Evaluation of Kidney Donors: Core Curriculum 2018

Deirdre Sawinski and Jayme E. Locke

Nearly 100,000 patients are waiting for a kidney transplant, yet each year only 11,000 undergo transplantation with a deceased donor kidney. Annual death rates among waitlist registrants range from 5% to 15%; many die before receiving a transplant. Not surprisingly, registrants turn to family and friends to become living kidney donors on their behalf. Living kidney donor selection practices aim to quantify lifetime risk for kidney failure based on a candidate's predonation demographic and health characteristics. It has been established that estimated lifetime risk for kidney failure varies considerably based on predonation comorbid conditions, and as such, it is of paramount importance that potential living donor candidates undergo proper medical, surgical, and psychosocial screening before donation. This installment of *AJKD*'s Core Curriculum in Nephrology provides readers with the tools necessary for proper evaluation of living kidney donor candidates.

Complete author and article information provided before references.

Am J Kidney Dis. 71(5): 737-747. Published online January 11, 2018.

doi: 10.1053/j.ajkd.2017.10.018

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Epidemiology of Living Kidney Donors in the United States

Kidney transplantation is recognized as the optimal therapy for end-stage kidney disease, and living donors are accepted as the ideal donor source. Despite a kidney transplant waiting list that has continued to grow yearly, with nearly 98,000 people waiting for a kidney transplant as of May 2017, the number of living kidney donors has remained at about 5,600 per year after several years of steady decline. The demographics of living kidney donors have changed over time. Although women still represent the majority (63.5%) of donors, there have been increases in the number of older donors (those aged 50-64 years) and donors with body mass index (BMI) $\geq 30\ kg/m^2$ and a decline in the percentage of African American donors. The reasons underpinning these trends in donation are complex and have been variously attributed to changes in the allocation system (such as Share-35, which gave priority to pediatric patients on the deceased donor waiting list), population-based health trends (increase in obesity and diabetes), and financial disincentives to donation.

Despite these obstacles, public opinion overwhelmingly supports living donation, with >73% of people surveyed nationally indicating that they would be willing to donate a kidney, especially if the recipient was a family member. The question remains of how best to engage with potential living donors. Work has been done to better educate potential recipients about the importance of transplantation and living donation through educational series such as "Explore Transplant." Others have explored using social media and mobile applications to solicit donors; use of a Facebook-based app was associated with a 6-fold increase in living donor inquiries compared with controls in one pilot study. The idea of a "living donor champion" program has also been tested as a means to increase living donation rates; participants go through a structured program that teaches them about living donation and coaches them on how to approach potential donors. Some transplantation centers have expanded this idea and borrowed from general internal medicine practices to create a "living donor navigator" who serves as an educator, advocate, and facilitator for the living donor evaluation process. Bringing the process to the patient and his or her community has also been trialed; Rodrigue et al tested the idea of doing home visits for living donors and found that this intervention also increased the rate of living donor inquiries, especially in populations with historically low living donor rates. Each transplantation center needs to critically evaluate the patient population it serves to decide which intervention will best facilitate living donation for their transplantation candidates.

Additional Readings

- Garonzik-Wang JM, Berger JC, Ros RL, et al. Live donor champion: finding live kidney donors by seperating the advocate from the patient. *Transplantation*. 2012;93(11):1147-1150.
- Kumar K, King EA, Muzaale AD. A Smartphone app for increasing live organ donation. *Am J Transplant*. 2016;16(12):3548-3553.
- Rodrigue JR, Paek MJ, Egbuna O, et al. Making house calls increases living donor inquiries and

evaluations for blacks on the kidney transplant waiting list. *Transplantation*. 2014;98(9):979-986.

Medical Evaluation of the Living Kidney Donor

Case: *A 27-year-old African American woman comes forward to be considered as a living kidney donor for her sister, who recently started dialysis therapy. She is blood group B, the same as her sister. Her medical and surgical history is notable for arthroscopic knee surgery 5 years ago. She had a normal pregnancy 2 years ago with a baby boy delivered at term. She smoked cigarettes for 5 years but quit when pregnant; she drinks alcohol socially. She works as a school guidance counselor. She is afebrile, with blood pressure (BP) of 120/85 mm Hg, pulse rate of 76 beats/min, and BMI of 32 kg/m^2. Physical examination findings are otherwise normal. Laboratory data reveal serum creatinine concentration of 0.6 mg/dL, and urinalysis is negative for blood or protein. Oral glucose tolerance test results are normal.*

Question: What evaluation is necessary to determine her suitability as a living kidney donor?

After a donor has contacted a transplantation center to start the living donor evaluation process, the purpose of the medical evaluation of the live kidney donor is to identify any conditions that might put the donor at increased risk for the development of chronic kidney disease (CKD) or end-stage kidney disease or places them at unacceptably high surgical or psychosocial risk. Table 1 includes a comprehensive list of essential live kidney donor medical testing.

Many centers begin the living donor evaluation process with a blood type determination and HLA antigen cross-match testing. Per the Organ Procurement and Transplantation Network (OPTN), donors must have blood type determined on 2 separate occasions before transplantation. ABO blood group incompatibility or HLA antigen reactivity with the intended recipient no longer necessitates the end of the donor evaluation because paired kidney exchange and desensitization programs help facilitate living donor transplants for incompatible donor-recipient pairs.

