Long-term Medical Outcomes of Living Kidney Donors

Arthur J. Matas, MD, and Andrew D. Rule, MD, MSc

Abstract

Historically, to minimize risks, living kidney donors have been highly selected and healthy. Operative risks are well-defined, yet concern remains about long-term risks. In the general population, even a mild reduction in glomerular filtration rate (GFR) is associated with cardiovascular disease, chronic kidney disease, and end-stage kidney disease (ESKD). However, reduction in GFR in the general population is due to kidney or systemic disease. Retrospective studies comparing donors with matched general population controls have found no increased donor risk. Prospective studies comparing donors with controls (maximum follow-up, 9 years) have reported that donor GFR is stable or increases slightly, whereas GFR decreases in controls. However, these same studies identified metabolic and vascular donor abnormalities. There are a few retrospective studies comparing donors with controls. Each has limitations in selection of the control group, statistical analyses, and/or length of follow-up. One such study reported increased donor mortality; 2 reported a small increase in absolute risk of ESKD. Risk factors for donor ESKD are similar to those in the general population. Postdonation pregnancies are also associated with increased risk of hypertension and preeclampsia. There is a critical need for long-term follow-up studies comparing donors with controls from the same era, geographic area, and socioeconomic status who are healthy, with normal renal function on the date matching the date of donation, and are matched on demographic characteristics with the donors. These data are needed to optimize donor candidate counseling and informed consent.

THE CONCERN WITH LIVING KIDNEY DONATION

For a patient with end-stage kidney disease (ESKD), a living donor (LD) kidney is the optimal treatment option, providing better patient and graft survival and quality of life than either dialysis or a deceased donor transplant. However, it does have a distinct disadvantage: LDs must undergo a major operative procedure associated with morbidity and mortality. In addition, there are concerns about the potential for adverse long-term medical consequences of living with a single kidney.[1-24]

In this review, we summarize current knowledge regarding these medical concerns, describe their physiologic basis and epidemiologic evidence, and, given these concerns, discuss donor care after donation and research needs.

LONG-TERM NON-LD OUTCOMES WITH REDUCED GLOMERULAR FILTRATION RATE

In humans, uninephrectomy results in loss of approximately 50% of kidney function; compensatory changes in the remaining kidney rapidly return glomerular filtration rate (GFR) to approximately 70% of initial function.[25] Observations from animal models and the general population have led to concerns about the long-term impact of reduced GFR. First, in the rat model, unilateral nephrectomy plus partial ablation of the remaining kidney results in hyperfiltration of the remaining glomeruli.[26-29] The hyperfiltration, although initally beneficial, ultimately leads to progressive dysfunction. In other species, however, subtotal nephrectomy does not uniformly lead to the same progressive loss of renal function.[30,31]

From the Transplantation Division, Department of Surgery, University of Minnesota, Minneapolis (A.J.M.); and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN (A.D.R.).

ARTICLE HIGHLIGHTS

- Living kidney donation is the optimal treatment for end-stage kidney disease, but there are concerns regarding medical risk to the donor.

- Some, but not all, studies report increased overall mortality, cardiovascular mortality, and kidney failure in living donors; however, even when present, the absolute risk is very small.

- Studies, to date, have not defined the risk attributable to donation.

- There remains a critical need for long-term follow-up studies comparing donors with controls from the same era and geographic area and who are healthy, with normal renal function on the date matching the date of donation.

- Donors need continued medical follow-up and encouragement for a continued healthy lifestyle because, similar to the general population, with aging many will develop kidney and cardiovascular disease risk factors such as obesity, hypertension, and diabetes.

Second, in the general population, even a mild reduction in renal function has been associated with all-cause mortality and cardiovascular mortality.[32-34] All forms of cardiovascular disease (CVD) are more common in patients with chronic kidney disease (CKD), including acute myocardial infarction, heart failure, stroke, peripheral artery disease, and atrial fibrillation. Supportive of these clinical observations, decreasing estimated GFR (eGFR), has been associated with increased cardiac hypertrophy and fibrosis of the left ventricle, as well as cardiac cell enlargement in the left ventricular wall.

Third, in the general population, reduced GFR and the slope of the GFR predict ESKD risk.[35-37]

Fourth, studies of children born with unilateral renal agenisis or a reduced number of functioning nephrons have reported development of focal segmental sclerosis and progressive renal failure.[38-40] However, in these cases it is not clear whether the remaining nephrons were normal. In contrast, some long-term follow-up studies after nephrectomy performed for unilateral disease have not found

progressive deterioration in renal function.[41-44] Andersen et al[41] compared the survival rates of 232 patients who underwent nephrectomy for benign disease (vs the overall Danish population). Follow-up ranged from 2 months to 26 years. If the remaining kidney was normal, survival was identical to that of the overall population. Baudoin et al[43] assessed patients (18-56 years old at the time of the study) who had undergone uninephrectomy in childhood. In general, their kidney function was maintained. However, those followed longer than 25 years (vs <25 years) had a higher incidence of kidney failure, higher blood pressure (BP), and increased urinary protein excretion. Narkun-Burgess et al[44] compared outcomes of 56 World War II veterans who lost a kidney because of trauma with those of other World War II veterans of the same age. The mortality rate was not increased in veterans who had lost a kidney; of the 28 living veterans (mean ± SD: age, 64±4 years; interval after kidney loss, 45±1 years), none had severe chronic kidney disease.

LONG-TERM OUTCOMES WITH KIDNEY DONATION

Challenges in Studying LD Outcomes

There are a variety of challenges to studying LD outcomes. The first is identifying an appropriate comparator group. Living donors are screened to be healthy at the time of donation, and reduced GFR is solely due to nephrectomy. The ideal possible control group would be those approved for donation but not actually donating, but there are likely insufficient numbers to detect differences in rare events. Neither is a clinical trial to randomize approved donors between actual donation vs nondonation feasible given the limited options for acceptable donors, the advantages of living donation, and the often close interpersonal relationships between the donor and recipient.

Single-center and registry studies from throughout the world comparing LDs with age-, sex-, and ethnicity-matched general population controls have found no increased risk of CVD, mortality, or ESKD in the

LDs.[1-22] In the absence of a completed donor evaluation, the best possible control group should be from the same era, geographic area, and socioeconomic status; have a health assessment corresponding to the date of donation (ruling out diseases precluding donation, and with normal renal function on the date corresponding to the date of donation); be matched on characteristics on the date corresponding to the date of donation (eg, body mass index [BMI], smoking history, family history of CKD or ESKD; and measurement and matching of BP and renal function [GFR and proteinuria]); and have decades of follow-up to detect long-term outcomes.

A second challenge is determining causation of any findings. Most long-term LD follow-up studies are retrospective observational studies that cannot discern whether any outcomes can be caused by donation. In addition, risk factors that have been associated with worse LD outcomes (eg, CKD or ESKD) are identical to those seen in the general population. The few prospective studies matching LDs to controls have not reported differences in clinical outcomes. As described later herein, retrospective studies that found an increased risk of ESKD or mortality in LDs compared with matched controls have significant limitations related to the choice of control groups. Until there are studies matching LDs to controls, as described previously herein, it will be difficult to attribute any poor LD outcomes directly to donation.

Metabolic and Hemodynamic Changes After Donation

In a prospective study, Kasiske et al[45,46] matched 200 LDs with 200 controls and reported on baseline and follow-up laboratory values. After 9 years, 133 LDs and 113 controls were still being followed.[46] Six months after donation, compared with baseline, measured GFR (mGFR) was 29% lower in LDs but unchanged in controls. Subsequently, mGFR was stable in LDs but declined in controls(-1.26 mL/min/1.73 m^2 per year). In a similar analysis, Lam et al[47] used administrative data to match 604 LDs

with 2214 controls. Median follow-up was 7 years (maximum, 15 years). From 6 weeks onward, eGFR increased in the LDs (0.35 mL/min/1.73 m^2 per year) and significantly decreased in the controls (-0.85 mL/min/1.73 m^2 per year).

