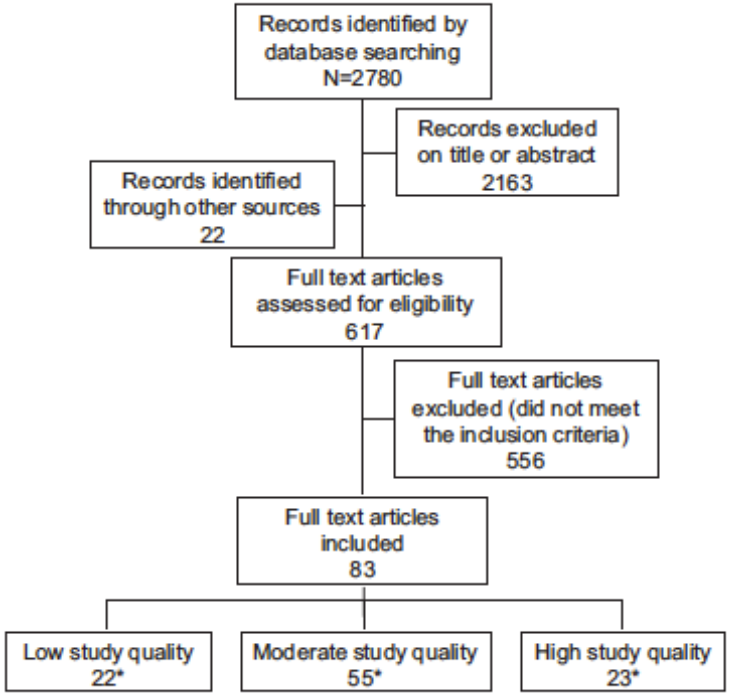

Identification
Screening
Eligibility
Included
Records identified through database searching (n =4099) (period 2011-2017: 1279)
Additional records identified through other sources (n = 2)
Records after duplicates removed (n = 0)
Records screened (n = 1281)
Records excluded (n = 1259)
Records excluded according to title (n=1133)
Records excluded no English language (n=1)
Records excluded according to abstract (n=123)
Records excluded review article (n=2)
Full-text articles assessed coming from KDIGO 2015 (n = 8)
Full-text articles assessed for eligibility (n = 22)
Full-text articles excluded, with reasons (n = 1)
Studies included in qualitative synthesis (n = 19)
Studies included in quantitative synthesis (meta-analysis) (n = 2)

Measuring GFR: A Systematic Review

Inga Soveri, MD, PhD,1 Ulla B. Berg, MD, PhD,2 Jonas Bjo¨ rk, PhD,3 Carl-Gustaf

Am J Kidney Dis. 2014;64(3):411-424

Systematic review with meta-analysis of cross-sectional diagnostic studies.



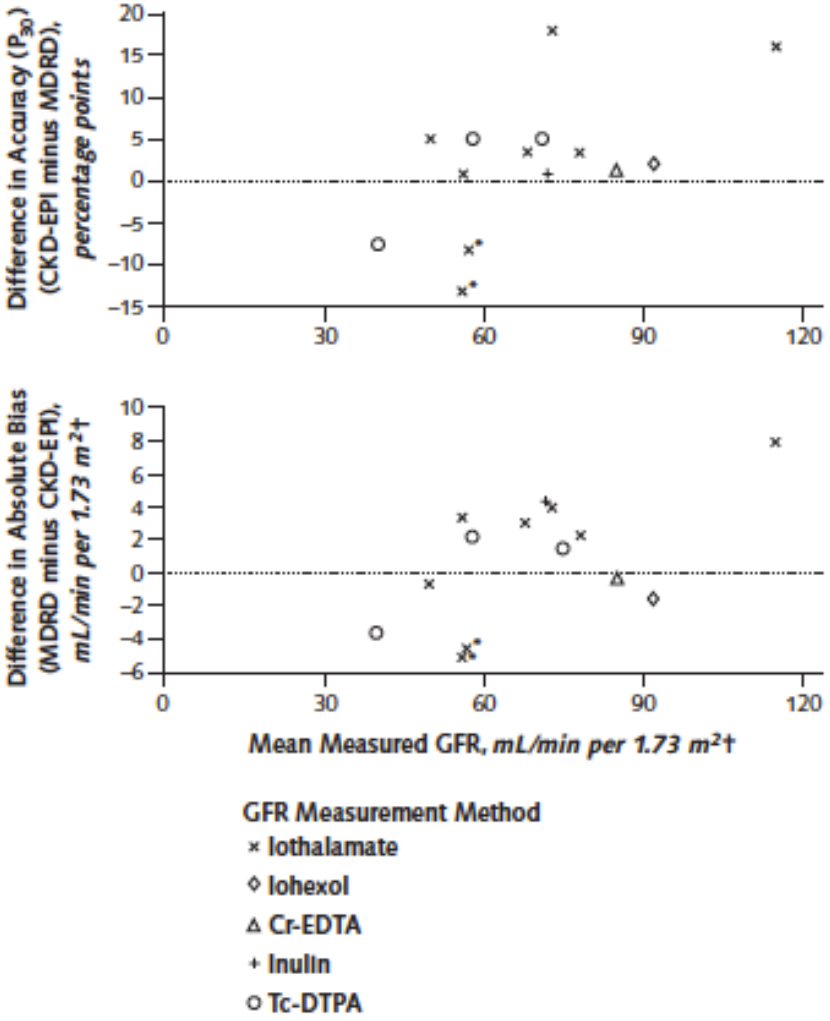
The scientific evidence to suggest that renal clearance of iohexol and plasma clearance of inulin can substitute for renal inulin clearance is limited. Limited evidence suggests that plasma clearance of DTPA is an inaccurate method and there is insufficient evidence to draw conclusions about the utility of plasma clearance of iothalamate. Strong scientific evidence suggests that endogenous creatinine clearance is an inaccurate method.

Table 9. Adjusted Model-Based Estimates of Mean Bias

Marker	Method	N[a]	GFR = 30	GFR = 60	GFR = 90
DTPA	R	80/46	4 (−3 to 12)	0 (−5 to 5)	−2 (−8 to 4)
	P	63/26	30 (19 to 40)	10 (3 to 18)	−8 (−17 to 1)
^{51}Cr-EDTA	R	88/110	−4 (−12 to 4)	−4 (−10 to 1)	−5 (−11 to 2)
	P	67/59	16 (7 to 25)	10 (3 to 16)	2 (−5 to 10)
Iohexol	R	15/32	−18 (−34 to −1)	−11 (−20 to −2)	−2 (−11 to 6)
	P	85/87	10 (2 to 19)	4 (−2 to 10)	0 (−6 to 7)
Iothalamate	R	194/354	7 (1 to 13)	6 (1 to 10)	5 (0 to 10)
	P	10/51	50 (27 to 73)	23 (7 to 39)	7 (−10 to 23)
Inulin	P	0/39	—[b]	—[b]	6 (−4 to 16)

Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review.

Earley A, Miskulin D, Lamb EJ, et al. Ann Intern Med 2012; 156: 785-795



A systematic search of MEDLINE, without language restriction, between 1999 and 21 October 201

Neither the CKD-EPI nor the MDRD Study equation is optimal across all populations and GFR ranges. Using a single equation for reporting estimated GFR requires a tradeoff to optimize performance at either higher or lower GFR ranges.

