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Impact of estimation versus direct measurement of predonation glomerular filtration rate on the eligibility of potential living kidney donors

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ABSTRACT

While direct measurements of glomerular filtration rate (GFR) provide the most accurate evaluation of pre-donation kidney function, guidelines do not systematically require the use of a reference method. We evaluated whether and to what extent relying upon creatinine-based estimating equations (eGFR) rather than direct measurement of GFR (mGFR) alters the selection of potential living donors. We compared the impact of 4 equations (the MDRD study equation, the CKD-EPI equation, the revised Lund-Malmo equation, and the full age spectrum [FAS] equation) on the evaluation of 2733 potential donors with GFR measured by reference methods. We also considered the impact of using either absolute or age-adapted GFR thresholds. The CKD- EPI and FAS equations had the best performances (P10 of 50.6% and 47.8%; P30 of 94.4% and 93.1%, respectively) and led to the lowest proportion of improperly evaluated candidates. Misclassification was more frequent when GFR adequacy was defined as an absolute threshold of 90 ml/min/1.73m2 as compared to an age-adapted definition (26% and 5%, respectively). Interpretation of eGFR according to an absolute threshold of 90 ml/min/1.73m^2 identified 1804 candidates eligible to donate, compared to 2648 when mGFR was interpreted with age-adapted thresholds. We conclude that creatinine-based estimates cannot substitute for direct GFR measurement to evaluate candidates for kidney donation. When reference methods for direct GFR measurement are not available, our data suggest that a strategy based on age-adapted eGFR values estimated with either the CKD-EPI or FAS equation should be preferred.

KEYWORDS: estimated GFR; living kidney donors; measured GFR

Renal transplantation from living donors is the best treatment for end-stage renal disease. Compared with deceased donors, kidneys from living donors provide better graft and patient survival.[1] Living donors are a significant, if not unique, source of kidneys in many geographic areas where deceased donation is scarce.[2] Prerequisites for living kidney donation have been recently reformulated by the Kidney Disease Improving Global Outcome (KDIGO) guidelines.[3] They recommend accepting living donation when the GFR is at least

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90 ml/min per 1.73 m^2 and to deny it for a GFR lower than 60 ml/min per 1.73 m^2. As for intermediate GFR values, eligibility has to be individually discussed using an end-stage renal disease risk estimate.[3] The GFR thresholds in the KDIGO guidelines for living kidney donors were chosen following values that define chronic kidney disease stages.[3] In the general population, those GFR values have been consistently found to be associated with higher risk of morbidity and mortality. Whether those thresholds portend the same excess of risk in a healthier population of donors is, however, unclear.

Importantly, the preferred technique to be used for predonation GFR evaluation is not clearly specified in the guidelines. By acknowledging that reference methods of GFR measurements are not necessarily accessible in every transplant center worldwide, the KDIGO group only recommends that each center should rely on the "best locally available" technique, including eGFR. This may be problematic given the potentially large discrepancy between estimated and measured GFR at the individual level in populations of living kidney donors.[4] In this regard several countries have adopted more stringent guidelines recommending direct measurement of predonation GFR with exogenous tracers (mGFR).[5-8] Beyond the traditional metrics (bias, precision, 30% accuracy) used to qualify a technique evaluating GFR, performance in terms of classification is also crucial in the context of living donation where the key question is to know whether an individual GFR value is high enough for proceeding further with the donation.

Beyond the way GFR is measured (or estimated), the question of the GFR threshold for kidney donation matters.[9] Currently, 2 approaches coexist to assess adequacy of individual GFR with kidney donation. The first is based on an absolute, 1-size-fits-all GFR threshold and is endorsed by the latest KDIGO guidelines (with the threshold of 90 ml/min per 1.73 m^2). The second takes into account the physiologic decline of GFR over time and is based on the range of normality defined for each age category. Whether and to what extent using GFR estimating equations rather than direct measurement of GFR differently impacts those 2 approaches are not known. Herein, we assembled a cohort of candidates for kidney donation who underwent conventional donor workup, including GFR measurements by a reference method, with the aim to evaluate the ability of creatinine-based equations in identifying GFRs suitable for donation.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF POTENTIAL DONORS

We included 2733 potential living kidney donors from 7 French transplant centers. Most were women (62%). Mean age was 50.6 ± 11.8 years and mean mGFR 96.1 ± 17.8 ml/ min per 1.73 m^2. Detailed characteristics of the cohort are presented in Table 1.

COMPARISONS OF GFR ESTIMATING EQUATIONS IN POTENTIAL DONORS

We evaluated the performances of 4 different creatinine- based equations: the modification of diet in renal disease (MDRD) study equation,10,11 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),12 the revised Lund- Malmo (LM)13 equation, and the FAS14 equation. Results are summarized in Table 2. Over the full range of mGFR, the CKD- EPI and the FAS equations had the best analytical performance. The CKD-EPI equation had the lowest root-mean square error (15.4 [95% confidence interval, 14.8-16.0]), highest percentage of eGFR values within 10% of mGFR (50.7%), highest percentage of eGFR values within 30% of mGFR (94.4%), and lowest absolute bias (-1.1 ml/min per 1.73 m2). The FAS equation had the highest Lin's Concordance Correlation Coefficient (Lin's CCC) and correlation coefficient (0.58 and 0.59, respectively). We also studied equations' performances around the threshold of 90 ml/min per 1.73 m2. Results are summarized in Table 2. Performances of equations greatly varied according to this

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threshold with no obvious superiority for one equation in particular across the whole range of GFR. Ranges of mGFR were very different from those of eGFR. Although 50% of potential donors had mGFR values between 84 and 107 ml/min per 1.73 m2 (quartile 2 and quartile 3; range, 23 ml/min per 1.73m2), eGFR values varied from 59 to 135 ml/min per 1.73 m2 (range, 76 ml/min per 1.73 m2), irrespective of the equation considered.

