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Brief Communication

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

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The value of estimated glomerular filtration rate (eGFR) in living kidney donors screening is unclear. A recently published web-based application derived from large cohorts, but not living donors, calculates the probability of a measured GFR (mGFR) lower than a determined threshold. Our objectives were to validate the clinical utility of this tool in a cohort of living donors and to test two other strategies based on chronic kidney disease epidemiology collaboration (CKD-EPI) and on MDRD-eGFR. GFR was measured using ^{51}Cr- ethylene-diamine tetraacetic acid urinary clearance in 311 potential living kidney donors (178 women, mean age 50 $\pm$ 11.6 years). The web-based tool was used to predict those with mGFR < 80 mL/min/1.73 m^2. Inputs to the application were sex, age, ethnicity, and plasma creatinine. In our cohort, a web-based probability of mGFR <90 mL/min/1.73 m^2 higher than 2% had 100% sensitivity for detection of actual mGFR <80 mL/min/1.73 m^2. The positive predictive value was 0.19. A CKD-EPI-eGFR threshold of 104 mL/min/1.73 m^2 and an MDRD-eGFR threshold of 100 mL/min/1.73 m^2 had 100% sensitivity to detect donors with actual mGFR <80 mL/min/1.73 m^2. We obtained similar results in an external cohort of 354 living donors. We confirm the usefulness of the web-based application to identify potential donors who should benefit from GFR measurement.

Abbreviations: ^{51}Cr-EDTA, ^{51}chromium-ethylene-diamine tetraacetic acid; AUC, area under the curve; CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; ESRD, end stage renal disease; mGFR, measured GFR; Posttest *(number)*, posttest probability of having mGFR lower than *(number)* calculated from the web-based application developed by Huang et al; SD, standard deviation

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Introduction

Several studies have shown that living kidney donors are at risk of end stage renal disease (ESRD) (1–6), emphasizing the need for precise predonation screening. A recent study estimated ESRD risk at 15 years in the absence of donation by using several variables. Among all the variables, an estimated GFR (eGFR) before donation below 90 mL/min/1.73 m^2 was significantly associated with increased ESRD risk. This risk was markedly

increased when eGFR decreased below 60 mL/min/1.73 m^2 (3). Several guidelines already consider that a GFR lower than 80 mL/min/1.73 m^2 could be a contraindication to donation (7–13); however, whether or not GFR should be measured rather than estimated in this population remains controversial (7–13). GFR can be estimated using Cockcroft (14), MDRD (15), or chronic kidney disease epidemiology collaboration (CKD-EPI) (16) formulas or calculated using urinary clearance of endogenous markers such as creatinine. The "gold standard" remains GFR measurement determined by the clearance of exogenous markers such as ^{51}Cr-ethylene-diamine tetraacetic acid (^{51}Cr-EDTA) (17), iohexol, or inulin (18).

GFR estimation is usually used as a screening test but is rarely sufficient to authorize donation without further renal function evaluation (8). Urinary creatinine clearance is accepted by some guidelines (8) but has its own limitations due to 24-h urine collection imprecision and tubular secretion of creatinine (18). In contrast, GFR measurement from exogenous markers is much more accurate but its cost and availability limit its use and its role in living donors screening has yet to be defined.

There is a need for a strategy to identify potential donors who should undergo GFR measurement. Recently, Huang et al developed a new tool to help transplantation centers estimate the probability that a potential donor will have a measured GFR (mGFR) higher or lower than a defined threshold (19). The authors suggest that this application could be used to identify donors requiring GFR measurement. The probabilities used to develop the tool were calculated from large cohorts, including National Health and Nutrition Examination Survey (NHANES) and CKD-EPI, but were not applied to a cohort of potential living kidney donors. Our objectives were to validate the clinical utility of this new tool in screening of living donors by comparing its results to systematically measured GFR. We also tested two other simple strategies based on CKD-EPI and MDRD-eGFR. Finally, we tested our results in an external cohort of living donors.

Materials and Methods

Living donors

We conducted an observational retrospective study including all potential living kidney donors who underwent predonation GFR measurements screened in our adult renal transplantation unit (Necker Hospital, Paris, France) between January 2008 and December 2015. We obtained approval of the Institutional Ethical Review Board for this study (number: REF2013-11-10). After donation, donors were seen once a year in consultation for clinical evaluation and plasma creatinine measurement to estimate GFR.

External cohort

Potential living kidney donors included in the external cohort were screened between January 2011 and March 2016 at the Physiology Department of the University Hospital of Lyon, (France) and between April 2008 and November 2015 at the Physiology Department at Bichat Hospital, Paris (France). GFR was measured with inulin or iohexol clearance for potential donors screened in Lyon and with ^{51}Cr-EDTA clearance for potential donors screened at Bichat Hospital, Paris.

