# Living Donor Evaluation and Selection

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**Abstract**

Living donors are frequently used for kidney transplantation in the United States. This option offers a superior patient and graft survival over deceased donor transplantation. It is also an excellent solution to close the widening gap between patients awaiting renal transplantation and number of transplants done. Organ Procurement and Transplantation Network (OPTN) has specified the minimum general and kidney-specific requirements for suitability as a living kidney donor. Transplant programs across the United States have specific medical criteria for living donation which may be beyond the minimum specified by OPTN. Although living kidney donation is deemed safe, a thorough evaluation to assess medical suitability, infectious and malignancy transmission risk, and assessment of residual organ reserve in the donor is required. This chapter covers all aspects of medical evaluation of the living kidney donor in detail. In general, most programs are now more willing to accept donors with treated hypertension, obesity, or a history of kidney stones provided that certain conditions are met. Such aspects of medically complex living kidney donors are also presented here. Certain recipient conditions that should prompt genetic testing in related living donor candidates are also discussed. Other OPTN requirements such as psychosocial evaluation of living donors and their follow-up by the donor center are also highlighted.

**Keywords**

Living kidney donor · Infection transmission · Malignancy transmission · Psychosocial evaluation · Independent living donor advocate

**Abbreviations**

| | |
|---|---|
| AER | Albumin excretion rate |
| AUA | American Urologic Association |
| BMI | Body mass index |
| CMS | Centers for Medicare and Medicaid Services |
| DTAC | Disease Transmission and Advisory Committee |
| ESRD | End-stage renal disease |
| KDIGO | Kidney Disease Improving Global Outcomes |
| NAT | Nucleic acid test |
| OPTN | Organ procurement and transplantation network |
| PHS | Public Health Service |
| SRTR | Scientific Registry of Transplant Recipients |
| TBMN | Thin basement membrane nephropathy |
| UNOS | United Network for Organ Sharing |
| WHO | World Health Organization |

## Introduction

As per UNOS (United Network for Organ Sharing), there are more than 100,000 patients awaiting renal transplantation as shown in Fig. 1. Living kidney donation can help lessen this widening gap. However, living donation rates have declined progressively for more than a decade. This decrease has largely been driven by a reduction in the number of living related kidney donations, from 4340 in 2004 to 2693 as per 2014 Scientific Registry of Transplant Recipients (SRTR) annual report (Fig. 2).

There are short- and long-term risks of living donor nephrectomy. In order to address this, the Organ Procurement and Transplant Network (OPTN) has defined policies which outline the minimum general and kidney-specific requirements for

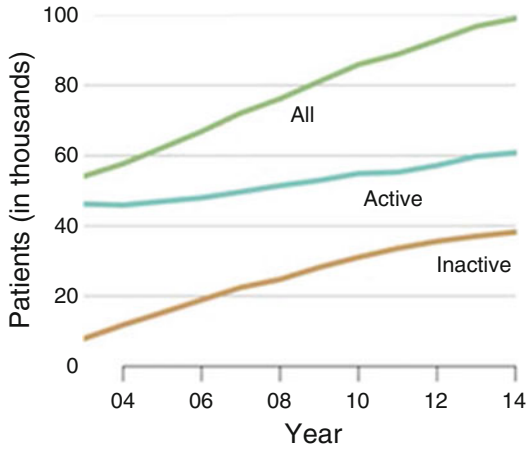


**Fig. 1** Adults awaiting renal transplantation (Reference: American Journal of Transplantation Volume 16, Issue S2, pages 11–46, 11 Jan 2016 doi: 10.1111/ajt.13666. http://onlinelibrary.wiley.com/doi/10.1111/ajt.13666/full#ajt13666-fig-0001)

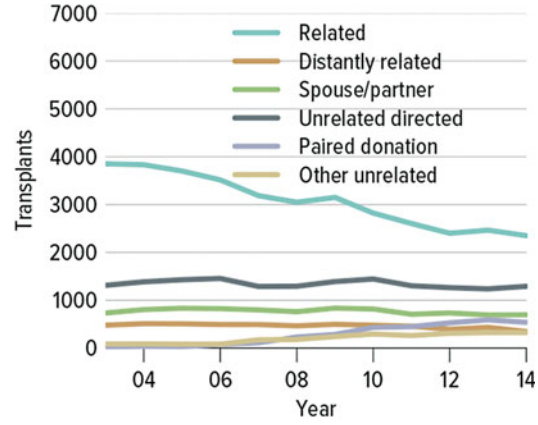


**Fig. 2** Kidney transplants from living donors, by donor relation (Reference: American Journal of Transplantation Volume 16, Issue S2, pages 11–46, 11 Jan 2016 doi: 10.1111/ajt.13666. http://onlinelibrary.wiley.com/doi/10.1111/ajt.13666/full#ajt13666-fig-0001)

suitability as a living kidney donor. These minimum requirements along with additional criteria are generally incorporated into center-specific protocols that are based on local expertise and center-specific risk threshold and then targeted to individual donor candidates on a case-by-case basis. Policy 14 by OPTN pertains to living donation and extensively details all pertinent living donor requirements. It encompasses psychosocial evaluation of living donors, independent living donor advocate requirements, informed consent requirements, and medical evaluation. This chapter will primarily cover medical evaluation of living donor since other aspects are covered in detail elsewhere in this book.

The first step to evaluation of a living donor begins with checking the living donor and recipient blood type to assess compatibility. The blood type and crossmatch compatibility are the primary criteria for biological compatibility of the donor and recipient. HLA typing of the donor is also pursued to assess residual immunologic risk that may exist beyond verifying compatibility of anti-human globulin CDC and flow crossmatches. With this added information, often times a zero-mismatched donor is preferentially used in case there are multiple living donor options available. Also any low-intensity donor-specific antibodies can be picked up easily in the recipient once HLA typing of the donor is known. Those living donor recipient pairs which are biologically incompatible should be counseled about the options of living donor kidney exchanges and chains. Based on center-specific protocols, desensitization of the intended recipient for both ABO incompatibility and HLA antibodies may also be pursued.