Table 1. Baseline characteristics of potential donors (n = 2733)

ıracteristic	ue
of women	)4 (62.0)
an age, yr (SD)	6 (11.8)
› > 40 yr	)9 (80.5)
an weight, kg (SD)	0 (14.1)
an height, cm (SD)	7.4 (9.0)
an BMI, kg/m² (SD)	3 (4.1)
an BSA, m² (SD)	9 (0.20)
Obese	5 (11.9)
an mGFR, ml/min per 1.73 m² (SD)	1 (17.8)
an creatinine, mmol/l (SD)	5 (13.9)
an MDRD, ml/min per 1.73 m² (SD)	3 (17.4)
an CKD-EPI, ml/min per 1.73 m² (SD)	1 (14.9)
an FAS, ml/min per 1.73 m² (SD)	6 (18.8)
an LM, ml/min per 1.73 m² (SD)	5 (12.4)

BMI, body mass index; BSA, body surface area; obese, BMI > 30 kg/m². Values are n (%) unless otherwise defined.

IMPACT OF EGFR FOR DONOR SELECTION: THE ABSOLUTE THRESHOLD APPROACH

The KDIGO guidelines identified 2 thresholds (90 and 60 ml/ min per 1.73 m²) to guide the clinical decision for donor eligibility. Table 3 displays the proportions of misclassified subjects at 90 and 60 ml/min per 1.73 m².

At the threshold of 90 ml/min per 1.73 m², detailed classification of living donor candidates by mGFR and eGFR is presented in Supplementary Table S1. The MDRD and LM equations had the highest percentage of misclassification at 33.7% and 35.7%, respectively, whereas both the CKD-EPI and the FAS equations misclassified 26% of potential donors.

For a threshold of 60 ml/min per 1.73 m², the percentage of misclassification was overall lower (Table 3). At this threshold detailed classification of living donor candidates by mGFR and eGFR is presented in Supplementary Table S2.

Misclassification is illustrated in Figure 1 for the CKD-EPI and FAS equations. Black dots represent potential donors with discordant eGFR at threshold of 90 (upper graphs) or 60 (lower graphs).

Table 2 Comparison of the performances of the 4 estimating GFR equations

Full mGFR range 46.5- 183 ml/min per 1.73 m²	**MDRD [29-167]**	**CKD-EPI [31-139]**	**LM [27-126]**	**FAS [33-168]**
RMSE	18.9 (18.3, 19.6)	15.4 (14.8, 16.0)	18.2 (17.7, 18.8)	16.9 (16.3, 17.5)
P10	41.4 (41.5, 41.5)	50.7 (50.7, 50.7)	41.7 (41.7, 41.7)	47.8 (47.8, 47.8)
P30	90.0 (90.0, 90.0)	94.4 (94.4, 94.4)	92.9 (92.9, 92.9)	93.1 (93.1,93.1)
Proportional bias	0.95 (0.94, 0.96)	1.02 (1.01, 1.02)	0.92 (0.91, 0.92)	1.00 (0.98, 1.00)
Absolute bias	-6.7 (-7.4, -6.1)	-1.1 (-1.6, -0.4)	-10.6 (-11.2, -10.6)	-2.5 (-3.2, -1.9)
Relative bias	-0.05 (-0.06, 0.05)	-0.00 (0.00, 0.01)	-0.09 (-0.10, -0.09)	-0.01 (-0.02, -0.00)
Lin's CCC	0.46 (0.43, 0.49)	0.56 (0.53, 0.58)	0.44 (0.41, 0.46)	0.58 (0.55, 0.60)
Correlation	0.49	0.57	0.57	0.59
P value	<0.001	<0.001	<0.001	<0.001
mGFR < 90 ml/min per 1.73 m² (n = 1036)	**MDRD [29-164]**	**CKD-EPI [31-121]**	**LM [27-112]**	**FAS [33-139]**