GFR measurement and estimation

GFR was assessed through a continuous ^{51}Cr-EDTA (GE Healthcare, Little Chalfont, UK) infusion method. A priming dose of 0.5 μCi/kg body weight of ^{51}Cr-EDTA was injected intravenously, followed by a constant ^{51}Cr-EDTA infusion. After allowing 1 h for equilibration of the tracer in the extracellular fluid, urine was collected and discarded. Average renal ^{51}Cr-EDTA clearance was assessed during six consecutive 30-min clearance periods. Blood was drawn at the midpoint of each clearance period with the last collection 300 min after injection of the priming dose. The radioactivity measurements in 1-mL plasma samples and in urine samples were carried out on a Packard Cobra 3-inch crystal γ-ray well counter (PerkinElmer, Waltham, MA). Inulin clearance and iohexol clearance are described in Data S1. GFR was estimated using CKD-EPI (20) and MDRD formulas (15) at donation and during follow-up. Plasma creatinine measurement was performed using an enzymatic method (Thermo Fisher Scientific, Waltham, MA) on Konelab 20i automat (Thermo Fisher Scientific) before donation in both cohorts.

Use of the web-based application

The web-based application calculates, for a given donor, its probability to have an mGFR lower than 60, 70, 80, and 90 mL/min/1.73 m^2. The web-based application performs a two-step calculation. First, it calculates the pretest probability to have an mGFR lower than 60, 70, 80, and 90 mL/min/1.73 m^2 based on sex, age, and ethnicity. This calculation was developed in the NHANES cohort using GFR calculated from cystatin measurement. Then, using data derived from the CKD-EPI cohort and concordance between eGFR and mGFR, the web-based application refines the pretest probability by taking into account creatinine measurements with or without cystatin. This gives the posttest probability value. Pretest and posttest probabilities were calculated using the web-based application, available on the CKD-EPI website (http://ckdepi.org/equations/donor-candidate-gfr-calculator/). The web-based application allows the user to alter the pretest probability according to the familial medical history of the donor (19). We did not modify the pretest probabilities to calculate the posttest probabilities. For both cohorts, the posttest probability was calculated based only on enzymatic creatinine because cystatin measurements were not available. The posttest probability of having an mGFR lower than 90, 80, 70, or 60 mL/min/1.73 m^2 are referred to as posttest 90, posttest 80, posttest 70, and posttest 60, respectively. For example, a white woman aged 30 with a plasma creatinine of 0.8 mg/dL (eGFR CKD-EPI 99 mL/min/1.73 m^2; eGFR MDRD 85 mL/min/1.73 m^2) has a posttest probability to have a measured GFR lower than 90 mL/min/1.73 m^2 of 3%.

Statistical analysis

Data processing was done using Excel (2011; Microsoft, Redmond, WA), and statistical analyses were performed using Prism GraphPad (version 6; Prism GraphPad, San Diego, CA). We plotted the distributions of mGFR, eGFR (CKD-EPI), and eGFR (MDRD). We calculated the arithmetic median difference (with interquartile range) between eGFR and mGFR for each value of eGFR.

We checked the validity of the web-based calculator in our main cohort by stratifying pretest probabilities according to age and sex as previously done by Huang et al (19). Our goal was to identify all the donors with an mGFR <80 mL/min/1.73 m^2, a threshold considered by some guidelines as a contraindication to donation (7–13). For this reason, we measured the sensitivity and specificity of different values of posttest 90, posttest 80, posttest 70, and posttest 60 to detect an mGFR <80 mL/min/1.73 m^2. We also measured the sensitivity and specificity of different

eGFR values, estimated with the MDRD or CKD-EPI formulas to detect potential donors with an mGFR <80 mL/min/1.73 m^2. These thresholds were tested in an external cohort.

Global diagnostic performance was measured by calculating the area under the receiver operating characteristics curve. We compared eGFR 1 year after donation in our main cohort for each strategy used to screen donors at the time of donation with 100% sensitivity to detect mGFR <80 mL/min/1.73 m^2. We calculated the Pearson correlation coefficient between predonation eGFR (calculated using MDRD or CKD-EPI formulas) and predonation mGFR.