A general practice and public health perspective favors adopting the CKD-EPI equation in North America, Europe, and Australia and using it as a comparator for new equations in all locations.

Cystatin-C is associated with partial recovery of kidney function and progression to chronic kidney disease in living kidney donors: Observational study.

Bang JY, Kim SO, Kim SG, Song JG, Hwang GS.

Medicine (Baltimore). 2017 Feb;96

Retrospective design

All patients who underwent donor nephrectomy between January 2006 and November 2014 at Asan Medical Center. A total of 1669 patients were identified for this study. A total of 1648 KT donors and 13,834 healthy nondonors were included in the final analysis.

(Defect: follow-up period of KT donors was relatively short)

PRKF (partial recovery of kidney function) is associated with progression to CKD after donor nephrectomy.

Cys-C concentration is a useful early marker to detect PRKF and CKD.

The CKD incidence and risk are significantly higher in KT donors than in healthy nondonors.

Independent variables related to PRKF were: male sex, age at donation, intraoperative Cys-C concentration, and the preoperative albumin level.

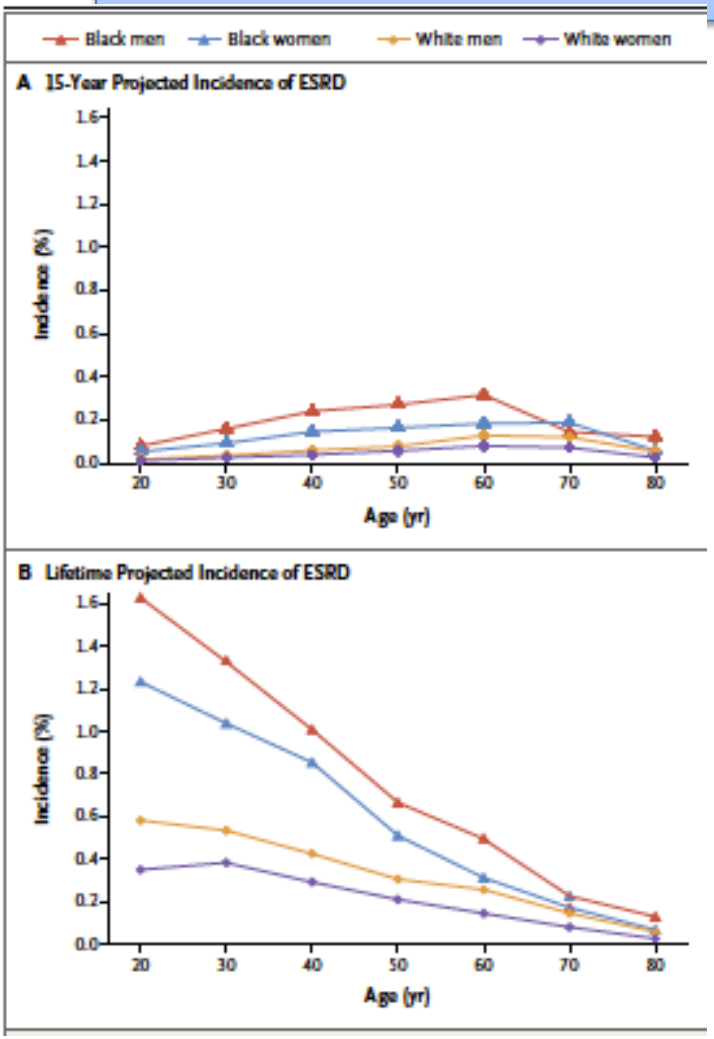
The predictors of CKD were age at donation, intraoperative Cys-C concentration,

and PRKF.

Chronic Kidney Disease Prognosis Consortium Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate.

Grams ME, Sang Y, Levey AS

N Engl J Med 2016 4; 374



4.933.314 participants from seven cohorts were followed for a median of 4 to 16 years.

They developed a tool that simultaneously incorporates multiple health characteristics to estimate a person's probable long-term risk of ESRD if that person does not donate a kidney.

For a 40-year-old person with health characteristics that were similar to those of age-matched kidney donors, the 15-year projections of the risk of ESRD in the absence of donation varied according to race and sex; the risk was 0.24% among black men, 0.15% among black women, 0.06% among white men, and 0.04% among white women.

Risk projections were higher in the presence of a lower estimated glomerular filtration rate, higher albuminuria, hypertension, current or former smoking, diabetes, and obesity. In the model-based lifetime projections, the risk of ESRD was highest among persons in the youngest age group, particularly among young blacks.

The 15-year observed risks after donation among kidney donors in the United States were 3.5 to 5.3 times as high as the projected risks in the absence of donation.

Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate.

