**Title:**

Measured vs estimated glomerular filtration (eGFR) rate in the assessment of living kidney donors: eGFR has its limitations

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In this issue of the Journal, Berglund and colleagues have published reassuring data indicating a decline in glomerular filtration rate (GFR) in living kidney donors of

-0.42 mL/min/1.73m2 per year which is within the range that would be expected for a normal healthy population (1). Changes in GFR over time were measured by plasma clearance of iohexol compared to the use of four widely used models for estimating GFR based on serum creatinine concentration. In considering the application of estimated GFR (eGFR) in the assessment of living kidney donors, we should remember that these equations were originally developed for the diagnosis and monitoring of chronic kidney disease (CKD) rather than stratification of individuals within the normal range for GFR (2). Steady state serum creatinine concentration depends on both the rate of generation of serum creatinine from skeletal muscle and the rate of renal clearance by glomerular filtration and tubular secretion. The mathematical models based on creatinine use demographic variables to predict skeletal muscle mass and creatinine production. The accuracy of the estimate is best for subjects with body composition in the middle of the range for the population where the equations were derived with progressively less accuracy with deviation from the median. A consequence is that for a given individual or population while the accuracy of an estimated GFR may be poor, the precision can be sufficient to track changes. The original MDRD study was a study of low protein diet in a cohort of individuals with CKD where the majority had GFR of less than

60 mL/min/1.73 m2 with mean GFR of 39.8 mL/min/1.73m2. There was increased bias and loss of precision at above 60 mL/min due to the relatively small number of subjects in that range (3). Hence, best practice in reporting MDRD eGFR is to cap values at a maximum of 60 mL/min/1.73 m2. In the current study, around 85% of the GFR measurements were at least 60 mL/min/1.73m2 (1). The CKD-EPI equation was developed to cover the full normal range of GFR (4) with further refinement by adding cystatin C (as an endogenous biomarker produced by all nucleated cells) to creatinine (5). Application of the eGFR equations outside the populations where they were derived may lead to inaccuracy. A clear example of this is use of the correction factor for Black ethnicity in the MDRD and CKD-EPI equations which was established in African American populations. Several studies conducted in Africa suggest that this correction factor is not appropriate in indigenous African populations where values closer to exogenous tracer-measured GFR or creatinine clearance are obtained without the correction for Black ethnicity (6).

The aim of GFR measurement in living kidney donors is to ensure that the donor will be left with sufficient nephron mass to avoid end-stage renal failure during their life expectancy and ensure adequate renal function in the recipient. In this context, the accuracy of the measurement is much more critical than that required in the diagnosis and monitoring of CKD. A number of guidelines, including those published recently by KDIGO (7) advise the use of eGFR as an initial screening tool followed by use of an exogenous filtration marker such as iohexol or 51Cr-EDTA.

In considering cut-off GFR: how comfortable are we that GFR measurement or estimation is actually within the guideline range? For values close to the guideline, the accuracy of the eGFR equations within an individual is probably insufficient and repeating the value will confirm precision rather than accuracy of the estimate. Even in resource-poor settings, measurement of GFR using an exogenous tracer would be best practice. In environments where tracers cannot be measured locally, there is the option of using a dried blood spot method with iohexol measurements done remotely (8).

The precision of tracer-measured GFR is highly relevant. The coefficient of variation of plasma iohexol clearance in the current study (1) was low at <10% (1) but coefficients of variation (CV) for 51Cr-EDTA have been reported to range between 9.6%-23.7% (9). It is important to know the CV of the assay in use at your centre in interpreting likely accuracy for values close to the guideline cut-off. In some circumstances, it may be appropriate to repeat testing to confirm results close to the guideline cut-off for GFR, with three measurements in the event of discrepant results. Correction for body surface area is a further area of controversy where a standard equation is unlikely to predict the value accurately for all individuals and will inevitably introduce bias in individuals at the extremes of body composition.

In the current study (1) all of the eGFR equations apart from MDRD appeared to over-estimate GFR across the population. It is intriguing that the MDRD equation was a better predictor of both actual GFR values and rate of change in this population than the CKD-Epi equation which is counter to what would be predicted from previously published studies. The living kidney donors in the current study had lower BMI (26 vs 28 kg/m2) and were younger (41 vs 47 years) than the population used to derive the CKD-Epi equation (4) which may be factors in the discrepancy. In another recently published study, van London, *et al* found that the MDRD and

CKD-EPI equations under-estimated GFR when compared to

125I-iothalamate clearance and that eGFR underestimated the slope of decline in GFR between 3 months and 5 years after donation (10). These observations serve as a note of caution in use of the eGFR equations outwith the populations where they were derived to inform high stakes decisions. Estimated GFR is not sufficiently accurate to inform the selection of potential living kidney donors.

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