Kasiske et al[48] also found that 36 months after donation, LDs (compared with matched controls) had abnormalities of bone metabolism: significantly reduced tubular phosphate reabsorption, serum phosphate concentrations, and serum 1,25-dihydroxyvitamin D3 concentrations. In contrast, LDs had significantly higher 25-hydroxyvitamin D concentrations and higher concentrations of both bone resorption and bone formation. At 9 years, urine protein, urine albumin, glucose, hemoglobin A$_{1c}$, insulin, and lipoprotein levels; BP; and carotid-femoral pulse wave velocity did not differ between groups. However, parathyroid hormone, homocysteine, and uric acid levels were higher in LDs, and their mean small artery elasticity was significantly lower. Kasiske et al[46] concluded that the LDs remained healthy at 9 years but that the long-term implications of the metabolic and vascular differences needed to be determined.

In a study comparing 68 LDs and 56 controls, Moody et al[49] found that at 12 months LDs had significant increases in uric acid, parathyroid hormone, fibroblast growth factor, and high-sensitivity C-reactive protein levels. In addition, detectable highly sensitive troponin T levels and microalbuminuria were significantly more common in LDs. Although there were differences in cardiac structure at 12 months, after 5 years of follow-up, there was no difference between LDs (n=50) and controls (n=45) in left ventricular mass as well as other parameters of cardiac structure or function or ambulatory BP.[50]

Hypertension Outcome

There are conflicting reports of LD hypertension risk. In a 1995 meta-analysis, Kasiske et al[2] compared 3124 uninephrectomized patients (60% were LDs) and 1703 controls. They found that nephrectomy did not

TABLE 1. CVD and Mortality in Kidney Donors Compared With Matched Controls[a]

Author, year	Country	Era	Donors/controls, No.	Follow-up, median [25%, 75%], y	Donor CVD	Donor Mortality
Garg et al,[18] 2008	Canada	1993-2005	1278/6369	Mean ± SD = 6.0±3.2	↔	↔
Segev et al,[19] 2010	United States	1994-2009	80,347/9458	6.3 [3.2, 9.8]	↔	
Berger et al,[20] 2011[b]	United States	1990-2010	219/219		↔	
Garg et al,[21] 2012	Canada	1992-2019	2028/20,280	Median = 6.5; maximum = 17	↔	↓
Reese et al,[22] 2014[c]		1996-2006	3368/3368	7.8 [5.1, 10.2]	↔	↔
Mjoen et al,[23] 2014	Norway	1963-2007	1901/32,621	15 [1.5, 43.9]	↑	↑
Chaudry et al,[54] 2020	Denmark	1996-2017	1262/12,620	7 [3.3, 12.1]	↔	↓
Munch et al,[55] 2020	Denmark					
General population		1996-2018	1103/11,030	7.8 [3.9, 12.1]	↓	↓
Blood donors		1995-2017	1007/260,494	7.9 [4.0, 12.2]	↔	↔
Grupper et al,[56] 2017	Israel	2000-2016	215/215	Mean ± SD = 5.5±3.7	↔	
Krishnan et al,[57] 2020	UK	2001-2013	9750/19,071	8.4 [6.0, 11.3]	↓	↓
Janki et al,[58] 2020	The Netherlands	1981-2010	761/1522	8.0 [5.1, 11.9]	↔	↓
Lin et al,[59] 2019	Taiwan	1997-2010	1082/1081			↔
Kim et al,[60] 2020	Korea	1982-2016	1237/4387	Median = 11	↔	↔

[a]CVD = cardiovascular disease.
[b]Aged 70 years or older at donation.
[c]Aged 55 years or older at donation.

increase the prevalence of hypertension; however, there was a small increase in systolic BP (2.4 mm Hg), which rose slowly with duration of follow-up (1.1 mm Hg per decade); there was also a small increase in diastolic BP, but this did not change with duration of follow-up.

Three prospective studies comparing LDs with controls found no increased hypertension risk for the LDs.[46,47,49] In addition, Najarian et al[1] studied greater than 20-year outcome of LDs (n=66) compared with their siblings and reported no differences between groups. Garg et al,[18] using administrative data, matched 1278 LDs with 6359 controls. With mean follow-up of 6 years (range, 1-13 years), LDs were diagnosed as having hypertension more frequently (16.3% vs 11.9%). However, Garg et al noted that a possible explanation for this difference was that the LDs were seen more frequently by their primary care physicians. A small study of African American individuals (103 LDs and 235 controls; mean follow-up, 6.8 years) reported a significant increased risk of hypertension in LDs (40.8%) vs controls (17.9%).[51] More recent studies of LDs compared with controls have continued to have conflicting results: increased risk or no difference.[52-59] Many authors noted,

similar to Garg et al, that the observation of increased risk of hypertension may have been related to closer follow-up of LDs.

CVD and Mortality Outcomes

Older studies comparing LDs with matched controls found no difference in CVD or mortality (Table 1).[18-22] However, most were limited by relatively short follow-up. In contrast, in 2014, Mjøen et al[23] reported that LDs, compared with selected healthy controls, had significantly increased all-cause and cardiovascular mortality. They reported that the increased mortality risk was seen after 15 years, and they attributed the differences in their study from previous analyses to the longer follow-up.

More recently, 7 studies (from 6 different countries) comparing LDs with matched controls found either no difference between groups or decreased mortality in the LDs (Table 1).[54-60] O'Keeffe et al,[61] in a meta-analysis and review of intermediate- and long-term LD follow-up studies, concluded that CVD and mortality were not increased after donation. Similarly, in a methodological review of the single paper reporting increased risk, Janki et al[62] found "key differences with respect to the comparability of donors and non-donors that could have led to overestimation of the risk in donors."

CKD and ESKD Risk Compared With Controls

Two studies, 1 from Norway (Mjøen et al[23]) and 1 from the United States (Muzaale et al[24]), reported increased ESKD in LDs. In the study by Mjøen et al,[23] 9 of 1901 LDs developed ESKD; in the study by Muzaale et al,[24] 99 of 96,217 LDs developed ESKD. As such, in both studies the absolute ESKD risk was small. In fact, Muzaale et al noted that the LDs had a much lower estimated lifetime risk of ESKD than did the general population (presumably because LDs are healthier than the average person in the general population). Mjøen et al reported that the estimated hazard ratio for ESKD in LDs was 11.38. Muzaale et al reported an 8-fold increase in risk. The authors of both papers stated that they would

continue performing LD nephrectomies and that their observations would improve predonation counseling and informed consent.

In a review by the ERA-EDTA-DESCARTES group, Maggiore et al[63] point out that any increased risk must be taken in context with the actual risk in controls, stating "what matters most to donors is the increase in long-term 'absolute' risk." They point out that an 11- or 8-fold increase over a close-to-zero reference hazard "yields only minor increases in the absolute risk." On a related note, since 1988 in the United States there have been 164,052 LD transplants.[64] In data from October 16, 1987, through November 3, 2020, the US Scientific Registry of Transplant Recipients has records of 633 LDs (0.4%) that have developed ESKD.[65]

A major limitation of both of the previously mentioned studies is that they did not match for family history of CKD. In the study by Mjøen et al,[23] all 9 LDs with ESKD were first-degree relatives of the recipient; in the study by Muzaale et al,[24] 83 of the 99 were related to the recipient. Numerous general population studies have reported that relatives of individuals with ESKD have an increased risk of ESKD.[66-68] Wainright et al,[69] in an analysis of the US Organ Procurement and Transplantation Network database, reported that LDs who were first-degree relatives of the recipient had a significantly increased risk of ESKD (highest in identical twins) compared with LDs who were distant relatives or were unrelated to the recipient.

In addition to lack of matching for LD-recipient relationship, there are numerous other limitations to the studies by Mjøen et al[23] and Muzaale et al,[24] including statistical analyses, controls and donors were from a different era and a different environment, differing lengths of follow-up, and different methods for identifying cases of ESKD.[70-76] The detailed methodologic reviews of both of these studies by Janki et al[62] suggested that the lack of comparability between donors and controls may have led to an overestimation of donor risk.

Three subsequent studies (number of LDs and length of follow-up shown in Table 1), each with mean or median follow-up less than 10 years, found no difference between LDs and matched controls in ESKD risk.[58-60] Each study also had limitations, including short follow-up, lack of matching for family history of CKD/ESKD, small event numbers, lack of matching for other CKD and/or CVD risk factors (eg, BMI), lack of controls from the same era and environment as the LDs, and lack of known normal renal function in controls at the time corresponding to the donation date.

