

Estimated GFR for Living Kidney Donor Evaluation

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All living kidney donor candidates undergo evaluation of GFR. Guidelines recommend measured GFR (mGFR), using either an endogenous filtration marker or creatinine clearance, rather than estimated GFR (eGFR), but measurement methods are difficult, time consuming and costly. We investigated whether GFR estimated from serum creatinine (eGFRcr) with or without sequential cystatin C is sufficiently accurate to identify donor candidates with high probability that mGFR is above or below thresholds for clinical decision making. We combined the pretest probability for mGFR thresholds <60, <70, ≥80, and ≥90 mL/min per 1.73 m² based on demographic characteristics (from the National Health and Nutrition Examination Survey) with test performance of eGFR (categorical likelihood ratios from the Chronic Kidney Disease Epidemiology Collaboration) to compute posttest probabilities. Using data from the Scientific Registry of Transplant Recipients, 53% of recent living donors had predonation eGFRcr high enough to ensure ≥95% probability that predonation mGFR was ≥90 mL/min per 1.73 m², suggesting that mGFR may not be necessary in a large proportion of donor candidates. We developed a Web-based application to compute the probability, based on eGFR, that mGFR for a donor candidate is above or below a range of thresholds useful in living donor evaluation and selection.

Abbreviations: AUC, area under the curve; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; GFR, glomerular filtration rate; eGFR, estimated GFR; eGFRcr,

GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from the combination of serum creatinine and cystatin C; eGFRcys, GFR estimated from cystatin C; LR, likelihood ratio; mGFR, measured GFR; NA, not assessed; NHANES, National Health and Nutrition Examination Survey; OPTN, Organ Procurement and Transplantation Network; SE, standard error; SRTR, Scientific Registry of Transplant Recipients

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Introduction

All living kidney donor candidates undergo an evaluation of glomerular filtration rate (GFR). Guidelines specify a value of GFR above or below a threshold as a main criterion to accept or decline candidate donors, although there is variation in both the recommended threshold to permit donation and the method by which GFR should be assessed (1–7). Some guidelines recommend that GFR be measured by clearance of an exogenous filtration marker (measured GFR [mGFR]) using urinary, plasma or radionuclide imaging clearance protocols; other guidelines accept urinary creatinine clearance (CrCl), although it is less accurate than clearance of exogenous filtration markers (1,2,6). All clearance measurement methods are difficult and time consuming and incur additional cost, and they may be less reliable in routine care than is seen in standardized settings (8).

GFR estimated from serum creatinine (eGFRcr) can be easily calculated, and eGFRcr is commonly used in settings other than donor evaluations to make clinical decisions (9). Recently, it has been shown that GFR estimated from the combination of serum creatinine and cystatin C (eGFRcr-cys) is generally more accurate than eGFRcr and is recommended as a confirmatory test for decreased eGFRcr in some nondonor settings (9,10). It is unclear whether eGFR can be used to guide donor selection, and some current guidelines recommend not using eGFR, given imprecision in the estimate (2,5). Notably, the current policies that govern transplant practice in the United States do not recognize the use of eGFR alone as an appropriate modality for assessment of predonation GFR and require a clearance measurement of either an exogenous filtration marker or creatinine (6). We investigated whether the use of eGFRcr, with or without sequential eGFRcr-cys, might be sufficiently accurate to identify a candidate donor with an mGFR value above or below a threshold that could be used

either to screen donor candidates prior to full evaluation or to accept or decline candidate donors in the absence of mGFR. Our purpose was to provide a tool to assist transplant centers in the use of eGFR to improve the efficiency of evaluation of donor candidates.

Methods

Study design

The reference test was mGFR, and the index tests were eGFR based on sequential use of creatinine (eGFRcr) and creatinine and cystatin C (eGFRcr and eGFRcr-cys, respectively). We combined information on a candidate donor's likelihood of having mGFR below or above a certain threshold (pretest probability) with test performance of eGFR (likelihood ratios [LRs]) to compute posttest probabilities for this threshold. Transplant centers policies differ on mGFR thresholds used to accept or decline donor candidates; therefore, we considered mGFR thresholds of <60, <70, ≥ 80 , and ≥ 90 mL/min per 1.73 m^2 . We presented the results according to a participant's age (18–44, 45–64, and 65–80 years), sex (men, women) and race (black, nonblack). We then examined scenarios for clinical decision making at a hypothetical transplant program that has the following policies: (1) Decisions may be based on eGFR if the posttest probabilities of mGFR below or above a threshold are $\geq 95\%$; (2) mGFR ≥ 90 mL/min per 1.73 m^2 is acceptable for donation, whereas mGFR <60 mL/min per 1.73 m^2 is not acceptable. Finally, we simulated decisions for a large sample of recent U.S. kidney donors based on eGFRcr obtained prior to donation for mGFR thresholds of ≥ 80 and ≥ 90 mL/min per 1.73 m^2 . We are not aware of a large representative sample of living kidney donor candidates with measurements of GFR, creatinine and cystatin C. Consequently, we used other study populations to provide information on pretest probabilities of mGFR thresholds and eGFR test performance.