Medical evaluation of the donor includes a comprehensive general medical history and physical examination with a particular focus on kidney disease history and risk factors. Donors should be queried for genetic or familial kidney diseases, a history of acute or chronic kidney injury, proteinuria, hematuria, recurrent urinary tract infections, congenital genitourinary anomalies, or episodes of stone disease. Potential donors should be asked about hypertension and diabetes, including gestational diabetes or gestational hypertension. Both prescription and over-the-counter medications should be reviewed, with particular attention to nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and any herbal medications or supplements. Social history taking should include assessment of adequate supports for postoperative recovery, substance use (eg, alcohol, tobacco, and illicit drugs), psychiatric disease history, travel history, and behaviors meeting Public Health Service (PHS) high-risk criteria (eg, injection drug use, commercial sex work, and history of jail time). Assessment of the adequacy of health insurance for mandated postdonation follow-up is also important because donors lacking such resources are at increased

Table 1. Living Donor Evaluation Testing

Condition	Test	Exclusion
Compatibility	ABO verification	ABO incompatible[a]
	HLA antibody screening	HLA antigen incompatible[a]
Kidney function	24-h urine collection	GFR < 80 mL/min
	Iothalamate-based GFR measurement	GFR < 80 mL/min
	Urinalysis	Proteinuria, hematuria
	Urine albumin-creatinine ratio	>30 mg
	Imaging; CT or MRI	Solitary kidney
Blood pressure	2 clinic readings	≥140/90 mm Hg
	24-h ambulatory monitoring	Sustained readings ≥ 140/90 mm Hg
Diabetes	Fasting glucose	≥126 mg/dL
	Oral glucose tolerance testing	Glucose ≥ 200 mg/dL at 2 h
	HbA_{1c}	≥6.5%
Hyperlipidemia	Fasting lipid panel	Metabolic syndrome[a]
Transmissible infection	RPR	Positive result without treatment
	HIV antibody	HIV antibody positive[a]
	HCV nucleic acid testing	HCV viral load positive[a]
	HBV nucleic acid testing	HBV DNA positive
Cancer	Age/history-driven screening	Active malignancy

Abbreviations: CT, computed tomography; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RPR, rapid plasma reagin.
[a]Relative exclusions to donation.

risk for not completing postdonation visits and laboratory testing. Family history should review diabetes and hypertension in first-degree relatives in addition to familial kidney disease. A comprehensive physical examination is required, with particular attention to BP and BMI. Many centers routinely use ambulatory BP monitoring to screen for occult hypertension.

Case, continued: *Your 30-year-old patient has had several family members come forward to be evaluated as donors. She is not yet on dialysis therapy and is anxious to undergo transplantation preemptively. Both her brother and her sister have contacted the donor team, but she is concerned about her brother's suitability. He was in jail overnight after a charge of driving under the influence 6 months ago and may be using other illegal substances.*

Question 1: What do you advise her?

a) Tell her not to worry about catching an infectious disease from her brother if he ends up being her donor; PHS increased risk designation only applies to deceased donors and no one has ever contracted human immunodeficiency virus (HIV) or hepatitis C virus (HCV) from a living donor transplant.
b) Inform her that all living donors are screened not only for transmissible infections at the time of evaluation, but again no more than 28 days before the planned surgery.
c) Inform her that all living donors are screened by a health care professional with appropriate mental health training and that this will be thoroughly investigated before he can be approved as a donor.
d) Tell her not to worry, her brother will definitely not be approved as a donor.

For answer, see Appendix.

Mandated laboratory testing for living donor candidates includes assessment of kidney function using serum creatinine concentration and glomerular filtration rate (GFR). Most commonly, this is achieved through a 24-hour urine collection. Urinalysis and measurement of urine albumin-creatinine ratio are performed to screen for proteinuria and hematuria. Routine preoperative laboratory testing such as a complete blood cell count, full chemistry panel, and coagulation studies are also performed. Premenopausal women should be screened for pregnancy with a test for beta human chorionic gonadotropin (hCG). Many centers will perform oral glucose tolerance testing for donors at increased risk for diabetes. Required donor infectious disease testing include HIV, HCV, and hepatitis B virus nucleic acid testing within 28 days of the planned surgery; many centers will additionally screen for cytomegalovirus, syphilis, or tuberculosis. Donors should have age-appropriate cancer screenings, including but not limited to Papanicolau smear, mammograms, and colonoscopies.

Imaging studies vary by evaluating center but always include some assessment of kidney size and anatomy, usually using magnetic resonance imaging or computed tomography angiography. Chest radiographs are also included as part of the evaluation.

Relative contraindications to living donation vary by transplantation center. Hypertension is controversial; some centers will accept donors with well-controlled hypertension without evidence of end-organ damage (eg, left ventricular hypertrophy), while others exclude any donors using antihypertensive medications. Centers may also have different thresholds for hypertension on the basis of donor race and be more reluctant to approve those who are both hypertensive and African American. BMI cutoffs for donation also vary by center protocol, but generally donors must have BMI < 35 kg/m^2, and at many centers, <30 kg/m^2, due to the risks for developing metabolic syndrome at higher BMI. Living donors have to be adults. At some centers, the minimum age for donation is 21 years, while others will accept candidates as young as 18 years of age. There is no upper limit for donors in terms of age, but many candidates of advanced age have medical issues that preclude donation. Diabetes is always a contraindication to living donation; other absolute contraindications include active cancer, uncontrolled psychiatric disease, and abuse of alcohol or drugs. Living donor candidates with abnormal kidney function (GFR < 80 mL/min) or suspicion for glomerular disease (hematuria or proteinuria) are not permitted to donate. Payment of donors or attempts to coerce donors is not permitted.

A key member of the living donor team is the independent living donor advocate, who is charged with "the protection of living donors and prospective donors." The independent living donor advocate evaluates all prospective living donors and assesses the donor's ability to make an informed choice to donate. He or she serves as an advocate for donor autonomy in the process, and as such, functions independently of the medical evaluation team.

Additional Reading

► Lentine KL, Kasiske BL, Levey AS, et al. Summary of Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on the evaluation and care of living kidney donors. *Transplantation*. 2017;101(8):1783-1792.

