TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Health outcomes among non-Caucasian living kidney donors: knowns and unknowns

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Keywords
health status disparities, hypertension, kidney failure, living donors, mortality, race.

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Conflict of interest
The authors have no conflicts of interest related to this work.

Received: 13 November 2012
Revision requested: 14 December 2012
Accepted: 15 February 2013
Published online: 27 March 2013

doi:10.1111/tri.12088

Summary

The growth in living kidney donation has been accompanied by greater racial diversity. Most information on post-donation health comes from single-center studies of dominantly Caucasian cohorts. Recent linkage of U.S. donor registration data with death records demonstrated higher mortality risks among African American donors, but importantly, no differences in death compared with demographically matched, healthy controls. Within the donor population, some recent studies have also identified higher likelihoods of post-donation hypertension, diabetes mellitus and kidney failure in African American and Hispanic donors. Thus, based on concerns for higher risks of long-term end-organ damage, it may be reasonable to consider race within the living donor selection process, such as use of more stringent exclusion criteria among non-Caucasian living donors with baseline elevated blood pressure. Recently identified associations of coding variants in the apolipoprotein L1 (APOL1) gene with nondiabetic renal failure in African Americans raise promise of APOL1 genotyping as a novel tool for risk stratifying African American potential donors, but more data are needed to understand implications for post-donation outcomes. To tailor counseling and informed consent, focused attention to long-term medical outcomes among non-Caucasian living donors is needed, and should include assembly of healthy non-donor controls for assessment of attributable risks of donation.

The growth and diversification of living kidney donation

In the context of the organ shortage, kidney transplantation from living donors has increased markedly in the last several decades. The number of live donor kidney transplants in the United States (U.S.) rose from 2000 annual transplants in the late 1980s to approximately 6000 transplants per year since 2001 [1]. In 2006, more than 27 000 healthy individuals underwent living donation at registered transplant centers across the world, including nearly 1500 live donors in the United Kingdom (U.K.), Germany and The Netherlands [2]. When scaled for population size, rates of live donor transplantation in Norway, the Netherlands and Switzerland of 16–17 procedures per million population (pmp) in 2006 ranked 6th to 8th internationally, following the U.S. rate of 21 pmp [2]. Underlying this expansion of living donation are changes in donor demographic and clinical characteristics. Donation from persons who are biologically unrelated to their recipient is increasingly common, and the average age at donation is rising [3]. The fastest growing modality for live donor transplantation is kidney paired donation, rising from 2 cases in the year 2000 to more than 600 cases reported to the Organ Procurement and Transplantation Network (OPTN) in 2011 [4–7]. In 2004, the Netherlands instituted a paired exchange system in all their transplant centers, which may explain the recent increase in living kidney donation in that country [8].

Living donors are also becoming more racially and ethnically diverse. In the U.S., the fraction of non-Caucasian living kidney donors rose from 24% in 1988 to 30% in 2011, with a notable increase among Hispanic donors, who comprised 14% of live donors in 2011 compared with 9% in 1988 [1] (Fig. 1). Currently 12% of U.S. living kidney donors are African American [1]. Information from other countries with large transplant registries includes non-Caucasian race among 12.8% of living donors with reported ethnicity in the Canadian Organ Replacement Register (CORR) in 1996–2006, although notably race information was unknown for 38% of Canadian live donors in this period [9]. According to the ANZDATA registry, 12% of living donors in Australia and New Zealand in 2004–2009 were non-Caucasian [10]. The growing organ shortage has also correlated with trends towards more common acceptance of live donors with certain baseline medical complexities, including pre-donation hypertension and obesity [11,12], which in turn may vary by donor ethnicity. Even after evaluation and selection, obesity is more common among approved U.S. non-Caucasian kidney donors, such that in 2008, body mass index (BMI) was >30 kg/m^2 in 25.6% of African American and 22.6% of Hispanic compared with 18.1% of Caucasian donors [11]. Emerging data from the Renal and Lung Living Donors Evaluation (RELIVE) consortium study of living donors at 3 U.S. Center in 1963 to 2007 is consistent with OPTN data, in that among donors aged 60 years and younger, African American donors were more likely than non-African Americans to have obesity or both obesity and hyperglycemia at donation [13].