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RMSE	14.1 (13.2, 14.9)	13.7 (13.1, 14.3)	10.6 (10.0, 11.0)	13.6 (12.8, 14.3)
P10	47.6 (44.5, 50.6)	42.5 (39.5, 45.5)	56.5 (53.4, 59.5)	48.3 (45.2, 51.3)
P30	91.8 (90.1, 93.5)	91.3 (89.6, 93.0)	97.0 (96.0, 98.0)	93.1 (91.6, 94.7)
Proportional bias	1.02 (1.00, 1.03)	1.09 (1.08, 1.10)	0.98 (0.98, 0.99)	1.03 (1.02, 1.04)
Absolute bias	0.72 (-0.14, 1.57)	6.34 (5.6, 7.09)	-1.56 (-2.2, -0.93)	2.05 (1.23, 2.87)
Relative bias	**0.02 (0.00, 0.02)**	0.08 (0.07, 0.09)	-0.01 (-0.02, -0.00)	0.03 (0.02, 0.04)
mGFR ≥ 90 ml/min per 1.73 m² (n = 1697)	**MDRD [58-152]**	**CKD-EPI [61-130]**	**LM [57-119]**	**FAS [56-162]**
RMSE	21.4 (20.5, 22.3)	16.3 (15.5, 17.2)	21.5 (20.6, 22.4)	18.5 (17.8, 19.4)
P10	37.8 (35.5, 40.1)	55.7 (53.4, 58.1)	32.8 (30.5, 35.0)	47.7 (45.3, 50.1)
P30	88.9 (87.4, 90.4)	96.3 (95.4, 97.2)	90.5 (89.1, 91.9)	93.1 (91.9, 94.3)
Proportional bias	0.90 (0.89, 0.91)	0.96 (0.95, 0.96)	0.86 (0.85, 0.86)	0.95 (0.95, 0.96)
Absolute bias	-11.4 (-12.3, 10.6)	--5.7 (-6.4, -4.9)	-16.1 (-16.8, -15.4)	-5.8 (-6.6, -4.9)
Relative bias	-0.10 (-0.11, 0.09)	--0.04 (-0.05, -0.04)	-0.14 (-0.15, -0.14)	-0.04 (-0.05, -0.04)

P10, percentage of eGFR values within 10% of mGFR; P30, percentage of eGFR values within 30% of mGFR; RMSE, root mean square error,
Values are mean, and values in parentheses are 95% confidence intervals. Values in brackets represent the minimum and maximum value of each equation estimating GFR.

Table 3 Proportions of misclassified potential donors for absolute GFR thresholds of 90 and 60 ml/min per 1.73 m²

GFR threshold (ml/min per 1.73 m²)	GFR estimating equation			
	MDRD	CKD-EPI	LM	FAS
90 ml/min per 1.73 m²	33.7 (32.2-35.2)	26.1 (24.7-27.5)	35.7 (34.2-37.3)	26.0 (24.7-27.4)
60 ml/min per 1.73 m²	2.6 (2.2-3.2)	1.2 (0.9-1.6)	1.8 (1.4-2.3)	2.0 (1.6-2.5)

GFR, glomerular filtration rate.
Values are percents with 95% confidence intervals in parentheses.

IMPACT OF EGFR FOR DONOR SELECTION: THE AGE-ADAPTED APPROACH

We summarized the percentage of misclassification in Table 4. The MDRD and LM equations had higher percentages of misclassification (11.6% and 7.8%, respectively) than the CKD-EPI and FAS equations (4.9% and 5.2%, respectively). Detailed classification of living donor candidates by mGFR and eGFR is presented in Supplementary Table S3.

Among the 85 potential donors with abnormally low mGFRs for age, 27 (31.7%) and 30 (35.3%) were correctly identified with the CKD-EPI and FAS equations, respectively. For 43 potential donors (50.5%) the MDRD equation showed the best sensitivity to detect those "ineligible donors" (Supplementary Table S3 and Figure 2).

Alternatively, we identified potential donors who would have been considered with abnormally low GFRs according to creatinine-based estimates (i.e., people with low eGFR but "good" mGFR). Results are presented in Figure 3. Among the 314 potential donors with low MDRD for age, 43 (13.6%) had low mGFRs for age. Among the 104 potential donors with low CKD-EPI for age, 27 (25.9%) had low mGFRs for age. Among the 115 potential donors with low FAS for age, 30 (26.1%) had low mGFRs for age. Among the 200 potential donors with low LM for age, 36 (18%) had normal mGFRs for age. Hence, the positive predictive value of low eGFR for age to predict low mGFR for age was at best 26.1% for the FAS equation (Supplementary Table S3).

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EGFR VERSUS MGFR: THE NET RESULT ON THE NUMBER OF ELIGIBLE DONORS

Differences in eligibility of potential donors according to the method of GFR evaluation (estimated vs. measured GFR) and according to the method of GFR interpretation (absolute vs. age-adapted threshold) are presented in Table 5. Considering age-adapted normality, use of eGFR resulted for all equations in a lower number of eligible donors (ranging from -19 to -229 donors for the CKD-EPI and MDRD equations, respectively). Considering the fixed threshold of 90 ml/min per 1.73 m^2, the number of eligible donors was higher for the CKD-EPI equation as compared with mGFR (+107). For all other equations the number of eligible donors was lower. For a threshold of 60 ml/min per 1.73 m^2 the number of eligible donors was constantly lower for eGFR as compared with mGFR.
Importantly, numbers of eligible donors according to eGFR equations and GFR interpretation contain falsely selected candidates (i.e., potential donors with eGFR higher than the threshold but mGFR lower than the threshold). For example, 2629 candidates were considered eligible to donation by the CKD-EPI equation, using age-adapted thresholds. That represents -19 donors compared with mGFR. Yet, among those 2629 candidates 58 had a low mGFR for age and should not have been accepted.