Specific Risks of Living Kidney Donation

Case, continued: *The candidate donor's father is deceased and was on dialysis therapy for several years before he died; his cause of end-stage kidney disease is unknown. Her mother is alive and has well-controlled hypertension. She wants to help her sister, but expresses concerns about her own risk for developing kidney disease in the future. She asks if there is any "extra" testing she can do that will help us decide.*

Question: What do you tell her about her risk for end-stage kidney disease should she choose to donate?

Donors must be counseled about the risks, both short and long term, associated with living kidney donation, including risks related to the surgery itself and long-term health risks due to having reduced renal mass. Currently, living kidney donation is mostly performed using a laparoscopic approach, and as such, the upfront surgical mortality associated with the procedure is low. The most common causes of early surgical mortality include bleeding and blood clots. Longer term data for donor mortality from the United States and Canada suggest that donor longevity is similar to the general population. However, at least one study from Norway demonstrated an increased risk for death among donors followed up for more than 2 decades.

Progression to end-stage kidney disease among living kidney donors is of great concern to patients and clinicians alike; although prior living donors are given priority access to deceased donor kidneys should they progress to end-stage kidney disease themselves, modern selection practices aim to avoid this occurrence. Available data suggest that although well-selected living kidney donors are at increased risk for end-stage kidney disease, the absolute magnitude of this risk is small. Data from the OPTN, which tracks all transplantations performed in the United States, was linked to data from the Centers for Medicare & Medicaid Services (CMS) to ascertain the development of end-stage kidney disease among former living kidney donors and then compared with end-stage kidney disease rates among a segment of the general population enrolled in the National Health and Nutrition Examination Survey (NHANES). During a median follow-up of 7.6 years, only 99 former living donors developed end-stage kidney disease. A more recent study encompassing all living kidney donors from 1987 to 2015 identified additional donors who had progressed to end-stage kidney disease ($n = 331$), but the projected rate of end-stage kidney disease by 20 years of follow-up was only 34 per 10,000. As in previous analyses, men, African Americans, and biologically related donors were at greatest risk for the development of end-stage kidney disease.

The risk for end-stage kidney disease for living kidney donors is not uniform among all candidates. Not surprisingly, risk is greater in younger donors because they have more life-years ahead of them in which to develop end-stage kidney disease or other complications of donation. Although younger donors are often the easiest to clear from a medical perspective, they can be the most challenging to counsel about long-term risk. Using data from the CARDIA (Coronary Artery Risk Development in Young Adults) Study, our group developed a risk calculator to model risk for the development of CKD in young donors. For example, among 30-year-old European American potential donors without comorbid conditions or family history of first-degree relative with diabetes or hypertension, the 25-year risk for CKD was 0.62% to 1.08%, whereas among 30-year-old African Americans, the baseline rate was higher (1.08%-1.86%). The addition of known risk factors such obesity or smoking increased that rate, but the greatest driver of risk was the presence of genetic variants in the apolipoprotein L1 gene (*APOL1*; see later section for further discussion of genetic risk).

The majority of live donor nephrectomies in the United States are performed laparoscopically, and as experience with this procedure grows, few are converted to open procedures. The 90-day all-cause mortality is estimated to be 1 in 3,000 (0.03%). The reported complication rate ranges from 4.2% to 10.6% and includes pain, infection (eg, urinary tract, pneumonia, and surgical site), damage to the donated kidney or surrounding structures, blood clots (eg, deep venous thrombosis and pulmonary embolism), allergic reaction to anesthesia, and lymphocele. A meta-analysis by Yuan et al estimated surgical times to be 51 minutes longer for laparoscopic compared to open nephrectomy. In contrast, perioperative blood loss was significantly greater for the open compared to laparoscopic approach. Differences in reoperation rates based on surgical approach are conflicting. On average, laparoscopic nephrectomy has been associated with shorter length of stay compared to the open technique. Moreover, laparoscopic nephrectomy has been associated with reduction in time to return to work, improved functional status, and lower pain scores compared to open nephrectomy.

Because historically the majority of living kidney donors have been women and many are of childbearing age, there has been concern regarding the effect of kidney donation on future pregnancy outcomes. A national study of living donors from Norway demonstrated a small but increased risk for preeclampsia among pregnancies occurring after living donation (5.7% vs 2.6%; $P = 0.026$), but the absolute number of events in the cohort ($n = 22$) was small. A single-center study from the United States comparing pre- and postdonation pregnancy outcomes demonstrated a significant increase in adverse events (eg, preterm delivery, gestational diabetes, gestational hypertension, and preeclampsia) in postdonation pregnancies, but this rate was not higher than that observed in the general population. A Canadian study matched donors with nondonors and demonstrated increased odds of both gestational hypertension and preeclampsia (odds ratio, 2.4; 95% confidence interval [CI], 1.2-5.0) among women living kidney donors. Taken collectively, these data indicate that there is likely a real increase in risk for adverse pregnancy outcomes for prior living kidney donors, but importantly, the magnitude of this increased risk is small. However, these data should be incorporated into decision making for women who wish to be evaluated as donors but have not yet completed their families.

Important but often overlooked complications of living donation are the emotional and financial consequences of donation. Data from a multicenter living donor cohort study demonstrated that although most (95%) donors rated the experience of donation positively, some

had negative experiences. Donors who experienced medical complications from donation, had psychological difficulties predonation, or whose donated kidneys failed were more likely to have had a negative experience with donation. Importantly, 20% of donors reported some degree of financial difficulty surrounding donation, which has led to calls for greater financial neutrality for donors.

Additional Readings

- Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009;360(5):459-469.
- Mjoen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. *Kidney Int*. 2014;86(1):162-167.
- Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. *JAMA*. 2014;311(6):579-586.
- Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA*. 2010;303(10):959-966.