Grams ME, Sang Y, Levey AS

N Engl J Med 2016 4; 374

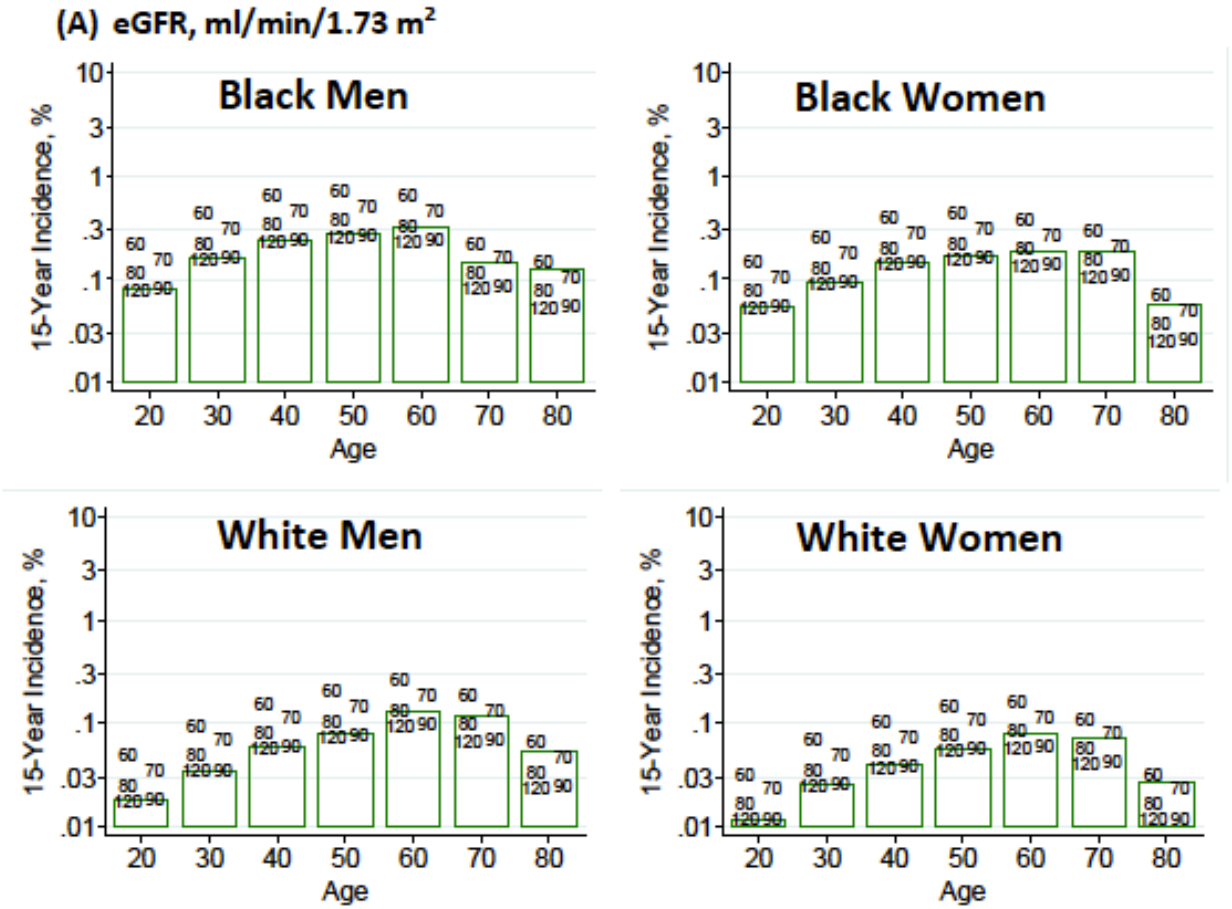


Figure S1: 15-Year incidence (%) of ESRD in the United States in the absence of kidney donation for the "base-case" scenario (green bars) with alteration of a single risk factor

Estimated or Measured GFR in Living Kidney Donors Work-up?

Gaillard F, Flamant M, Lemoine S, Baron S

Am J Transplant. 2016

Observational retrospective study

311 living kidney donors who underwent predonation GFR measurements between 2008 -2015.

The web-based tool (Grams ME NEJM 2015) was used to predict those with mGFR < 80 mL/min/1.73 m2. Inputs to the application were sex, age, ethnicity, and plasma creatinine.

Table 6: Comparison of CKD-EPI, MDRD, and posttest 90 thresholds identified in the main cohort to detect potential living kidney donors with an mGFR lower than 80 mL/min/1.73 m^2 in the validation cohort

	CKD-EPI	MDRD	Posttest 90
AUC (95% CI)	0.85 (0.80–0.91)	0.85 (0.79–0.90)	0.84 (0.79–0.89)
Tested threshold	104 mL/min/1.73 m^2	100 mL/min/1.73 m^2	2%
Sensitivity (95% CI)	0.95 (0.86–0.99)	0.92 (0.81–0.97)	0.95 (0.86–0.99)
Specificity (95% CI)	0.51 (0.45–0.56)	0.54 (0.48–0.60)	0.47 (0.42–0.53)
Positive predictive value	0.28	0.28	0.27
Negative predictive value	0.98	0.97	0.98
Reduction of GFR measurements	43%	45%	40%

AUC, area under the curve; CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration.

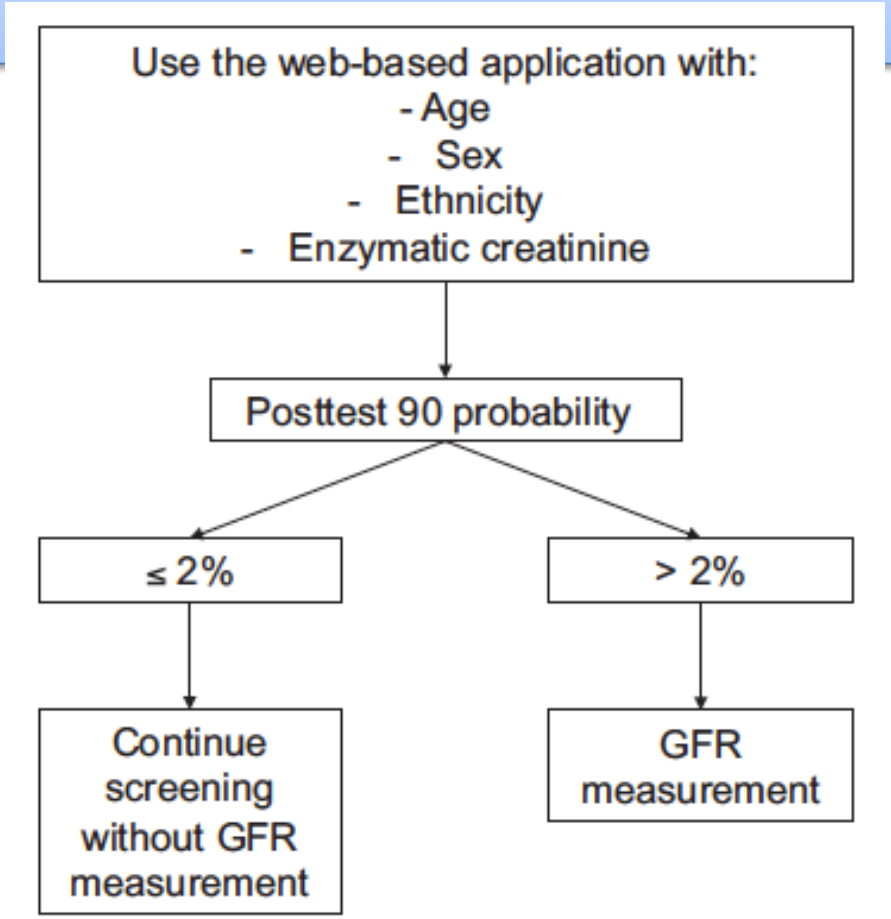
A web-based probability of mGFR <90 mL/min/1.73 m2 higher than 2% had 100% sensitivity for detection of actual mGFR <80 mL/min/ 1.73 m2. The positive predictive value was 0.19.

A CKD-EPI-eGFR threshold of 104 mL/min/1.73 m2 and an MDRD-eGFR threshold of 100 mL/min/1.73 m2 had 100% sensitivity to detect donors with actual mGFR <80 mL/min/1.73 m2

Estimated or Measured GFR in Living Kidney Donors Work-up?

Gaillard F, Flamant M, Lemoine S, Baron S

Am J Transplant. 2016



Proposed algorithm to determine whether or not to measure GFR in living kidney donors.

Estimated nephron number of the remaining donor kidney: impact on living kidney donor outcomes.

Schachtner T, Reinke P.