Results

Description of the population

Three hundred eleven potential living kidney donors were included in the main cohort analysis. Their characteristics are summarized in Table 1. The distributions of mGFR, CKD-EPI-eGFR, and MDRD-eGFR are plotted in Figure 1(A). Median arithmetic difference between CKD-EPI-eGFR, eGFR, and mGFR or MDRD-eGFR and mGFR are plotted in Figure 1(B and C), respectively. Pretest probability risk stratification according to age and sex are reported in Table S1. The percentage of correct classification of eGFR (estimated by MDRD or CKD-EPI) compared to mGFR are summarized in Table S2. For MDRD, correct classification of mGFR, overestimation and underestimation are 30%, 28%, and 41%, respectively. For CKD-EPI, correct classification of mGFR, overestimation and underestimation are 31%, 39%, and 30%, respectively.

Diagnostic performance of the web-based application in detection of mGFR lower than 80 mL/min/1.73 m^2

We measured the sensitivity and specificity of posttest probabilities calculated from the web-based application to detect mGFR <80 mL/min/1.73 m^2. Results are summarized in Table 2. Posttest 80 had a sensitivity of 0.95 (95% confidence interval [CI] 0.83–0.99). This means that some donors who had a posttest 80 equal to zero (that is to say a null probability of having mGFR <80 mL/min/1.73 m^2 according to the web-based application) had a measured GFR <80 mL/min/1.73 m^2. Comparatively, the posttest 90 had a sensitivity of 1 (95% CI 0.92–1); this test detected all potential donors with mGFR <80 mL/min/1.73 m^2. This means that all the potential donors with an mGFR <80 mL/min/1.73 m^2 had a posttest 90 higher than 2%. The specificity of posttest 90 is 0.32, meaning that among the potential donors with an mGFR ≥80 mL/min/1.73 m^2, 32% had a posttest 90 lower than 2%. Using the posttest 90 as criterion, 27% of the GFR measurements could have been safely avoided as these donors actually had a measured GFR ≥80 mL/min/1.73 m^2. Sensitivity and specificity of posttest 90 at thresholds higher or lower than 2% are summarized in Table S3.

Diagnostic performances of MDRD and CKD EPI

To determine the thresholds of MDRD and CKD EPI that give similar diagnostic performance as the web-based application, we estimated GFRs using plasma enzymatic creatinine measurements. Area under the curve (AUC) was 0.79 for CKD-EPI and 0.81 for MDRD. CKD-EPI and MDRD-eGFR also achieved 100% sensitivity for detection of an mGFR <80 mL/min/1.73 m^2 at thresholds of 104 mL/min/1.73 m^2 for CKD-EPI-eGFR and 100 mL/min/1.73 m^2 for MDRD-eGFR. This means that all the potential donors with an mGFR <80 mL/min/1.73 m^2 had a CKD-EPI eGFR lower than 104 mL/min/1.73 m^2 or an MDRD-eGFR lower than 100 mL/min/1.73 m^2. Specificities at these thresholds are 0.33 for CKD-EPI and 0.35 for MDRD. Correlation coefficients between MDRD-eGFR or CKD-EPI-eGFR and measured GFR are 0.51 and 0.53, respectively. GFR measurement could have been

Table 1: Characteristics of the potential kidney donors included in the analysis in the main cohort

Demographic and health characteristics at donor evaluation	All	Donors	Non Donors	Men	Women	White	African
n (%)	311 (100%)	287 (92%)	24 (8%)	133 (43%)	178 (57%)	281 (90%)	30 (10%)
Age, years (IQR)	51.2 (16.4)	51.0 (16.6)	53.5 (13.5)	48.9 (17.5)	52.2 (15.9)	51.6 (15.5)	42.9 (20.8)
mGFR mL/min/1.73 m^2 (IQR)	93.3 (20.9)	93.4 (20.7)	89.9 (22.1)	93.2 (18.8)	93.1 (21.2)	93.1 (21.0)	96.0 (20.9)
eGFR MDRD mL/min/1.73 m^2 (IQR)	91.1 (21.6)	91.4 (22.1)	87.9 (19.1)	91.4 (21.8)	91.1 (21.5)	91.1 (21.8)	109.5 (27.2)
eGFR CKD-EPI mL/min/1.73 m^2 (IQR)	96.6 (19.7)	96.6 (20.3)	96.7 (22.4)	95.2 (18.5)	96.4 (18.5)	95.2 (18.3)	109.8 (28.2)
BMI kg/m^2 (IQR)	25.1 (5.5)	25.1 (5.5)	24.3 (5.7)	26.4 (4.6)	24.9 (5.5)	24.7 (5.2)	28.0 (7.2)
Albuminuria mg/L (IQR)	7.4 (7.2)	7.5 (7.1)	6.3 (7.5)	7.9 (7.8)	6.9 (7.5)	7.5 (7.1)	7.5 (7.2)
SBP mmHg (IQR)	122.0 (14.3)	122.0 (14.0)	123.0 (14.0)	123.5 (12.8)	123.5 (12.3)	124.7 (11.1)	120.5 (17.8)
Hypertension ≥ 140/90 mmHg (%)	17 (5.4%)	13 (4.5%)	4 (17%)	8 (6%)	9 (5%)	10 (4%)	2 (7%)
Smoking history (%)	108 (35%)	100 (35%)	8 (33%)	53 (40%)	55 (31%)	100 (36%)	8 (27%)

CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mGFR, measured glomerular filtration rate; SBP, systolic blood pressure.