While living donors gain no direct medical benefits from donation, they do deserve accurate information on the short- and long-term outcomes of donation, tailored to their individual characteristics. Given that most countries including the U.S. do not currently maintain national registries that effectively track long-term health outcomes after living organ donation, much of the information on long-term postdonation outcomes has been drawn from single-center, retrospective studies. Available data are consistent with the view that live kidney donation does not pose excessive short- or long-term health risks, but retrospective studies may be challenged by selection bias, missing data and loss to follow-up [14]. The largest U.S. cohort study to achieve high ascertainment of donor vital status and renal survival reported no adverse impacts of live kidney donation of life-span or end-stage renal disease (ESRD) risk compared with general population registry controls [15]. However, more than 98% of donors in this cohort were Caucasian, thus potentially limiting the generalizability of the findings to donors of other racial and ethnic groups. Recently, observation of higher relative rates of postdonation medical conditions in non-Caucasian donors have emerged in research studies, including measures of hypertension, diabetes, chronic kidney disease, ESRD and mortality [16–20]. However, the direct impact of donation upon the health outcomes otherwise expected for healthy persons are not well defined, especially for the non-Caucasian donor.

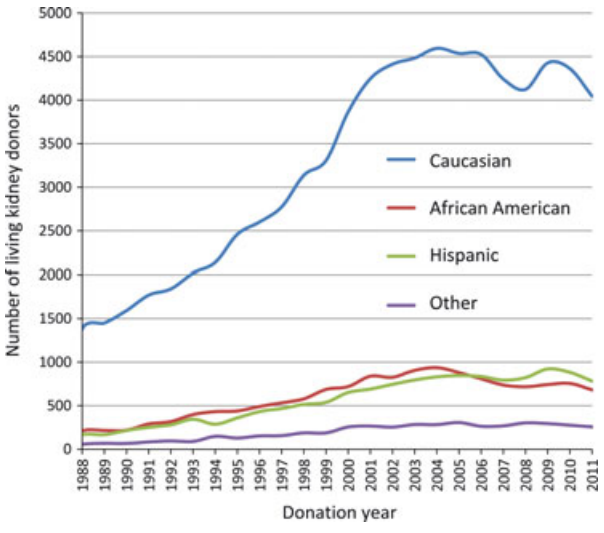

Figure 1 Annual counts of living kidney donors in the United States according to donor race. Based on data from the Organ Procurement and Transplantation Network [1].

As policies for the medical evaluation, informed consent and follow-up of living donors receive intensified scrutiny and debate, such as in the 2010 European Union directive on standards of quality and safety in transplantation [21] and the new living donor policies passed by the United Network for Organ Sharing (UNOS) that take effect February 2013 [22], it is important to consider the state of evidence on live donor health outcomes and knowledge gaps in need of more attention. A 2010 consensus conference convened to evaluate 'Living Kidney Donor Follow-up: State-of-the-Art and Future Directions' identified non-Caucasian donors as a leading subgroup in need of focused attention because of inadequate understanding of donation-related risks. In the current article, we review available evidence on health outcomes after living kidney donation including mortality, hypertension, diabetes and kidney failure, with particular attention to outcomes and knowledge gaps for the non-Caucasian donor.

Post-donation mortality

Per the current OPTN/SRTR Annual Data Report, the number of living donor deaths within 30 days of donation and classified as donation-related in the U.S. were: 0 in 2005, 1 in 2006, 0 in 2007, 1 in 2008, and 1 in 2009 [3]. The number (and percentage) of living donor deaths from any cause within 1 year of donation were: 2 (0.03%) in 2005,

5 (0.08%) in 2006, 3 (0.05%) in 2007, 3 (0.05%) in 2008, and 2 (0.05%) in 2009 [3]. Recent linkage of OPTN registration data for 80 347 living donors in 1994 – 2009 with the Social Security Death Master File (SSDMF) produced a 90-day mortality estimate of 3.1 per 10 000 that did not change significantly over the 15-year study period [24]. Peri-operative mortality was higher in African American compared with Caucasian and Hispanic donors (7.6 vs. 2.6 and 2.0 per 10 000, $P = 0.04$) (Table 1). Other subgroups with relative surgical mortality differences included men compared with women (5.1 vs. 1.7 per 10 000, $P = 0.007$), and those with pre-donation hypertension (36.7 vs. 1.3 per 10 000, $P < 0.001$, although this is based on only 2 deaths in the hypertensive group).

Because the OPTN collects living donor follow-up information for only two years, with recent cohorts from 2004 to 2008 characterized by 24% to 50% missing one-year vital status [24], inferences on longer-term donor morbidity and mortality have generally been drawn from retrospective, single-center studies with comparison to general population-based survival estimates [15,25]. The conclusion that 'kidney donors live longer' than members of the general population has been popularized for several decades, but with obvious confounding by the fact that living donors undergo medical evaluation and selection for good health at the time of donation.

