**Item S1: Detailed methods.**

Participants were recruited between November 2007 and May 2011, from four geographical regions of Australia: Top End (of Northern Territory), Central Australia, Far North Queensland and Western Australia. Participants were Indigenous Australians aged 16 years and above, from urban, rural and remote centres within the above four geographical regions across the following 5 pre-defined strata: (i) “healthy” group: with no diabetes, CKD or albuminuria; (ii) participants with diabetes or albuminuria and eGFR (MDRD-4) >90 ml/min/1.73 m$^2$; (iii) eGFR 60-90 ml/min/1.73 m$^2$; (iv) eGFR 30-59 ml/min/1.73 m$^2$; (v) eGFR <15-29 ml/min/1.73 m$^2$.

Participants aged under 18 years (n=13) were excluded from the analyses presented in this paper as neither MDRD nor CKD-EPI equations have been validated in that age group. Indigenous Australians fulfilled the definition of ‘Aboriginal and/or Torres Strait Islander’ according to the standard method used in National Census data collection: “1) is of Aboriginal and/or Torres Strait Islander descent; 2) identifies as an Australian Aboriginal and/or Torres Strait Islander; and 3) is accepted as such by the community in which he or she lives or has lived”. Indigenous participants identified as: Aboriginal (71%), Torres Strait Islander (20%) or of both Aboriginal and Torres Strait Islander origin (9%). Exclusion criteria were: participants with rapidly changing kidney function, participants receiving dialysis, women who were pregnant or breastfeeding, and people with a history of allergy or adverse reaction to iodine-based contrast media. Participants with CKD and/or diabetes were recruited from participating Aboriginal Medical Services, primary care facilities and hospital specialist clinics. The identification and recruitment of the “healthy” group was through community networks, staff members of health services, word-of-mouth, self-referral and family members of participants. A comparator group of Australians of
Caucasian background was recruited across the above 5 pre-defined strata from Darwin, Northern Territory, Australia. This group was not intended to be a matched group for direct comparison with the Indigenous group, but rather a group in which the equation performance could be assessed in comparison to other published studies, thereby supporting the reference GFR methodology in the current study. The study was approved by the following Human Research Ethics Committees (HREC): the joint Menzies School of Health Research - Northern Territory Department of Health HREC, including approval by the Aboriginal sub-committee (which has absolute right of veto); Central Australian HREC; Western Australian Aboriginal Health Information and Ethics Committee, Royal Perth Hospital Ethics Committee; and Cairns and Hinterland Health Services District HREC.

Assessment of Reference GFR (mGFR)

Non-isotopic iohexol was injected (5.445 ml, including 0.445ml of prime volume in the tubing of the butterfly canula, 300 mg/ml “Omnipaque”) into an antecubital vein and flushed with 10 ml of normal saline. Using the contralateral arm, venous blood samples (5 ml) were collected for measurement of iohexol at 120, 180 and 240 min post injection. Blood samples were refrigerated, centrifuged within 4 hours and aliquoted for transportation on ice (or on dry ice or in liquid nitrogen “Biological Shipper” in remote locations) to storage at -80°C freezer. Slope-intercept GFR was calculated from the formula: Slope-intercept GFR (mL/min) = k × Iohexol dose (μg)/C0 (μg/mL) where k is the slope of the semilog plot of plasma Iohexol concentration versus time (plotted using 3 points, refer above), and C0 is the calculated Iohexol concentration at time zero (intercept). This value was multiplied by 1.73 and divided by the body surface area (BSA, calculated from the equation BSA =
0.20247 × height (metres)\(^{0.725}\) × weight (kg)\(^{0.425}\).\(^2\) The BSA-slope intercept GFR value (mL/min/1.73m\(^2\)) was corrected by the Brochner-Mortensen correction factor = (0.990778 × GFR) - (0.001218 × GFR\(^2\)) providing a reference GFR value (mGFR, mL/min/1.73 m\(^2\)).\(^3\) Iohexol was measured by Austin Health, Melbourne, Australia using a validated HPLC assay modified from Niculescu-Duvaz et al.\(^4\) Precision studies showed a coefficient of variation of 1.0% or less, and inaccuracy [100−(100 x measured value/target value)] of ± 4.5% or less. Elimination of iohexol was determined to be linear, thus 27 participants with two rather than 3 time-point values for iohexol were included in the analysis, but an additional 7 participants with eGFR<30 mL/min/1.73 m\(^2\) and only two time-points were excluded as they may not have reached terminal elimination phase.\(^5\)