Pretest probability of having mGFR above or below a threshold for kidney donation

To estimate pretest probabilities, we studied 4122 participants aged 18–80 years from the 1999–2002 cycles of the National Health and Nutrition Examination Survey (NHANES). NHANES provides a cross-sectional, multistage, stratified, clustered probability sample of the U.S. civilian noninstitutionalized population and is conducted by the National Center for Health Statistics (11). Although mGFR is not available in NHANES, we used an acceptable alternative of eGFRcr-cys to derive prevalence estimates (pretest probabilities) and 95% confidence intervals of various thresholds of mGFR according to a participant's age, sex and race. The 1999–2002 cycles of NHANES are the most recent cycles with standardized creatinine and cystatin C measurements, and eGFRcr-cys is more accurate than eGFRcr or GFR estimated from cystatin C (eGFRcys) for estimating mGFR (9,12–14). We performed the analyses in Stata/SE 12.1 (Release 12, StataCorp LP., College Station, TX) using the survey commands and the surplus sera cystatin C weights to account for oversampling in the complex survey design, nonresponse and poststratification adjustment in NHANES (12,13,15). In sensitivity analyses, we restricted our analysis to 3046 (74%) participants without diabetes.

Performance of eGFR as a test to predict a threshold of mGFR

To assess test performance of eGFRcr and eGFRcr-cys, we used the development and internal validation data set for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equations. As described previously, this data set included 5352 participants in 13 research studies and clinical populations with a wide range of GFRs in whom mGFR, eGFRcr and eGFRcr-cys were determined within 1 week of each other (10). Detailed methods describing the GFR measurement procedure and measurements

of serum creatinine and cystatin C have been described previously (10). We studied participants aged 18–80 years ($n = 5345$). In sensitivity analyses, we restricted our analysis to 3619 (68%) participants without diabetes in development and internal validation data and to 1097 participants in four populations in the external validation data set.

We sorted mGFR, eGFRcr and eGFRcr-cys into eight categories of <30, 30–44, 44–59, 60–69, 70–79, 80–89, 90–104, and ≥ 105 mL/min per 1.73 m^2 . We then computed the proportion of correct classification, overestimation and underestimation of mGFR categories across the eight eGFR categories and noted agreement among eGFRcr and eGFRcr-cys categories. For comparison, we provided results on eGFRcys. We evaluated test performance for eGFRcr and eGFRcr-cys for predicting mGFR levels below the four thresholds by comparing the area under the curve (AUC) for each threshold. Because AUCs were similar among demographic subgroups, we used the test characteristics for the whole population to calculate the LRs.

We next calculated categorical LRs for the eight categories of eGFRcr and eGFRcr-cys in predicting mGFR below each of the four thresholds. Using the categorical LR allowed the LR to be calculated in several clinically relevant eGFR categories and used more information from the test results than LR positive or LR negative, which are based on a single threshold (16). The LR for each eGFR category was calculated as the proportion of participants who met the specified mGFR threshold (<60, <70, ≥ 80 , or ≥ 90 mL/min per 1.73 m^2) that had a test result within the eGFR category divided by the proportion of participants who did not meet the specified mGFR threshold that had a test result within the eGFR category. If the LR for an eGFR category was close to 1, then the probability that a participant met a threshold of mGFR after the eGFR test would differ little from the pretest probability before the eGFR test. If the LR for an eGFR category achieved a value far from 1 (e.g. >10 or <0.1), then the eGFR test would exert a large influence on the posttest probability of meeting or not meeting a threshold of mGFR. We calculated LRs in R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

Calculation of posttest probabilities

For each of the eight categories of eGFR values and each of the four mGFR thresholds, we computed the probability of meeting an mGFR threshold after an eGFR test by applying the LR from CKD-EPI to the pretest probabilities from NHANES. We computed posttest probabilities by application of Bayes' theorem: Posttest probability equaled posttest odds divided by (1 + posttest odds), in which posttest odds equaled pretest odds times LR and pretest odds equaled pretest probability divided by (1 – pretest probability). In practice, clinicians may have additional knowledge to refine their estimates of meeting an mGFR threshold before their measurement of eGFR. For this reason, we also computed posttest probabilities for a wider range of pretest probabilities (0.05–0.95). To demonstrate the use of these calculations for decision making in our hypothetical transplant center, we examined scenarios of decision making using eGFRcr with or without sequential eGFRcr-cys for white women aged 50 years with different values of eGFRcr and eGFRcr-cys. For use of eGFRcr-cys as a confirmatory test, the posttest probability of an mGFR threshold after an eGFRcr test becomes the pretest probability before the eGFRcr-cys test. To facilitate application in practice, we created a Web-based application, which is available on the CKD-EPI website (<http://ckdepi.org/equations/donor-candidate-gfr-calculator/>).