An advance in understanding the impact of donation on mortality was achieved with the comparison of long-term live donor mortality, as ascertained from linked SSDMF records, with mortality in a matched healthy non-donor cohort drawn from carefully screened participants in the third National Health and Nutrition Examination Survey (NHANES III) [23]. Importantly, to simulate the process of donor selection, the control group was assembled after excluding those with evidence of medical contraindications to kidney donation. Among the findings, age and sex-adjusted long-term mortality among Hispanic donors was not substantially different from that of Caucasian donors. African American donors experienced higher relative risks of death over 12 years in models adjusted for age and sex (HR 1.3, 95% CI 1.0–1.06) and for demographic factors plus systolic blood pressure (HR 2.0, 95% CI 1.3–3.0). However, long-term donor mortality was similar or lower than that of matched non-donor controls, including among sub-groups stratified by race.

Post-donation hypertension

Data from predominantly Caucasian cohorts suggest increased risk of blood pressure elevation and hypertension in prior donors over that expected with normal aging, which may reflect physiological alterations (hyperfiltration in the remaining kidney, changes in vascular tone and renin-angiotensin-aldosterone regulation) and/or heightened clinical follow-up [26,27]. A meta-analysis including data for 5145 donors estimated 6 mmHg higher weighted mean systolic blood pressure and 4 mmHg higher weighted mean diastolic blood pressure in donors compared with controls after an average of 7 years post-donation [26]. An administrative claims linkage study of 1278 (primarily Caucasian) living donors in Ontario by Garg *et al.* found a higher incidence of claims-based hypertension diagnoses (16.3% vs. 11.9%, HR 1.4, 95% CI 1.2–1.7) among living donors compared with matched controls who were screened for the absence of indications of baseline comorbidity (also identified through administrative claims) [27].

Racial variation in the burden and consequences of poor health outcomes among non-Caucasian persons in the general U.S. population are well established [28,29], but outcomes including hypertension among non-Caucasian donors have only recently begun to receive attention (Table 2). In a retrospective cohort study from the University of Minnesota, drug-treated hypertension was reported in 25% of 255 Caucasian donors assessed at an average of 12 years after donation [15]. By comparison, a notably higher prevalence of hypertension was identified in 41% of 39 African American donors at one center at an earlier average assessment time of 7 years post-donation [17]. Among a cohort of 38 Canadian Aboriginal donors evaluated at an average of 14 years after donation, 42% were hypertensive compared with 14% of Caucasian donor controls [18].

Linkage of OPTN living donor registration data to administrative billing claims from a private health insurer identified an overall frequency of hypertension diagnosis in 17.8% of the cohort at 5 years post-donation [19]. As compared with Caucasian donors, African American donors had approximately 50% increased relative risk of hypertension diagnosis (aHR 1.52, 95% CI 1.23–1.88) and Hispanic donors had approximately 36% increased relative risk (aHR 1.36, 95% CI 1.04–1.78). Preliminary data from a linkage of OPTN donor registration data with Medicare billing claims suggests that, while hypertension is more common among the donor population with Medicare compared with private insurance, consistently higher hypertension rates among African American donors generalizes to the Medicare-insured donor population [30]. A study of 103 African American donors at two centers suggested that the frequency of post-donation hypertension may exceed that of matched controls, noting a high proportion of previously undiagnosed hypertension identified through study encounters [31].

Post-donation diabetes

While a direct causal relationship between donor nephrectomy and diabetes mellitus is not postulated, recent studies

Table 1. Summary of recent studies including information on post-donation renal outcomes and mortality according to donor race.