Other blood and clinical measures

Venous blood was collected for creatinine 120mins-post iohexol.\(^1\) Serum creatinine was measured by Roche enzymatic assay (Melbourne Pathology, Melbourne Australia), with traceability to IDMS claimed by the manufacturer and supported by independent studies.\(^6\) For 12 participants for whom an enzymatic creatinine result was unavailable, creatinine was measured by their local laboratory (comparison of creatinine in local laboratory and research laboratory in n=666, mean difference - 0.31umol/L, r=0.983, p<0.0001).\(^1\) Estimates of GFR were calculated as follows (where Scr is serum creatinine concentration in μmol/L, age in years, eGFR in mL/min/1.73m\(^2\)): the adjusted MDRD-4 variable formula (for creatinine measurements traceable to the IDMS method and reported in μmol/L)

eGFR = 175 × [(Scr × 0.0113)\(^{1.154}\)] × (age)\(^{-0.203}\) × (0.742 if female) × (1.212 if African-American);\(^7\) the CKD-EPI formula:\(^8\)
eGFR = 141 × min(Scr × 0.0113/k, 1)^a × max(Scr × 0.0113/k, 1)^{-1.209} × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where k is 0.7 for females and 0.9 for males, ^a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1. The correction factor for African-Americans or blacks was not used for Indigenous Australians in either MDRD or CKD-EPI equations as there is no a-priori reason to consider the populations to be similar.

Body weight was recorded to the nearest 0.1 kg using a Seca digital portable scale (Model 767 and 841, Seca Deutschland, Hamburg, Germany). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Waist and hip circumference were measured in centimetres using a 2-metre non-stretch flexible steel tape (Model W606PM Lufkin, Texas, USA). Venous blood for HbA1c was collected 120 min-post iohexol. HbA1c and a urine albumin-creatinine ratio (ACR) were measured by local care providers. An interviewer-administered questionnaire and information from medical records (where available) were used to determine a history of diabetes, smoking and current medications. Diabetes was defined as a previous diagnosis of diabetes or HbA1c ≥6.5%. Urine albumin-creatinine ratio (ACR) was calculated. Microalbuminuria was defined as urine ACR ≥2.5 and ≤25 mg/mmol in men and ≥3.5 and ≤25 mg/mmol in women. Macroalbuminuria was defined as ACR > 25 mg/mmol. Albuminuria was defined as ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women.

Statistical Analysis
Data analysis was performed using STATA v10.0 (Stata Corporation, TX, USA). Data are presented as mean (standard deviation), geometric mean (95% confidence interval) or frequency, stratified by ethnicity (Indigenous or Caucasian) and mGFR group. Factorial analysis of variance was used to compare means for different ethnic and mGFR groups (for continuous variables) and logistic regression models were used to compare frequencies in different ethnic and mGFR groups (for categorical variables). For biochemical measures that were not normally distributed, geometric rather than arithmetic means were used, and generalized linear models were performed using the log of the variable.

Difference between mGFR and eGFR was calculated as (mGFR – eGFR) and percentage difference [(mGFR-eGFR)/mGFR x 100]. Bias was calculated as the average differences for a group. Precision was measured as interquartile range of the differences. Accuracy was calculated as percentage of estimates within 30% of mGFR. Confidence intervals were calculated by bootstrap methods, stratified by ethnic group and mGFR group (1000 bootstraps) for difference and percentage difference and by the binomial method for accuracy. Performance was determined for the whole group and stratified by ethnic group and mGFR group. Median bias was compared between Indigenous and Caucasian groups using the Kruskal-Wallis test. Accuracy was compared between Indigenous and Caucasian groups using the chi-squared test.

Works Cited