Special Considerations

Overview

Selection practices aim to quantify lifetime risk for kidney failure on the basis of a candidate's predonation demographic and health characteristics. It has been established that estimated lifetime risk for kidney failure varies considerably based on predonation comorbid conditions. The KDIGO (Kidney Disease: Improving Global Outcomes) guideline for assessing living donor risk recommends that: (1) transplantation centers determine and inform candidates of a quantitative threshold for "acceptable risk" for kidney failure after donation; (2) donor candidates with estimated risk under this threshold should be accepted by the transplantation center, with the decision to proceed to donation or not made by the candidate after being informed of the risks; and (3) based on the quantitative evidence-based framework they have developed, transplantation centers are justified in declining donor candidates with estimated risk over this threshold (Fig 1). Establishing an "acceptable risk" threshold requires working knowledge of baseline predonation risk, as well as postdonation risk for end-stage kidney disease.

Medically Complex Living Kidney Donors

Historically, living kidney donors were healthy and free of isolated medical abnormalities at the time of donation. More recently, and in parallel with the general US population, donor demographics have changed, and transplantation centers have relaxed selection criteria to include donors with isolated medical abnormalities such as prehypertension, hypertension, obesity, gestational diabetes, and metabolic syndrome, as well as the aged. At a general population level, individuals with isolated medical abnormalities are more likely to develop comorbid diseases

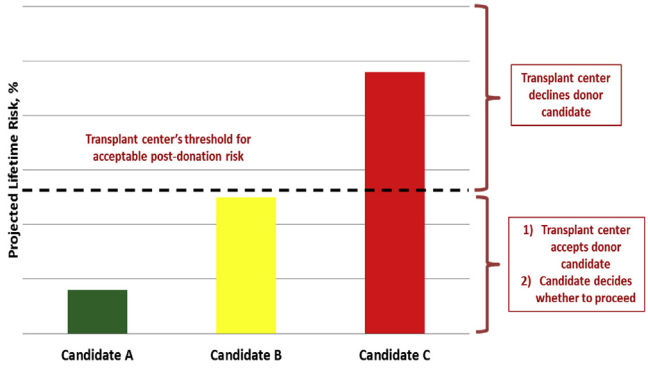

Figure 1. Defining an "acceptable risk" threshold for living kidney donation. Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) Living Kidney Donor Work Group. KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. *Transplantation*. 2017;101(suppl 8S):S1-S109 with permission of the copyright holder (KDIGO).

such as diabetes, hypertension, CKD, and end-stage kidney disease. It remains unclear what impact, if any, living donation will have on the development of these comorbid conditions, and as such, understanding risk among potential living kidney donors with predonation isolated medical abnormalities remains an area of ongoing research.

Prehypertension

Prehypertension has been defined by the 8th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) as intermediate systolic BPs (SBPs) of 120 to 139 mm Hg and diastolic BPs (DBPs) of 80 to 89 mm Hg. Approximately 30% of the general US population is defined as having prehypertension. Recent data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study demonstrated that 62.9% of African Americans in the study population met criteria for prehypertension compared to only 54.1% among European Americans, and that among prehypertension participants, moderately increased albuminuria was more common in African Americans. Prehypertension has been established as a risk factor for cardiovascular disease and end-stage kidney disease.

Additional Reading

- Glasser SP, Judd S, Basile J, et al. Prehypertension, racial prevalence and its association with risk factors: analysis of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Am J Hypertens*. 2011;24(2):194-199.

Hypertension

Hypertension is defined as clinic SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, out-of-clinic daytime mean ambulatory BP of SBP ≥ 135 mm Hg or DBP ≥ 85 mm Hg, or the

need for antihypertensive medication. Loss of kidney function (reduction in GFR) may accelerate the progression of hypertension over time secondary to physiologic alterations in the setting of uninephrectomy, including hyperfiltration in the remaining kidney, changes in vascular tone, and renin-angiotensin-aldosterone regulation. Importantly, hypertension is a known cause of CKD and end-stage kidney disease in the general population. A recent meta-analysis of 7 general US population cohorts found that for every 20–mm Hg increase in SBP, there was an associated 42% increased risk for end-stage kidney disease (adjusted hazard ratio [aHR], 1.42; 95% CI, 1.27-1.58), and use of antihypertensives was associated with 35% increased risk for end-stage kidney disease (aHR, 1.35; 95% CI, 1.01-1.82). Postdonation hypertension has been shown to be more common among African Americans (aHR, 1.52; 95% CI, 1.23-1.88), Hispanics (aHR, 1.36; 95% CI, 1.04-1.78), and older donors (aHR, 1.06; 95% CI, 1.06-1.07), and those having predonation hypertension had a significant increase in their need for antihypertensive agents after donation (aHR, 20.9; 95% CI, 8.8-49.3).

With regard to living kidney donors, Segev et al linked Scientific Registry of Transplant Recipients (SRTR) data to national death records and found higher perioperative mortality among donors who had predonation hypertension as compared with those who did not (36.7 vs 1.3 per 10,000). A smaller single-center Norwegian study with 25 years of follow-up comparing living donors with matched controls demonstrated that each 1–mm Hg increase in SBP was associated with increased risk for end-stage kidney disease. However, other studies have demonstrated no associated increased risk for end-stage kidney disease among carefully selected living donors (white, ≥55 years of age, and well controlled receiving a single antihypertensive). Although there remains heterogeneity in available outcomes data, most centers consider uncontrolled hypertension or hypertension with end-organ damage (eg, proteinuria, moderately increased albuminuria, left ventricular hypertrophy, and hypertensive retinopathy) as absolute contraindications to living donation.

Additional Readings

- Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med*. 2009;360(5):459-469.
- Mjoen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. *Kidney Int*. 2014;86(1):162-167.
- Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA*. 2010;303(10):959-966.