Reference	Data source/design	Racial composition of participants	Outcome, measures and post-donation assessment time	Outcomes by race within LKD samples	Comparison of LKD to non-LKD
Renal outcomes					
Gibney *et al.*, *Transplantation* 2007 [16]	Linkage of OPTN LKD registration (1993–2005) and U.S. transplant waitlist registration data (1993–2005)	8889 LKD: 14% AA; 68% Caucasian	Transplant waitlist registrations among prior LKD	Of 102 LKD waitlisted after donation in the period, 44% were AA (compared with 68% total C donors, $P < 0.0001$) and 40% were Caucasian (compared with 68% total C donors, $P < 0.0001$)	None
Ibrahim *et al.*, *N Engl J Med* 2009 [15]	Cohort study of LKD at one center in Minnesota, USA (1963–2007)	3698 LKD: 98.8% Caucasian	ESRD requiring dialysis or transplantation based on report of the LKD or recipient	11 LKD, at an average of 22.5 ± 10.4 years (180 cases PMPY) While only 45 (1.2%) of full LKD cohort were non-Caucasian, 3 of 11 (27.3%) LKD who developed ESRD were non-Caucasian	ESRD in LKD did not exceed national ESRD rate for Caucasian Americans (268 cases PMPY)
Lentine *et al.*, *N Engl J Med* 2010 [19]	Linkage of OPTN LKD registration data (1987–2007) with administrative billing claims from a U.S. private health insurer (2000–2007 claims)	4650 LKD: 76.3% Caucasian, 13.1% AA, 8.2% Hispanic, 2.4% other	CKD diagnosis in administrative billing claims Stage-specific coding examined in a sub-group of 2307 with insurance benefits after start of stage-specific coding Median time from donation to end of insurance: 7.7 years	CKD diagnosis: Overall, 5.2% at 5 years. Approximately twice as likely among AA (aHR 2.32, $P < 0.05$) or Hispanic (aHR 1.90, $P < 0.05$) compared to Caucasian LKD CKD stage 3 or higher in sub-analysis: More likely in AA (aHR, 3.60, $P = 0.009$) or Hispanic (aHR, 4.23, $P = 0.006$) vs Caucasian LKD Dialysis-requiring CKD in sub-analysis: 0.7% ($P = 0.02$ vs Caucasian) and 0.5% Hispanic ($P = 0.10$ vs Caucasian) LKD, compared with 0 cases among Caucasian LKD	None

Table 1. continued

Reference	Data source/design	Racial composition of participants	Outcome, measures and post-donation assessment time	Outcomes by race within LKD samples	Comparison of LKD to non-LKD
Cherikh *et al.*, *Am J Transplant* 2011 [20]	Linkage of OPTN LKD registration (1987–2003) and CMS ESRD registration data (1987–2009)	56 458 LKD: 13% AA, 71% Caucasian	ESRD defined by the CMS Medical Evidence Form 2728 (certification of ESRD)	Post-donation ESRD rate significantly higher in AA compared with Caucasian LKD: 0.423 vs. 0.086 per 1000 years at risk (RR 4.92, 95% CI 2.79–8.66)	Annual ESRD incidence rates of 0.998 and 0.273 per 1000 for AA and Caucasian Americans cited, but not adjusted for comorbidity
Mortality					
Segev *et al.*, *JAMA* 2010 [23]	Linkage of OPTN LKD registration data (1994–2009) with the SSDMF	80 347 LKD: 13% AA, 73% Caucasian Controls matched from NHANES III by age, gender, race, education, smoking history, BMI, and systolic BP, after exclusions for baseline comorbidity	Surgical mortality (within 90 day) based on SSDMF records Long-term death (up to 12 years) based on SSDMF	Surgical mortality higher in AA compared to Caucasian and Hispanic LKD (7.6 vs. 2.6 and 2.0 per 10 000) Risk of death over 12 years higher in AA compared with Caucasian LKD after adjustment for age and sex (HR 1.3, $P < 0.05$), and for demographics plus systolic BP (HR 2.0, $P < 0.05$)	Long-term LKD mortality not higher vs matched healthy controls from NHANES III, including among sub-groups stratified by race

AA, African American; CKD, chronic kidney disease; CMS, Centers for Medicare & Medicaid Services; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; LKD, living kidney donors; NHANES, National Health and Nutrition Examination Survey; OPTN, Organ Procurement and Transplantation Network; PMPY, per million per year; SSDMF, Social Security Death Master File.

Table 2. Summary of recent studies including information on post-donation medical outcomes according to donor race.