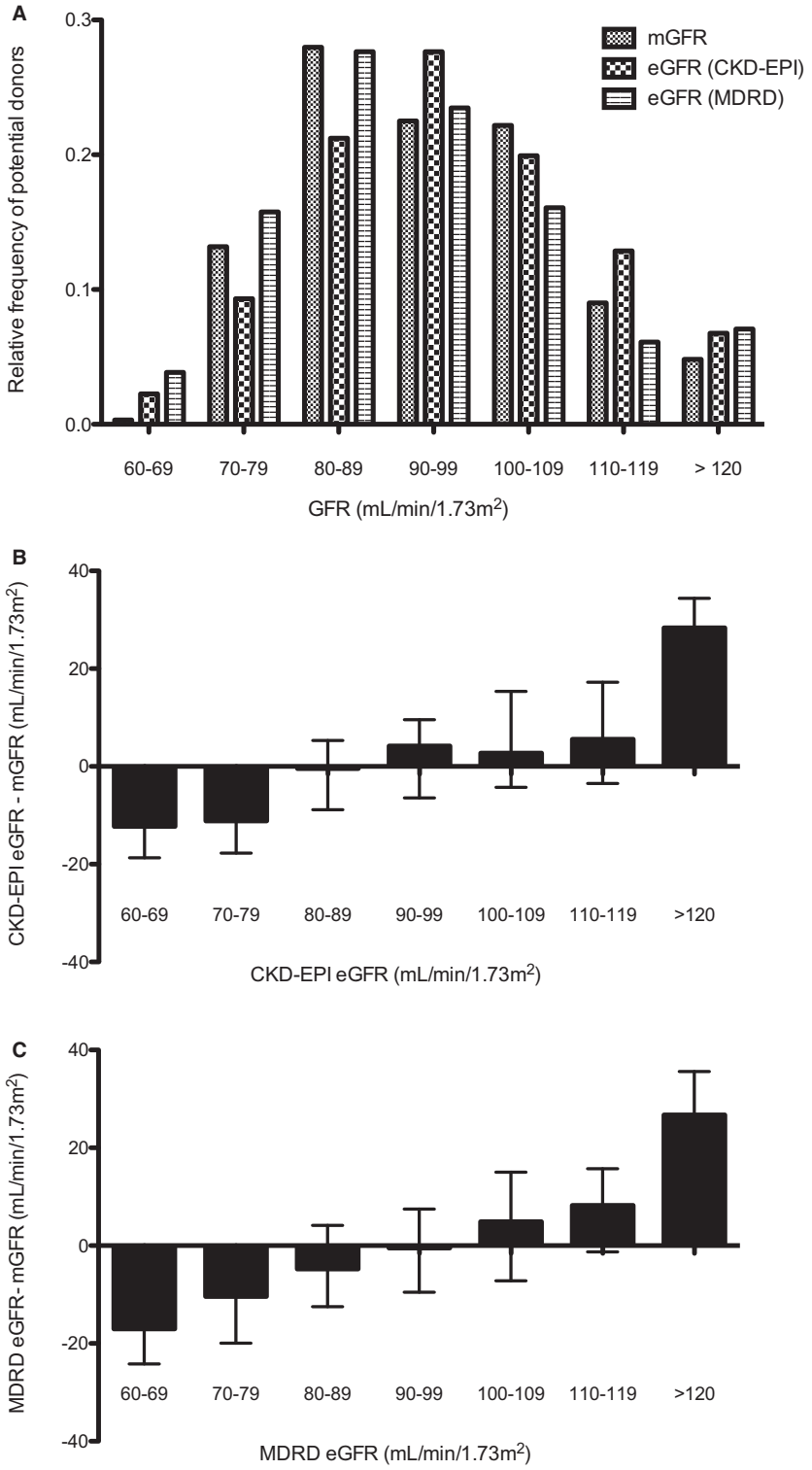

Figure 1: (A) Distribution of measured GFR, estimated GFR by CKD-EPI, and estimated GFR by MDRD in our cohort. (B) Median arithmetic difference and interquartile range between eGFR (CKD-EPI) and mGFR. (C) Median arithmetic difference and interquartile range between eGFR (MDRD) and mGFR. CKD-EPI, chronic kidney disease epidemiology collaboration; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