Computation of hypothetical test savings associated with use of eGFR to accept or decline donor candidates

Using our approach, we computed the posttest probability for mGFR thresholds ≥ 80 and ≥ 90 mL/min per 1.73 m^2 after an eGFRcr test using predonation information from a sample of U.S. living kidney donors extracted from the Scientific Registry of Transplant Recipients (SRTR) (17). The SRTR

data system includes data on all donors, waitlisted candidates and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight of the activities of the OPTN and SRTR contractors. We studied 35 384 donations between the year 2009 to the extraction date (March 4, 2015) because most creatinine assays in clinical laboratories were traceable to isotope dilution mass spectrometry methods during this period (18). We excluded donors with serum creatinine values <0.04 mg/dL and >4.0 mg/dL as erroneous, resulting in a final sample of 35 334 donations. We calculated the number and proportion of donors with ≥95% probability of having mGFR above the thresholds.

Results

Pretest probabilities for GFR thresholds for kidney donation in NHANES

Characteristics and pretest probabilities for GFR <60, <70, ≥80, and ≥90 mL/min per 1.73 m² for participants in NHANES are shown in Tables 1 and S1. The pretest probabilities vary more by age than by sex and race; for example, the pretest probabilities for GFR ≥90 mL/min per 1.73 m² for subgroups defined by sex and race ranged from 87% to 93% for those aged 18–44 years, from 61% to 70% for those aged 45–64 years and from 15% to 31% for those aged 65–80 years. Pretest probabilities in participants without diabetes are shown in Table S2 and are not meaningfully different than the estimates presented in Table 1.

Test performance for eGFR categories to predict a threshold of mGFR in CKD-EPI

Characteristics of participants in the CKD-EPI cohorts are shown in Tables S3 and S4. Classification by mGFR and

eGFR categories is shown in Tables 2, S5, and S6. The percentages of correct classification, overestimation, and underestimation for eGFR_{cr} compared with mGFR were 56%, 23% and 21%, respectively; corresponding percentages for eGFR_{cr-cys} compared with mGFR were 61%, 19% and 20%, respectively (Table 2). There were not substantial differences in AUCs among subgroups defined by age, sex or race or in the subgroup of CKD-EPI participants without diabetes (Tables S7 and S8).

Categorical LRs for each eGFR category and mGFR threshold are shown in Tables 3, S9, and S10. For all mGFR thresholds, categorical LRs for very low and very high categories of both eGFR_{cr} and eGFR_{cr-cys} were either >10 or <0.1, indicating that patients with eGFR values within those categories would have a substantial change from their pretest to posttest probability of mGFR below or above the given threshold. Results were similar in the subgroup without diabetes (Tables S11 and S12) and for participants in the validation data set (Table S13).

Computing posttest probabilities and use in clinical decision making

We applied the LR to pretest probabilities for participants of varying ages, sexes and races (Table 4). Pretest probabilities for mGFR <60 mL/min per 1.73 m² were low in NHANES except at older age (65–80 years), but low eGFR categories did not lead to very high (≥95%) posttest probabilities for mGFR <60 mL/min per 1.73 m² at any age (top panel of Table 4, no red shading). Conversely, pretest probabilities for mGFR ≥90 mL/min per 1.73 m² were high except at older age, leading to very high posttest probabilities except at older age (lower panel of Table 4,

Table 1: Pretest probabilities of four thresholds of GFR stratified by age, sex, and race in NHANES

	Prevalence, % (SE)	GFR mean (SE)	Pretest probabilities for GFR, % (95% CI)			
			<60	<70	≥80	≥90
All	100	100 (1)	5 (4–6)	9 (8–10)	83 (82–85)	71 (68–73)
Age, 18–44 years	55.8 (1.3)	111 (1)				
Black women	3.8 (0.5)	121 (2)	1 (0–2)	1 (0–2)	97 (95–100)	93 (89–96)
Black men	3.2 (0.4)	117 (2)	1 (0–3)	2 (1–3)	97 (95–99)	94 (91–97)
Nonblack women	24.7 (0.9)	111 (1)	0 (0–1)	1 (0–2)	96 (95–98)	87 (83–90)
Nonblack men	24.2 (1.5)	109 (1)	0 (0–1)	1 (0–1)	97 (94–98)	88 (83–93)
Age, 45–64 years	30.8 (1.2)	93 (1)				
Black women	1.9 (0.3)	99 (2)	5 (3–7)	8 (4–12)	83 (76–91)	70 (58–81)
Black men	1.3 (0.2)	97 (2)	4 (2–6)	7 (4–10)	83 (77–88)	68 (62–75)
Nonblack women	13.7 (1.0)	91 (1)	6 (3–10)	12 (7–17)	77 (71–83)	64 (58–70)
Nonblack men	13.9 (0.8)	94 (1)	1 (0–2)	6 (3–8)	82 (79–85)	61 (56–66)
Age, 65–80 years	13.4 (0.5)	71 (1)				
Black women	0.6 (0.1)	70 (2)	30 (21–39)	46 (36–57)	39 (28–49)	20 (13–27)
Black men	0.5 (0.1)	74 (2)	27 (19–36)	40 (30–49)	48 (39–57)	31 (22–40)
Nonblack women	7.0 (0.4)	70 (1)	27 (24–30)	47 (43–52)	34 (29–38)	16 (13–19)
Nonblack men	5.3 (0.3)	71 (1)	26 (22–29)	42 (38–46)	35 (31–39)	15 (12–18)

Data derived from 4122 persons aged 18–80 from the 1992–2002 cycle of NHANES. GFR estimated from the combination of serum creatinine and cystatin C. Units for GFR are mL/min/1.73 m². CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; SE, standard error.