Reference	Data source/design	Racial composition of participants	Outcome, measures and post-donation assessment time	Outcomes by race within LKD samples	Comparison of LKD to non-LKD
Hypertension					
Garg *et al.*, *Transplantation* 2008 [27]	Linkage of Ontario Organ Procurement Organization LKD registration data with provincial administrative health databases (1993–2005)	1278 LKD Among those with race information: 92% Caucasian, 5% Asian or Asian-Indian, <3% African Canadian, Hispanic or Aboriginal Canadian	HTN diagnosis in administrative billing claims Mean time from donation to followup: 6.2 years	16.3% in total sample (dominantly Caucasian; no racial stratification provided)	Diagnosed HTN more frequent in LKD vs non-LKD controls from the same data source matched by age, sex, neighborhood income and frequency of physician visits (HR 1.4, $P < 0.001$)
Ibrahim *et al.*, *N Engl J Med* 2009 [15]	Cohort study of LKD at one center in Minnesota, USA (1963–2007) In-person health assessment for a subset	255 of 3698 LKD in the period participated in the health assessment 99.2% Caucasian	Treatment with antihypertensive medication Mean time from donation to followup: 12.2 years	24.7% in this Caucasian sample	No difference in HTN among LKD vs prevalence of 28.8% in controls from NHANES (2003–2004, or 2005–2006) matched by age, sex, race and BMI ($P = 0.83$)
Storsley *et al.*, *Transplantation* 2010 [18]	Chart review of LKD at one center in Manatoba, Canada (1971–2007)	38 Aboriginal LKD (total in the period) 76 'randomly selected' Caucasian donor controls	HTN diagnosis based on physician- or nurse-report and use of antihypertensive medication Mean time from donation to followup: 14.6 years in Aboriginal and 13.4 years in Caucasian LKD	42% in Aboriginal vs 14% in Caucasian LKD controls ($P = 0.02$)	None
Nogueira *et al.*, *Transplantation* 2010 [17]	Sample of AA LKD at one center in Maryland, USA (1996–2002) In-person health assessment including BP measurement	39 of 192 AA LKD in the study period participated	Treatment with hypertensive medication for an indication of HTN, average systolic BP >= to 140 mmHg, or average diastolic BP >= 90 mmHg (3 measures)	41%	None

Table 2. continued

Reference	Data source/design	Racial composition of participants	Outcome, measures and post-donation assessment time	Outcomes by race within LKD samples	Comparison of LKD to non-LKD
Lentine *et al.*, *N Engl J Med* 2010 [19]	Linkage of OPTN LKD registration data (1987–2007) with administrative billing claims from a U.S. private health insurer (2000–2007 claims)	4650 LKD: 76.3% Caucasian, 13.1% AA, 8.2% Hispanic, 2.4% other	Diagnosis: HTN diagnosis in administrative billing claims Drug-treated HTN: pharmacy claim for antihypertensive medication Median time from donation to end of insurance: 7.7 years	Overall, 17.8% at 5 years. 52% relative increase in AA (aHR, 1.52, $P < 0.05$) and 36% relative increase in Hispanic (aHR 1.36, $P < 0.05$) vs Caucasian LKD	HTN prevalence at 5 years higher than NHANES (2005–2006) estimates in some subgroups, particularly Hispanic LKD
Doshi *et al.*, *Am J Transpl* 2012 [31]	Sample of AA LKD at 2 centers in Michigan, USA (1993–2006)	103 of 171 AA LKD in the period participated 235 non-donors were matched from CARDIA cohort by age, gender, baseline systolic BP and duration of followup, after exclusions for baseline comorbidity	Systolic BP >= 140 mmHg, diastolic BP >= 90 mmHg, or use of antihypertensive agent, ascertained at a study visit or from medical chart review Mean time from donation and CARDIA cohort entry: 6.8 and 6.4 years, respectively	40.8% in the AA LKD Among the AA LKD with HTN, 52.4% were untreated before study contact	HTN more frequent in LKD vs 17.9% prevalence among AA non-LKD controls ($P < 0.001$)
Diabetes mellitus					
Ibrahim *et al.*, *N Engl J Med* 2009 [15]	Cohort study of LKD at one center in Minnesota, USA (1963–2007) In-person health assessment for a subset	255 of 3698 LKD in the period participated in health assessment 99.2% Caucasian	Self-report Mean time from donation to followup: 12.2 years	3.1% in this Caucasian sample	No difference in DM among LKD vs prevalence of 5.9% in controls from NHANES (2003–2004, or 2005–2006) matched by age, sex, race and BMI ($P = 0.10$)
Storsley *et al.*, *Transplantation* 2010 [18]	Chart review of LKD at one center in Manatoba, Canada (1971–2007)	38 Aboriginal LKD (total in the period) 76 'randomly selected' Caucasian donor controls	DM diagnosis based on physician- or nurse-report and use of oral glucose lowering medication or insulin Mean time from donation to followup: 14.6 years in Aboriginal and 13.4 years in Caucasian LKD	19% in Aboriginal vs 2% in Caucasian LKD controls ($P = 0.005$)	None
Lentine *et al.*, *N Engl J Med* 2010 [19]	Linkage of OPTN LKD registration data (1987–2007) with administrative billing claims from a U.S. private health insurer (2000–2007 claims)	4650 LKD: 76.3% Caucasian, 13.1% AA, 8.2% Hispanic, 2.4% other	Diagnosis: DM diagnosis in administrative billing claims Drug-treated DM: pharmacy claim for oral glucose lowering medication or insulin Median time from donation to end of insurance: 7.7 years	Drug-treated DM: More than twice as likely in AA (aHR 2.74, $P < 0.05$) or Hispanic (aHR 1.24, $P < 0.05$) vs Caucasian LKD	DM prevalence at 5 years did not exceed NHANES (2005–2006) estimates in subgroups of similar age, sex and race