Table 2: Comparison between posttest strategies to detect potential living kidney donors with an mGFR lower than 80 mL/min/1.73 m^2

	Posttest 90	Posttest 80	Posttest 70	Posttest 60
AUC (95% CI)	0.78 (0.72–0.85)	0.80 (0.73–0.87)	0.81 (0.73–0.88)	0.68 (0.58–0.78)
Maximum sensitivity (95% CI 95)	1 (0.92–1)	0.95 (0.83–0.99)	0.90 (0.77–0.97)	0.45 (0.29–0.61)
Threshold to achieve 100% sensitivity	>2%	N/A	N/A	N/A
Specificity (95% CI)	0.32 (0.26–0.38)	0.38 (0.32–0.44)	0.57 (0.50–0.63)	0.90 (0.86–0.94)
Reduction of GFR measurements	27%	N/A	N/A	N/A

AUC, area under the curve; CI, confidence interval; N/A, not applicable.

avoided for 28% of potential donors using the CKD-EPI threshold and for 29% of potential donors using the MDRD threshold. The negative predictive values are 100% for the three strategies. It means that when the posttest 90 is lower than 2% or the MDRD-eGFR is higher than 100 mL/min/1.73 m^2 or the CKD-EPI eGFR is higher than 104 mL/min/1.73 m^2 the probability to have a measured GFR <80 mL/min/1.73 m^2 is equal to zero. Similarly, positive predictive values are 19% for the CKD-EPI and MDRD strategies and 18% for posttest 90. It means that when the posttest 90 is higher than 2% or the MDRD-eGFR is lower than 100 mL/min/1.73 m^2 or the CKD-EPI eGFR is lower than 104 mL/min/1.73 m^2 the probability to have a measured GFR <80 mL/min/1.73 m^2 is equal to 18% or 19%, respectively.

Comparison of MDRD, CKD-EPI, and web-based strategy to detect an mGFR lower than 80 mL/min/1.73 m^2

We compared the web-based strategy to the MDRD and CKD-EPI strategies. To summarize, for each of the three strategies (posttest 90, MDRD, and CKD-EPI), thresholds were chosen such that AUC is around 0.80 (95% CI 0.72–0.85) (Figure 2), sensitivity is 1 (95% CI 0.92–1), specificity around 0.33, and reduction of GFR measurements around 28%. The comparison is summarized in Table 3.

Kidney function 1 year after donation

Each strategy classified potential donors as theoretically requiring GFR measurement or not. We wondered if this classification was also relevant regarding eGFR evolution during follow-up. Whatever the strategy applied, donors who theoretically did not require GFR measurement had similar eGFR at baseline and similar eGFR during follow-up. Similarly, potential donors who theoretically required GFR measurement had similar eGFR at baseline and similar eGFR during follow-up regardless of the strategy. Results are summarized in Table 4.

External cohort validation

We tested the MDRD, CKD-EPI, and posttest 90 thresholds in an external cohort. Characteristics of potential donors included in the external cohort are summarized in Table 5. As summarized in Table 6, the three strategies have comparable performances and results are closed to those found in the development cohort. AUC ranges from 0.84 to 0.85 (95% CI 0.79–0.89), sensitivity ranges from 0.92 to 0.95 (95% CI 0.86–0.99), specificity ranges from 0.47 to 0.54, and the expected reduction of GFR measurement ranges from 40% to 45%.

Discussion

We evaluated three strategies, including a tool developed by Huang et al (19), to identify potential kidney donors who should undergo GFR measurement. The three strategies were tested assuming that an mGFR <80 mL/min/1.73 m^2 is a clinically relevant level to contraindicate donation (7,13). When applied to our cohort of living donors with systematic GFR measurement, the web-based application had good diagnostic performance (AUC of 0.78). Moreover, of the probabilities calculated with the web-based application, posttest 90 2% was the only one able to detect all potential donors with an mGFR <80 mL/min/1.73 m^2. MDRD, CKD-EPI, and posttest 90 strategies had similar abilities to detect potential living kidney donors with an mGFR <80 mL/min/1.73 m^2 and identified comparable groups in terms of eGFR evolution 1 year after donation. When applied to an external cohort, the MDRD, CKD-EPI, and posttest 90 thresholds had comparable diagnostic performance (AUC of 0.84) and sensitivity (0.95) to the development cohort, as shown by the 95% CIs overlap.