Table 2: Cross-classification of eGFRcr and eGFRcr-cys with mGFR in CKD-EPI

	mGFR, mL/min/1.73 m ²								Total
	<30	30–44	45–59	60–69	70–79	80–89	90–104	≥105	
eGFRcr									
<30	710 (13%)	121 (2%)	7 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	840 (16%)
30–44	210 (4%)	537 (10%)	178 (3%)	24 (0%)	7 (0%)	1 (0%)	1 (0%)	1 (0%)	959 (18%)
45–59	16 (0%)	200 (4%)	446 (8%)	128 (2%)	61 (1%)	23 (0%)	12 (0%)	2 (0%)	888 (17%)
60–69	2 (0%)	27 (1%)	153 (3%)	124 (2%)	100 (2%)	49 (1%)	18 (0%)	5 (0%)	478 (9%)
70–79	2 (0%)	8 (0%)	50 (1%)	77 (1%)	87 (2%)	63 (1%)	44 (1%)	20 (0%)	351 (7%)
80–89	0 (0%)	4 (0%)	14 (0%)	28 (1%)	56 (1%)	69 (1%)	53 (1%)	39 (1%)	263 (5%)
90–104	0 (0%)	2 (0%)	11 (0%)	17 (0%)	51 (1%)	68 (1%)	109 (2%)	155 (3%)	413 (8%)
≥105	1 (0%)	1 (0%)	5 (0%)	7 (0%)	18 (0%)	44 (1%)	156 (3%)	921 (17%)	1153 (22%)
Total	941 (18%)	900 (17%)	864 (16%)	406 (8%)	380 (7%)	318 (6%)	393 (7%)	1143 (21%)	5345 (100%)
eGFRcr-cys									
<30	776 (15%)	144 (3%)	2 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	923 (17%)
30–44	150 (3%)	580 (11%)	187 (3%)	19 (0%)	3 (0%)	1 (0%)	2 (0%)	0 (0%)	942 (18%)
45–59	11 (0%)	156 (3%)	488 (9%)	119 (0%)	40 (1%)	15 (0%)	3 (0%)	3 (0%)	835 (16%)
60–69	2 (0%)	11 (0%)	126 (2%)	143 (3%)	106 (2%)	28 (1%)	17 (0%)	3 (0%)	436 (8%)
70–79	1 (0%)	7 (0%)	43 (1%)	90 (2%)	115 (2%)	78 (1%)	36 (1%)	8 (0%)	378 (7%)
80–89	0 (0%)	1 (0%)	7 (0%)	18 (0%)	69 (1%)	88 (2%)	59 (1%)	32 (1%)	274 (5%)
90–104	0 (0%)	0 (0%)	8 (0%)	14 (0%)	42 (1%)	77 (1%)	137 (3%)	145 (3%)	423 (8%)
≥105	1 (0%)	1 (0%)	3 (0%)	3 (0%)	5 (0%)	30 (1%)	139 (3%)	952 (18%)	1134 (21%)
Total	941 (18%)	900 (17%)	864 (16%)	406 (8%)	380 (7%)	318 (6%)	393 (7%)	1143 (21%)	5345 (100%)

Concordant classifications are shaded in green. Data derived from 5345 persons aged 18–80 years. For eGFRcr, correct classification, overestimation, and underestimation of mGFR is 56%, 23%, and 21% respectively; for eGFRcr-cys, correct classification, overestimate, and underestimate of mGFR is 61%, 19%, and 20%, respectively. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFRcr, GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from the combination of serum creatinine and cystatin C; mGFR, measured GFR.

green shading). For all mGFR thresholds, posttest probabilities were higher for eGFRcr-cys than eGFRcr.

Table 5 shows the application of LRs to a wide range of pretest probabilities (5–95%), as could be seen in clinical practice. Posttest probabilities for other mGFR thresholds can be computed using our Web-based application.

Table 6 shows examples of clinical decision making using eGFRcr with or without sequential eGFRcr-cys for a hypothetical nonblack woman aged 50 years in a transplant center using the framework for decision making described above. The top panel shows scenarios in which the candidate donors have high eGFRcr, and the clinical decision is whether to accept the candidate for donation without a confirmatory test. In the absence of clinical information, results from NHANES indicate that the pretest probability for mGFR ≥90 mL/min per 1.73 m² is 64%. If the eGFRcr is 110 mL/min per 1.73 m² (example A), the posttest probability exceeds the threshold of 95% for acceptance without a GFR measurement. In example B, the eGFRcr is 95 mL/min per 1.73 m², and the posttest probability does not exceed the 95% threshold. If the eGFRcr-cys is the same as eGFRcr (example B), the posttest probability exceeds the threshold, and the candidate could be accepted without an mGFR test. If the eGFRcr-cys is substantially lower (example C), an mGFR test would be required. In the bottom panel, examples D–F show scenarios in which the candidates have low eGFRcr, and the clinical decision is whether candidates can be rejected without a confirmatory test.