AA, African American; CARDIA, Coronary Artery Risk Development in Young Adults; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; LKD, living kidney donors; NHANES, National Health and Nutrition Examination Survey.

have suggested racial variation in the frequency of post-donation diabetes mellitus (Table 2). Diabetes was identified in 3.1% of 255 Caucasian donors from the University of Minnesota cohort at an average of 12 years after donation [15]. In contrast, 19% of a small cohort of Canadian Aboriginal donors were found to be diabetic at an average of evaluation time of 14 years post-donation, compared with 2% of Caucasian donor controls [18]. In a linkage of private insurance claims to OPTN living donor registrations, the estimated prevalence of diabetes diagnoses at five years post-donation was 4.0% with higher risks of diabetes requiring drug therapy in both African American (aHR 2.31, 95% CI 1.33–3.98) and Hispanic donors (aHR 2.94, 95% CI 1.57–5.51) [19]. However, the estimated prevalence of diabetes at five years after donation did not exceed that in subgroups from NHANES defined by age, race and gender.

As the presence of diabetes mellitus at the time of donor evaluation should exclude living donation by clinical practice guidelines [22,32,33], these patterns that race-related factors (possibly genetic or environmental) predispose to the onset diabetes over time (possibly genetic or environmental), and also emphasize the variable long-term predictive value of a 'normal' donor evaluation for all dimensions of health. As previously stated, obesity is more common among non-Caucasian donors [11], and in turn is a strong risk factor for diabetes [34]. Further study of the associations of pre-donation obesity, post-donation weight gain, genetic/familial, and environmental factors with post-donation health outcomes, including the development of diabetes, is warranted.

Post-donation renal outcomes

The rate of ESRD after kidney donation was assessed among 3698 living donors in the retrospective University of Minnesota cohort based on reports of donors and their recipients. ESRD requiring dialysis or transplantation was identified in 11 donors at an average of 22.5 $\pm$ 10.4 years post-donation, producing a rate of 180 cases per million per year (PMPY), which did not exceed the national ESRD rate for Caucasian Americans of 268 cases PMPY [15]. However, while only 1.2% donors in the full cohort where non-Caucasian race, notably 3 of 11 (27%) donors who developed ESRD were non-Caucasian (Table 1), supporting the need for more attention to renal outcomes among racially diverse donors. Additionally, population-based comparison groups cannot be used to assess attributability of sequelae such as ESRD directly to donation, as donors are clearly more healthy than the general population.

OPTN survey data collected at an average of 5 months post-donation for live donors in 2000–2005 showed no appreciable differences in serum creatine or estimated glomerular filtration rate (eGFR) among African American compared with Caucasian donors in this early post-donation period [35]. In contrast, based on linkage of OPTN registry data with administrative billing claims with an average time from donation to end of followup of 7.7 years, diagnosed chronic kidney disease after donation was approximately twice as likely among African American (aHR 2.32, 95% CI 1.48–3.62) or Hispanic (aHR 1.90, 95% CI 1.05–3.43) compared with Caucasian donors [19]. Subanalysis after the introduction of stage-specific billing codes for chronic kidney disease found higher risk of diagnoses of chronic kidney disease stage 3 or higher among donors who were African American (aHR, 3.60, 95% CI 1.37–9.39) or Hispanic (aHR 4.23, 95% CI 1.52–11.75) [19]. While ESRD was identified in a small number of cases, the pattern of diagnosis suggested racial variation: 2 of 271 African American (0.7%, $P = 0.02$ vs Caucasian) and 1 of 197 Hispanic (0.5%, $P = 0.10$ vs Caucasian) donors, compared with no cases among 1786 Caucasian donors. Preliminary data have also suggested that race may interact with medical conditions in impacting long-term renal function. In a small study of 36 obese living kidney donors at the University of Maryland assessed at an average of 7 years, the absolute decrement in eGFR was greater in African American obese donors, as compared with non-African American obese donors (33.3 $\pm$ 9.6 vs 22.7 $\pm$ 12.7 ml/min/1.73 m^2, respectively; $P = 0.016$) [36].

