Risk-Factor Profile of Living Kidney Donors: The Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry 2004-2012

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Background. Recent literature suggests that living kidney donation may be associated with an excess risk of end-stage kidney disease and death. Efforts to maximize access to transplantation may result in acceptance of donors who do not fit within current guidelines, potentially placing them at risk of adverse long-term outcomes. **Methods.** We studied the risk profile of Australian and New Zealand living kidney donors using data from the Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry over 2004 to 2012. We compared their predonation profile against national guidelines for donor acceptance. **Results.** The analysis included 2,932 donors (mean age 48.8 ± 11.2 years, range 18–81), 58% female and 87% Caucasian. Forty (1%) had measured glomerular filtration rate less than 80 mL/min; 32 (1%) had proteinuria >300 mg/day; 589 (20%) were hypertensive; 495 (18%) obese; 9 (0.3%) were diabetic while a further 55 (2%) had impaired glucose tolerance; and 218 (7%) were current smokers. Overall 767 donors (26%) had at least one relative contraindication to donation and 268 (9%) had at least one absolute contraindication according to national guidelines. **Conclusions.** Divergence of current clinical practice from national guidelines has occurred. In the context of recent evidence demonstrating elevated long-term donor risk, rigorous follow-up and reporting of outcomes are now mandated to ensure safety and document any change in risk associated with such a divergence.

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Kidney transplantation is the optimal treatment for the majority of patients with end-stage kidney disease (ESKD), affording improved survival[1,2] and quality of life[3] compared with dialysis at reduced cost.[4] Compared with deceased donor transplantation, living donor transplantation reduces waiting time, allows elective rather than emergency surgery, and is associated with superior patient and graft survival.[5,6] Living donor transplantation is therefore the preferred treatment for ESKD in many centers.

Acceptance of living kidney donation as an ethical practice is contingent on knowledge and comprehension of risks by donors.[7] The short- and long-term outcomes of kidney donation have been reported in a large number of studies which provided reassurance of long-term safety.[8-13] However, those studies were generally based on historical cohorts of donors, from a single center or from a small group of centers, with incomplete follow-up. Significant variation in donor assessment and acceptance criteria among US transplant centers has been reported, suggesting such studies may not be representative of all donors.[14]

More recently, in 2 long-term population-based studies, donors were found to be over 10 times more likely to develop ESKD than healthy nondonors.[15,16] One of these studies also reported increased cardiovascular and all-cause mortality in donors.[15] These reports suggest the need to monitor donor acceptance patterns and long-term donor outcomes. Since 2004, the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry has prospectively collected data on all living kidney donors in Australia and New Zealand. We analyzed these data to determine the baseline characteristics of contemporary Australian and New Zealand living kidney donors.

MATERIALS AND METHODS

The ANZDATA Registry collects data on all patients receiving renal replacement therapy in Australia and New Zealand.

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Details of its collection methods are available on its website http://www.anzdata.org.au. In 2004, ANZDATA began collecting data on living kidney donors in Australia and New Zealand through the creation of the ANZDATA Living Kidney Donor Registry. Data are collected at baseline and then annually postdonation. Baseline data are reported by the transplant hospital, and follow-up data are reported either by the transplant hospital or by the current treating nephrologist depending on local practice. In this article, we report the baseline characteristics of donors.

We included all living kidney donors in Australia and New Zealand over 2004 to 2012 apart from pathologic donors (nondirected donors after surgical management of a pathological process, typically tumor nephrectomy). We determined the renal and cardiovascular risk profile of the donors. We defined renal risk factors as reported measured glomerular filtration rate (GFR) less than 80 mL/min per 1.73 m^2 by nuclear isotope dilution, and/or proteinuria greater than 300 mg/day assessed by 24-hour collection. In donors without a reported 24-hour urine protein measurement, we considered a spot urine albumin:creatinine ratio (ACR) less than 2.5 mg/mmol (men) or less than 3.5 mg/mmol (women), or a spot urine protein:creatinine ratio (PCR) less than 20 mg/mmol to be normal. Estimated GFR (eGFR) was calculated using the 4-variable MDRD equation.[17] We defined cardiovascular risk factors as: (1) overweight or obesity, defined as body mass index (BMI) 25 to 29.9 kg/m^2 or greater than 30 kg/m^2, respectively; (2) diabetes, defined as use of hypoglycaemic medication, fasting blood glucose greater than 7.0 mmol/L or 2-hour blood glucose greater than 11.0 mmol/L after a standard 75 g oral glucose load; (3) hypertension as defined by blood pressure of 140/90 mm Hg or greater or use of antihypertensive medication; and (4) currently smoking.