To date, the data suggest that increased risk of ESKD is limited to those who are first-degree relatives of the recipient. However, in the early days of kidney transplant as a treatment option, most LDs were related to the recipient. Since then, the number of unrelated LDs has increased substantially. It may be that with longer follow-up, increased risk will be observed in unrelated LDs.

Long-term Follow-up for CKD and ESKD in LDs

A common concern with most previous studies is that there was insufficient follow-up time. Steiner[74-76] emphasized that long-term follow-up is necessary to determine whether kidney donation is associated with ESKD risk because most LDs are relatively young at donation and most ESKD develops later in life. In addition, most kidney diseases progress slowly, so that short-term LD follow-up will identify only LDs developing rapidly progressive disease (eg, immunologic). Long-term follow-up is required to determine the impact of diseases associated with aging, specifically hypertension and diabetes (the 2 most common causes of ESKD in the US general population and the US LD population).[77] It is unknown whether the rate of progression of these diseases toward ESKD differs between LDs and matched controls. Yet, worldwide, there has been little systematic LD follow-up. The Norwegian data were collected from a single center and a national health care system.[23] In the United States, reporting of 2-year outcomes is required. However, even

within this short interval, only approximately 66% of LDs have complete data.[78]

Although LD survival longer than 50 years has been reported,[79] there are only a few studies that include a substantial number of LDs more than 20 years after donation. In these studies, the reported interval from donation to ESKD is directly related to the duration of follow-up. In the US study by Muzaale et al,[24] mean follow-up was 7.2 years and the mean interval from donation to ESKD was 8.6 years. In the Norwegian study, median follow-up was 15.1 years and the median interval from donation to ESKD was 18.7 years.[23] With longer follow-up in the University of Minnesota series[80] and in a Canadian series (J. Gill, J. Lesage, personal communication), mean interval from donation to ESKD was 27 years.

In the study with the longest follow-up, Keys et al[79] reported on 66 LDs donating 50 or more years earlier. Of the 66 LDs, 22 (33.3%) were still alive (current mean ± SD age, 78.5±7.25 years), 39 (59.1%) had died (mean ± SD age at death, 74.2±12.3 years), and 5 (7.6%) were lost to follow-up (mean ± SD age at last contact, 68.7±4.6 years). There were no differences among the 3 groups other than those who had died were older at donation. At last follow-up, the mean ± SD eGFR by Chronic Kidney Disease Epidemiology Collaboration for LDs currently alive was 60.2±13.4 mL/min/1.73 m^2, for those who died was 54.0±21.5 mL/min/1.73 m^2, and for those lost to follow-up was 55.6±7.5 mL/min/1.73 m^2; ESKD developed in 2 LDs (3.0%).

Onset of CKD Risk Factors After Donation

A critical question is whether LDs who subsequently develop risk factors for CKD—even years after nephrectomy—will have an accelerated course to CKD and kidney failure. Of particular concern are obesity, type 2 diabetes, and hypertension; each can occur later in life. There are few data to answer this question.

Issa et al[81] studied serial BMI after donation (median follow-up, 22 years) and reported that weight gain was associated with increased risk of hypertension and/or

TABLE 2. Web-Based Calculators for Estimating Risk of Adverse Outcomes in Kidney Donors

	Grams et al,[90] 2016	Massie et al,[91] 2017	Palzer et al,[93] 2020
Reference	Grams et al,[90] 2016	Massie et al,[91] 2017	Palzer et al,[93] 2020
Data source	7 General population cohorts	National donor registry	Single center
Follow-up	Median per cohort, 4-16 y	Not available	Median, 22.8 y (range, 0.8-56.4 y)
Predictor variables			
Age	X	X	X
Sex	X	X	X
Race	X	X	X
Myocardial infarction	X	X	X
Donor/recipient relationship		X	X
eGFR	X		X
Creatinine			X
Urinary albumin to creatinine ratio	X		
Smoking history	X		X
Systolic BP	X		X
Diastolic BP			X
Hypertension medications	X		
Non—insulin-dependent diabetes	X		
Glucose			X
Family history			
Hypertension			X
Hyperlipidemia			X
Recipient type 1 diabetes			X
Recipient type 2 diabetes			X
Outcomes predicted	15-y and lifetime risk of diabetes; proteinuria; kidney failure without eGFR <60, <45, <30 mL/min/1.73 m² donation	20-y donor risk of kidney failure	40-y donor risk of hypertension

BP = blood pressure; eGFR = estimated glomerular filtration rate.
From *Nat Rev Nephrol*,[96] with permission.

diabetes. Locke et al[82] studied the impact of obesity at the time of donation in 119,769 LDs in the United States. Maximum follow-up was 20 years. They found that for each unit increase in BMI higher than 27 there was an associated significant 7% increase in risk of ESKD. The risk was similar for male and female donors, African American and White donors, and across the baseline eGFR spectrum. In a separate analysis, Locke et al[83] also reported that high BMI at donation was associated with increased mortality.

In a study from the University of Minnesota, Ibrahim et al[84] reported that of 4014 LDs, 309 (7.7%) developed diabetes a median of 18 years after donation. At donation, those subsequently developing diabetes had a higher BMI, glucose level, and creatinine concentration; after donation, they had increased weight gain. The LDs developing diabetes were followed an average of 9.2 years (range, 0-37 years) after onset of diabetes. In the 7 years before the onset of diabetes there was no difference in slope of eGFR for those developing diabetes compared with those without. Onset of diabetes in LDs was associated with the development of proteinuria and hypertension. After the development of diabetes, eGFR decline exceeded that of nondiabetic LDs only for those who had concomitant proteinuria and hypertension.

Sanchez et al[85] reported that with median follow-up of 16 years after donation, 27% of LDs developed hypertension. Risk factors at donation included older age, higher BMI, higher systolic and diastolic BPs, hyperlipidemia, and smoking. Hypertension was associated with proteinuria, CKD, CVD, and mortality. Importantly, in the studies by Ibrahim et al[84] and Sanchez et al,[85] there was more than 15 years between donation and onset of new disease and less than 10 years of follow-up after new-onset disease, stressing the importance of additional long-term follow-up studies.

Risk Factors for CKD and ESKD and Risk Calculators

In the general population, numerous risk factors for the development of CKD and ESKD have been identified, including biological relationship to an individual with ESKD, smoking, BMI, sex, age, race/ethnicity, lower GFR, proteinuria, hematuria, hypertension, and diabetes.[86-89] Similar risk factors—identifiable at evaluation—have been found for LDs, including biological relationship to recipient, sex, age, race/ethnicity, BMI, lower GFR, and lower socioeconomic status.[16,69,82,90,91] In addition, also similar to the general population, it has recently been proposed that in African American individuals, APOL1 genotype may be a risk factor for long-term CKD and ESKD.[92]

Identification of risk factors present at the time of evaluation allows for the development of risk calculators that can be used to facilitate LD acceptance decisions and improve informed consent. Two such calculators have been developed. Using the University of Minnesota LD database, we developed a calculator to estimate the long-term risk of hypertension, diabetes, proteinuria, and eGFR less than 60, less than 45, and less than 30 mL/min/1.73 m^2 (Table 2) (shiny.biostat.umn.edu/transplant/kidneydonor).[16,93] Massie et al,[91] using the US national LD registry data, developed a prediction model to estimate the long-term risk of developing ESKD (Table 2) (transplantmodels.com/donesrd). In addition, Grams et al[90] developed a calculator, using data from 7 general population cohorts, that determines the projected risk of ESKD in the absence of donation (Table 2) (transplantmodels.com/esrdrisk). Each calculator has limitations based on the data available in the data set.[94,95] A calculator that could estimate long-term risks with and without donation (based on LDs and controls) is still needed.

Other Long-term LD Outcomes

In addition to the previously mentioned outcomes, other specific outcomes have been studied. In studies comparing LDs with matched controls, there were no differences between groups in microalbuminuia,[58] incidence of diabetes,[54,56,59] acute renal failure,[59] hyperlipidemia,[59] depression,[57] BMI,[58] cancer,[59,97] fractures,[98] or kidney stones.[99] In contrast, Grupper et al[56] reported that LDs were more likely to develop new-onset metabolic syndrome, mainly from increased triglycerides and impaired fasting glucose levels. Consistent with reports of elevated uric acid levels, Lam et al[100] reported that LDs had an increased incidence of gout.