Knowledge of postdonation ERSD based on large, diverse samples of U.S. donors has been advanced by recent database linkages. By integrating donor registration data with kidney transplant candidate registrations, Gibney *et al.* found that while African Americans composed 12% of U.S. living kidney donors in 1996–2007, they represented 43% of 148 prior donors listed for kidney transplantation after donation [16,37]. ESRD also developed earlier after donation among affected African American donors, at a median of 16 years post-donation compared with 21 years in Caucasian donors who required transplantation. Cherikh *et al.* recently linked OPTN donor registration data with Center for Medicare and Medicaid Services (CMS) ESRD reporting forms and found similar patterns, such that 47% of 126 prior donors who started maintenance dialysis after donating in 1987–2003 were African American [20]. The overall post-donation ESRD rate was 0.134 per 1000 years at risk, but this rate was significantly higher in African American compared with Caucasian donors (0.423 vs. 0.086 per 1000 years at risk; relative risk 4.92, 95% CI 2.79–8.66). While the authors report these rates 'compared favorably' with national ESRD incidence rates, national rates include persons with an array of medical comorbidities including hypertension and diabetes, and thus are not directly comparable to rates among healthy persons screened for baseline good health. As such, while it is clear that African American donors develop ESRD at higher rates

than Caucasian donors, African American individuals in general develop ESRD at higher rates than Caucasian individuals, and it remains unknown whether donating a kidney is associated with increased risk of ESRD.

Improving risk stratification among donors of African Descent: APOL1 genotyping

Epidemiological data from the general population demonstrate that end-organ damage from conditions such as hypertension, diabetes and obesity generally develop after a latency period [38,39]. Thus, several authors have advanced the importance of considering expected lifespan and the life-time risks of end-organ failure for the living donor. Based on lifetime risk patterns in the general population, Steiner estimated that some older donors with an isolated medical abnormality such as mild hypertension face similar or lower lifetime ESRD risk as that of young donors without baseline comboridity who have an expected lifespan of more than 50 years in which to develop ESRD [40]. Age-stratified selection of donors with baseline hypertension is recommended in the Amsterdam Forum clinical practice guidelines for the medical evaluation and care of the living donor but these guidelines do not formally discuss implications of race for donor selection [32]. Notably, as African Americans tend to donate at a younger average age and are more likely related to their recipient (and thus potentially more likely to carry familial or genetically-based ESRD risk factors) [41,42], demographic differences in long-term post-donation risks may occur as a result of donation patterns.

Based on the rationale that 'the risk of CKD [chronic kidney disease] and CVD [cardiovascular disease] is increased in individuals from certain racial backgrounds or ethnic groups and in those with elements of the metabolic syndrome' and that 'the risk of developing hypertension in a normotensive kidney donor is greater with black and Hispanic donors compared with Caucasians' a recent Consensus Document from the AST/ASTS/NATCO/UNOS Joint Societies Work Group on 'Evaluation of the Living Kidney Donor' recommended that hypertension in a non-Caucasian donor at any age should be considered a relative contraindication to donation [33]. However, 'relative contraindications' are not permissible in UNOS policy, and this recommendation is not formalized in the new medical evaluation policy adopted by UNOS in 2013 [22]. Further research is needed to inform selection practices for non-Caucasian donors with baseline medical abnormalities and possible familial risk factors.

To this end, recently identified associations of coding variants in the apolipoprotein L1 (APOL1) gene with non-diabetic ESRD risk may prove relevant to the evaluation and selection of African American kidney donors. APOL1 is a secreted lipoprotein with putative roles in autophagy and apoptosis. The heterozygous carrier state for either of two coding variants (G1, G2) is protective against the parasite *Trypanosoma brucei* that causes sleeping sickness endemic to sub-Saharan Africa, and this heterozygous advantage appears to have driven natural selection, such that at least one copy of G1 or G2 is present in approximately 37% of African American chromosomes, whereas the variants are virtually absent in persons of European descent [43]. In 2010, a case–control study from the 1000 Genomes Project first identified G1 and G2 as 'renal risk alleles' such that homozygosity or compound heterozygosity was associated with more than seven times of odds of ESRD in African Americans compared with zero risk alleles (OR 7.3), whereas a single copy of a risk allele bore a modest association with ESRD (OR 1.26) [43]. When recalculated as a relative risk rather than an odds ratio, the risk of developing ESRD was more than doubled by the presence of two risk alleles compared with zero risk alleles [44].