IMPACT OF SCREENING STRATEGY ON EVALUATION OF POTENTIAL DONORS YOUNGER THAN 40 YEARS

This population of potential donors is specific regarding the number of years to live with a single kidney and the fact that age-related GFR decline has not yet started in this age group.[9] We studied the performance of equations, the percentage of misclassifications, and the number of eligible donors for potential living kidney donors younger than 40. Conclusions remain in this subgroup of candidates. Performances were similar for the 4 equations (Supplementary Table S4). The CKD-EPI and FAS equations still had the lowest percentage of misclassification either at the age- adapted GFR threshold (Supplementary Tables S5 and S6) or fixed thresholds (Supplementary Tables S7, S8, and S9), and an age-adapted GFR threshold combined with the mGFR led to the highest number of eligible donors (Supplementary Table S10).

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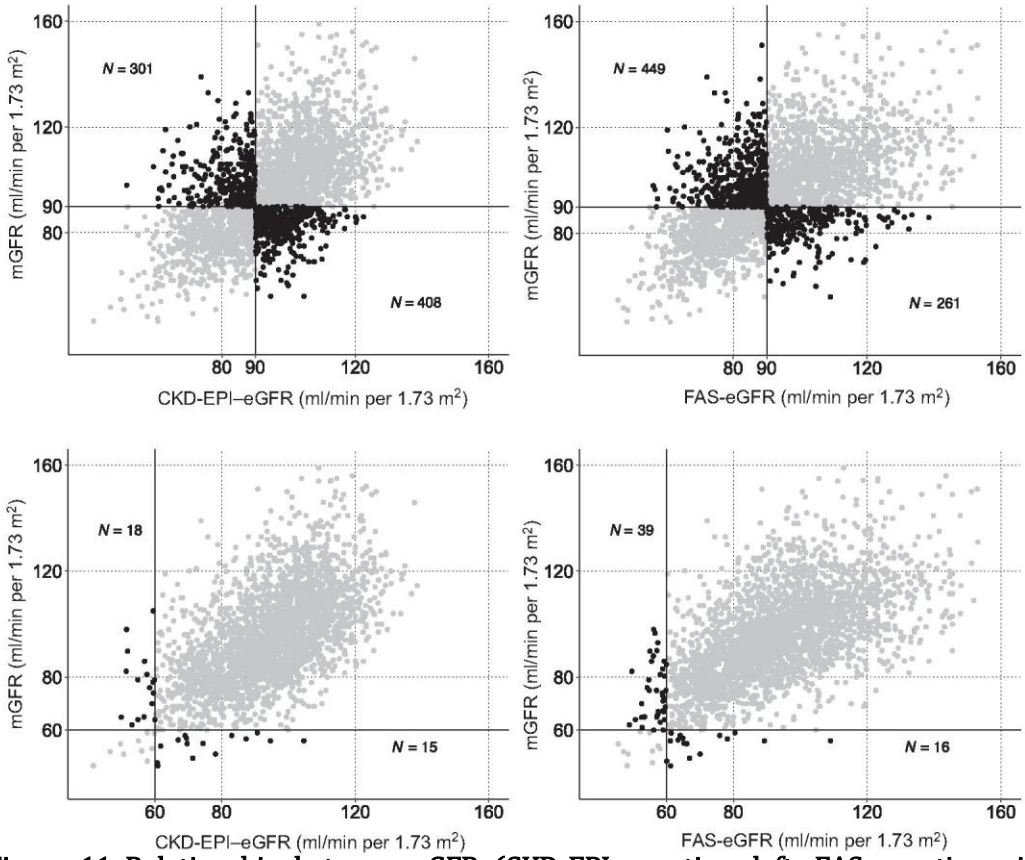

Figure 11 Relationship between eGFR (CKD-EPI equation, left; FAS equation, right) and mGFR in 2733 potential donors. Black dots represent misclassified individuals according to an absolute GFR threshold of 90 ml/min per 1.73 m² (upper graphs) or 60 ml/min per 1.73 m² (lower graphs).

Table 4. Proportions of misclassified potential donors for age-adapted GFR thresholds

GFR threshold (ml/min per 1.73 m²)	Equation estimating GFR			
	MDRD	CKD-EPI	LM	FAS
Age adapted	11.6 (10.6-12.6)	4.9 (4.2-5.6)	7.8 (6.9-8.7)	5.2 (4.5-5.9)

GFR, glomerular filtration rate.
Values are percents with 95% confidence intervals in parentheses.