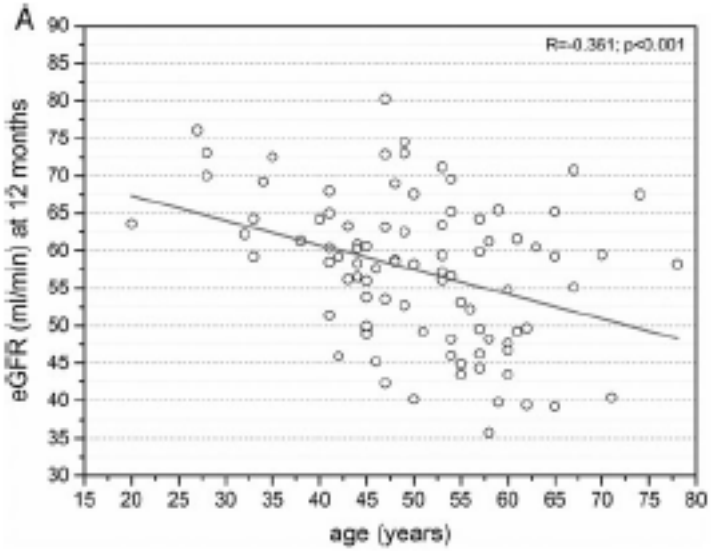
Nephrol Dial Transplant. 2016 Sep

91 living donors who underwent donor nephrectomy at Charité Campus Virchow Clinic

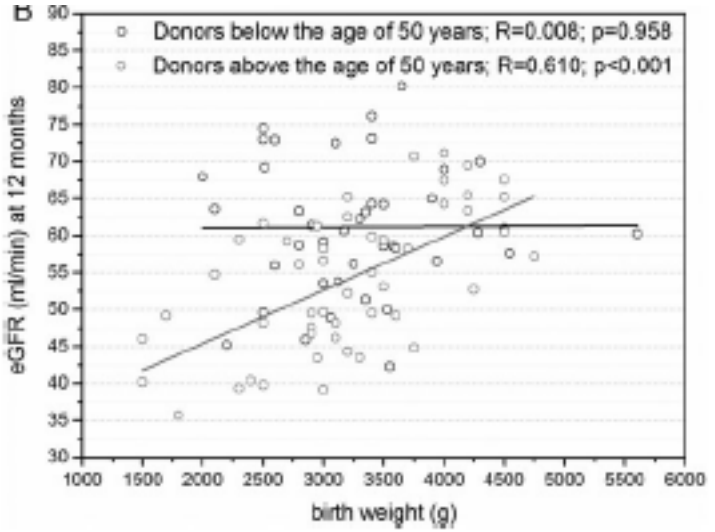
Calculation of nephron number

869 959 + [(donor birth weight . kg. 3: 34 kg) 257 426] nephron number per kidney

Age-adjusted nephron number: nephron number per kidney . 4500. donor age 18)]:



Moderate negative correlation between eGFR and donor age



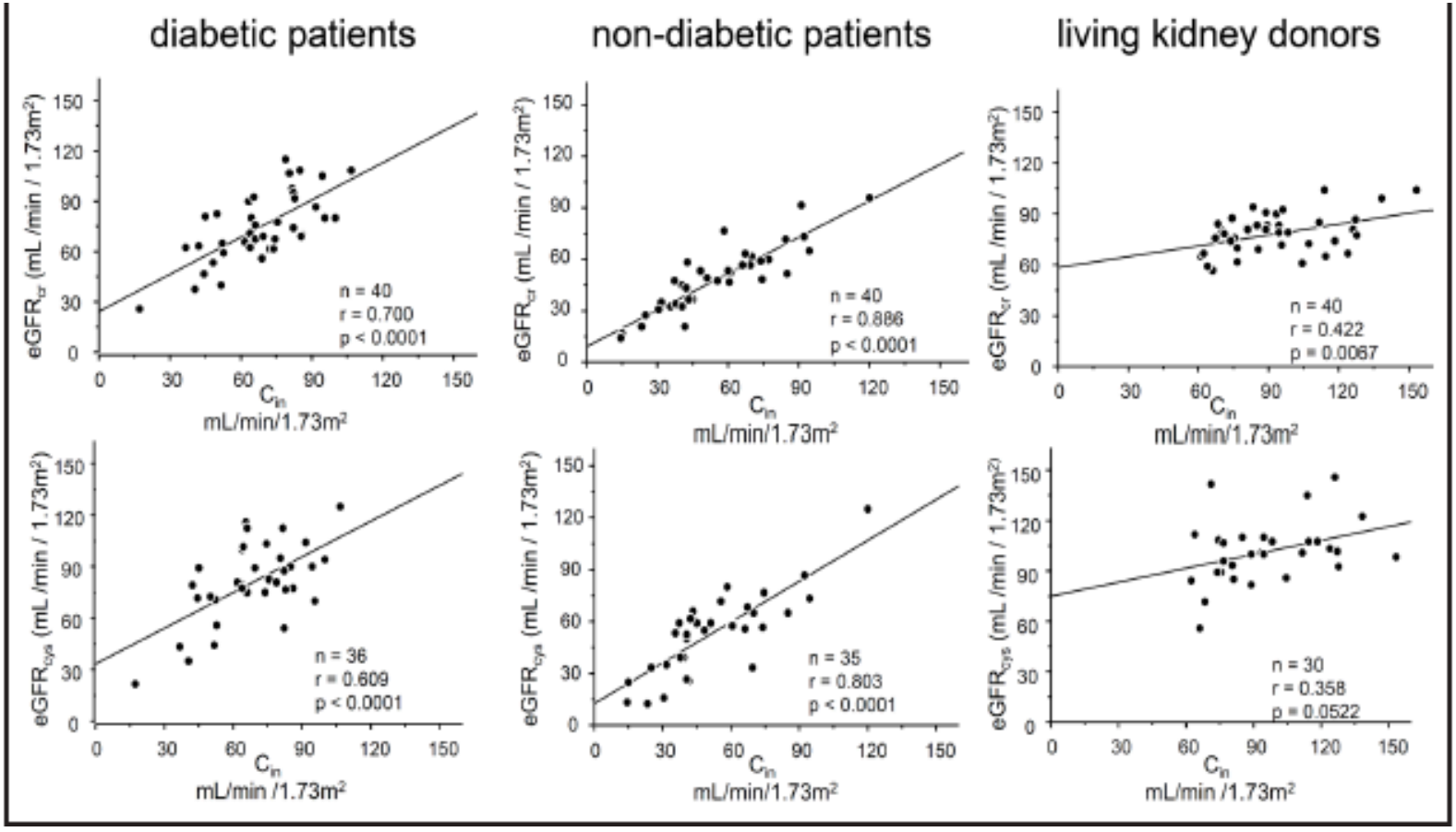
>50 years strong positive correlation between eGFR and donor birth weight (n = 49)

Comparison of the Estimated Glomerular Filtration Rate (eGFR) in Diabetic Patients, Non-Diabetic Patients and Living Kidney Donors.