Pregnancy After Donation

Pregnancy is associated with anatomical and physiologic effects on the kidney, including

hypertrophy and hyperfiltration.[101] Furthermore, pregnancies in women with CKD are associated with increased maternal and fetal complications. Thus, there have been concerns about pregnancies after donation. Unfortunately, there remains limited data on pregnancies among female LDs.

To date, the data suggest that pregnancy after donation, compared with pregnancy in the matched general population, is not associated with an increased risk of complications (maternal or fetal).[102,103] However, comparing pregnancies after donation with those before donation, Ibrahim et al noted that pregnancies after donation were associated with a higher-than-expected risk of hypertension and preeclampsia.[102] Reisaeter et al[103] reported similar findings. Garg et al[104] matched 85 LDs with 510 controls and reported that hypertension and preeclampsia were more common in LDs (11%) than in controls (5%). The increased risk of preeclampsia reported in these studies is similar to what has been seen in women with chronic hypertension, gestational diabetes, and a higher BMI. More recently, Davis et al[105] studied 59 LDs with pregnancies, matched (on age and race) 4:1 with first pregnancies in women with 2 kidneys and reported no differences in adverse events. However, there was a trend toward increased risk of preeclampsia in the LDs (odds ratio, 2.96; 95% confidence interval, 0.98 to 8.94), and for LDs younger than 30 years there was a 4-fold increased risk of preeclampsia (odds ratio, 4.09; 95% confidence interval, 1.07 to 15.59). In addition, Yoo et al[106] studied 56 LDs matched with 437 (propensity-matched) controls; there were no differences between groups in gestational hypertension, proteinuria, or preeclampsia.

In the only LD study reporting long-term outcomes for women with gestational hypertension or preeclampsia, Ibrahim et al[102] found that LDs with maternal complications, compared with LDs without complications, had similar eGFRs but were more likely to have proteinuria and/or hypertension.

These observations suggest that LD candidates of childbearing age should be informed and counseled about increased risks of hypertension and preeclampsia, and told that pregnancies after donation should be considered "higher risk," with stringent monitoring for hypertension and preeclampsia, and rapid institution of appropriate care.

POTENTIAL MECHANISMS FOR PROGRESSIVE DECLINE IN GFR AFTER KIDNEY DONATION

Underlying Disease or Disease Risk That Was Present Before Donation

One possibility for progressive decline in GFR after donation is underlying (subclinical) disease in the donor. Although LD evaluations are thorough, they are by no means comprehensive for all measures of kidney disease. Some kidney diseases are genetic and manifest later in life. The classic example is autosomal dominant polycystic kidney disease. Transplant programs have developed inclusion and exclusion criteria that should eliminate acceptance of most LDs with polycystic kidney disease. However, there are likely other genetic factors that contribute to disease risk.[107-113] Indeed, living kidney donors donating to a blood relative with ESKD have fewer nephrons than donors who are unrelated to the recipient.[114] Interestingly, although there is a lot of missing information in registry data, analysis of Organ Procurement and Transplantation Network data found that only a few LDs developing ESKD had the same disease as their recipient.[77] This observation is limited by uncertainty in the cause of ESKD because often no kidney biopsy was performed in the recipient. Regardless, comprehensive genetic testing for kidney disease is not generally performed in LDs, despite many being first-degree relatives of the recipient with ESKD.

In the general population, individuals of African American ancestry have an increased risk of ESKD. For example, in the United States, individuals with African American ancestry compose 13.4% of the general

population but 31.5% of the ESKD population. More than a decade ago, it was recognized that some of this increased risk was related to inheriting 2 copies of the G1/G2 variants of the apolipoprotein L1 gene (APOL1).[115] Importantly, the pathogenesis of the kidney injury is poorly understood, and most individuals of African ancestry with 2 copies do not get kidney disease. Doshi et al[92] studied the impact of APOLI genotype in 136 African American LDs. Of the 136 LDs, 19 (14%) had 2 APOL1 risk alleles and were classified as high risk; 117 (86%) had 0 or 1 risk allele and were classified as low risk. Predonation characteristics were similar between the groups, except that the high-risk group had a lower GFR before donation (P=.04). A median of 12 years after donation, LDs with the high-risk alleles had significantly lower eGFR (P=.02) and a faster decline in eGFR after adjusting for GFR before donation (P=.02). Two donors had developed ESKD; both had the high-risk genotype. Currently, there is a National Institutes of Health—sponsored trial (APOL1 Long-term kidney transplantation outcomes network [APOLLO]) studying the outcomes of kidney transplant from deceased and living donors with recent African American ancestry.[116] A secondary goal of the study is to determine whether the presence of the high-risk genotype in LDs is associated with worse outcomes after kidney donation.

Given that most individuals with 2 high-risk alleles do not develop kidney disease, there is a debate in the transplant literature as to whether to genotype LD candidates of African American ancestry. There is a second debate about whether those with 2 high-risk alleles should be accepted for donation. Some centers will accept older candidates, but not younger candidates, with 2 high-risk alleles and normal mGFR.

Kidney donor evaluations do not typically involve a kidney biopsy of the potential donor. This is based on the invasive and potentially harmful nature of kidney biopsies, which would likely discourage donation, and, more importantly, the perceived lack of clinical usefulness in donor evaluations. A donor evaluation that reveals a normal GFR and no hypertension, proteinuria, or active urine sediment would seemingly be reassuring that the kidney histology is "normal." However, careful morphometric study of kidney histology from biopsies obtained at the time of donation suggest otherwise. There is significant variation in the underlying microstructural features of nephrosclerosis (arteriosclerosis, global glomerulosclerosis, and interstitial fibrosis), nephron number, and nephron size among kidney LDs. This microstructural variation is only weakly correlated with the more accessible clinical and laboratory characteristics of LDs at the time of their evaluation.[117] More importantly, these microstructural features predict adverse kidney outcomes along pathways that are not detected by CKD risk factors or kidney function tests (including mGFR and 24h urine albumin). Specifically, larger glomerular volume and more interstitial fibrosis and tubular atrophy at the time of donation predict mGFR less than 60 mL/min/1.73 m^2 4 months after donation.[118] Larger and fewer nephrons predicts the development of detectable albuminuria (>5 mg/24 h), and arteriosclerosis predicts the onset of hypertension 4 months after donation.[118] With a decade of follow-up, larger glomeruli predict eGFR less than 45 mL/min/1.73 m^2 and proteinuria, whereas low nephron number predicts a larger decline in eGFR after donation and eGFR less than 45 mL/min/1.73 m^2.[119] Relatedly, low birth weight is a surrogate for low nephron number and is predictive of albuminuria a decade after donation.[120] In the recipient of LD kidneys, death-censored graft failure over a mean of 6.3 years was predicted by more severe interstitial fibrosis and tubular atrophy, arteriolar hyalinosis, larger glomeruli, and larger tubules in the LD kidney at the time of donation.[121] The strength of these predictions is modest and probably does not warrant routine kidney biopsy of LDs. Nonetheless, they highlight the presence of microstructural kidney features that go undetected by current donor evaluations and yet are

predictive of adverse kidney outcomes in both the LD and the recipient after donation.

Detrimental Impact of Glomerular Hyperfiltration After Donation

Another possible etiology for LD ESKD is that, similar to the rat model, the resulting glomerular hyperfiltration leads to nephron damage. Early after donation, the GFR in the remaining kidney is approximately 70% of the GFR before donation due to compensatory hyperfiltration (increase in single-nephron GFR).[122] However, as noted previously herein, in the rat model progressive decline in renal function occurred only with additional damage to the remaining kidney; in other species, progressive decline in renal function was not seen after uninephrectomy. Lenihan et al[123] note that ESKD after donation is not commonly due to focal segmental glomerulosclerosis, which would have been expected if hyperfiltration were the pathogenesis. Importantly, physiologic modeling studies in LDs have suggested that the compensatory increase in single-nephron GFR after donation is not maladaptive.[122]

Impact of a Lower Baseline GFR After Donation

It is possible that the abrupt decrease in renal function associated with nephrectomy, followed by the somewhat variable age-related decline in GFR,[124] may lead to clinically relevant kidney disease in some LDs. However, the 2 studies cited previously herein comparing renal function in LDs and controls[46,47] found that there was an annual decline in GFR for the controls, whereas in the LDs the GFR either increased or was stable. Other studies, some with follow-up longer than 15 years, have reported small annual increases in eGFR.[125-128] In young LDs, annual increases in eGFR could be seen up to 25 years after donation.[128]

The new lower baseline GFR after donation can still be viewed as a loss of "renal reserve" such that with onset of kidney disease later in life (unrelated to the donation) there is earlier progression to ESKD. In other words, an LD developing kidney disease starts off with a lower GFR than an individual with 2 kidneys. If the slope of decline in GFR from a disease is the same in these 2 individuals, the LD will develop ESKD sooner than the nondonor. Indeed, this likely possibility was first suggested by Kido et al,[129] who noted that for 9 LDs developing ESKD, eGFR was stable until development of new-onset disease (eg, kidney disease, diabetes). This observation was confirmed in a larger series.[80]

These latter observations are important for candidate evaluation and acceptance and LD follow-up. Some new-onset diseases (eg, immunologic) are unpredictable; however, early detection and intervention may slow their course. But the 2 most common causes of LD ESKD in the United States are type 2 diabetes and hypertension.[77] Both are diseases associated with lifestyle and both develop with aging. The data suggest that every effort should be made to encourage LDs to live a healthy lifestyle.