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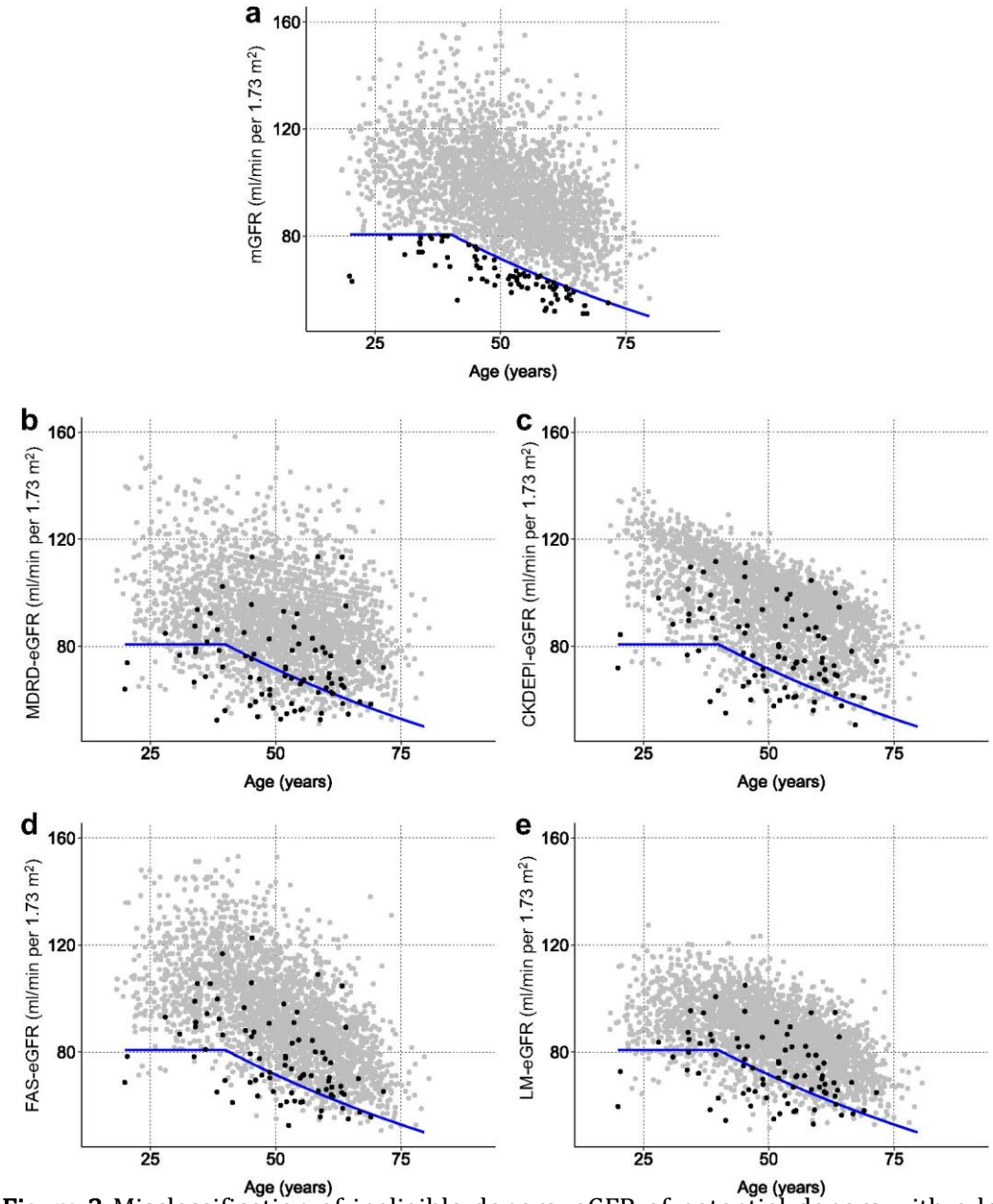

Figure 2 Misclassification of ineligible donors: eGFR of potential donors with a low mGFR for age among 2733 potential donors. Black dots represent individuals with abnormally low mGFR for age. (a) Relationship between age and mGFR. (b-e) Relationship between age and GFR estimated by 4 equations. Solid blue line represents the lower limit of GFR normality for age.

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DISCUSSION

Our study has focused on the relationship between the method to evaluate predonation kidney function and the way to interpret it. We show that the impact of eGFR on eligibility for donation varies according to the approach used for assessing GFR adequacy (absolute or age-adapted threshold) and that those results are also applicable to potential donors younger than 40.

Diagnostic performances of the FAS and CKD-EPI equations were found to be better than those of the MDRD and revised LM equations. This is not surprising because the CKD-EPI was developed to improve the MDRD equation in populations with GFRs higher than 60 ml/min per 1.73 m^2.[12] Performances of the different equations could be considered as optimal at first glance, especially regarding the accuracy within 30%. However, in the specific situation of living kidney donation a high level of precision is crucial, and the accuracy within 30% is certainly too permissive: an individual GFR value of 100 ml/min per 1.73 m^2 is usually not considered as being equivalent to 70 ml/min per 1.73 m^2 or to 130 ml/min per 1.73 m^2. In this context, accuracy within 10 seems to be a better parameter to consider. Importantly, only 50.6% (in the best scenario) of eGFRs reached this level of performance in our cohort. In the same vein, we observed that 50% of potential donors had mGFR values between 84 and 107 ml/min per 1.73 m^2 (quartile 2 and quartile 3; interquartile range, 23 ml/min per 1.73 m^2), whereas the corresponding eGFR values varied from 59 to 135 ml/min per 1.73 m^2 (interquartile range, 76 ml/min per 1.73 m^2) irrespective of the equation considered. This magnitude of discrepancy can be seen as a first indication that eGFR and mGFR are not interchangeable for the screening of potential donors. Of note, GFR was indexed to body surface area. Such a strategy has several limitations,[15-18] especially for obese donors, but the impact on donor eligibility still has to be investigated.