We compared the risk factor profile of donors with the local Caring for Australasians with Renal Impairment (CARI) Guidelines for donor acceptance.[18-21] These guidelines suggest relative and absolute contraindications to donation based on renal and cardiovascular risk factors (among other considerations); a summary of these is shown in Table 1. It should be noted that these suggestions were only published in 2010 and were therefore not available when the majority of donors in this study were assessed.

Finally, we explored the variation in donor acceptance patterns between different transplant hospitals and between different age groups. All analyses were conducted using State/IC version 13.1 (StataCorp, College Station, TX).

TABLE 1.

CARI suggestions for acceptance of living kidney donors (abbreviated)

Renal function
Glomerular filtration rate <80 mL/min/1.73 m^2 relative contraindication
Proteinuria
>300 mg/day relative contraindication
Hypertension
Blood pressure ≥140/90 mmHg relative contraindication; absolute contraindication if treated with >2 drugs, presence or end-organ damage or other cardiovascular risk factors
Obesity
Body mass index >30 kg/m^2 relative contraindication; absolute contraindication in the presence of an additional cardiovascular risk factor
Glucose metabolism
Diabetes mellitus, impaired glucose tolerance or history of gestational diabetes all absolute contraindications

RESULTS

There were 3012 living kidney donors in Australia and New Zealand in the 9-year period of 2004 to 2012. Eighty (3%) were donors after nephrectomy performed primarily because of a pathologic process, typically a renal cell carcinoma less than 3 cm in diameter, and were excluded, leaving 2932 donors in the study.

The baseline characteristics of the donors are shown in Table 2. One thousand seven hundred forty-three (59%) donors were biologically related to the recipient, including 792 parents, 654 siblings, 134 children, and 163 other relatives. The 1189 (41%) unrelated donors included 737 spouses/partners, 219 friends, and 233 other unrelated donors.

Glomerular filtration rate was measured by radionuclide scanning in 1565 (53%) donors, timed creatinine clearance in 505 (17%), iohexol/iothalamate clearance in 81 (3%), "other" methods (predominantly eGFR using a creatinine-based estimation formula) in 347 (12%) and was not reported in 434 (15%). Forty (1%) donors had a GFR measured by radionuclide scanning or iohexol/iothalamate clearance less than 80 mL/min per 1.73 m^2. In addition, GFR less than 80 mL/min per 1.73 m^2 was recorded for 15 (3%) of those assessed by creatinine clearance and 112 (41%) in those assessed by eGFR, although these methods have poor accuracy compared with measured GFR in potential donors.[22]

Twenty-four–hour urine protein excretion was reported in 2273 (78%), among whom 32 (1%) excreted greater than 300 mg daily. Of the remaining 659 (22%) donors, ACR or PCR was reported for 300 (10%), of whom 14 had an ACR or PCR between 1 and 3 times the upper limit of normal.

Cardiovascular risk factors were common. Hypertension was reported in 294 (10%) donors, of whom 55 were taking 2 antihypertensive drugs and 10 were taking more than 2 drugs. A further 295 (10%) donors had a reported systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater, such that in total 589 (20%) donors were classified as hypertensive. Donors included current (218, 7%) and former (947, 32%) smokers.

Nine donors were reported to be diabetic. Of the 2878 donors reported to be nondiabetic, an oral glucose tolerance test result was reported for 1499 (52%) donors. Two donors met criteria for diabetes and 65 had impaired glucose tolerance or impaired fasting glucose. An additional 4 donors had a history of gestational diabetes. The Registry does not currently collect donor hemoglobin A1c. Donor BMI ranged from 16.4 to 46.6 kg/m^2 with a mean of 26.5 kg/m^2. One thousand two hundred sixty-one (45%) donors were overweight (BMI, 26-30 kg/m^2) with a further 495 (18%) deemed obese (BMI, >30 kg/m^2). Of the 1429 (49%) donors who did not undergo an oral glucose tolerance test, 59% were overweight or obese.