Tsuda A, Ishimura E, Uedono H, Kidney Blood Press Res. 2016;41

40 diabetic patients, 40 nondiabetic patients, and 40 living kidney donors

The estimated GFR of eGFRcr and eGFRcys were inaccurate in living kidney donors. This result also suggests that each eGFR would be inaccurate in healthy subjects with eGFR more than 60 ml/min/1.73m2

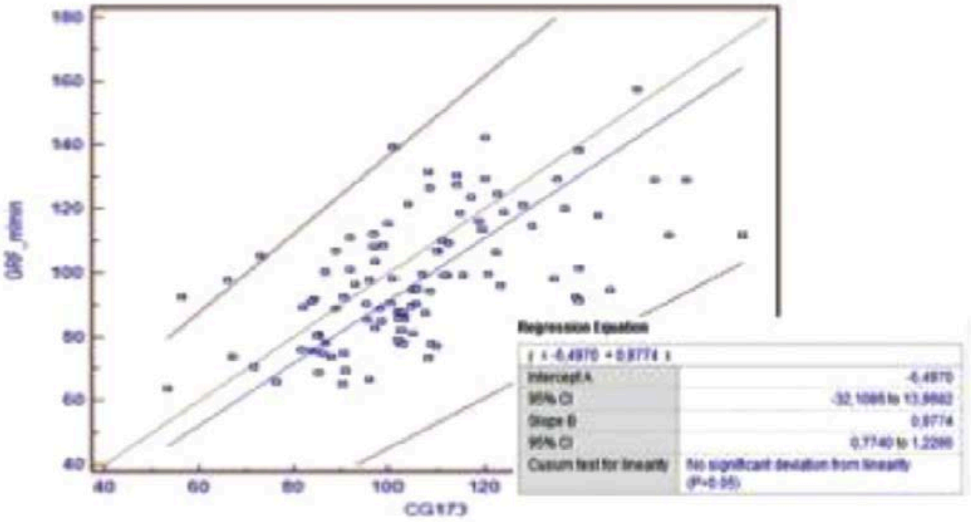


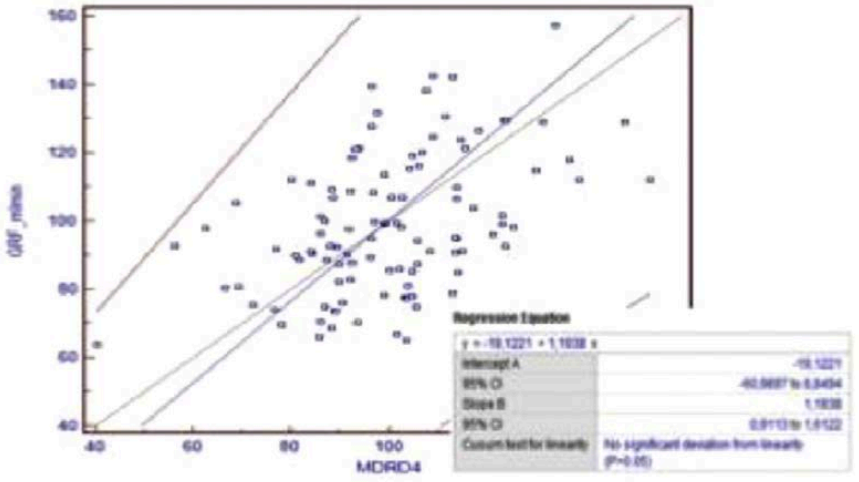
Assessment of the Renal Function in Potential Donors of Living Kidney Transplants: Expanded Study.

Macías LB, Poblet MS, Pérez NN, Transplant Proc. 2015 Nov;47

105 potential kidney donors

The EDTA-Cr51vis compared with the CCr values in 24-hour urine and eGFR based on creatinine (Cockcroft-Gault, MDRD4, MDRD6, and CKD-EPI).





eGFR for MDRD-4 and MDRD-6 formulas show the highest approximation to mGFR for EDTACr51. This might represent the best option if the direct GF measure is not available.

Estimated GFR for Living Kidney Donor Evaluation.
Huang N, Foster MC, Lentine KL
Am J Transplant. 2016 Jan;16(1):171-80

35 334 living kidney donors in the United States (from 2009 to 2015)

Using pretest probabilities from NHANES (4122) and eGFR categorical LRs from CKD-EPI (5352)

		mGFR thresholds	
	n	≥80	≥90
All, n (%)	35 334	25 985 (74)	18 566 (53)
Age, 18–44 years			
Black women	1693	1610 (95)	1507 (89)
Black men	1245	1194 (96)	1158 (93)
Nonblack women	10 232	9499 (93)	8357 (82)
Nonblack men	7053	6594 (93)	5522 (78)
Age, 45–64 years			
Black women	674	459 (68)	286 (42)
Black men	381	229 (60)	92 (24)
Nonblack women	8777	4190 (48)	1183 (13)
Nonblack men	4546	2205 (49)	461 (10)
Age, 65–80 years			
Black women	17	2 (12)	0 (0)
Black men	11	1 (9)	0 (0)
Nonblack women	462	1 (0)	0 (0)
Nonblack men	243	1 (0.4)	0 (0)

18 566 (53%) would have had eGFR high enough to ensure 95% probability that mGFR was 90 mL/min per 1.73m2 and would not have been required to undergo mGFR testing using CrCl or an exogenous filtration marker.

http://ckdepi.org/equations/donor-candidate-gfr-calculator/

Limitations: the data are based on NHANES and CKD-EPI study populations rather than studies in kidney donor candidates

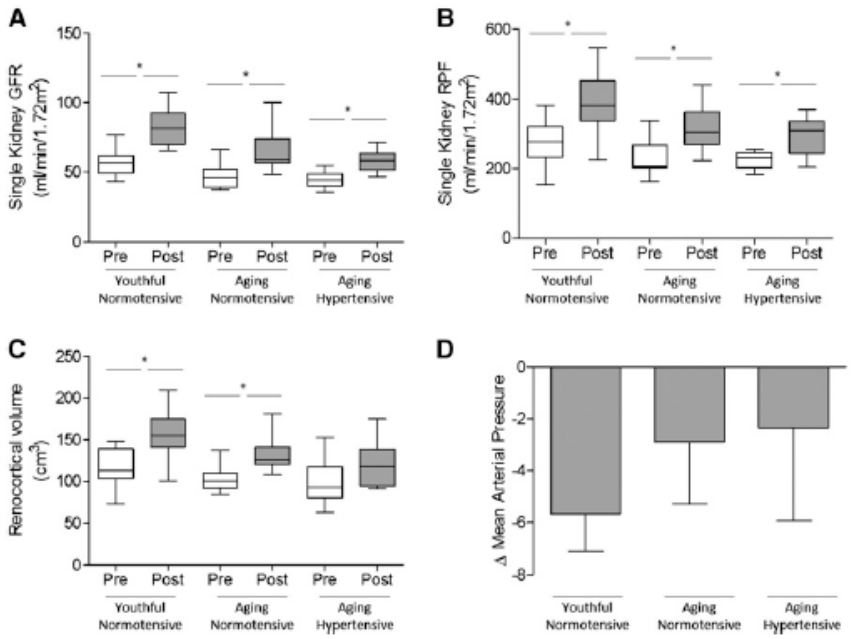
The association of predonation hypertension with glomerular function and number in older living kidney donors.

Lenihan CR, Busque S, Derby G

J Am Soc Nephrol. 2015 Jun;26(6):1261-7

51 living donors to undergo physiologic, morphometric, and radiologic evaluations before and after kidney donation

Donors ages 50 years old, preexisting hypertension was associated with a reduction in NFG (number of functioning glomeruli)



No difference in glomerular volume or 6-month postdonation hyperfiltration capacity or compensatory hypertrophy in those donors with hypertension compared with their normotensive controls.

Glomerular filtration rate estimation in prospective living kidney donors: preliminary study.