Obesity

Obesity ($BMI > 30\ kg/m^2$) is strongly correlated with increased risk for CKD because data from a population-based case-control study conducted in Sweden and US studies (Framingham Offspring cohort and Hypertension Detection and Follow-up Program) have shown that higher weight for height is associated with increased risk for CKD. Beyond CKD, obesity has been linked with end-stage kidney disease, with reported risks among obese persons 1.16- to 3.57-fold higher than for persons considered normal weight. Moreover, obesity has been associated with proteinuria, moderately increased albuminuria, and glomerulopathy. High waist-to-hip ratio has an associated 1.29- to 2.74-fold increased odds of CKD and rapid decline in kidney function; central fat distribution is associated with a 1.7-fold increased risk for moderately increased albuminuria, 2-fold higher odds of CKD, and rapid decline in estimated GFR; and liver adiposity (higher fat content) is associated with 1.8- to 6.14-fold increased odds of CKD.

In parallel with trends in the general population, the mean BMI of living donors has increased over time, from $24.3\ kg/m^2$ in the 1970s to $27.3\ kg/m^2$ in the 2000s. Currently, >25% of all living kidney donors are obese compared to <8% in the 1970s. Determining candidacy for living kidney donation among obese individuals remains challenging because the appropriate BMI cutoff above which donation is no longer safe is unknown. Most centers have implemented a "one-size-fits-all" approach to setting BMI limits (eg, individuals with $BMI \geq 35\ kg/m^2$ are excluded from donation) rather than a personalized approach that accounts for individual baseline differences. Recent data have emerged linking predonation obesity with postdonation end-stage kidney disease risk. Specifically, Ibrahim et al reported results from a single-center study of 3,956 donors and found that higher BMI was associated with 10% increased risk for proteinuria (aHR, 1.10; 95% CI, 1.06-1.13) and 3% risk for reduced GFR (<60 mL/min; aHR, 1.03; 95% CI, 1.01-1.04). Donors with higher BMI were also more likely to experience a composite end point of GFR < 30 mL/min or end-stage kidney disease (aHR, 1.08; 95% CI, 1.04-1.07). However, the study was limited by lack of generalizability because no African Americans were included and fewer than 100 obese donors were studied. Most recently, our group linked SRTR data to CMS claims and identified 119,769 living kidney donors. Risk for end-stage kidney disease 20 years postdonation was 93.9 per 10,000 for obese versus 39.7 for nonobese living kidney donors. However, it is important to note that both studies were limited by a lack of appropriate nondonor controls to assess end-stage kidney disease risk directly attributable to the donation itself.

Additional Reading

- 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.

Case: *A 42-year-old man would like to be evaluated as a living kidney donor to his 10-year-old daughter with focal segmental glomerulosclerosis. He is normotensive, but his BMI is 35 kg/m² and his evaluation laboratory testing is notable for a fasting glucose concentration of 115 mg/dL. His wife has been previously evaluated and declined because she has lupus; there are no other available family members.*

Question 2: Would you permit him to donate and how would you describe his risk for end-stage kidney disease?

a) Not permit him to donate. His risk for end-stage kidney disease is prohibitively high. His daughter will have to wait for a deceased donor transplant, which she should get quickly through Share-35.
b) Ask him to do an oral glucose tolerance test; if the result is normal, he is at low risk for diabetes and can proceed to donation without further testing.
c) Ask him to lose weight to BMI < 30 kg/m² and check an oral glucose tolerance test at that time. Counsel him that he is at increased risk for end-stage kidney disease after donation but that risk is acceptable to your transplantation center.

For answer, see Appendix.

Impaired Fasting Glucose

Impaired fasting glucose in the setting of a normal 2-hour oral glucose tolerance test result is not an absolute contraindication to living kidney donation. In contrast, most US centers do not accept donors with diabetes or impaired glucose tolerance. The physiology of impaired fasting glucose and impaired glucose tolerance differ; specifically, isolated impaired fasting glucose is the result of hepatic insulin resistance with normal peripheral insulin sensitivity, whereas isolated impaired glucose tolerance results from increased peripheral insulin resistance. The presence of either impaired fasting glucose or impaired glucose tolerance increases the risk for diabetes by 5% to 10% per year depending on ethnicity and family history. Despite the correlation between prediabetes and the subsequent development of diabetes, during the last 20 years, there has been a trend among US centers toward accepting more living donors with glucose problems. This is significant because hyperfiltration, which occurs in the setting of uninephrectomy, is known to play an important role in the progression of diabetic nephropathy. Animal studies have demonstrated progression of kidney disease among diabetic animals after nephrectomy. Among humans, the Framingham Study demonstrated increased risk for CKD among patients with impaired fasting glucose and impaired glucose tolerance. Moreover, the development of gestational diabetes has an associated 37-fold increased risk for the subsequent development of type 2 diabetes mellitus, and as such, all female potential donors with a history of gestational diabetes should undergo a 2-hour oral glucose tolerance test.

Additional Reading

- Fox CS, Larson MG, Leip EP, et al. Glycemic status and development of kidney disease: the Framingham Heart Study. *Diabetes Care.* 2005;28(10):2436-2440.

Metabolic Syndrome

Metabolic syndrome, as defined by the National Cholesterol Education Program's Adult Treatment Panel, requires evidence of at least 3 of the following 5 measures: (1) BMI ≥ 25 kg/m², (2) SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, (3) triglyceride concentration ≥ 150 mg/dL, (4) high-density lipoprotein cholesterol concentration < 40 mg/dL in males or <50 mg/dL in females, and (5) fasting blood glucose concentration ≥ 100 mg/dL. According to data from NHANES, the prevalence of metabolic syndrome in the general US population is 34%. It has been established that both metabolic syndrome and each of its components are independently associated with increased risk for cardiovascular disease and incident CKD. Emerging data from the Renal and Lung Living Donors Evaluation (RELIVE) consortium demonstrate that African American donors were more likely to be obese and have hyperglycemia at the time of donation, suggesting that a higher rate of metabolic syndrome may exist among African American kidney donors. Further, a recent study examined the association between metabolic syndrome and kidney function in 410 living kidney donors. The study determined that donors with metabolic syndrome were more likely to have long-term histologic changes on implant biopsy specimens, and this finding was associated with impaired kidney function recovery among recipients. The study was limited by lack of donor follow-up and the absence of nondonor controls to assess attributable risk, and as such, it is unclear what role metabolic syndrome may play in the development of postdonation comorbid conditions in living kidney donors.