CONCLUSION

Counseling Donor Candidates

In addition to counseling about perioperative risks, LD candidates should be counseled about the potential long-term risks. Counseling should include information on the 2 studies that reported increased ESKD and their limitations and that current data suggest that any increased risk may be limited to first-degree relatives of the recipient because related donors have been followed longer than unrelated donors. Women of childbearing age should be informed about the increased risk of gestational hypertension and preeclampsia associated with pregnancies after donation.

All LD candidates should be informed that the decision to donate should be accompanied by a commitment to a healthy lifestyle as well as regular health maintenance visits that screen for early kidney disease and kidney disease risk factors. Screening, followed by intervention if necessary, may minimize long-term risks.

Long-term Donor Care

Historically, there was a debate as to whether LDs should be followed closely after donation. One school of thought was that donation should be treated similar to an appendectomy: once the LD had recovered from the surgery, there should be no emphasis on long-term follow-up. The rationale was that LD candidates are told that donation is safe; recommending follow-up that differed from normal adult preventive care would send a message that LDs should worry about long-term risks. Alternatively, some suggested that given the limited information about outcomes after uninephrectomy, LD follow-up should include more frequent follow-up visits than would normally be required for preventive care. We have now learned that type 2 diabetes and hypertension are the 2 most common causes of ESKD after living donation. We also know that treatment of new-onset CKD can often slow the progression. As discussed previously herein, living donation should be paired with a lifetime commitment to a healthy lifestyle.

The Need for Additional Studies

It has been more than 65 years since the first successful LD transplant. At that time, the justification for considering an LD transplant was the knowledge that individuals born with a single kidney could live a normal life. Since that early era, much has been learned about CKD, risk factors for CKD, and the association of relatively small decreases in GFR with increased morbidity and mortality. However, most of this information has come from studies of populations whose decreased GFR is due to kidney or systemic disease. In contrast, decreased GFR in LDs is solely due to nephrectomy. As described previously herein, although there are numerous reports about LD outcomes, there are few data on outcomes compared with appropriately matched controls and with sufficient follow-up time to meaningfully assess attributable risk. These data are needed to optimize donor candidate counseling and informed consent; and, importantly, LDs themselves are asking for this information.[130-133] The information will also contribute to knowledge as to whether nephron loss alone is a risk factor for morbidity and mortality or these risks are seen only when nephron loss is due to an underlying disease process.

POTENTIAL COMPETING INTERESTS

Dr Rule receives royalties from UpToDate and serves as a section editor for *Mayo Clinic Proceedings*. Dr Matas reports no competing interests.

ACKNOWLEDGMENTS

Correspondence: Address to Arthur Matas, MD, 420 Delaware St SE, Mayo Mail Code 195, Minneapolis, MN 55455 (matas001@umn.edu; Twitter: @AndrewRuleMD).

ORCID
Arthur J. Matas: https://orcid.org/0000-0001-9957-639X

REFERENCES

1. Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. *Lancet.* 1992; 340(8823):807-810. https://doi.org/10.1016/0140-6736(92)92683-7
2. Kasiske BL, Ma JZ, Louis TA, Swan SK. Long-term effects of reduced renal mass in humans. *Kidney Int.* 1995;48(3):814-819. https://doi.org/10.1038/ki.1995.355
3. Gossmann J, Wilhelm A, Kachel HG, et al. Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. *Am J Transplant.* 2005; 5(10):2417-2424. https://doi.org/10.1111/j.1600-6143.2005.01037.x
4. Torres VE, Offord KP, Anderson CF, et al. Blood pressure determinants in living-related renal allograft donors and their recipients. *Kidney Int.* 1987;31(6):1383-1390. https://doi.org/10.1038/ki.1987.153
5. Rizvi SA, Naqvi SA, Jawad F, et al. Living kidney donor follow-up in a dedicated clinic. *Transplantation.* 2005;79(9):1247-1251. https://doi.org/10.1097/01.tp.0000161666.05236.97
6. Fehrman-Ekholm I, Dunér F, Brink B, Tydén G, Elinder CG. No evidence of accelerated loss of kidney function in living

kidney donors: results from a cross-sectional follow-up. *Transplantation*. 2001;72(3):444-449. https://doi.org/10.1097/00007890-200108150-00015

7. Ramcharan T, Matas AJ. Long-term (20-37 years) follow-up of living kidney donors. *Am J Transplant*. 2002;2(10):959-964.

8. El-Agroudy AE, Sabry AA, Wafa EW, et al. Long-term follow-up of living kidney donors: a longitudinal study. *BJU Int*. 2007;100(6):1351-1355. https://doi.org/10.1034/j.1600-6143.2002.21013.x

9. Goldfarb DA, Matin SF, Braun WE, et al. Renal outcome 25 years after donor nephrectomy. *J Urol*. 2001;166(6):2043-2047.

10. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tydén G, Groth CG. Kidney donors live longer. *Transplantation*. 1997;64(7):976-978. https://doi.org/10.1097/00007890-199710150-00007

11. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009;360(5):459-469. https://doi.org/10.1056/NEJMoa0804883

12. Okamoto M, Akioka K, Nobori S, et al. Short- and long-term donor outcomes after kidney donation: analysis of 601 cases over a 35-year period at Japanese single center. *Transplantation*. 2009;87(3):419-423. https://doi.org/10.1097/TP.0b013e318192dc95

13. Fehrman-Ekholm I, Nordén G, Lennerling A, et al. Incidence of end-stage renal disease among live kidney donors. *Transplantation*. 2006;82(12):1646-1648. https://doi.org/10.1097/01.tp.0000250728.73268.e3

14. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. *N Engl J Med*. 2010;363(8):724-732. https://doi.org/10.1056/NEJMoa1000950

15. Fournier C, Pallet N, Chergaoui Z, et al. Very long-term follow-up of living kidney donors. *Transpl Int*. 2012;25(4):385-390. https://doi.org/10.1111/j.1432-2277.2012.01439.x

16. 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(9):2885-2893. https://doi.org/10.1681/ASN.2015091018

17. Mjøen G, Reisaeter A, Hallen S, et al. Overall and cardiovascular mortality in Norwegian kidney donors compared to the background population. *Nephrol Dial Transplant*. 2012;27(1):443-447. https://doi.org/10.1093/ndt/gfv397

18. Garg AX, Prasad GV, Thiessen-Philbrook HR, et al. Donor Nephrectomy Outcomes Research (DONOR) Network. Cardiovascular disease and hypertension risk in living kidney donors: an analysis of health administrative data in Ontario, Canada. *Transplantation*. 2008;86(3):399-406. https://doi.org/10.1097/TP.0b013e31817ba9e3

19. Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA*. 2010;303(10):959-966. https://doi.org/10.1001/jama.2010.237

20. Berger JC, Muzaale AD, James N, et al. Living kidney donors ages 70 and older: recipient and donor outcomes. *Clin J Am Soc Nephrol*. 2011;6(12):2887-2893. https://doi.org/10.2215/CJN.04160511

21. Garg AX, Meirambayeva A, Huang A, et al. Cardiovascular disease in kidney donors: matched cohort study. *BMJ*. 2012;344:e1203. https://doi.org/10.1136/bmj.e1203