Gozdowska J, Urbanowicz A TransplantProc. 2014 Oct;46(8):2592

25 prospective kidney donors (aged 28e 64 years)

The precision of GFR estimation by all methods is unsatisfactory (30% margin of reference held in < 50% of cases)
CKDEPI estimation equations are the most precise methods of GFR estimation in this analysis; in addition, CKD-EPI cystatin C and combined creatinine/cystatin C estimators are robust to overweight/obesity.

Table 3. Subgroup Analysis of Relationship Between Estimated and Measured Glomerular Filtration Rate (GFR) According to Normal Versus Elevated Body Mass Index (BMI)

	^{99m}Tc-*DTPA* (Corrected for Body Surface Area)					
	Normal BMI			Elevated BMI		
Parameter	Regression Coefficient	R^2	*P*	Regression Coefficient	R^2	*P*
CKD-EPI creatine	0.55	0.30	.12	−0.01	<0.01	NS
CKD-EPI cystatin C	0.30	0.09	NS	0.28	0.08	NS
CKD-EPI cystatin C/creatine	0.47	0.20	NS	0.21	0.04	NS
Cockcroft- Gault	−0.07	<0.01	NS	−0.38	0.15	NS
MDRD (short)	0.37	0.13	NS	−0.27	0.07	NS
MDRD (full)	0.06	<0.01	NS	−0.17	0.03	NS
Mayo quadratic	−0.32	0.1	NS	−0.49	0.24	.06
Nankivell	−0.07	<0.01	NS	−0.11	0.01	NS
BTP White	0.34	0.11	NS	−0.48	0.23	.06
Serum creatine	−0.55	0.30	.13	−0.18	0.03	NS
Serum cystatin C	−0.35	0.12	NS	−0.59	0.34	<.02
Serum BTP	0.45	0.2	NS	−0.43	0.19	.09

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; NS, not significant.

Table 4. Equation Bias (Mean Difference Between Measured and Estimated Glomerular Filtration Rate [GFR]) and Accuracy of GFR Estimates (% of Estimates Within 30% of the Measured GFR)

Parameter	Bias (mL/min; Mean ± SD)	Accuracy (%)
CKD-EPI creatine	1.2 (29.1)	28
CKD-EPI cystatin C	26.8 (36.7)	32
CKD-EPI cystatin C/creatine	17.6 (31.1)	44
Cockcroft-Gault	16.1 (46.3)	44
MDRD (short)	−0.6 (34.1)	44
MDRD (full)	4.7 (34)	48
Mayo quadratic	5.6 (41.1)	32
Nankivell	11.6 (33.4)	36
BTP White	−44 (37.2)	4

Abbreviations: BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

Comparison of estimated GFR and measured GFR in prospective living kidney donors.Bhuvanakrishna T, Blake GM,
Int Urol Nephrol. 2015 Jan;47(1):201-8

508 consecutive potential living kidney donors.

Table 3 Sensitivity, specificity, positive predictive value and negative predictive value for each eGFR equation to identify potential living kidney donors with mGFR < 80 mL/min/1.73 m^2

eGFR equation	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MDRD	50/84 (60 %)	353/424 (83 %)	50/121 (41 %)	353/387 (91 %)
CKD-Epi	33/84 (39 %)	404/424 (95 %)	33/53 (62 %)	404/455 (89 %)
CG	37/84 (44 %)	404/424 (95 %)	37/57 (65 %)	404/451 (90 %)

Numbers of subjects in numerator and denominator for the calculations of sensitivity, specificity, PPV and NPV (% in brackets)

CG Cockcroft–Gault, *CKD-Epi* Chronic Kidney Disease Epidemiology Collaboration, *eGFR* estimated GFR, *GFR* glomerular filtration rate, *MDRD* Modification of Diet in Renal Disease, *mGFR* measured GFR

Among subjects with mGFR results below the threshold of 80 mL/min/1.73 m2 , 40 % had a MDRD, 61 % a CKD-Epi and 56 % a CG eGFR above threshold such that they would have been wrongly recommended for donation.

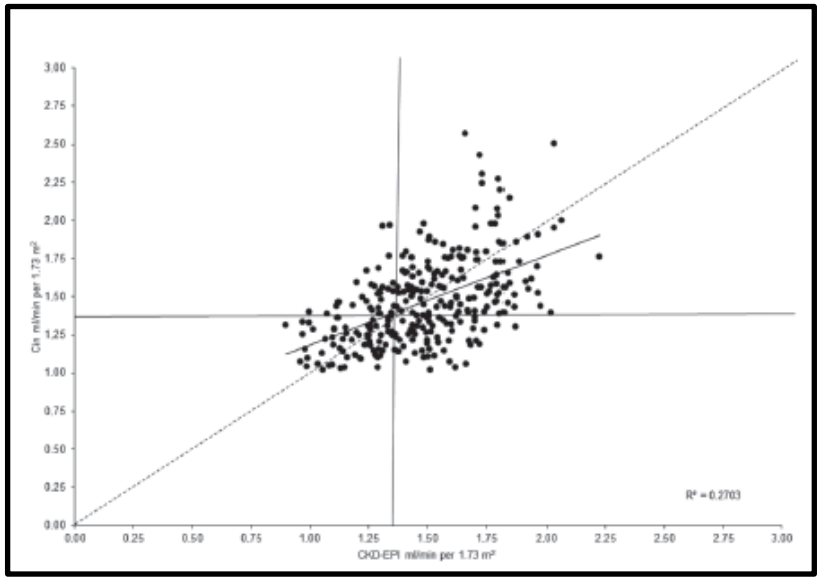
Among subjects with an mGFR result above threshold, 17 % had a MDRD, 5 % a CKD-Epi and 5 % a CG eGFR below threshold such that they would have been wrongly rejected as suitable donors

The relationship between estimated GFR based on the CKD-EPI formula and renal inulin clearance in potential kidney donors.

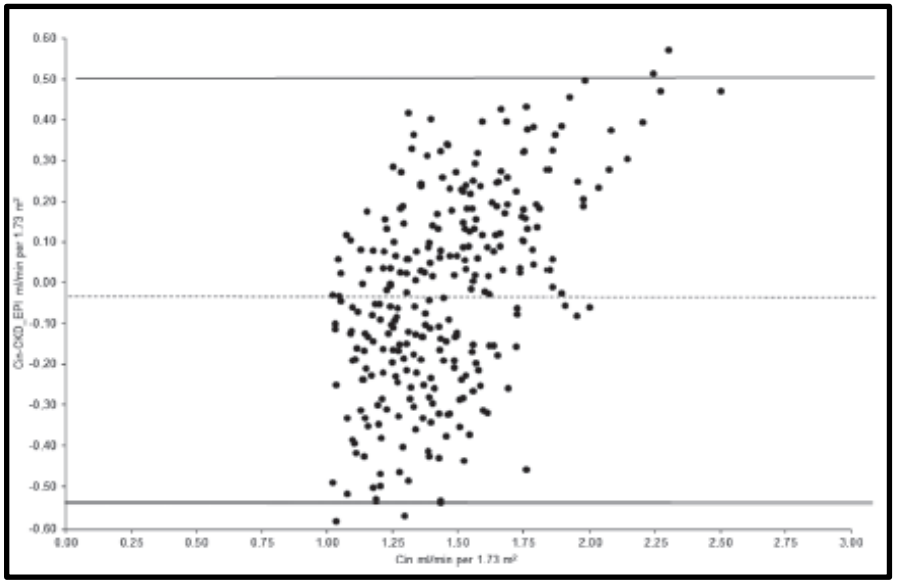
Schück O, Teplan V, Maly J,

Clin Nephrol. 2014 Dec;82(6):353-7

287 potential kidney donors with a mean age of 48 ± 10 years.