The presence of multiple cardiovascular risk factors within individual donors was common (Table 3). One thousand six hundred eighty-nine (58%) donors had no reported

TABLE 2.

Baseline characteristics of donors (n = 2932)

Characteristic	Value
Age: mean ± SD, y	48.8 ± 11.2
Sex	
Female	1692 (58%)
Male	1240 (42%)
Race	
White	2546 (87%)
Australian indigenous	14 (<1%)
Asian	200 (7%)
Māori or Pacific Islander	91 (4%)
Other	44 (2%)
Not reported	23 (<1%)
Measured GFR[a], mL/min	
<80	40 (2%)
80–99	484 (29%)
≥100	1130 (68%)
Not reported	1278 (44%)
24 h urinary protein excretion	
≤300 mg	2241 (77%)
>300 mg	32 (1%)
Not reported	659 (22%)
Glucose metabolic status[b]	
Normal	2811 (96%)
Impaired fasting glucose	10 (<1%)
Impaired glucose tolerance	55 (2%)
Diabetes	11 (<1%)
Unknown	45 (2%)
Body mass index, kg/m^2	
<18.5 (underweight)	17 (<1%)
18.5–24.9 (normal)	1044 (36%)
25–29.9 (overweight)	1263 (43%)
≥30 (obese)	493 (17%)
Not reported	115 (4%)
Hypertension[c]	589 (20%)
Cigarette smoking	
Current	218 (7%)
Former	947 (32%)
Never	1737 (59%)
Not reported	29 (1%)

[a] Glomerular filtration rate measured by radionuclide scanning or iothalamate clearance.
[b] Glucose metabolic status as determined by standard oral glucose tolerance test (n = 1499, 52%) or self-report.
[c] Hypertension was defined as reported blood pressure ≥140/90 mmHg or use of antihypertensive medication.

cardiovascular risk factors. One hundred eighty-eight (6%) donors had 2 cardiovascular risk factors and 3 (<1%) had 3 risk factors. If overweight was considered a cardiovascular risk factor, the majority of donors had at least 1 risk factor.

Based on the CARI suggestions for donor acceptance, 767 (26%) donors had at least 1 relative contraindication to donation and 268 (9%) at least 1 absolute contraindication (Table 4). The majority of these contraindications were due to donor hypertension or obesity in combination with another cardiovascular risk factor. There was significant variation between transplant hospitals in acceptance patterns (Figure 1). All hospitals accepted donors with 1 or more relative contraindications, and all but 6 hospitals accepted donors with one or more absolute contraindications.

TABLE 3.

Cardiovascular risk factors

Cardiovascular Risk Factors	N	%
None	1689	58
Unable to be determined[a]	176	6
Smoking	162	6
Smoking + diabetes	1	<1
Diabetes	2	<1
Obesity	315	11
Obesity + smoking	29	1
Obesity + diabetes	2	<1
Hypertension	397	14
Hypertension + smoking	16	<1
Hypertension + diabetes	4	<1
Hypertension + obesity	136	5
Hypertension + obesity + diabetes	1	<1
Hypertension + obesity + smoking	2	<1

[a] Missing data in 1 or more fields prevented categorization.
A BMI of ≥25 kg/m^2 was considered high.

Older donors were more likely to have relative or absolute contraindications to donation (Table 4 and Figure 2), although even in donors who were younger than 40 years, a significant minority had contraindications to donation. There was no clear association between donor relationship to recipient, recipient sensitization or waiting time and the risk profile of

TABLE 4.