The web-based application provides the probability that a potential donor will have an mGFR lower than 60, 70, 80, or 90 mL/min/1.73 m^2. In clinical practice, it is difficult to use such probabilities to guide the decision of whether or not to perform the GFR measurement without an understanding of their significance. Therefore, precise evaluation of the web-based tool among donors is needed prior to its widespread use. Our results strengthen the usefulness of this new web-based application and validate its clinical utility. First, we obtained similar risk stratification in our main cohort as in the cohort of Huang et al (19), suggesting that the web-based tool can be applied to living donors. Second, we validated our results in an external cohort of living donors. We identified a threshold of posttest 90 lower than 2% under which no donors had an mGFR <80 mL/min/1.73 m^2. Posttest 80 and posttest 70 had similar diagnostic performance to posttest 90 (AUC of 0.78 and 0.81, respectively) but had lower

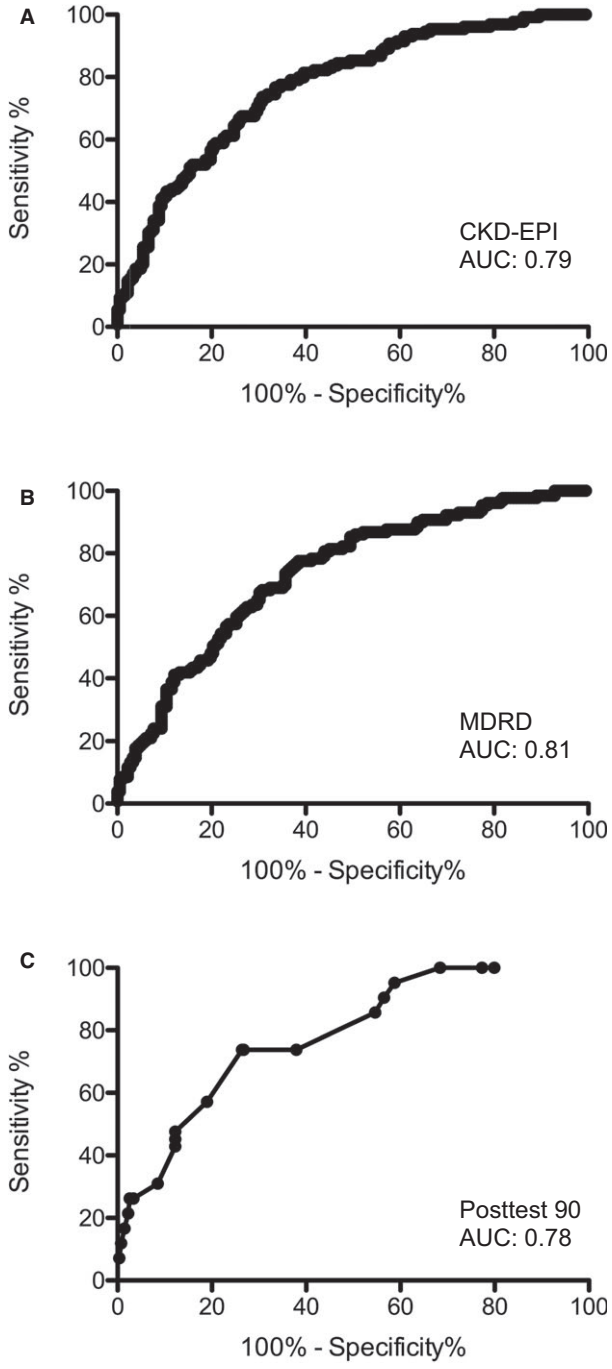

Figure 2: ROC curves and area under the curve (AUC) for a CKD-EPI threshold of 104 mL/min/1.73 m^2 (A), a MDRD threshold of 100 mL/min/1.73 m^2 (B), and a posttest 90 threshold of 2% (C). CKD-EPI, chronic kidney disease epidemiology collaboration.

sensitivity. It is noteworthy that three donors had a posttest 80 equal to 0 and yet had a measured GFR <80 mL/min/1.73 m^2. This is probably due to the fact that the real probability is not 0 but lower than 1%. As our main cohort consisted of more than 311 potential donors, we could detect an event with a probability as low as 1/311 (0.3%). As we wanted to detect a maximum of potential donors with an mGFR <80 mL/min/1.73 m^2, we conducted the analysis with the posttest 90.

The sensitivity of posttest 90 in the external cohort tends to be lower (0.95). However, this difference is not significant when comparing 95% CIs of sensitivity in the two cohorts. Overall diagnostic performance estimated by the AUC was comparable in both cohorts. However, we observed a significantly higher specificity in the external cohort, which further increased the reduction of GFR measurements.

We also demonstrate that this tool can be used safely even in the absence of cystatin measurement, which was not available in our cohort and which may not be available everywhere as a routine bioassay (16).