22. Reese PP, Bloom RD, Feldman HI, et al. Mortality and cardiovascular disease among older live kidney donors. *Am J Transplant*. 2014;14(8):1853-1861. https://doi.org/10.1111/ajt.12822

23. Mjøen G, Hallan S, Harmann A, et al. Long-term risks for kidney donors. *Kidney Int*. 2014;86(1):162-167. https://doi.org/10.1038/ki.2013.460

24. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. *JAMA*. 2014;311(6):579-586. https://doi.org/10.1001/jama.2013.285141

25. Pabico RC, McKenna BA, Freeman RB. Renal function before and after unilateral nephrectomy in renal donors. *Kidney Int*. 1975;8(3):166-175. https://doi.org/10.1038/ki.1975.96

26. Shimamura T, Morrison AB. A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. *Am J Pathol*. 1975;79(1):95-106.

27. Kaufman JM, Siegel NJ, Hayslett JP. Functional and hemodynamic adaptation to progressive renal ablation. *Circ Res*. 1975;36(2):286-293. https://doi.org/10.1161/01.res.36.2.286

28. Purkerson ML, Hoffsten PE, Klahr S. Pathogenesis of the glomerulopathy associated with renal infarction in rats. *Kidney Int*. 1976;9(5):407-417. https://doi.org/10.1038/ki.1976.50

29. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol*. 1981;241(1):F85-F93. https://doi.org/10.1152/ajprenal.1981.241.1.F85

30. Robertson JL, Goldschmidt M, Kronfeld DS, Tomaszewski JE, Hill GS, Bovee KC. Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. *Kidney Int*. 1986;29(2):511-519. https://doi.org/10.1038/ki.1986.29

31. Bourgoignie JJ, Gavellas G, Hwang KH, Disbrow MR, Sabnis SG, Antonovych TT. Renal function of baboons (*Papio hamadryas*) with a remnant kidney, and impact of different protein diets. *Kidney Int Suppl*. 1989;27:S86-S90.

32. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305. https://doi.org/10.1056/NEJMoa041031

33. Fox CS, Matsushita K, Woodward M, et al. Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380(9854):1662-1673. https://doi.org/10.1016/S0140-6736(12)61350-6

34. Carmena R, Ascaso JF, Redon J. Chronic kidney disease as a cardiovascular risk factor. *J Hypertens*. 2020;38(11):2110-2121. https://doi.org/10.1097/HJH.0000000000002506

35. Kovesdy CP, Coresh J, Ballew SH, et al; CKD Prognosis Consortium. Past decline versus current eGFR and subsequent ESRD risk. *J Am Soc Nephrol*. 2016;27(8):2447-2455. https://doi.org/10.1681/ASN.2015060687

36. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311(24):2518-2531. https://doi.org/10.1001/jama.2014.6634

37. Tangri N, Kitsios GD, Inker LA, et al. Risk prediction models for patients with chronic kidney disease: a systematic review. *Ann Intern Med*. 2013;158(8):596-603. https://doi.org/10.7326/0003-4819-158-8-201304160-00004

38. McGraw M, Poucell S, Sweet J, Baumal R. The significance of focal segmental glomerulosclerosis in oligomeganephronia. *Int J Pediatr Nephrol*. 1984;5(2):67-72.

39. Kiprov DD, Colvin RB, McCluskey RT. Focal and segmental glomerulosclerosis and porteinuria associated with unilateral renal agenesis. *Lab Invest*. 1982;46(3):275-281.

40. Thorner PS, Arbus GS, Celermajer DS, Baumal R. Focal segmental glomerulosclerosis and progressive renal failure associated with a unilateral kidney. *Pediatrics*. 1984;73(6):806-810.

41. Andersen B, Hansen JB, Jorgensen SJ. Survival after nephrectomy. *Scand J Urol Nephrol*. 1968;2(2):91-94. https://doi.org/10.3109/00365596809136977

42. Robitaille P, Mongeau JG, Lortie L, Sinnassamy P. Long-term follow-up of patients who underwent unilateral nephrectomy in childhood. *Lancet*. 1985;1(8441):1297-1299. https://doi.org/10.1016/s0140-6736(85)92792-8

43. Baudoin P, Provoost AP, Molenaar JC. Renal function up to 50 years after unilateral nephrectomy in childhood. *Am J Kidney Dis*. 1993;21(6):603-611. https://doi.org/10.1016/s0272-6386(12)80032-1

44. Narkun-Burgess DM, Nolan CR, Norman JE, Page WF, Miller PL, Meyer TW. Forty-five year follow-up after

uninephrectomy. *Kidney Int.* 1993;43(5):1110-1115. https://doi.org/10.1038/ki.1993.156

45. Kasiske BL, Anderson-Haag T, Israni AK, et al. A prospective controlled study of living kidney donors: three-year follow-up. *Am J Kidney Dis.* 2015;66(1):114-124. https://doi.org/10.1053/j.ajkd.2015.01.019

46. Kasiske BL, Anderson-Haag TL, Duprez DA, et al. A prospective controlled study of metabolic and physiologic effects of kidney donation suggests that donors retain stable kidney function over the first nine years. *Kidney Int.* 2020;98(1):168-175. https://doi.org/10.1016/j.kint.2020.01.017

47. Lam NN, Lloyd A, Lentine KL, et al. Changes in kidney function follow living donor nephrectomy. *Kidney Int.* 2020;98(1):176-186. https://doi.org/10.1016/j.kint.2020.03.034

48. Kasiske BL, Kumar R, Kimmel PL, et al. Abnormalities in biomarkers of mineral and bone metabolism in kidney donors. *Kidney Int.* 2016;90(4):861-868. https://doi.org/10.1016/j.kint.2016.05.012

49. Moody WE, Ferro CJ, Edwards NC, et al. CRIB-Donor Study Investigators. Cardiovascular effects of unilateral nephrectomy in living kidney donors. *Hypertension.* 2016;67(2):368-377. https://doi.org/10.1161/HYPERTENSIONAHA.115.06608

50. Price AM, Moody WE, Stoll VM, et al. Cardiovascular effects of unilateral nephrectomy in living kidney donors at 5 years. *Hypertension.* 2021;77(4):1273-1284. https://doi.org/10.1161/HYPERTENSIONAHA.120.15398

51. Doshi MD, Goggins MO, Li L, Garg AX. Medical outcomes in African American live kidney donors: a matched cohort study. *Am J Transplant.* 2013;13(1):111-118. https://doi.org/10.1111/j.1600-6143.2012.04303.x

52. Holscher CM, Haugen CE, Jackson KR, et al. Self-reported incident hypertension and long-term kidney function in living kidney donors compared with healthy nondonors. *Clin J Am Soc Nephrol.* 2019;14(10):1493-1499. https://doi.org/10.2215/CJN.04020419

53. Haugen AJ, Hallan S, Langberg NE, et al. Increased long-term risk for hypertension in kidney donors: a retrospective cohort study. *Transpl Int.* 2020;33(5):536-543. https://doi.org/10.1111/tri.13576

54. Chaudry M, Gislason GH, Fosbøl EL, Køber L, Gerds TA, Torp-Pedersen C. Hypertension, cardiovascular disease and cause of death in Danish living kidney donors: matched cohort study. *BMJ Open.* 2020;10(11):e041122. https://doi.org/10.1136/bmjopen-2020-041122

55. Munch P, Christiansen CF, Birn H, Erikstrup C, Nørgaard M. Is the risk of cardiovascular disease increased in living kidney donors? a Danish population-based cohort study. *Am J Transplant.* 2021;21(5):1857-1865. https://doi.org/10.1111/ajt.16384

56. Grupper A, Angel Y, Baruch A, et al. Long term metabolic and renal outcomes of kidney donors compared to controls with excellent kidney function. *BMC Nephrol.* 2019;20(1):30. https://doi.org/10.1186/s12882-019-1214-4

57. Krishnan N, Mumford L, Lipkin G, et al. Comparison of medium-term outcomes of living kidney donors with longitudinal healthy control in the United Kingdom. *Transplantation.* 2020;104(3):e65-e74. https://doi.org/10.1097/TP.0000000000003082

58. Janki S, Dehghan A, van de Wetering J, et al. Long-term prognosis after kidney donation: a propensity score matched comparison of living donors and non-donors from two population cohorts. *Eur J Epidemiol.* 2020;35(7):699-707. https://doi.org/10.1007/s10654-020-00647-y