Implications of baseline factors

	Contraindication Status (%)[a]				
Characteristics	None	Relative	Absolute	Unclear	Total
All donors	1063 (36)	767 (26)	268 (9)	834 (28)	2932
Donor age, y					
18–24	23 (43)	6 (11)	4 (8)	20 (38)	53
25–34	131 (49)	33 (12)	18 (7)	86 (32)	268
35–44	290 (42)	133 (19)	41 (6)	229 (33)	693
45–54	365 (38)	253 (26)	75 (8)	269 (28)	962
55–64	218 (29)	250 (34)	93 (13)	182 (24)	743
65–74	34 (17)	85 (42)	37 (18)	45 (22)	201
75–84	2 (20)	7 (70)	0 (0)	1 (10)	10
Donor relationship to recipient					
Sibling	250 (38)	139 (21)	52 (8)	213 (33)	654
Parent	253 (32)	250 (32)	88 (11)	201 (25)	792
Child	61 (46)	23 (17)	7 (5)	43 (32)	134
Spouse/partner	260 (35)	209 (28)	72 (10)	196 (27)	737
Other related	63 (39)	44 (27)	14 (9)	42 (26)	163
Friend	90 (41)	47 (21)	20 (9)	62 (28)	219
Other unrelated	86 (37)	55 (24)	15 (6)	77 (33)	233
Recipient peak PRA (%)					
0–49	972 (36)	713 (27)	246 (9)	740 (28)	2671
50–79	41 (32)	23 (18)	14 (11)	50 (39)	128
80–100	34 (36)	25 (26)	7 (7)	29 (31)	95
Recipient years on dialysis					
<6 mo	491 (37)	317 (24)	111 (8)	394 (30)	1313
6 mo to 1 y	154 (37)	120 (29)	40 (10)	105 (25)	419
1 to 4 y	364 (35)	290 (28)	108 (10)	291 (28)	1053
≥5 y	54 (37)	40 (27)	9 (6)	44 (30)	147

[a] According to CARI recommendations.

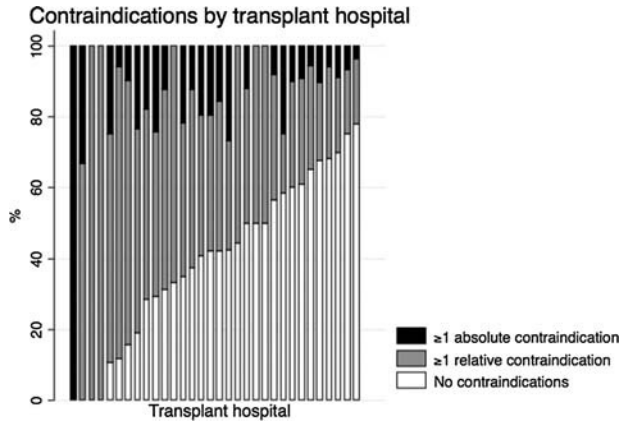

FIGURE 1. Proportion of donors with absolute, relative, or no contraindications by transplant hospital. Donors who could not be classified due to missing data are excluded.

donors, with approximately 10% of each subgroup studied having a contraindication (Table 4). However, parental donors were the donor group least likely to have no contraindications (32%). There was no clear change in donor risk profile over time (Figure 3).

DISCUSSION

One third of all living kidney donors in Australia and New Zealand during the past 9 years had a relative or absolute contraindication to donation, according to local and international guidelines.[7,23] This was due to the presence of one or more renal or cardiovascular risk factors identified before donation, most commonly obesity, hypertension, or smoking.

Many studies have reported on the long-term outcomes of kidney donation and provided reassuring results. For example, the Donor Nephrectomy Outcomes Research Network has reported that donors are not at increased risk of cardiovascular disease,[8] need for acute dialysis,[9] fracture risk,[10] or reduction in quality of life.[24] Analyses of administrative datasets in the United States have demonstrated acceptably low risk of postdonation death,[11] depression,[12] and cancer,[13] which compare favourably with nondonor controls.

However, a recent population-based study comparing US donors with healthy matched controls from the National

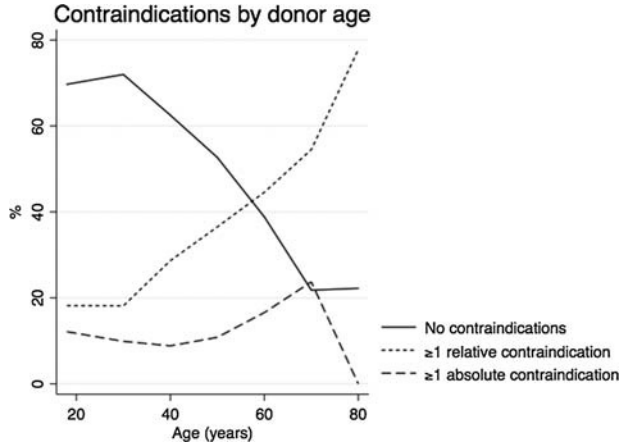

FIGURE 2. Proportion of donors with absolute, relative, or no contraindications by donor age. Donors who could not be classified due to missing data are excluded.

