LETTER TO THE EDITORS

Lifetime end-stage kidney disease risk estimation in living kidney donor candidates remains a challenge

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Dear Editors,

The recent Kidney Disease Improving Global Outcome (KDIGO) guideline recommends incorporating a 'multi-parameter' prediction tool to quantify the lifetime end-stage kidney disease (ESKD) risk for living kidney donor candidate (LKDC) assessment [1]. Three such risk calculators with different limitations are now available [2–4] (Table 1). Only the calculator by Grams *et al.* [2] provides lifetime (albeit predonation) ESKD risk estimates and is endorsed by KDIGO. We read with interest the publication by Gaillard *et al.* [5], having recently reported similar findings from Australia [6]. Like Gaillard *et al.*, we observed higher predonation 15-year risk but similar lifetime ESKD risk in declined compared with accepted LKDC using the Grams calculator. In contrast to Gaillard *et al.*, only 1% of our accepted versus 15% of declined LKDC exceeded a 1% predonation lifetime ESKD risk threshold, suggesting the utility of the calculator for risk stratification. In both studies, however, there remained a significant overlap in risk estimates between accepted and declined LKDC cohorts.

We wish to emphasize the need for cautious use of the Ibrahim calculator [3] to estimate lifetime risk and highlight the paradoxical effect of donor age. Gaillard *et al.* [5] reported higher 15-year but similar 40-year postdonation risk in their declined versus accepted LKDC using the Ibrahim calculator. As the median age was 10 years older in their declined LKDC, they were likely disadvantaged when 40-year postdonation risk was used to compare their long-term risk with accepted LKDC. In fact, the 30-year postdonation risk of ESKD or eGFR <30 ml/min/1.73 m^2 in younger, accepted LKDC was 2.5-fold higher compared with the 20-year risk in their declined LKDC (Table 1). More importantly, Gaillard *et al.* did not explain the exclusion of 10 of their 27 declined LKDC for the 40-year risk estimation. The Ibrahim calculator does not provide 40-year risk for male LKDC age over 61 (as donors were unlikely to have lived beyond 100 years of age), the likely explanation for the exclusion of their 10 declined LKDC. Furthermore, with a median age of 59 and an average life expectancy of 82 years in France [5], any risk estimation beyond 25 years would be inappropriate for the majority of their declined LKDC. In our cohort [6], we employed an alternative approach by reporting the postdonation risk at age 78–82 as a surrogate for lifetime risk. Interestingly, while the 15-year risk was statistically higher (but unlikely clinically relevant) in declined versus accepted LKDC, the lifetime risk was paradoxically lower (Table 1). The shorter life expectancy of older, declined LKDC and consequent lower postdonation ESKD risk is the likely explanation [7,8]. However, interpretation of our findings requires caution as the Ibrahim calculator was derived from a single-centre cohort of accepted donors with no obesity, no (pre)-diabetes and no hypertension (unless controlled on a maximum of a single antihypertensive without end-organ damage). The validity for estimating risk in declined LKDC with clear contraindications is therefore questionable, highlighting its limitation in the assessment of medically complex LKDC.

As acknowledged by KDIGO, risk calculators have limitations and should be used with care. Prediction tools, developed from relatively short-term follow-up, are particularly unreliable in providing lifetime ESKD risk estimates for younger LKDC. Uncaptured risk factors cast uncertainties on their broader utility. 61% of our declined LKDC were declined for universally accepted risk factors that were not part of the Grams

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Table 1. Comparison of three end-stage kidney disease risk calculators for living kidney donor candidates and risk estimates of living kidney donor candidates in studies by Gaillard *et al.* and Lee *et al.*