We evaluated whether using eGFR instead of mGFR could modify the final decision of donation according to the 2 most common ways to interpret GFR adequacy. When adequacy was judged through an absolute fixed threshold, we observed significant discrepancies between eGFR and mGFR. For example, at a threshold of 90 ml/min per 1.73 m^2 the CKD-EPI and FAS equations, which turned out to have the best performance, misclassified one-fourth of potential donors. This result is in accordance with our previous findings.[4] On the other hand, when adequacy was judged through age-adapted thresholds, as recommended by some guidelines,[5-8] misclassification was improved down to 5.0%, suggesting that this approach might be acceptable in situations where mGFR is not available. This needs to be tempered, however, given the relative inability of GFR estimating equations to detect abnormally low mGFR for age. Among the 85 potential donors who had such abnormal mGFRs in our cohort, only 50.5%, 42.4%, and 35.3% of them were properly identified by the MDRD, LM, and FAS equations, respectively. The figure was even worse for the CKD-EPI equation, with only 27 (31.7%) potential donors adequately pinpointed.

Interestingly, the degree of misclassification is similar between an approach that would be based on a fixed GFR threshold of 60 ml/min per 1.73 m^2 and the approach based on age-adapted thresholds. Obviously, 60 ml/min per 1.73 m^2 is, however, far too low to be applicable for the screening of the youngest potential donors. This further underlines the relevance of an age-adapted approach for determining the adequacy of predonation GFR at the individual level. In our previous work on this subject we studied a population of effective living kidney donors so that postdonation GFR evolution was used as a read-out of baseline GFR evaluation.[9] Age is associated with the number of nephrons,[19] and we previously reported that age was an important parameter to interpret GFR because older donors had lower GFRs than younger donors.[9] On the contrary, in the present study we included all potential living kidney donors who underwent predonation GFR evaluation to simulate the impact of the GFR evaluation method and GFR interpretation on eligibility to donation. By doing so, not only did we confirm our previous observation on the importance of age (in a different population), but we also observed that the combination of mGFR with an age-adapted approach leads to the selection of the highest number of candidates. At a time when many countries are facing stagnation or even decline in living kidney donation,[20] that combination is of particular clinical and epidemiologic relevance.

Our study has to be understood with its limitations. First, potential donors of our cohort may not be

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perfectly representative of countries other than France, and consequently generalizability of our results may be questioned. Normal GFR references may be different in other populations, notably in Asia.[21,22] Second, we aggregated mGFR values obtained from different methods of GFR measurement. Although they are all considered as reference methods, inulin, ^{51}Cr-EDTA, and iohexol measured clearances are not strictly equivalent.[23] Moreover, the performances of equations including cystatin C could not be evaluated in the absence of cystatin C values in this cohort. Third, measured creatinine clearance is sometimes considered to estimate GFR when mGFR is not available. However, such measured creatinine clearances were not available in our cohort, and the real performance of this method in living kidney donation could thus not be tested. However, today 24-hour urinary creatinine clearance is not considered as a reference method to measure GFR because of a systematic bias (overestimation due to tubular secretion) and, more importantly in the context of living donation, a high degree of imprecision.[23] Fourth, even though we included all potential donors who underwent predonation screening, potential donors who did not undergo GFR measurement were not evaluated. In fact, those potential donors who did not undergo GFR measurement were denied donation because of a reason unrelated to GFR. Hence, our cohort represents *stricto sensu* all potential donors for whom the value of GFR could have changed the decision. We assumed abnormally low GFRs for age as a possible contraindication to donation. Finally, beyond age- adapted GFR thresholds and overall GFR measurement, the usefulness of differential renal function evaluation for each kidney needs to be addressed.

In conclusion, the KDIGO guidelines on the evaluation of living kidney donors recommend the use of absolute, fixed GFR thresholds without specifying the method to be used for GFR evaluation. This recommendation is mainly justified by the observation that reference methods to measure GFR are not necessarily available in all transplant centers. One may argue, however, that simple and rigorous methods, such as plasma clearance of iohexol,[24] exist and can easily be implemented. In this regard our data show that mGFR by providing the highest number of eligible donors should remain the gold standard for potential donor evaluation. In situations where eGFR is the only resource to evaluate GFR adequacy with donation, we suggest preferentially relying on a strategy based on age-adapted GFR values estimated with either the CKD- EPI or FAS equations.