Additional Reading

- Taler SJ, Messersmith EE, Leichtman AB, et al. Demographic, metabolic, and blood pressure characteristics of living kidney donors spanning five decades. *Am J Transplant.* 2013;13(2):390-398.

Aged Donor

Compensatory hyperfiltration in the remaining kidney is to be expected after nephrectomy, however, the aging process may impair compensation and reduce postdonation GFR. It is therefore critical to accurately assess predonation GFR in aged donors, and as such, GFR measured using iothalamate may complement 24-hour urine collection.

Additional Reading

- 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.

Hematuria

Hematuria is abnormal and if it is present, living kidney donor candidates should be evaluated to determine whether the hematuria is secondary to correctable causes (eg, urinary tract infection, recent intercourse, and menses), malignancy, or a glomerular disease (eg, immunoglobulin A nephropathy and thin basement membrane disease). Microscopic hematuria is typically defined as microscopic evidence of more than 2 to 5 red blood cells per high-power field of urinary sediment on 2 to 3 separate occasions unrelated to exercise, trauma, sexual activity, or menstruation. No consensus exists on hematuria workup for living donor candidates, but a recent Canadian protocol recommends: (1) urine culture and cytology, 24-hour urine calcium measurement, and metabolic stone profile; and (2) if the cause remains unknown after completing the first step, perform cystoscopy and native biopsy. Consensus-based recommendations on the management of Alport syndrome and thin basement membrane nephropathy suggest that individuals with the latter are safe to donate in the setting of normal BP and kidney function and no evidence of proteinuria.

Additional Reading

- Savige J, Gregory M, Gross O, et al. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol*. 2013;24(3):364-375.

Kidney Stones

Kidney stones are common; 10% to 15% of the general population is estimated to be at risk for developing kidney stones in their lifetime. The risk for developing a kidney stone after living kidney donation in donors who did not have a stone history is the same as for selected nondonors. One or more episodes of kidney stones has been associated with 2-fold higher risk for end-stage kidney disease. However, no data are available regarding rates of recurrent stones or long-term kidney function in donors with and without kidney stones before donation. Living donor candidates with a history of kidney stones should have a comprehensive evaluation to elucidate the cause, including a 24-hour urine collection to assess urine pH, as well as calcium, oxalate, uric acid, citrate, and sodium excretion; review of available imaging studies to quantify stone burden; measurement of intact parathyroid hormone concentration; examination of urine sediment; and a detailed dietary history. Additionally, potential living donors should be screened for conditions that predispose to recurrent nephrolithiasis, including primary hyperparathyroidism, medullary sponge kidney, type I renal tubular acidosis, and chronic urinary tract infections, or conditions predisposing to chronic diarrhea, such as irritable bowel disease, gastric bypass, and short gut syndrome.

APOL1 Renal-Risk Variants and Living Kidney Donation

Case, continued: *The patient was offered the option to undergo screening for APOL1 allelic variants, which she decided to have done. She was found to be heterozygous for the G1 allele. Using our risk calculator, we estimated that her 25-year risk for developing CKD was 4.1% (95% CI, 2.72%-5.46%). We discussed this risk projection with her in the context of her risk factors for developing kidney disease and which ones were modifiable. She indicated that she was still interested in serving as a living donor and was therefore asked to lose weight to BMI < 30 kg/m^2. She returned to the donor evaluation clinic 6 months later, having lost 30 lbs and now with BP of 112/76 mm Hg. She elected to proceed with donation and was approved by the selection committee.*

African Americans have been shown to be at increased risk for CKD and end-stage kidney disease both within the general population and among previous living kidney donors. The reasons for this observation are multiple and include genetic differences, such as variants in *APOL1*. Individuals with 2 *APOL1* risk alleles carry a 15% lifetime risk for kidney disease, but having *APOL1* genetic variants alone is insufficient to guarantee the development of CKD, and it is thought that a second insult is required. There is concern that living donor nephrectomy may serve as a possible "second hit" for these individuals. Screening of African American living donor candidates is neither mandated nor universally accepted, and the practice varies on a center-level basis. There is concern that incorporating genetic testing for *APOL1* into the living donor evaluation may worsen already disparate access to living donor kidney transplantation among African Americans and that restricting a patient's ability to donate on the basis of genetic testing alone may be unfounded because not all individuals with *APOL1* genetic variants develop kidney disease. However, there have been at least 2 reports of living kidney donors with *APOL1* risk alleles who subsequently developed end-stage kidney disease themselves. We believe that *APOL1* genetic data are valuable and can enhance current CKD/end-stage kidney disease risk prediction algorithms (Fig 2). However, *APOL1* testing in kidney transplantation remains controversial. Given the equipoise that surrounds the testing of African American living donor candidates for *APOL1* risk variants, the National Institutes of Health is embarking on a multicenter prospective trial (*APOL1* Long-term Kidney Transplantation Outcomes Network) to screen African American kidney donors and recipients