	Grams *et al.* [2] (NEJM 2016)		Ibrahim *et al.* [3] (JASN 2016)		Massie *et al.* [4] (JASN 2017)
Sample size	~5 million (7 multinational cohorts)		3674 (single US centre)		~134 00 (US population)
Actual donors?	No		Yes (white only)		Yes
Median/mean follow-up (years)	4–16		11–20		16.6
Lifetime risk estimation	Yes		No		No
Postdonation risk?	No		Yes		Yes
Outcome estimated	ESKD		Composite of ESKD and eGFR <30		ESKD
Number of variables captured	10		10		5
Risk estimates from actual LKDC	Accepted	Declined	Accepted	Declined	
15-year risk (%)					Risk estimates not reported from Gaillard *et al.* for comparison
Gaillard *et al.* [5]†	0.14 (0.13–0.16)	0.25 (0.16–0.35)	1.43 (1.29–1.57)	2.21 (1.77–2.64)	
Lee *et al.* [6]‡	0.10 (0.07–0.14)	0.14 (0.09–0.31)	2.1 (2.0–2.2)	2.1 (0.7–2.1)¶	
Lifetime risk (%)§					
Gaillard *et al.*†	0.59 (0.52–0.66)	0.72 (0.38–1.06)	11.11 (10.2–12.0)	4.43 (3.57–5.28)	
Lee *et al.*‡	0.35 (0.22–0.56)	0.39 (0.23–0.80)	8.7 (4.4–18.7)	4.4 (2.1–12.7)¶	

US, United States; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); LKDC, living kidney donor candidates.

†Data presented as mean (95% confidence interval).

‡Data presented as median (interquartile range).

¶Declined versus accepted in Lee *et al.*; two-tailed Mann–Whitney *U* test; $P < 0.05$.

§In Gaillard *et al.*, 30-year and 20-year postdonation risk estimates (Ibrahim *et al.*) are presented as a surrogate for lifetime risk for a median age of 49 and 59, respectively. In Lee *et al.*, postdonation risk estimates at age 78–82 are presented as a surrogate for lifetime risk. LKDC aged <38 were excluded (eight accepted and seven declined), as risk estimation beyond 40 years was not possible.

algorithm [6]. Although KDIGO has proposed projection of postdonation risk by multiplying predonation risk estimates by 3.5- to 5.3-fold [2], the lack of precise donation-attributable risk estimation adds further complexity in communicating the risk to LKDC. Furthermore, other investigators have reported donation-attributable risk to be 8- to 11-fold based on actual ESKD events [9,10]. To put this in context, the vast majority of accepted donors in both studies had a lower predonation lifetime risk than the risk of death (0.9%) from a traffic accident in the United States [11]. What remains unclear is the postdonation risk, on which LKDC's decision-making is based for informed consent. All LKDC should be made aware that precise individualization of lifetime risk remains a challenge for their altruistic act, despite recent advances in risk stratification.

REFERENCES

1. Lentine KL, Kasiske BL, Levey AS, *et al.* Summary of kidney disease: improving global outcomes (KDIGO) clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation* 2017; **101**: 1783.
2. Grams ME, Sang Y, Levey AS, *et al.* Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med* 2016; **374**: 411.
3. Ibrahim HN, Foley RN, Reule SA, *et al.* Renal function profile in white kidney donors: the first 4 decades. *J Am Soc Nephrol* 2016; **27**: 2885.
4. Massie AB, Muzaale AD, Luo X, *et al.* Quantifying postdonation risk of ESRD in living kidney donors. *J Am Soc Nephrol* 2017; **28**: 2749.
5. Gaillard F, Baron S, Timsit MO, *et al.* What is the significance of end-stage renal disease risk estimation in living kidney donors? *Transpl Int* 2017; **30**: 799.
6. Lee D, Manzoor M, Harley G, *et al.* Use of a new end stage kidney disease risk calculator in the Kidney Disease Improving Global Outcomes guideline to evaluate the impact of different living kidney donor candidate assessments. *Nephrology* 2017. https://doi.org/10.1111/nep.13074. [Epub ahead of print]
7. Anjum S, Muzaale AD, Massie AB, *et al.* Patterns of end-stage renal disease caused by diabetes, hypertension, and glomerulonephritis in live kidney donors. *Am J Transplant* 2016; **16**: 3540.
8. Steiner RW. A very different paradigm for living kidney donor risk. *Am J Transplant* 2017; **17**: 1701.
9. Muzaale AD, Massie AB, Wang MC, *et al.* Risk of end-stage renal disease following live kidney donation. *JAMA* 2014; **311**: 579.
10. Mjoen G, Hallan S, Hartmann A, *et al.* Long-term risks for kidney donors. *Kidney Int* 2014; **86**: 162.
11. Risk Science Centre and Centre for Bioethics and Social Sciences in Medicine, University of Michigan. http://www.nsc.org/learn/safety-knowledge/Pages/injury-facts-chart.aspx

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