Since that time, a growing body of literature has further defined associations of APOL1 mutations with focal segmental glomerulosclerosis (FSGS)/HIV-associated nephropathy (HIVAN) histopathologies, proteinuria, low eGFR, and younger age at dialysis among African Americans in the general population [45–47]. Although the pathobiological mechanism by which APOL1 variants contribute to kidney disease has not been delineated, APOL1 expression has been identified in podocytes and renal proximal tubular cells in persons without kidney disease [48], whereas biopsies from patients with HIVAN or FSGS show reduced podocyte and tubular expression of APOL1 along with de novo expression in renal arterioles, suggesting possible roles of APOL1 variants in podocyte dysfunction, tubulointerstitial injury and/or arteriopathy [48,49]. The presence of 2 APOL1 risk alleles in a deceased kidney donor has also been associated with nearly four times the relative risk of allograft loss (aHR 3.84) compared with 0 or 1 risk alleles [50].

Based on the rationale that first degree relatives are often considered as potential donors, and that close relatives of African American ESRD patients with APOL1-related kidney failure are likely to share one or more APOL1 risk alleles, Cohen *et al.* have proposed a screening program of self-identified African American potential live donors wherein the presence of two risk alleles constitutes a strong relative contraindication to donation [44]. While more data and followup are needed to evaluate how use of APOL1 in the risk stratification and selection of potential living donors impacts rates of donor candidacy and outcomes in both donors and recipients, APOL1 variation warrants attention as a potential explanatory factor in the current higher relative frequency of ESRD in living donors of African descent. Future research should also attempt to discriminate risk related to genetics from environmental, cultural and lifestyle factors.

Racial disparities in insurance and quality of healthcare

There is substantial evidence of disparities in health care access and treatment according to race and payer in the general population. African American individuals are less likely to have a regular primary care provider and are more likely to turn to the emergency room for care [51–53]. AHRQ's 'Health Care Coverage Analyses of the 2006 National Healthcare Quality and Disparities Reports' identified many racial and ethnic disparities among individuals with the same type of insurance as well as among the uninsured [53]. Overall, African Americans fared worse on more than one-third of process measures of ambulatory care quality and access. In a recent study of Medicaid beneficiaries in North Carolina, African American patients with hypertension were less likely to have their blood pressure controlled despite equal access to care [54]. Race related differences have also been identified in the early care of chronic kidney disease complications, such as anemia and bone and mineral metabolism, and in the timeliness of nephrology referral and preparation for renal replacement therapy [55]. A recent study examined insurance status at donation based on OPTN survey information for U.S. donors in 2004–2006 [56]. Among the 67% with reported insurance status, 18% of donors lacked insurance at donation. Importantly, lack of health insurance varied according to donor demographic traits, such that 21% of African American donors were uninsured, including 32% of African American male donors aged 18–34 years old. However, disparities in access to and quality of care by race and payer, and implications for long-term donor health outcomes, have not been explored among kidney donors and deserve further study.

Race and the need for organ donors: balancing risks with organ supply disparities

A competing pressure with the potential need for more selective approval of non-Caucasian donors is the acuity of the organ shortage in non-white populations. In 2009, the incident ESRD rate in African American persons in the U.S. was 3.5 times that of Caucasians, and incident ESRD among Hispanics was 1.5-times that of non-Hispanics [57]. Similarly in the U.K., the incidence of ESRD among the African Caribbean population is three to fourfold that of Caucasians [58]. African American ESRD patients also have decreased access to transplantation and longer waiting times once on the waitlist [59,60]. Younger African American ESRD patients have twice the death rate of younger Caucasian ESRD patients, emphasizing the need for transplantation in younger patients who will benefit the most from this treatment modality [61]. Furthermore, review of U.S. transplant referral data has shown that African American transplant candidates are less likely to identify potential living donors, and their potential living donors are less likely to donate for reasons including medical exclusions [62]. A new national registry study of incident adult ESRD patients in the U.K. identified a particular racial disparity in access to live donor transplantation among persons aged <50 years, such that black persons had 69% lower adjusted odds of live donor transplantation (aOR 0.31) within 3 years of dialysis initiation compared with Caucasians in this age group [63]. Live donor and recipient race are nearly completely correlated; 95% of African American donors donate to African American recipients [41]. Given the even more dramatic need for live donors for non-Caucasian recipients, it is critical that the goal of increasing the organ supply is carefully balanced against the responsibility to select only appropriate donors who are not expected to face excessive risks of adverse health events. To tailor counseling and informed consent, focused attention to long-term medical outcomes among non-Caucasian living donors is needed, and should include assembly of healthy, non-donor controls for assessment of attributable risks of donation as an important priority.

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