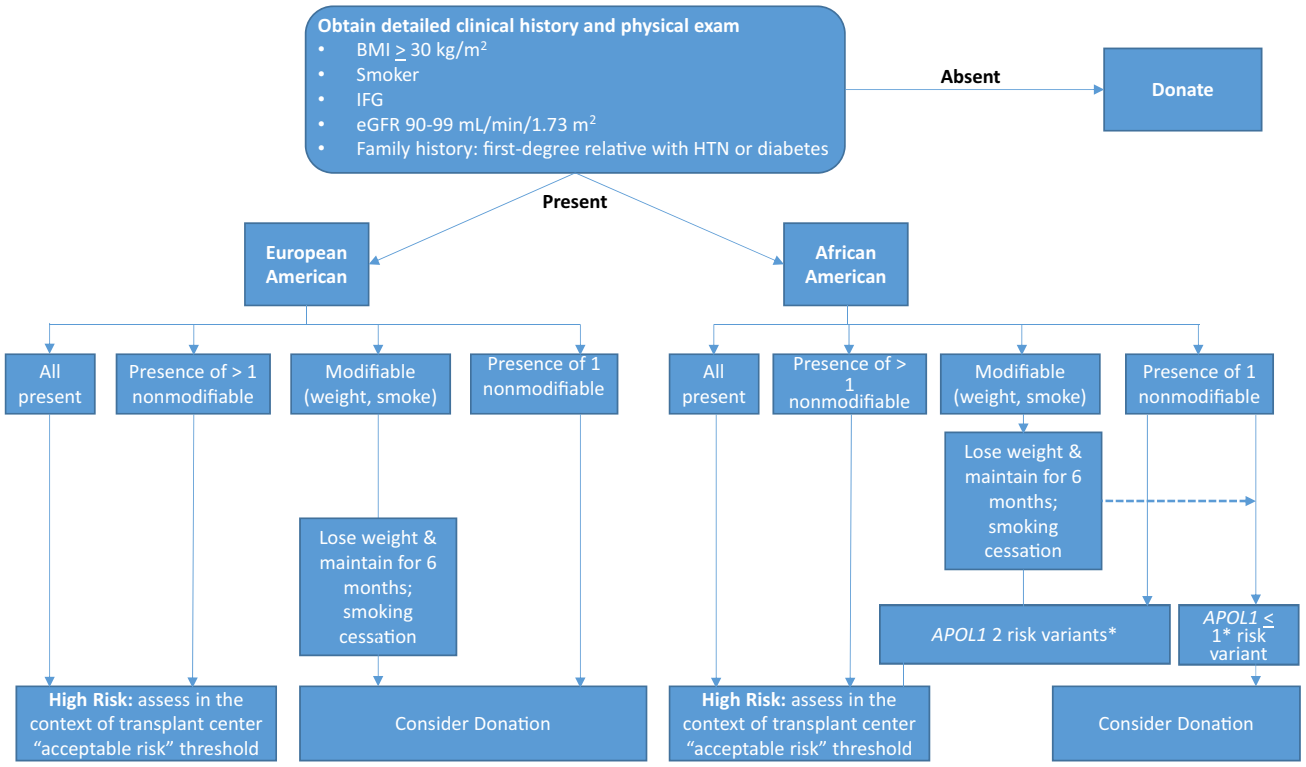

Figure 2. Algorithm for selection of the young potential living kidney donor candidate.**APOL1* genetic testing is recommended but not required. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HTN, hypertension; IFG, impaired fasting glucose.

for *APOL1* and assess the impact on renal outcomes for donors and recipients.

Additional Reading

- Locke JE, Sawinski D, Reed RD, et al. Apolipoprotein L1 and chronic kidney disease risk in young potential living kidney donors. *Ann Surg.* 2017;doi:10.1097/SLA.0000000000002174.

Altruistic Living Kidney Donors

Altruistic donors are characterized by donation to a stranger or someone with whom the donor has no previous relationship and for which they receive no direct benefit. The transplantation community has traditionally been skeptical of these donors' motivation to donate and their psychological well-being, but this nontraditional living donor source has become more accepted, increasing 8-fold from 20 transplants in 2000 to 163 transplants in 2015 and accounting for just over 3% of all living donors in 2014. Although the concept of altruistic donation has become widely accepted in the United States, it is important to note that altruistic donors lack a predonation connection to the recipient and are less likely to report having had personal experiences with transplantation or medicine before contacting the transplantation center than their traditional counterparts. They are also less likely to report having received support for their decision to donate when compared with traditional donors, with some even reporting resistance from spouses or other family members. Although medical risks may not differ between traditional and altruistic or nondirected living kidney donors, these findings highlight the need for more in-depth psychosocial evaluation of altruistic or nondirected living kidney donors. A national consensus conference held to discuss practice guidelines for approval and care of these donors concluded that initial screening of nondirected or altruistic donors should cover medical history, as well as knowledge of nondirected donation and donor-related issues. This conference emphasized that many potential altruistic donors have a limited understanding of these issues and often withdraw from consideration after learning more. A study at the University of Minnesota found that among individuals who expressed an initial interest in nondirected donation, 60% had no further contact with the transplantation center after receiving further information or participating in discussions about nondirected donation. However, encouragingly, recent data suggest that altruistic donors are more likely to complete postdonation follow-up screening compared with their traditional counterparts, suggesting that current predonation screening practices may be adequate.

Additional Readings

- Adams PL, Cohen DJ, Danovitch GM, et al. The nondirected live-kidney donor: ethical considerations and practice guidelines: a National Conference Report. *Transplantation*. 2002;74(4):582-589.
- Maple H, Chilcot J, Burnapp L, et al. Motivations, outcomes, and characteristics of unspecified (nondirected altruistic) kidney donors in the United Kingdom. *Transplantation*. 2014;98(11):1182-1189.
- Reed RD, Shelton BA, MacLennan PA, Sawinski D, Locke JE. Living kidney donor phenotype and likelihood of postdonation follow-up. *Transplantation*. 2018;102(1):135-139.