59. Lin SY, Lin CL, Sung FC, et al. Risk of subsequent health disorders among living kidney donors. *Medicine (Baltimore).* 2019;98(7):e14494. https://doi.org/10.1097/MD.0000000000014494

60. Kim Y, Yu MY, Yoo KD, et al. Long-term mortality risks among living kidney donors in Korea. *Am J Kidney Dis.* 2020;75(6):919-925. https://doi.org/10.1053/j.ajkd.2019.09.015

61. O'Keeffe LM, Ramond A, Oliver-Williams C, et al. Mid- and long-term health risks in living kidney donors: a systematic review and meta-analysis. *Ann Intern Med.* 2018;168(4):276-284. https://doi.org/10.7326/M17-1235

62. Janki S, Steyerberg EW, Hofman A, IJzermans JN. Live kidney donation: are concerns about long-term safety justified? a methodological review. *Eur J Epidemiol.* 2017;32(2):103-111. https://doi.org/10.1007/s10654-016-0168-0

63. Maggiore U, Budde K, Heemann U, et al; ERA-EDTA DESCARTES working group. Long-term risks of kidney living donation: review and position paper by the ERA-EDTA DESCARTES working group. *Nephrol Dial Transplant.* 2017;32(2):216-223. https://doi.org/10.1093/ndt/gfw429

64. Data. Organ Procurement and Transplantation Network. Accessed January 2021. https://optn.transplant.hrsa.gov/data/

65. *SRTR custom data request. Scientific Registry of Transplant Recipients.* Hennepin Healthcare Research Institute; Requested November 2, 2020. Data as of September 30, 2020.

66. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. *J Am Soc Nephrol.* 1998;9(7):1270-1276. https://doi.org/10.1681/ASN.V971270

67. O'Dea DF, Murphy SW, Hefferton D, Parfrey PS. Higher risk for renal failure in first-degree relatives of white patients with end-stage renal disease: a population-based study. *Am J Kidney Dis.* 1998;32(5):794-801. https://doi.org/10.1016/s0272-6386(98)70135-0

68. Skrunes R, Svarstad E, Reisæter AV, Vikse BE. Familial clustering of ESRD in the Norwegian population. *Clin J Am Soc Nephrol.* 2014;9(10):1692-1700. https://doi.org/10.2215/CJN.01680214

69. Wainright JL, Robinson AM, Wilk AR, Klassen DK, Cherikh WS, Stewart DE. Risk of ESRD in prior living kidney donors. *Am J Transplant.* 2018;18(5):1129-1139. https://doi.org/10.1111/ajt.14678

70. Gill JS, Tonelli M. Understanding rare adverse outcomes following living kidney donation. *JAMA.* 2014;311(6):577-579. https://doi.org/10.1001/jama.2013.285142

71. Kasiske BL. Outcomes after living kidney donation: what we still need to know and why. *Am J Kidney Dis.* 2014;64(3):335-337. https://doi.org/10.1053/j.ajkd.2014.04.013

72. Matas AJ, Woodle ES, Gaston RS, Forsythe JL, Wadström J, Stegall MD. Kidney donors at increased risk? additional studies are needed. *Kidney Int.* 2014;86(3):650. https://doi.org/10.1038/ki.2014.146

73. Kaplan B, Ilahe A. Quantifying risk of kidney donation: the truth is not out there (yet). *Am J Transplant.* 2014;14(8):1715-1716. https://doi.org/10.1111/ajt.12804

74. Steiner RW. Normal for now' or 'at future risk': a double standard for selecting young and older living kidney donors. *Am J Transplant.* 2010;10(4):737-741. https://doi.org/10.1111/j.1600-6143.2010.03023.x

75. Steiner RW. Moving closer to understanding the risks of living kidney donation. *Clin Transplant.* 2016;30(1):10-16. https://doi.org/10.1111/ctr.12652

76. Steiner RW. "You can't get there from here": critical obstacles to current estimates of the ESRD risks of young living kidney donors. *Am J Transplant.* 2019;19(1):32-36. https://doi.org/10.1111/ajt.15089

77. Matas AJ, Hays RE, Ibrahim HN. A case-based analysis of whether living related donors listed for transplant share ESRD causes with their recipients. *Clin J Am Soc Nephrol.* 2017;12(4):663-668. https://doi.org/10.2215/CJN.11421116

78. Henderson ML, Thomas AG, Shaffer A, et al. The national landscape of living kidney donor follow-up in the United States. *Am J Transplant.* 2017;17(12):3131-3140. https://doi.org/10.1111/ajt.14356

79. Keys DO, Jackson S, Berglund D, Matas AJ. Kidney donor outcomes $\geq$ 50 years after donation. *Clin Transplant.* 2019;33(10):e13657. https://doi.org/10.1111/ctr.13657

80. Matas AJ, Berglund DM, Vock DM, Ibrahim HN. Causes and timing of end-stage renal disease after living kidney donation.

Am J Transplant. 2018;18(5):1140-1150. https://doi.org/10.1111/ajt.14671

81. Issa N, Sánchez OA, Kukla A, et al. Weight gain after kidney donation: association with increased risks of type 2 diabetes and hypertension. *Clin Transplant.* 2018;32(9):e13360. https://doi.org/10.1111/ctr.13360

82. Locke JE, Reed RD, Massie A, et al. Obesity increases the risk of end-stage renal disease among living kidney donors. *Kidney Int.* 2017;91(3):699-703. https://doi.org/10.1016/j.kint.2016.10.014

83. Locke JE, Reed RD, Massie AB, et al. Obesity and long-term mortality risk among living kidney donors. *Surgery.* 2019;166(2):205-208. https://doi.org/10.1016/j.surg.2019.03.016

84. Ibrahim HN, Berglund DM, Jackson S, Vock DM, Foley RN, Matas AJ. Renal consequences of diabetes after kidney donation. *Am J Transplant.* 2017;17(12):3141-3148. https://doi.org/10.1111/ajt.14416

85. Sanchez OA, Ferrara LK, Rein S, Berglund D, Matas AJ, Ibrahim HN. Hypertension after kidney donation: incidence, predictors, and correlates. *Am J Transplant.* 2018;18(10):2534-2543. https://doi.org/10.1111/ajt.14713

86. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S. Influence of smoking and obesity on the development of proteinuria. *Kidney Int.* 2002;62(3):956-962. https://doi.org/10.1046/j.1523-1755.2002.00506.x

87. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int.* 1996;49(3):800-805. https://doi.org/10.1038/ki.1996.111

88. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int.* 2003;63(4):1468-1474. https://doi.org/10.1046/j.1523-1755.2003.00868.x

89. Praga M, Hernández E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. *Kidney Int.* 2000;58(5):2111-2118. https://doi.org/10.1111/j.1523-1755.2000.00384.x

90. Grams ME, Sang Y, Levey AS, et al. Chronic kidney disease prognosis consortium. kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374(5):411-421. https://doi.org/10.1056/NEJMoa1510491

91. Massie AB, Muzaale AD, Luo X, et al. Quantifying postdonation risk of ESRD in living kidney donors. *J Am Soc Nephrol.* 2017;28(9):2749-2755. https://doi.org/10.1681/ASN.2016101084

92. Doshi MD, Ortigosa-Goggins M, Garg AX, et al. APOL1 genotype and renal function of black living donors. *J Am Soc Nephrol.* 2018;29(4):1309-1316. https://doi.org/10.1681/ASN.2017060658

93. Palzer EF, Vempati S, Helgeson ES, Matas AJ. Long-term living kidney donor risk: a web-based calculator. *J Am Soc Nephrol.* 2020;31(12):2968-2969. https://doi.org/10.1681/ASN.2020081238

94. 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 (Carlton).* 2018;23(7):616-624. https://doi.org/10.1111/nep.13074

95. 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(8):799-806. https://doi.org/10.1111/tri.12931

96. Matas AJ, Rule AD. Risk of kidney disease after living kidney donation. *Nat Rev Nephrol.* 2021;17(8):509-510. https://doi.org/10.1038/s41581-021-00407-5

97. Lentine KL, Vijayan A, Xiao H, et al. Cancer diagnoses after living kidney donation: linking U.S. Registry data and administrative claims. *Transplantation.* 2012;94(2):139-144. https://doi.org/10.1097/TP.0b013e318254757d