Computation of hypothetical test savings associated with use of eGFRcr to accept or decline donor candidates

From 2009 until March 2015, there were 35 334 living kidney donors in the United States with data available to compute eGFRcr (Table S14). Using pretest probabilities from NHANES and eGFR categorical LRs from CKD-EPI, Table 7 shows that 18 566 (53%) would have had eGFR high enough to ensure 95% probability that mGFR was ≥90 mL/min per 1.73 m² and would not have been required to undergo mGFR testing using CrCl or an exogenous filtration marker according to the policies for our hypothetical transplant center. For an mGFR threshold of ≥80 mL/min per 1.73 m², 25 985 (74%) would not have been required to undergo mGFR tests. Large test savings were also observed when LRs were computed using CKD-EPI participants without diabetes (Table S15) or CKD-EPI participants in the validation data set (Tables S16 and S17). Test savings would be greater if one accounted for evaluated candidates who did not proceed with kidney donation.

Discussion

Application of eGFR to the evaluation and selection of living kidney donors is controversial, in part due to concerns about insufficient accuracy in the relationship of eGFR to mGFR to accept or decline donor candidates (2,5). In many clinical settings other than kidney donation, eGFR rather than mGFR is considered sufficient for clinical decision making;

Table 3: Categorical likelihood ratios of eGFR categories for mGFR thresholds

mGFR thresholds	eGFR categories	LRs for eGFRcr	LRs for eGFRcr-cys
<60	<30	409	900
	30–44	27	36
	45–59	2.9	3.6
	60–69	0.60	0.46
	70–79	0.20	0.150
	80–89	0.07	0.03
	90–104	0.03	0.02
	≥105	0.01	<0.005
<70	<30	602	662
	30–44	68	112
	45–59	5.8	9.1
	60–69	1.3	1.31
	70–79	0.46	0.43
	80–89	0.15	0.08
	90–104	0.06	0.04
	≥105	0.01	0.01
≥80	<30	<0.005	<0.005
	30–44	0.01	0.006
	45–59	0.08	0.05
	60–69	0.33	0.23
	70–79	1.1	0.90
	80–89	3.0	3.5
	90–104	7.7	11
	≥105	66	162
≥90	<30	<0.005	<0.005
	30–44	0.005	0.005
	45–59	0.04	0.02
	60–69	0.12	0.12
	70–79	0.55	0.33
	80–89	1.3	1.2
	90–104	4.4	5.0
	≥105	35.1	63

If the LR for an eGFR category is close to 1, then the probability that a participant met a threshold of mGFR after the eGFR test differed little from their pretest probability before the eGFR test. If the LR for an eGFR category achieved a value far from 1 (e.g. >10 or <0.1), then the eGFR test exerts a greater influence on the posttest probability of meeting or not meeting a threshold of mGFR. Units of GFR are mL/min/1.73 m². CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; eGFRcr, GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from the combination of serum creatinine and cystatin C; LR, likelihood ratio; mGFR, measured GFR.

however, it is argued that donation is a higher stakes decision in which more accuracy is needed and that eGFR is less accurate at higher values of GFR (9). In the current study, we demonstrated circumstances in which eGFRcr alone or sequential use of eGFRcr then eGFRcr-cys may be sufficiently accurate to identify mGFR above or below thresholds used for decision making. Using data from the SRTR, we demonstrated that 53% and 74% of living donors had predonation eGFRcr high enough to ensure ≥95% probability that predonation mGFR would be ≥90 and

≥80 mL/min per 1.73 m², respectively, suggesting that mGFR may not be necessary in a large proportion of donor candidates. To facilitate application of our results, we produced a Web-based application that enables clinicians to compute posttest probability for mGFR thresholds between 60 and 90 mL/min per 1.73 m², based on the eGFR values of participants of different ages, sex, and race. Transplant centers could use these data to develop policies for use of eGFRcr and/or eGFRcr-cys without requiring confirmation by mGFR based on clearance of an exogenous filtration marker or creatinine.

Evaluation of GFR is only one part of the evaluation of living donor candidates. The evidence base for the traditionally accepted mGFR thresholds for decision making has not been evaluated rigorously, and the thresholds vary across transplant centers. Consequently, transplant centers make decisions about donor candidacy with the understanding that there is some uncertainty in ascertainment of GFR. In principle, measuring GFR would be preferred for donor evaluation and will likely be required for many donor candidates, but there are good reasons to consider strategies that reduce reliance on mGFR. First, timed urine collections for measurement of CrCl—available in all centers and used by many programs (7)—are inconvenient and prone to error due to undercollection or overcollection, and even when the procedure is performed properly, the results are limited by large systematic bias and imprecision (19). Some studies show that eGFRcr is as accurate or more accurate than measured CrCl in potential donors (20,21). Measurement of urinary or plasma clearance after administration of an exogenous filtration is more accurate than measured CrCl but requires specialized personnel and equipment and is more difficult, time consuming and expensive (22,23). Second, GFR measurement methods using exogenous filtration markers are not standardized across transplant centers, and measurement error is an important concern (19). Radionuclide imaging protocols are generally less accurate than urinary or plasma clearance protocols (24). In contrast, GFR estimation from endogenous filtration markers is simpler than GFR or CrCl measurement and is not affected by GFR measurement error and, with use of multiple markers, may approach the accuracy of mGFR (25,26). Indeed, concordance between eGFRcr and eGFRcys but discordance with mGFR may suggest measurement error in mGFR.