Significant correlation between the values of Cin and those estimated using the CKD-EPI formula.



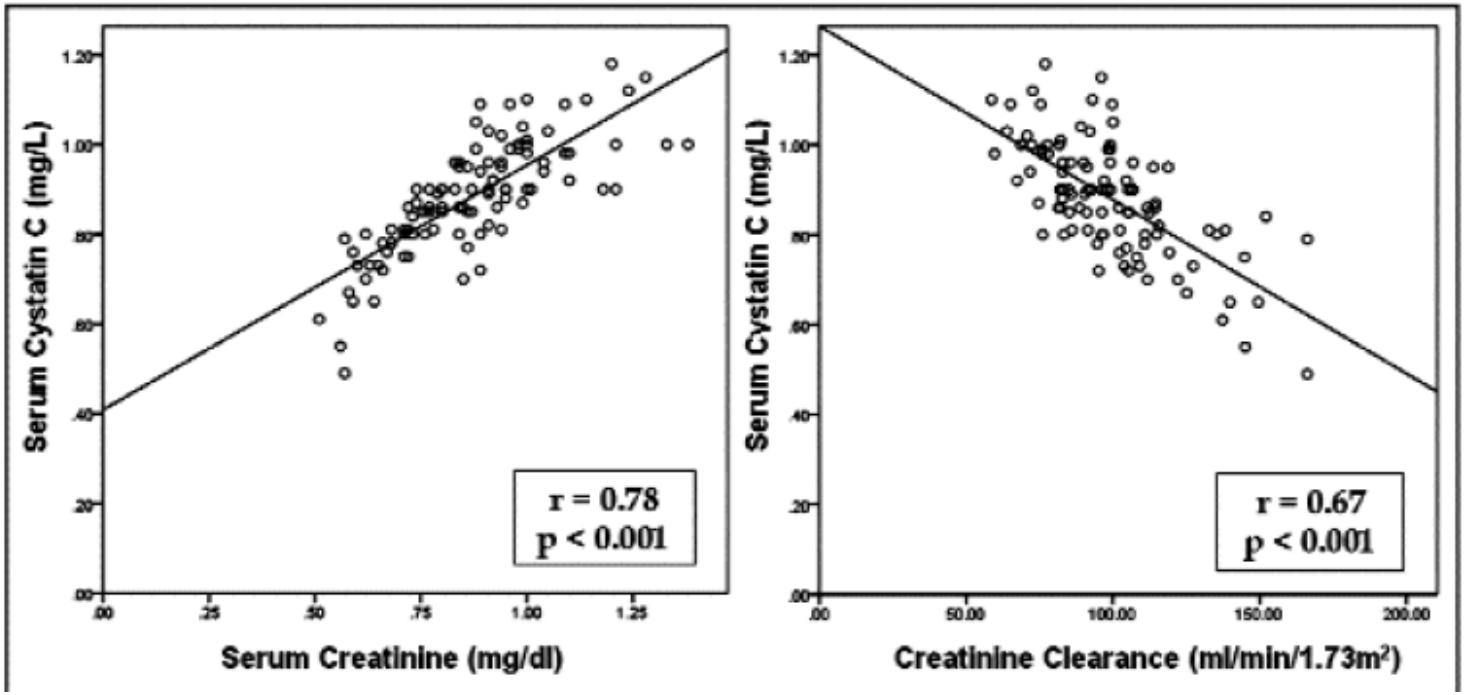
High 2SD (0.52 mL/s/1.73 m2) suggestes that eGFR using the CKD-EPI formula cannot beused as an alternative to accurate GFR determination in potential kidney donors

Cystatin C levels in healthy kidney donors and its correlation with GFR by creatinine clearance.

J Ayub S, Khan S, Ozair U, Zafar MN.

Pak Med Assoc. 2014 Mar;64(3):286-90

103 potential healthy kidney donors were enrolled



S.CysC showed significant correlation with CCL, CCG and MRDR. The GFR assessed by CCL in our population was lower than reported in western studies comparable to that reported from India. This may be a reflection of difference in muscle mass between South Asian and European population.

Comparison of estimating equations for the prediction of glomerular filtration rate in kidney donors before and after kidney donation

Chung BH, Yu JH, Cho HJ, Kim JI PLoS One. 2013 Apr 9;

207 potential kidney donors and 108 uninephric donors

eGFR CKD-EPI showed better performance than other GFR estimating equations including eGFR MDRD in the prediction of renal function.

In the uninephric state after kidney donation, the overall performance of eGFR CKD-EPI was inferior to eGFR MDRD, which suggests that the eGFR MDRD is more appropriate for the estimation of renal function during follow-up of uninephric kidney donors.

CKD-EPI instead of MDRD for candidates to kidney donation

Lujan PR, Chiurchiu C, Douthat W

Transplantation. 2012 Sep 27;94(6):637-41

85 adults candidates for living-related kidney donation.

TABLE 2. Overall performance of studied equations

Variable	CKD-EPI	MDRD
Mean, mL/min/1.73 m^2	108	102
Bias, mL/min/1.73 m^2	3.3	10.2
Precision, mL/min/1.73 m^2	22	28
Accuracy, %	100	89
Median, mL/min/1.73 m^2	112	99
IQR	98–123	86–118
ΔIQR	25	32

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IQR, interquartile range; MDRD, modification of diet in renal disease.

CKD-EPI presented lower bias), higher precision and higher accuracy (100% vs. 89%) than MDRD