98. Garg AX, Pouget J, Young A, et al. Donor Nephrectomy Outcomes Research (DONOR) Network. Fracture risk in living kidney donors: a matched cohort study. *Am J Kidney Dis.* 2012;59(6):770-776. https://doi.org/10.1053/j.ajkd.2012.01.013

99. Murad DN, Nguyen H, Hebert SA, et al. Outcomes of kidney donors with pre- and post-donation kidney stones. *Clin Transplant.* 2021;35(2):e14189. https://doi.org/10.1111/ctr.14189

100. Lam NN, McArthur E, Kim SJ, et al. Donor Nephrectomy Outcomes Research (DONOR) Network; Donor Nephrectomy Outcomes Research DONOR Network. Gout after living kidney donation: a matched cohort study. *Am J Kidney Dis.* 2015;65(6):925-932. https://doi.org/10.1053/j.ajkd.2015.01.017

101. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. *Clin J Am Soc Nephrol.* 2012;7(12):2073-2080. https://doi.org/10.2215/CJN.00470112

102. Ibrahim HN, Akkina SK, Leister E, et al. Pregnancy outcomes after kidney donation. *Am J Transplant.* 2009;9(4):825-834. https://doi.org/10.1111/j.1600-6143.2009.02548.x

103. Reisaeter AV, Røislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and birth after kidney donation: the Norwegian experience. *Am J Transplant.* 2009;9(4):820-824. https://doi.org/10.1111/j.1600-6143.2008.02427.x

104. Garg AX, Nevis IF, McArthur E, et al; DONOR Network. Gestational hypertension and preeclampsia in living kidney donors. *N Engl J Med.* 2015;372(2):124-133. https://doi.org/10.1056/NEJMoa1408932

105. Davis S, Dylewski J, Shah PB, et al. Risk of adverse maternal and fetal outcomes during pregnancy in living kidney donors: a matched cohort study. *Clin Transplant.* 2019;33(1):e13453. https://doi.org/10.1111/ctr.13453

106. Yoo KD, Lee H, Kim Y, et al. Maternal and fetal outcomes of pregnancies in kidney donors: a 30-year comparative analysis of matched non-donors in a single center. *Kidney Res Clin Pract.* 2018;37(4):356-365. https://doi.org/10.23876/j.krcp.18.0050

107. Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int.* 2019;95(4):914-928. https://doi.org/10.1016/j.kint.2018.10.031

108. Friedman DJ, Pollak MR. APOL1 nephropathy: from genetics to clinical applications. *Clin J Am Soc Nephrol.* 2021;16(2):294-303. https://doi.org/10.2215/CJN.15161219

109. Prakash S, Gharavi AG. Assessing genetic risk for IgA nephropathy: state of the art. *Clin J Am Soc Nephrol.* 2021;16(2):182-184. https://doi.org/10.2215/CJN.19491220

110. Rich SS. Genetic contribution to risk for diabetic kidney disease. *Clin J Am Soc Nephrol.* 2018;13(8):1135-1137. https://doi.org/10.2215/CJN.07240618

111. Tin A, Köttgen A. Genome-wide association studies of CKD and related traits. *Clin J Am Soc Nephrol.* 2020;15(11):1643-1656. https://doi.org/10.2215/CJN.00020120

112. Domingo-Gallego A, Pybus M, Bullich G, et al. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. *Nephrol Dial Transplant.* 2022;37(4):687-696. https://doi.org/10.1093/ndt/gfab019

113. Lemaire M, Noone D, Lapeyraque AL, Licht C, Frémeaux-Bacchi V. Inherited kidney complement diseases. *Clin J Am Soc Nephrol.* 2021;16(6):942-956. https://doi.org/10.2215/CJN.11830720

114. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol.* 2017;28(1):313-320. https://doi.org/10.1681/ASN.2016020154

115. Freedman BI, Kopp JB, Langefeld CD, et al. The apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephrol.* 2010;21(9):1422-1426. https://doi.org/10.1681/ASN.2010070730

116. Freedman BI, Moxey-Mims MM, Alexander AA, et al. APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO): design and rationale. *Kidney Int Rep.* 2019;5(3):278-288. https://doi.org/10.1016/j.ekir.2019.11.022

117. Denic A, Alexander MP, Kaushik V, et al. Detection and clinical patterns of nephron hypertrophy and nephrosclerosis among apparently healthy adults. *Am J Kidney Dis*. 2016;68(1):58-67. https://doi.org/10.1053/j.ajkd.2015.12.029

118. Issa N, Vaughan LE, Denic A, et al. Larger nephron size, low nephron number, and nephrosclerosis on biopsy as predictors of kidney function after donating a kidney. *Am J Transplant*. 2019;19(7):1989-1998. https://doi.org/10.1111/ajt.15259

119. Merzkani MA, Denic A, Narasimhan R, et al. Kidney microstructural features at the time of donation predict long-term risk of chronic kidney disease in living kidney donors. *Mayo Clin Proc*. 2021;96(1):40-51. https://doi.org/10.1016/j.mayocp.2020.08.041

120. Berglund D, MacDonald D, Jackson S, et al. Low birthweight and risk of albuminuria in living kidney donors. *Clin Transplant*. 2014;28(3):361-367. https://doi.org/10.1111/ctr.12321

121. Issa N, Lopez CL, Denic A, et al. Kidney structural features from living donors predict graft failure in the recipient. *J Am Soc Nephrol*. 2020;31(2):415-423. https://doi.org/10.1681/ASN.2019090964

122. Lenihan CR, Busque S, Derby G, Blouch K, Myers BD, Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. *J Clin Invest*. 2015;125(3):1311-1318. https://doi.org/10.1172/JCI78885

123. Lenihan CR, Myers BD, Tan JC. Glomerular function and structure in living donors: lessons from single nephron studies. *Curr Transplant Rep*. 2016;3:24-32. https://doi.org/10.1007/s40472-016-0092-y

124. Hommos MS, Glassock RJ, Rule AD. Structural and functional changes in human kidneys with healthy aging. *J Am Soc Nephrol*. 2017;28(10):2838-2844. https://doi.org/10.1681/ASN.2017040421

125. Cho HJ, Choi SW, Bae WJ, et al. Change in renal function following laparoscopic donor nephrectomy using 99 mTc-diethylenetriaminepentaacetic acid scan. *World J Urol*. 2015;33(5):719-723. https://doi.org/10.1007/s00345-014-1408-0

126. Fehrman-Ekholm I, Kvarnström N, Söfteland JM, et al. Post-nephrectomy development of renal function in living kidney donors: a cross-sectional retrospective study. *Nephrol Dial Transplant*. 2011;26(7):2377-2381. https://doi.org/10.1093/ndt/gfr161

127. Courbebaisse M, Gaillard F, Tissier AM, et al. Association of mGFR of the remaining kidney divided by its volume before donation with functional gain in mGFR among living kidney donors. *Clin J Am Soc Nephrol*. 2016;11(8):1369-1376. https://doi.org/10.2215/CJN.12731215

128. Matas AJ, Vock DM, Ibrahim HN. GFR ≤25 years postdonation in living kidney donors with (vs. without) a first-degree relative with ESRD. *Am J Transplant*. 2018;18(3):625-631. https://doi.org/10.1111/ajt.14525

129. Kido R, Shibagaki Y, Iwadoh K, et al. How do living kidney donors develop end-stage renal disease? *Am J Transplant*. 2009;9(11):2514-2519. https://doi.org/10.1111/j.1600-6143.2009.02795.x

130. Associated Press. *Healthbeat: as more people donate a kidney, a push to better track how donors fare long-term*. https://medicalxpress.com/news/2011-11-kidney-donors-fare.html

131. Shelton DL. *Living kidney donors push for better data on risks*. http://www.wnep.com/health/ct-met-living-donor-risks-20110731,0,421984.story?page=1

132. Hanson CS, Chapman JR, Gill JS, et al. Identifying outcomes that are important to living kidney donors: a nominal group technique study. *Clin J Am Soc Nephrol*. 2018;13(6):916-926. https://doi.org/10.2215/CJN.13441217

133. Ruck JM, Van Pilsum Rasmussen SE, Henderson ML, Massie AB, Segev DL. Interviews of living kidney donors to assess donation-related concerns and information-gathering practices. *BMC Nephrol*. 2018;19(1):130. https://doi.org/10.1186/s12882-018-0935-0