We anticipate two potential strategies for the application of our results to increase efficiency of the donor evaluation and selection and to reduce costs. As we have illustrated in this study, one strategy would be to use eGFRcr at the transplant center as a first test and possibly eGFRcr-cys as a confirmatory test in which posttest probabilities of sufficient magnitude could be used to accept or decline donor candidates. In this scenario, measured GFR would be used only when eGFR did not provide sufficiently high probability of an mGFR above or below the threshold of interest. Our analysis of SRTR data showed that more than half of

Table 4: Examples of posttest probabilities from application of likelihood ratios to NHANES

NHANES categories	Pretest probabilities of mGFR <60	Posttest probabilities of mGFR <60			
		If eGFRcr 30–44	If eGFRcr 45–59	If eGFRcr-cys 30–44	If eGFRcr-cys 45–59
All	5%	58%	13%	65%	16%
Age, 18–44 years					
Black women	1%	21%	3%	21%	3%
Black men	1%	21%	3%	34%	5%
Nonblack women	0%	5%	1%	7%	1%
Nonblack men	0%	10%	1%	13%	1%
Age, 45–64 years					
Black women	5%	58%	13%	66%	16%
Black men	4%	53%	11%	61%	13%
Nonblack women	6%	63%	15%	70%	19%
Nonblack men	1%	21%	3%	34%	5%
Age, 65–80 years					
Black women	30%	92%	55%	94%	61%
Black men	27%	91%	51%	93%	57%
Nonblack women	27%	91%	51%	93%	57%
Nonblack men	26%	90%	50%	93%	55%

NHANES categories	Pretest probabilities of mGFR ≥90	Posttest probabilities of mGFR ≥90			
		If eGFRcr 90–104	If eGFRcr ≥105	If eGFRcr-cys 90–104	If eGFRcr-cys ≥105
All	71%	91%	99%	92%	99%
Age, 18–44 years					
Black women	93%	98%	100%	98%	100%
Black men	94%	99%	100%	99%	100%
Nonblack women	87%	97%	100%	97%	100%
Nonblack men	88%	97%	100%	97%	100%
Age, 45–64 years					
Black women	70%	91%	99%	92%	99%
Black men	68%	90%	99%	91%	99%
Nonblack women	64%	89%	98%	90%	99%
Nonblack men	61%	87%	98%	89%	99%
Age, 65–80 years					
Black women	20%	52%	89%	55%	94%
Black men	31%	66%	94%	69%	97%
Nonblack women	16%	45%	86%	49%	92%
Nonblack men	15%	43%	85%	46%	92%

Shading corresponds to transplant center decision making for the hypothetical example given in text. Shading shows combinations where posttest probabilities of mGFR <60 are ≥95%, indicating donor candidates who could be rejected without mGFR tests; green shading shows combinations where posttest probabilities of mGFR ≥90 are ≥95%, indicating donor candidates who could be accepted without mGFR tests. Unshaded cells indicate donor candidates who would require mGFR testing for decision making. Units of GFR are mL/min/1.73 m². eGFRcr, GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from serum creatinine and cystatin C; mGFR, measured GFR; NHANES, National Health and Nutrition Examination Survey.

accepted candidates would not have required an mGFR test according to the policies of our hypothetical transplant center, improving the efficiency of evaluation. Another strategy is to use eGFR to screen donor candidates prior to evaluation at the transplant center, particularly candidates who live far from transplant centers, thereby avoiding unnecessary evaluations.

If transplant centers decide to implement eGFR tests, we anticipate that each center would determine the specific

algorithm for clinical decision making. For the hypothetical transplant center that we described, we considered mGFR thresholds of ≥90 and <60 mL/min per 1.73 m² to accept and decline potential donors and posttest probabilities ≥95% for these thresholds for clinical decision making. The thresholds for mGFR and posttest probabilities for acceptance and rejection could be higher or lower depending on the transplant program policies or could vary by demographic and clinical characteristics of the donor candidates, as has been recommended (27). Thresholds for posttest

Table 5: Examples of posttest probabilities for a wide range of pretest probabilities

Pretest probabilities of mGFR <60	Posttest probabilities of mGFR <60			
	If eGFRcr 30–44	If eGFRcr 45–59	If eGFRcr-cys 30–44	If eGFRcr-cys 45–59
0.05	58%	13%	65%	16%
0.1	75%	24%	80%	28%
0.2	87%	42%	90%	47%
0.3	92%	55%	94%	60%
0.4	95%	66%	96%	70%
0.5	96%	74%	97%	78%
0.6	98%	81%	98%	84%
0.7	98%	87%	99%	89%
0.8	99%	92%	99%	93%
0.9	100%	96%	100%	97%
0.95	100%	98%	100%	99%