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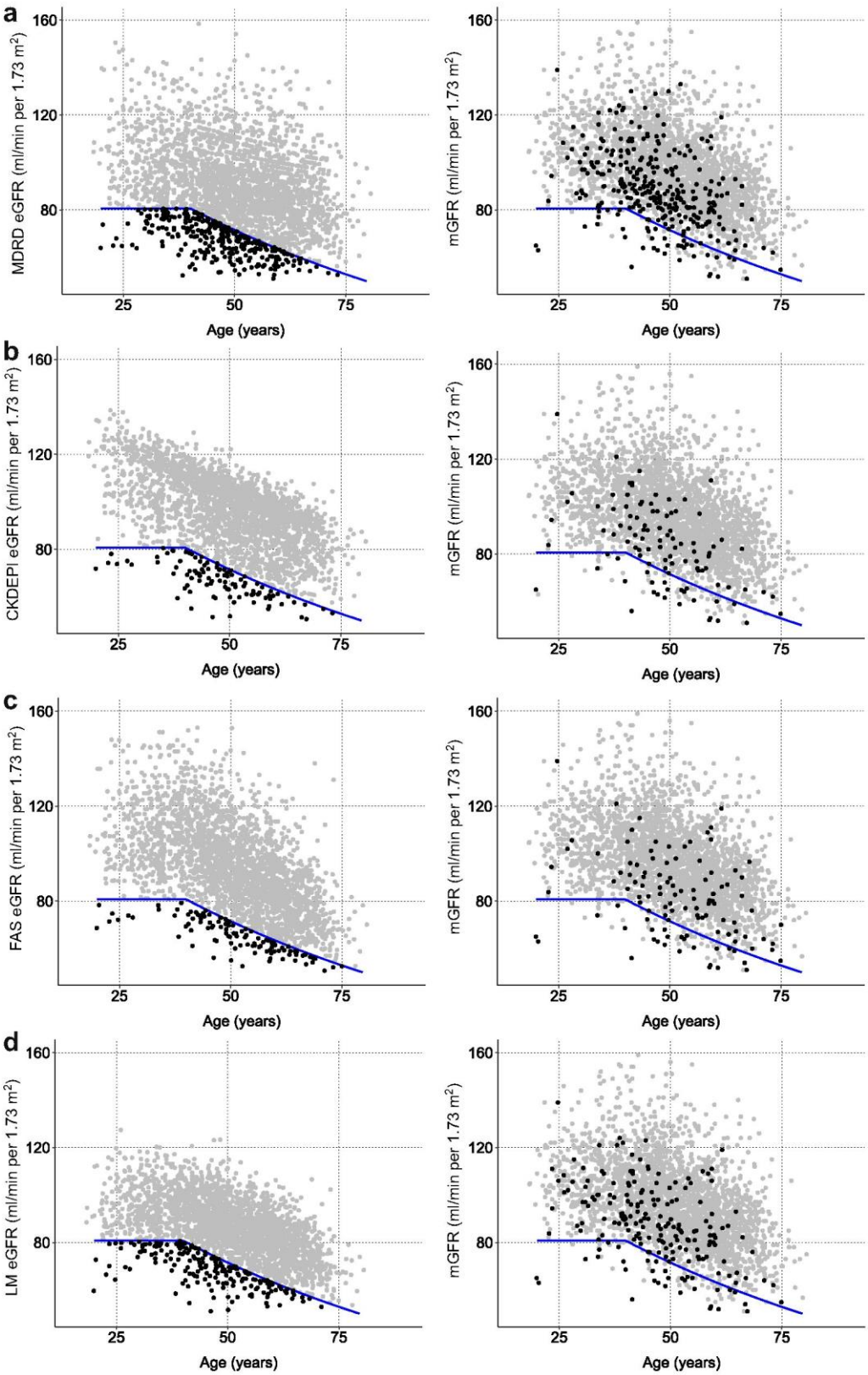

Figure 3 **Misclassification of eligible donors: mGFR of potential donors with a low eGFR for age among 2733 potential donors. Black dots represent potential donors with abnormally low eGFR for age. Relationship between age and mGFR (right column) or eGFR (left column) given by (a) the MDRD equation, (b) the CKD-EPI equation, (c) the FAS equation, and (d) the LM equation. Solid blue line represents the lower limit of normal GFR for age.**

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Table 5. Simulation of the numbers of eligible donors according to the methods of GFR evaluation and GFR interpretation

	-adapted threshold			nl/min per 1.73 m²			nl/min per 1.73 m²		
	ible	/ersus mGFR	e positive	ible	/ersus mGFR	e positive	ible	/ersus mGFR	e positive
;R	8			7			7		
RD	9	)		9	3		0		
)-EPI	9			4	)7		4		
	8			9	3		4		
	3	5			l		1		

Are considered eligible to donation, donors with normal GFR for age (for age-adapted approach), or donors with GFR higher than the absolute threshold. Difversus mGFR is the difference in the number of eligible donors by using eGFR. False positive refers to the number of eligible donors selected by eGFR contains some false-positive candidates, that is, candidates with eGFR compatible with donation and mGFR not compatible with donation.

METHODS

POTENTIAL LIVING KIDNEY DONORS

We conducted a retrospective multicentric observational study on candidates for living kidney donation between 2007 and 2017. Seven transplantation centers participated in the study (Bordeaux, Clermont-Ferrand, Grenoble, Lyon, Paris-Necker, Toulouse, and Nantes). Data were recorded anonymously. We included all potential donors who underwent predonation GFR measurement irrespective of whether they finally donated a kidney or not.
Our study complies with all the items of the modified STROBE statement (https://www.strobe-statement.org) except item 13 (regarding the necessity to report the number of individuals at each stage of the study), which could not be entirely fulfilled. According to French law, anonymous retrospective studies do not require institutional review board approval.