HCV Antibody–Positive Nucleic Acid Test–Negative Living Kidney Donors

Chronic HCV infection is a recognized risk factor for the development of CKD and has been linked with a multitude of glomerular diseases, including focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and cryoglobulinemia, in addition to being an established risk factor for systemic diseases such as diabetes, which is an important contributor to kidney disease burden worldwide. HCV infection also accelerates the progression to end-stage kidney disease. Historically, HCV infection has been a contraindication for living donation given concerns surrounding disease transmission to the recipient and risk for subsequent kidney disease in the donor. Since the approval of highly effective direct-acting antivirals for the treatment of HCV infection in 2013, there has been renewed interest in the prospect of permitting candidates who have either cleared the infection spontaneously (HCV antibody positive and nucleic acid testing negative) or those who have been successfully treated to serve as living kidney donors. The most recent version of the KDIGO guidelines listed this as a potentially acceptable practice on the basis of "expert opinion"; they propose that living donors with HCV should have an evaluation of liver fibrosis after direct-acting antiviral therapy and achievement of a sustained viral response measured at 12 and 24 weeks after therapy. There are now several case reports in the literature of using HCV antibody–positive and nucleic acid testing–negative living donors, but the practice has not been widely adopted and concerns regarding potential for disease transmission and donor safety remain.

Additional Reading

- Cruzado JM, Gil-Vernet S, Castellote J, et al. Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. *Am J Transplant*. 2013;13(10):2773-2774.

HIV-Positive Living Kidney Donors

Passage of the HIV Organ Policy Equity Act in 2013 created the opportunity for HIV-positive individuals to serve as living kidney donors, and the US Department of Health and Human Services established the safeguards and research criteria for use of HIV-positive organs in 2015. Under these provisions, HIV-positive living donors must first meet all center-specific HIV-independent criteria for living donation and in addition have a CD4 count ≥ 500 cells/μL, undetectable viral load, and no history of invasive opportunistic infections and undergo a native kidney biopsy. There is reasonable concern in the transplantation and nephrology community regarding the safety of living donation for HIV-positive individuals. HIV infection is a risk factor for the development of CKD and HIV-positive individuals remain at increased risk for end-stage kidney disease compared to the general population despite the widespread adoption of antiretroviral therapy. To date, no living HIV-positive person has been a kidney donor and attempts have been made to model the risk for end-stage kidney disease that they may face. One simulation projected an end-stage kidney disease risk ranging from 1.8 to 25.5 per 10,000 persons at risk; this risk varied greatly based on metrics of viral control, presence of other comorbid conditions, age, and race. African Americans had the highest risk for end-stage kidney disease among all potential donor cohorts. This wide range in risk highlights the fact that HIV-positive persons are not a homogeneous group and that other factors, including *APOL1* renal-risk variants or other genetic variants, may play an important role in their long-term risk for end-stage kidney disease.

Additional Reading

- Muzaale AD, Althoff KN, Sperati CJ, et al. Risk of end-stage renal disease in HIV-positive potential live kidney donors. *Am J Transplant*. 2017;17(7):1823-1832.

Postdonation Care and Follow-up

The transplantation center is mandated to follow up all living kidney donors for at least 2 years after donation; however, life-long medical care with an established primary care physician is the ideal. Living donors should have their BP checked at least once yearly, along with determination of kidney function as measured by serum creatinine and screening for proteinuria using urinalysis or urine albumin-creatinine ratio. Younger age, African American race, lack of insurance, living far away from a transplantation center, or having donated at a high-volume center have all been established as risk factors for lack of living donor follow-up. Because current health care legislation prohibits denying coverage to patients on the basis of pre-existing conditions, such as living donation, living donors should not have increased difficulty obtaining health insurance, but this could change, and transplantation centers need to remain vigilant to ensure that their donors have access to appropriate medical care and follow-up after donation.

Additional Reading

- Lentine KL, Kasiske BL, Levey AS, et al. Summary of Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on the evaluation and care of living kidney donors. *Transplantation*. 2017;101(8):1783-1792.

Article Information

Authors' Full Names and Academic Degrees: Deirdre Sawinski, MD, and Jayme E. Locke, MD, MPH.

Authors' Affiliations: Division of Nephrology, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA (DS); and Division of Transplantation, Department of Surgery, University of Alabama at Birmingham School of Medicine, Birmingham, AL (JEL).

Address for Correspondence: Jayme E. Locke, MD, MPH, 701 19th St S, LHRB 748, Birmingham, AL 35294. E-mail: jlocke@uabmc.edu

Support: This research was supported in part by National Institutes of Health grant K23-DK103918 (Principal Investigator, Dr Locke).

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received June 12, 2017, in response to an invitation from the journal. Evaluated by 3 external peer reviewers, with direct editorial input from the Feature Editor. Accepted in revised form October 10, 2017.

APPENDIX

Answer to Question 1: In this case both (b) and (c) are correct. The PHS–increased risk donor designation applies to both living and deceased donors and is made by review of social factors that increase a donor's risk for disease transmission in the window period. Although the majority of reported transmissions involve HCV and the source is predominantly deceased donors, there has been at least 1 documented case of a living donor transmitting HIV. Evaluation of living donors includes screening for behaviors that would designate that person as "PHS increased risk." Furthermore, the evaluation of donors includes a comprehensive assessment by a trained mental health professional with particular attention to substance use and abuse behaviors.

Answer to Question 2: Although we have focused on the medical considerations around living kidney donation, it is important to respect and understand the potential donor's perspective and autonomy in decision making. Being declined as a donor candidate can have a negative psychological impact and, depending on whom the intended recipient is, larger ramifications for the donor's overall well-being. In this particular instance of a parent donating to a child, we would favor answer (c); using this approach, we are counseling him about his increased health risks associated with donation while providing guidance on how to mitigate those risks to the best of his ability.