TABLE 3. Performance of equations according GFR 90 mL/min per 1.73 m^2 or less

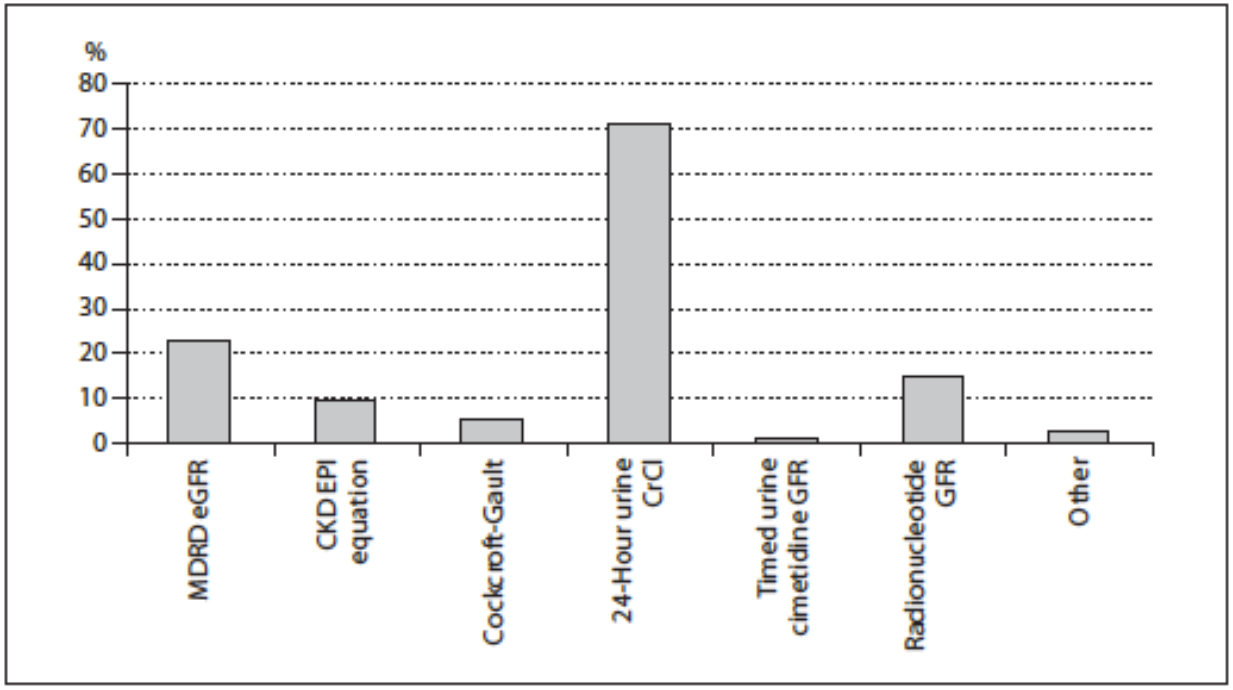
Variable	CKD-EPI	MDRD
ROC, AUC[a]	0.975	0.877
ROC, SE	0.015	0.039
AUC, 95% CI	0.915–0.996	0.788–0.938
Sensitivity[b]	94.3 (86.0–98.4)	92.9 (84.1–97.6)
Specificity[b]	93.3 (68.0–98.9)	80.0 (51.9–95.4)
PPV[b]	98.5 (91.9–99.8)	95.6 (87.6–99.0)
NPV[b]	77.8 (52.4–93.5)	70.6 (44.1–89.6)
Misclassified donors, %[b]	5.9	21.2

Only 5.9% of the subjects had to be rejected as a donor with CKD-EPI instead of 21.2% were misclassified using MDRD. Results showed better performance for CKD-EPI which misclassified smaller number of subjects

Practice patterns in evaluation of living kidney donors in United Network for Organ Sharing-approved kidney transplant centers.

Brar A, Jindal RM, Abbott KC, Hurst FP, Salifu MO. Am J Nephrol. 2012;35(5

37-question electronic survey to gather information about living kidney donor evaluation and selection processes. Respondents from 72 centers completed the

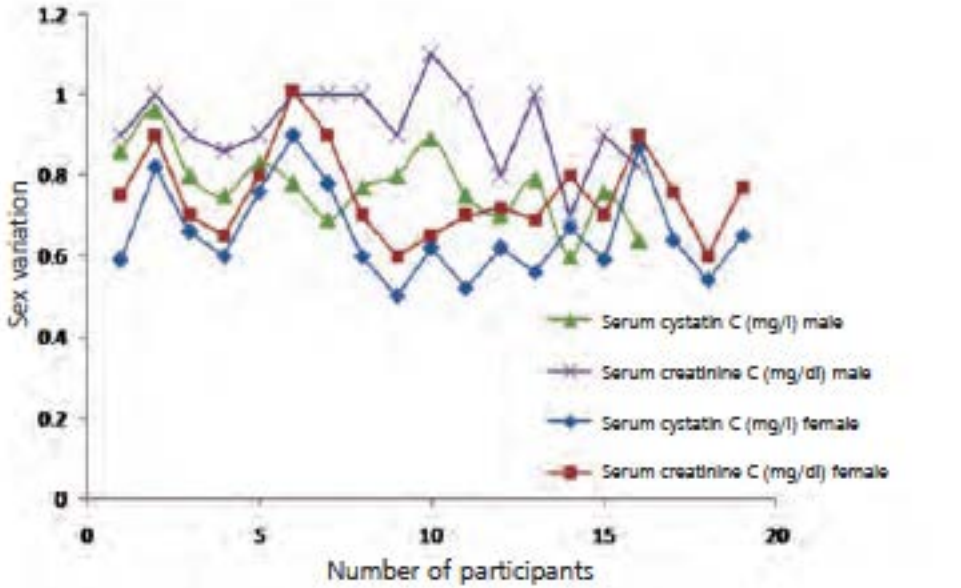


24-hour urine measuring creatinine clearance (CrCl) was the most common screening method for glomerular filtration rate
66%of the centers used a cut-off of 80 ml/min for exclusion of living kidney donors.

Cystatin C as a marker of glomerular filtration rate in voluntary kidney donors.
Jaisuresh K, Sharma RK, Mehrothra S, Kaul A, Jain A.
Exp Clin Transplant. 2012 Feb;10(1):14-7

35 voluntary kidney donors

Serum cystatin C showed significant correlation with serum creatinine (r =0.864; P < .001), with GFR-Cockcroft-Gault (r = - 0.50; P = .002), GFR-MDRD (r = - 0.59; P < .001), and gGFR-double plasma sampling method (r = - 0.59; P < .001).



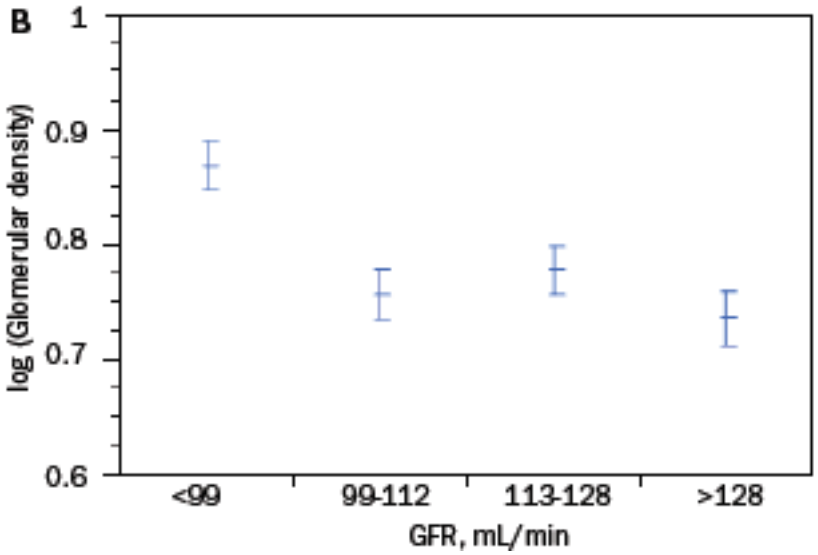
Significant sex difference in the estimated SCysC levels with lower levels in women similar to SCr

Association of kidney function and metabolic risk factors with density of glomeruli on renal biopsy samples from living donors

Rule AD, Semret MH, Amer H, Cornell LD

Mayo Clin Proc. 2011 Apr;86(4):282-90.

biopsy samples of 54 donors



Increased GFR was independent predictors of decreased glomerular density