Pretest probabilities of mGFR ≥90	Posttest probabilities of mGFR ≥90			
	If eGFRcr 90–104	If eGFRcr ≥105	If eGFRcr-cys 90–104	If eGFRcr-cys ≥105
0.95	99%	100%	100%	100%
0.9	98%	100%	99%	100%
0.8	95%	99%	98%	100%
0.7	91%	99%	96%	100%
0.6	87%	98%	94%	100%
0.5	81%	97%	91%	99%
0.4	74%	96%	88%	99%
0.3	65%	93%	82%	99%
0.2	52%	89%	73%	98%
0.1	33%	79%	54%	95%
0.05	19%	64%	36%	90%

Shading corresponds to transplant center decision making for the hypothetical example given in text. Red shading shows combinations in which posttest probabilities of mGFR <60 are ≥95%, indicating donor candidates who could be rejected without mGFR tests. Green shading shows combinations in which posttest probabilities of mGFR ≥90 are ≥95%, indicating donor candidates who could be accepted without mGFR tests. Unshaded cells indicate donor candidates who would require mGFR testing for decision making. Units of GFR are mL/min/1.73 m². eGFRcr, GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from serum creatinine and cystatin C; mGFR, measured GFR.

probabilities to accept or decline donor candidates without further testing could also vary according to other factors, such as ease of measuring GFR and cost. Decisions as to whether to use cystatin C in addition to creatinine may also vary by center or patient characteristics. We have considered eGFRcr-cys as a second test prior to mGFR, but decisions about the requirement for GFR measurement could be made using only GFRcr without measurement of cystatin C. Alternatively, eGFRcys may be more appropriate in donor candidates in whom eGFRcr is likely to be biased due to variation in non-GFR determinants of the serum creatinine concentration, such as creatinine generation by diet (e.g. vegetarians, use of creatine supplements) or by muscle (e.g. amputees, body builders) or drugs that inhibit tubular secretion of creatinine (e.g. cimetidine, ranitidine or possibly fenofibrate). Although we used pretest probabilities based on demographic groups in NHANES, we would anticipate that clinicians would adjust pretest probabilities based on additional information. A donor candidate without risk factors for kidney disease, for example, may have a

higher probability of mGFR ≥90 mL/min per 1.73 m² than the average participant of the same age, sex and race in NHANES. Conversely, a donor candidate with a strong family history of kidney disease, history of hypertension or use of nonsteroidal anti-inflammatory agents may have a lower probability of mGFR ≥90 mL/min per 1.73 m².

Prior studies in potential transplant donors have shown misclassification of mGFR by eGFR and concluded that eGFR was not useful for kidney donor evaluation (28,29). Our results are consistent in that we showed only 56% and 61% agreement of eGFRcr and eGFRcr-cys with mGFR categories, respectively. The other studies did not consider using both eGFRcr and eGFRcr-cys sequentially, and they did not compute categorical LRs for discreet categories of eGFR that leverage more information available in an eGFR.

Strengths of our study include use of NHANES as a nationally representative population to determine pretest probabilities; use of the CKD-EPI creatinine and creatinine-

Table 6: Examples of decision making using eGFR for white women aged 50 years using sequential testing with eGFRcr and eGFRcr-cys

Patient 1: White woman aged 50 years with higher GFR			
Example	A	B	C
Pretest probability of mGFR ≥90	64%	64%	64%
eGFRcr value	110	95	95
Posttest probability of mGFR ≥90	98%	89%	89%
Transplant center decision	Accept without confirmatory test	Require confirmatory test	Require confirmatory test
eGFRcr-cys value	NA	95	75
Posttest probability of mGFR ≥90		99%	89%
Transplant center decision		Accept without mGFR test	Require mGFR test

Patient 2: White woman aged 50 years with lower GFR			
Example	D	E	F
Pretest probability of mGFR <60	6%	6%	6%
eGFRcr value	25	40	40
Posttest probability of mGFR <60	96%	63%	63%
Transplant center decision	Reject without confirmatory test	Require confirmatory test	Require confirmatory test
eGFRcr-cys value	NA	40	50
Posttest probability of mGFR <60		98%	84%
Transplant center decision		Reject without mGFR test	Require mGFR test

In the top panel, the clinical decision to be made is whether the candidate donor can be accepted without the use of confirmatory tests (eGFRcr-cys or mGFR). In the bottom panel, the clinical decision to be made is whether the candidate donor can be rejected without use of confirmatory tests (eGFRcr-cys or mGFR).

For use of eGFRcr-cys as a confirmatory test, the posttest probability from the eGFRcr becomes the pretest probability for eGFRcr-cys. Confirmatory testing is not required if posttest probability based on eGFRcr is ≥95%. mGFR testing is not required if posttest probability is ≥95%.

Posttest probabilities are computed from pretest probability based on NHANES overall population and the likelihood ratio for eGFRcr in the Chronic Kidney Disease Epidemiology Collaboration overall population.

Units of GFR are mL/min/1.73 m².

eGFR, estimated glomerular filtration rate; eGFRcr, GFR estimated from serum creatinine; eGFRcr-cys, GFR estimated from serum creatinine and cystatin C; mGFR, measured glomerular filtration rate; NA, not assessed.

cystatin C equations, which have been validated extensively and are recommended by current guidelines; use of standardized assays for creatinine and cystatin C to determine pretest probabilities and test performance; use of rigorous statistical methods appropriate for diagnostic test evaluation for continuous variables; demonstration of good performance characteristics for eGFR compared with mGFR; and provision of clinical examples and simulations using data from a national registry of recent kidney donors. In addition, we developed a Web-based application that enables widespread clinical use.