GFR MEASUREMENT

^{51}Cr-EDTA. For Paris-Necker, Bordeaux, Grenoble, and Nantes GFR was measured with ^{51}Cr-EDTA in standardized conditions in the morning. For Paris-Necker and Bordeaux GFR was assessed through a continuous ^{51}Cr-EDTA (GE Healthcare SAS, Vélizy-Vil- lacoublay, France) infusion method. A priming dose of 0.5 mC/kg body weight of ^{51}Cr-EDTA was injected i.v. followed by a constant ^{51}Cr-EDTA infusion. Average renal ^{51}Cr-EDTA clearance was assessed during 6 (7 for Bordeaux) consecutive 30-minute (45 minutes for Nancy) clearance periods. Blood was drawn at the midpoint of each clearance period with the last collection 300 minutes after injection of the priming dose. The radioactivity measurements in 1-ml plasma samples and in urine samples were carried out on a 3-inch crystal γ-ray well counter (Packard Cobra, CANBERRA PACKARD Central Europe GmbH, Vienna, Austria).
Inulin. For Toulouse, Lyon, and Clermont-Ferrand GFR was measured with inulin clearance. Inulin clearance was performed with a loading dose of 30 mg/kg and a maintenance dose of inulin of 40 mg/kg (Inutest 25%; Fresenius, Kabi, Austria). Urine was collected every 30 minutes, and blood tests were performed in the middle of each period of urine collection (3 or 4 periods). The inulin clearance was calculated in each period to obtain the average. Measurements of plasma and urine polyfructosan concentrations were performed using an enzymatic method.
Iohexol. For Lyon GFR was measured with iohexol. Iohexol plasma clearance, after i.v. injection of 5 to 10 ml of iohexol (300 mg, Omnipaque; GE Healthcare). The syringe was weighted before and after injection to calculate the injected dose, and blood was collected at 120, 180, and 240 minutes. Serum iohexol concentration was measured by high-performance liquid chromatography. The GFR was calculated from plasma clearance with the Brochner-Mortensen correction.

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GFR ESTIMATION

Creatinine was measured by enzymatic isotope dilution mass spectrometry-traceable methods. GFR was estimated using 4 equations: MDRD,[10,11] CKD-EPI,[12] FAS,[14] and revised LM.[13]

STATISTICAL ANALYSIS

Data processing was done using Excel (2011, Microsoft, Redmond, WA), and statistical analyses were performed using R (R Core Team, 2017, R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean and SD.

We compared the performances of 4 equations estimating GFR with bias (constant bias eGFR-mGFR, proportional bias eGFR/mGFR, relative bias [eGFR-mGFR)/mGFR]), accuracy (within 10% and within 30%), and precision (root mean square error) and Lin's CCC.[25] Lin's CCC evaluates the degree to which pairs of observations (e.g., eGFR and mGFR) fall on the 45° line through the origin. The CCC contains a measurement of precision ρ and accuracy: CCC = ρ Cb, where ρ is the Pearson correlation coefficient, which measures how far each observation deviates from the best-fit line and is a measure of precision, and C_b is a bias correction factor that measures how far the best-fit line deviates from the 45° line through the origin and is a measure of accuracy.

The proportion of potential donors with discordant eGFR and mGFR at a fixed threshold represents the sum of the percentage of potential donors with eGFR higher and mGFR lower than the threshold and of the percentage of potential donors with eGFR lower and mGFR higher than the threshold. For age-adapted thresholds we used the previously published definition of low GFR for age (107.3/ 1.33 [x 0.988$^{(age-40)}$ when age > 40)],[26] which is very close to the age threshold proposed by the British guideline.[8] The proportion of potential donors with discordant eGFR and mGFR for age represents the sum of the percentage of potential donors with eGFR higher and mGFR lower than normal for age and of the percentage of potential donors with eGFR lower and mGFR higher than normal for age.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Comparison of eGFR and mGFR on the classification of potential donors at the fixed GFR threshold of 90 ml/min per 1.73 m^2. Table S2. Comparison of eGFR and mGFR on the classification of potential donors at the fixed GFR threshold of 60 ml/min per 1.73 m^2. Table S3. Comparison of eGFR and mGFR on the classification of potential donors at age-adapted GFR threshold.

Table S4. Comparison of the performances of the 4 equations estimating GFR for potential donors < 40 years.

Table S5. Comparison of eGFR and mGFR on the classification of potential donors at age-adapted GFR threshold for potential donors < 40 years.

Table S6. Proportions of misclassified potential donors for age- adapted GFR thresholds, for potential donors < 40 years.

Table S7. Comparison of eGFR and mGFR on the classification of potential donors at the fixed GFR threshold of 60 ml/min per 1.73 m^2 for potential donors < 40 years.

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Table S8. Comparison of eGFR and mGFR on the classification of potential donors at the fixed GFR threshold of 90 ml/min per 1.73 m^2 for potential donors < 40 years.
Table S9. Proportions of misclassified potential donors for absolute GFR thresholds of 90 and 60 ml/min per 1.73 m^2 for potential donors < 40 years.
Table S10. Simulation of the numbers of eligible donors according to the methods of GFR evaluation and GFR interpretation for potential donors younger than 40.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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