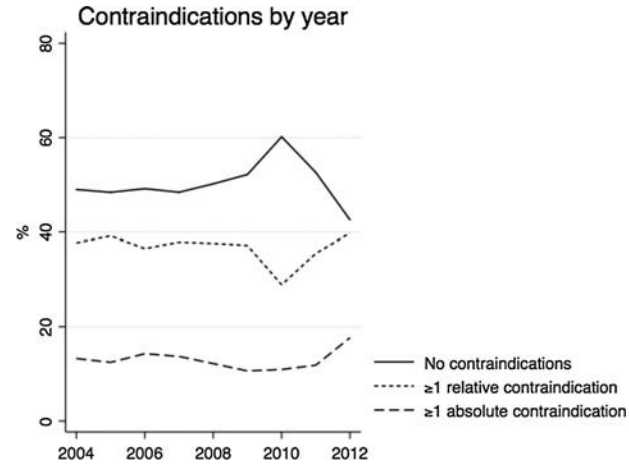

FIGURE 3. Proportion of donors with absolute, relative, or no contraindications by year of donation. Donors who could not be classified due to missing data are excluded.

Health and Nutrition Examination Survey reported a substantially increased risk of ESKD in donors.[16] The rate of ESKD in donors was estimated at 30.8 per 10 000 patient-years compared with 3.9 per 10 000 patient-years in matched nondonors. A similar study in the Norwegian population produced similar findings, with a hazard ratio for ESKD of 11.38 (95% confidence interval, 4.4-29.6) compared with nondonors.[15] The latter study also reported increased all-cause and cardiovascular mortality, with hazard ratios of 1.30 and 1.40, respectively. It can be argued that both studies had less than perfect control groups.[25,26] Importantly, absolute risks of excess ESKD and mortality were low. Nevertheless, these studies clearly define the risk of ESKD in patients deemed acceptable for living kidney donation.

There is strong biologic plausibility for an excess of renal and cardiovascular risk after kidney donation. Living donors are at increased risk of hypertension, with a mean increase in blood pressure of 6/4 mm Hg[27] and a 1.4 times increase in hypertension diagnoses.[28] Donors also commonly experience low-grade proteinuria.[29] The reduction in GFR caused by nephrectomy is partially compensated by the remaining kidney, and average long-term kidney function has been reported to approximate 70% of predonation GFR.[29-31] Among the general population, low eGFR has been associated with increased cardiovascular and all-cause mortality,[32] with risk logarithmically related to magnitude of reduction in eGFR below 70 mL/min. It is worth noting that with a lower GFR threshold of 80 mL/min for kidney donation, many donors would be expected to have a postdonation GFR less than 70 mL/min. Whether donors whose eGFR falls below 70 mL/min postdonation incur cardiovascular and mortality risks similar to those seen in the general population remains to be seen; it is plausible that a reduced GFR due to surgical reduction in nephron mass has different implications from a reduced GFR due to an underlying disease process.

Evidence for the impact of donor obesity on outcomes is limited. In the short-term, obese donors are likely to have a longer length of hospital stay.[33] In the long-term, obesity in the general population is a risk factor for the development of chronic kidney disease,[34,35] diabetes,[36] and ESKD,[37] and in nondonors undergoing nephrectomy, obesity is associated with the development of proteinuria and renal insufficiency.[38]

Donors with metabolic syndrome are more likely to have abnormal histologic findings on implantation biopsy and have a protracted recovery of renal function after donation, raising concerns about inferior long-term kidney health.[39] Clinical practice guidelines on donor acceptance suggest different BMI cutoffs, reflecting the lack of strong evidence in this area.[23]

A large proportion of Australian and New Zealand donors were hypertensive. Hypertension was reported in 10%, and reported blood pressure was consistent with a diagnosis of hypertension in a further 10%. These numbers are substantially higher than the US data.[11,33] This is concerning given that hypertension is a well-established complication of kidney donation,[27,28,40] and an established risk factor for chronic kidney disease progression,[41] short-term donor complications,[33] and donor mortality.[11] Furthermore, the majority of hypertensive donors in our study had additional cardiovascular risk factors.