Interestingly, we also found relevant thresholds of MDRD and CKD-EPI in our cohort that resulted in good overall diagnostic performances. The thresholds ensured that no potential donor with an eGFR higher than 100 mL/min/1.73 m^2 (MDRD) or 104 mL/min/1.73 m^2 (CKD-EPI) had a measured GFR <80 mL/min/1.73 m^2. The relatively high thresholds of MDRD and CKD-EPI to achieve 100% sensitivity to detect an mGFR <80 mL/min/1.73 m^2 are probably due to the low correlation between mGFR and eGFR. MDRD and CKD-EPI show similar patterns of underestimation of mGFR for lower values of eGFR and overestimation of mGFR for higher values of eGFR. Similarly to posttest 90, when MDRD and CKD-EPI were tested in an external cohort, we obtained comparable sensitivity with significantly increasing specificity. Overall diagnostic performance of the three strategies was comparable in the two cohorts.

The fact that CKD-EPI and MDRD show similar diagnostic performance to the posttest 90 strategy is probably due to the fact that these three strategies are based on analysis of similar parameters: age, sex, ethnicity, and plasma creatinine.

We also compared eGFR evolution 1 year after donation between the three strategies. Whatever the strategy (MDRD, CKD-EPI, and posttest 90), potential donors who required GFR measurement had similar eGFR evolution. Potential donors who did not require GFR measurement also had similar eGFR after 1 year regardless of the strategy. This confirms that the three strategies identify comparable groups in terms of eGFR evolution. Of note, the group of potential donors who were identified as requiring GFR measurements had significantly lower eGFR at 1 year than did the group of potential donors not requiring GFR measurement. This could be due to the fact that eGFR at donation is an important determinant of eGFR after donation (21), and confirms the ability of the three

Table 3: Comparison of CKD-EPI, MDRD, and posttest 90 to detect potential living kidney donors with an mGFR lower than 80 mL/min/1.73 m^2

	CKD-EPI	MDRD	Posttest 90
AUC (95% CI)	0.79 (0.73–0.86)	0.81 (0.76–0.87)	0.78 (0.72–0.85)
Sensitivity (95% CI)	1 (0.92–1)	1 (0.92–1)	1 (0.92–1)
Specificity (95% CI)	0.33 (0.28–0.39)	0.35 (0.28–0.39)	0.32 (0.26–0.38)
Threshold to achieve 100% sensitivity	<104 mL/min/1.73 m^2	<100 mL/min/1.73 m^2	>2%
Positive predictive value	0.19	0.19	0.18
Negative predictive value	1	1	1
Reduction of GFR measurements	28%	29%	27%

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

Table 4: Comparison of mGFR and eGFR at baseline and 1 year after donation

Donors requiring GFR measurement	CKD-EPI <104 mL/min/1.73 m^2 (n = 124)	Posttest >2% (n = 125)	MDRD <100 mL/min/1.73 m^2 (n = 112)
Baseline			
MDRD	85.2 (79.7–94.9)	85.7 (79.9–95.3)	83.9 (79.0–92.3)
CKD-EPI	89.7 (81.9–98.3)	89.9 (81.9–98.4)	88.4 (81.5–97.1)
mGFR	90.5 (88.4–92.6)	90.3 (87.9–92.6)	90.7 (88.6–92.8)
1 year postdonation			
MDRD	54.7 (49.1–60.5)	55.1 (49.4–61.2)	54.6 (49.1–60.7)
CKD-EPI	57.8 (50.4–63.1)	57.9 (50.5–63.4)	57.6 (50.4–63.5)
Donors not requiring GFR measurement	**CKD-EPI >104 mL/min/1.73 m^2 (n = 32)**	**Posttest <2% (n = 31)**	**MDRD >100 mL/min/1.73 m^2 (n = 44)**
Baseline			
MDRD	107.5 (100.5–124)	107 (100.2–120.5)	108.7 (105.0–121.3)
CKD-EPI	112.4 (107.5–119.1)	112.7 (108.4–119.4)	107.0 (101.3–115.0)
mGFR	113.3 (101.4–118.9)	112.5 (101.1–119.1)	104.5 (93.8–115.5)
1 year postdonation			
MDRD	69.6 (62.1–76.4)	67.4 (61.2–76.6)	65.8 (59.4–75.5)
CKD-EPI	75.7 (67.9–85.1)	76.3 (67.4–85.4)	68.1 (63.1–79.5)

CKD-EPI, chronic kidney disease epidemiology collaboration; mGFR, measured glomerular filtration rate.