Our study also has limitations. First, the data on pretest probabilities of mGFR categories and categorical LRs for eGFR versus mGFR that we used to determine posttest probabilities are based on NHANES and CKD-EPI study populations rather than studies in kidney donor candidates. In the absence of data from a representative study of kidney donor candidates, it was necessary to use data from other sources. Systematic differences between donor candidates and our study populations may limit the application of our results; however, we noted little difference in eGFR test performance among participants in the CKD-EPI data set across age, race, sex, presence or absence of diabetes, or participation in the development and internal validation data set or external validation data set. Furthermore, our

Web-based application allows clinicians to input alternative pretest probabilities for mGFR that are thought to be more accurate than those derived from NHANES. Nonetheless, we suggest studies of the performance of eGFRcr, eGFRcys, and eGFRcr-cys in kidney donor candidates. Of note, performance measures of estimating equations are not as high when the range of mGFR is restricted, so further validation of our calculator will require evaluation in donor candidates rather than accepted donors. Second, mGFR is not available in NHANES and serum cystatin C is not available in SRTR. Third, eGFRcr is less accurate in participants with alterations in non-GFR determinants of the serum CrCl, and the CKD-EPI equations are not as accurate in racial groups other than white and black or in regions other than North America, Europe and Australia (30). Fourth, our estimate of test savings was restricted to donor candidates who were accepted and underwent kidney donation but did not include candidates who did not undergo donation and did not include information on whether the evaluation included mGFR or CrCl.

In summary, our results suggest that eGFRcr and eGFRcr-cys could often be used for decision making to accept or decline living kidney donor candidates without requiring a measurement of GFR. We proposed a strategy for kidney donor evaluation, but we anticipate that transplant centers

Table 7: Number of donors in the SRTR in whom eGFRcr would have been sufficient for clinical decision making without mGFR testing, computed from participants in NHANES and all participants in CKD-EPI

	n	mGFR thresholds	
		≥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)

Data from SRTR 2009–2015. Posttest probabilities computed from pretest probability based on NHANES and likelihood ratio for eGFRcr in CKD-EPI. mGFR testing is not required if posttest probability is ≥95%. Data for using eGFR to correctly predict mGFR thresholds are shown as n (%). CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; eGFRcr, GFR estimated from serum creatinine; mGFR, measured GFR; NHANES, National Health and Nutrition Examination Survey; SRTR, Scientific Registry of Transplant Recipients.

might implement a wide variety of strategies for which the Web-based calculator that we developed could be useful as part of the evaluation process. We suggest assessment of strategies using eGFR to determine their impact on the practice of kidney donor evaluation.

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Supporting Information

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

Table S1: Demographic and clinical characteristics of NHANES in all participants and in participants without diabetes.

Table S2: Pre-test probabilities of four thresholds of GFR stratified by age, sex and race in NHANES participants without diabetes.

Table S3: Demographic and clinical characteristics in CKD-EPI development and internal validation cohort in all participants and in participants without diabetes.

Table S4: Demographic and clinical characteristics of CKD-EPI external validation cohort in all participants and in participants without diabetes.

Table S5: Cross classification of eGFRcr with eGFRcr-cys in CKD-EPI.

Table S6: Cross classification of eGFRcys with mGFR and eGFRcr-cys in CKD-EPI.

Table S7: AUCs of eGFRcr, eGFRcr-cys for mGFR thresholds in CKD-EPI in all participants.

Table S8: AUCs of eGFRcr, eGFRcr-cys for mGFR for CKD-EPI in participants without diabetes.

Table S9: Contingency table and LR for eGFRcr in CKD-EPI in all participants.

Table S10: Contingency table and LR for eGFRcr-cys in CKD-EPI in all participants.

Table S11: Contingency table and LR for eGFRcr in CKD-EPI in participants without diabetes.

Table S12: Contingency table and LR for eGFRcr-cys in CKD-EPI participants without diabetes.

Table S13: Categorical LRs of eGFR categories for mGFR thresholds in the CKD-EPI external validation cohort.

Table S14: Demographic and clinical characteristics of Scientific Registry of Transplant Recipients (SRTR) cohort.

Table S15: Number of donors in Scientific Registry of Transplant Recipients (SRTR) in whom eGFRcr would have been sufficient for clinical decision making without mGFR testing, computed from participants in NHANES and non-diabetic participants in CKD-EPI.

Table S16: Number of donors in Scientific Registry of Transplant Recipients (SRTR) in whom eGFRcr would have been sufficient for clinical decision making without mGFR testing, computed from participants in NHANES and all participants in CKD-EPI external validation cohort.

Table S17: Number of donors in Scientific Registry of Transplant Recipients (SRTR) in whom eGFRcr would have been sufficient for clinical decision making without mGFR testing, computed from participants in NHANES and non-diabetic participants in CKD-EPI external validation cohort.