A history of smoking was also common in this cohort, with 7% of donors current and 32% former smokers. ANZDATA collects neither cumulative exposure nor duration of abstinence in former smokers, so it is not possible to determine magnitude of smoking-associated risk or risk of return to smoking postdonation. As with hypertension, the majority of currently smoking donors also had additional cardiovascular risk factors, particular overweight or obesity.

Living kidney donors who proceed to donation in Australasia appear to have a relatively high-risk profile which, in the majority of cases, represents either relative or absolute contraindications to donation according to local CARI guidelines.[7] In terms of guideline adherence, the guidelines were published in 2010, postdating acceptance of many donors in this study, and provide "suggestions for clinical care" rather than direct recommendations due to perceived limitations of the existing literature. Similar variations between guidelines and practice in donor acceptance criteria have been well documented elsewhere.[42,43] Consistent with these reports, we found substantial variability between centers, suggesting differences in assessment and/or tolerance of risk. Variability by center exhibited a gradation of risk factor acceptance, rather than clear polarisation into centers with either low or high thresholds. It is unlikely that such variation can be explained by unmeasured donor factors. It is unclear why centers accept so many donors with relative and absolute contraindications. Possibilities include uncertainties in the evidence base underpinning the CARI recommendations, availability of additional data not reported to ANZDATA (eg ambulatory blood pressure measurement), or the use of discretion in donors considered unlikely to develop long-term complications despite the presence of risk factors.

Older donors have a lower life expectancy than younger ones. Younger donors therefore have potential to develop and be exposed to renal and cardiovascular risk factors for a longer period of time than older donors, resulting in an increased lifetime risk of developing ESKD or premature mortality.[44] It may therefore be reasonable to have a lower threshold for acceptance of older donors. Accordingly, we found that older donors were more likely to have risk factors than younger donors. Similar findings were reported in the RELIVE retrospective study of donors from three major US transplant centers.[45] However, even young donors in our study frequently had risk factors, with around one-third of donors under 40 having at least one relative or absolute contraindication to donation.

A key strength of our study is that the data were collected prospectively and represent all living donors in both Australia and New Zealand over 2004 to 2012. This provides a comprehensive survey of donor acceptance patterns across both countries, avoiding the selection bias that may occur in single- or multicenter studies (in which high performing units are typically overrepresented) and retrospective studies (in which donors with poor outcomes may be more likely to be lost to follow-up). Our study also has a number of limitations. We have analyzed registry data that had some missing data (especially for measured GFR and proteinuria), and we cannot determine whether these factors were not measured or simply not reported to ANZDATA. Several important aspects of cardiovascular risk assessment are not captured, including lipids, quantification of smoking exposure, family history of vascular disease, more sophisticated assessment of hypertension (24-hour monitoring), measurement of left ventricular mass or stress testing for ischemia, some or all of which may have been performed and used to inform the decision to proceed to donation. No information was available on weight loss counselling in overweight and obese donors. Although psychological assessments are routine in donor assessment in Australasia, the Registry does not capture either psychological acceptability or motivation to donate, both of which may impact appetite for risk and outcome.

As the first publication from this Registry, we included only predonation data and have not analyzed outcome data after donation. Although annual follow-up data are sought for all donors, complete data are available for a minority of donors at present. We plan to increase capture of follow-up data in the future, and to link the Registry with hospitalization and mortality data sets. However, these projects are beyond the scope of the current analysis.

In summary, we have reported the baseline characteristics of 2932 living kidney donors in Australia & New Zealand over 2004 to 2012. These donors exhibit a higher prevalence of renal and cardiovascular risk factors than that recommended by local and international guidelines. Given these risk factors, along with recent studies suggesting elevated long-term donor risk, we believe our findings mandate tight follow-up of this cohort and justify the ongoing collection of both baseline and follow-up donor data in Australian and New Zealand and in other countries. Such data are required to define donor profile and donor outcomes to provide potential donors and clinicians with accurate, contemporary estimates of risk associated with living kidney donation.

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