Table 5: Characteristics of the potential kidney donors included in the analysis in the external cohort

Demographic and health characteristics	All	Men	Women	White	African
n (%)	354 (100%)	143 (40%)	211 (60%)	327 (92%)	27 (8%)
Age, years (IQR)	48.0 (17.0)	45 (17.0)	50.1 (19.9)	48.2 (17.8)	43 (16)
mGFR mL/min/1.73 m^2 (IQR)	92.0 (18.3)	94.0 (16.0)	90.2 (18.5)	92.3 (17.8)	85.5 (21.7)
eGFR MDRD mL/min/1.73 m^2 (IQR)	98.6 (25.1)	101.8 (26.4)	97.8 (24.3)	98.8 (24.9)	112.3 (28.5)
eGFR CKD-EPI mL/min/1.73 m^2 (IQR)	101.6 (20.3)	103.4 (19.3)	99.2 (20.2)	100.3 (18.3)	114 (28.2)
BMI kg/m^2 (IQR)	25.4 (6.2)	26.4 (4.5)	24.6 (6.8)	25.2 (6.3)	26.7 (4.5)

CKD-EPI, chronic kidney disease epidemiology collaboration; IQR, interquartile range; mGFR, measured glomerular filtration rate.

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.

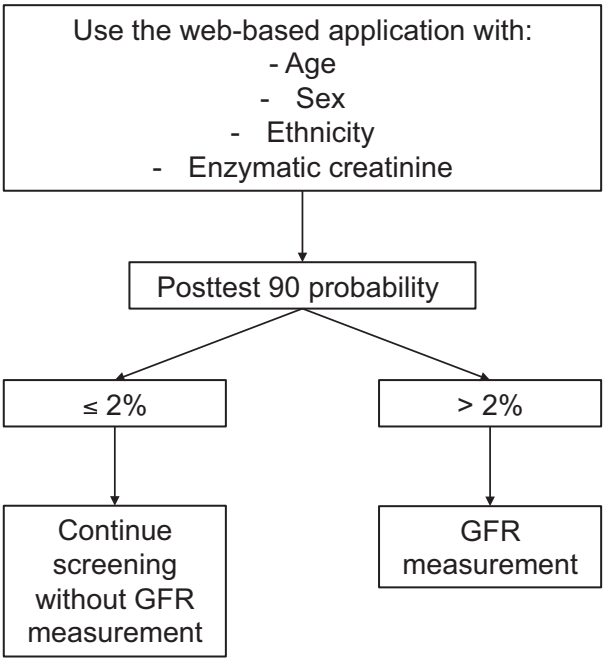

Figure 3: Proposed algorithm to determine whether or not to measure GFR in living kidney donors. The first step consists of calculating the posttest 90 probability with the web-based application at: http://ckdepi.org/equations/donor-candidate-gfr-calculator/. If the probability is higher than 2%, GFR measurement should be performed because mGFR below 80 mL/min/1.73 m^2 cannot be excluded. mGFR, measured GFR.

strategies to identify homogeneous groups with mGFRs higher or lower than 80 mL/min/1.73 m^2.

In the main cohort, use of any one of the three strategies would have permitted a reduction by approximately 28% in the number of GFR measurements. This reduction increased to nearly 45% in the external cohort, leading to a significant reduction of the cost of screening without hampering the safety of the donors.

Our work has some limitations. We focused on GFR, which is part of the decision to accept or decline donation, but not the unique acceptance criterion. A recent work (3) suggests using several health characteristics and biological dosage to evaluate ESRD risk for donors before donation. This new strategy could lead to different GFR thresholds for different donors. However, acceptance criteria based on ESRD risk calculation before donation are not yet available and the question of measured GFR in ESRD risk calculation is unanswered. Moreover, our study mainly includes white donors. Even though we validated our results in a second cohort, these results may be different in populations differing from the one of our study. Last, due to sample size limitations we could not study our results in different subgroups stratified according to age and ethnicity. Therefore, we suggest that the three strategies should be studied in other transplantation centers.

In conclusion, we recommend calculating posttest 90 for each potential kidney donor, and we suggest that those potential donors with a posttest 90 higher than 2% should be evaluated by GFR measurement, as summarized in Figure 3.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Data S1: Supplemental material.

Table S1: Risk stratification in the main cohort. Pretest probabilities stratification according to age and sex. mGFR, measured GFR. Data are presented as mean and SD for mGFR values. Data are presented as mean and 95% CI for pre-test probabilities.

Table S2: Cross-classification of eGFR (MDRD up and CKD-EPI bottom) compared to measured GFR in the main cohort. Concordant classifications are shaded in gray.

Table S3: Sensitivity and specificity of different posttest 90 values to detect potential donors with an mGFR lower than 80 mL/min/1.73 m^2.