According to a recent publication by Grams et al. (2016), for a 40-year-old person with a similar profile to age-matched healthy donors, the 15-year projections of the risk of end-stage renal disease (ESRD) in the absence of donation vary according to race and sex; the risk was 0.24% among black men, 0.15% among black women, 0.06% among white men, and 0.04% among white women. The 15-year observed risks after donation among kidney donors in the United States were 3.5–5.3 times as high as the projected risks in the absence of donation. An online risk assessment tool developed by the same authors is also available at www.transplantmodels.com/esrdrisk to evaluate, counsel, and accept living kidney donor candidates. The incidence of 90-day all-cause perioperative mortality is considered very low at 0.03% based on a study by Segev et al. (2010) of more than 80,000 living donors where 25 deaths were recorded. Table 1 shows a more recent cohort of living kidney donor deaths recorded in the United States and also lists the causes.

**Table 1** Living kidney donor deaths from 2010 to 2014 (Adapted from Table 3.1 from SRTR 2014 Report)

| | Days after donation | | |
|---|---|---|---|
| **Cause** | **0–30** | **31–90** | **91–365** |
| Suicide | **1** | **1** | **4** |
| Accident/homicide | **0** | **0** | **5** |
| Medical | **3** | **2** | **1** |
| Cancer | **0** | **0** | **1** |
| Unknown | **0** | **1** | **1** |
| **TOTAL** | **4** | **4** | **12** |

## Medical Evaluation of Living Donor

General donor history requirements as specified by OPTN policy 14 pertaining to living donation are listed below. All living kidney donors should be queried for a personal history of significant medical conditions which include but are not limited to:

(a) Hypertension
(b) Diabetes
(c) Lung disease
(d) Heart disease
(e) Gastrointestinal disease
(f) Autoimmune disease
(g) Neurologic disease
(h) Genitourinary disease
(i) Hematologic disorders
(j) Bleeding or clotting disorders
(k) History of cancer including melanoma
(l) History of infections
(m) Active and past medications with special consideration for known nephrotoxic medications or chronic use of pain medication
(n) Allergies
(o) An evaluation for coronary artery disease

Additionally, potential living donors should be queried for kidney-specific personal history:

(a) Genetic renal diseases
(b) Kidney disease, proteinuria, hematuria
(c) Kidney injury
(d) Diabetes including gestational diabetes
(e) Nephrolithiasis
(f) Recurrent urinary tract infections

Family history should focus on the following elements:

(a) Coronary artery disease and any cancer
(b) Kidney disease
(c) Diabetes
(d) Hypertension
(e) Kidney cancer

Social history should include:

(a) Occupation
(b) Employment status
(c) Health insurance status
(d) Living arrangements
(e) Social support
(f) Smoking, alcohol and drug use and abuse
(g) Psychiatric illness, depression, suicide attempts
(h) Increased risk behavior as defined by the US Public Health Services (PHS) Guideline

Physical exam should focus on:

(a) Height
(b) Weight
(c) BMI
(d) Vital signs
(e) Examination of all major organ systems
(f) Blood pressure taken on at least two different occasions or 24-h or overnight blood pressure monitoring

General laboratory and imaging studies that need to be pursued include:

(a) Complete blood count with platelet count
(b) Blood type and subtype

(c) Prothrombin time (PT) or international normalized ratio
(d) Partial thromboplastin time (PTT)
(e) Metabolic testing (to include electrolytes, BUN, creatinine, transaminase levels, albumin, calcium, phosphorus, alkaline phosphatase, bilirubin)
(f) HCG quantitative pregnancy test for premenopausal women without surgical sterilization
(g) Chest X-ray
(h) Electrocardiogram (ECG)

Kidney-specific tests include:

(a) Fasting blood glucose.
(b) Fasting lipid profile (cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol).
(c) Glucose tolerance test or glycosylated hemoglobin in first-degree relatives of diabetics and in high-risk individuals.
(d) Urinalysis or urine microscopy.
(e) Urine culture if clinically indicated.
(f) Measurement of urinary protein and albumin excretion.
(g) Measurement of glomerular filtration rate by isotopic methods or a creatinine clearance calculated from a 24-h urine collection.
(h) Hospitals must develop and comply with a written protocol for polycystic kidney disease or other inherited renal disease as indicated by family history.
(i) Patients with a history of nephrolithiasis or nephrolithiasis (>3 mm) identified on radiographic imaging must have a 24-h urine stone panel measuring: calcium, oxalate, uric acid, citrate, creatinine, and sodium.
(j) Determine on kidney imaging study: size of both kidneys, presence of lesions (cyst, mass, stone), anatomical defects or variants, and assessment of which kidney is suitable for donation.

## Transmissible Disease Screening

Infectious disease testing must be performed in a CLIA-certified laboratory or in a laboratory meeting equivalent requirements as determined by Centers for Medicare and Medicaid Services (CMS) using FDA-licensed, approved, or cleared tests. Testing must include all the following:

1. CMV (cytomegalovirus) antibody
2. EBV (Epstein-Barr virus) antibody
3. HIV antibody (anti-HIV) testing or HIV antigen/antibody (Ag/Ab) combination test as close as possible, but within 28 days prior to organ recovery
4. Hepatitis B surface antigen (HBsAg) testing as close as possible, but within 28 days prior to organ recovery
5. Hepatitis B core antibody (anti-HBc) testing as close as possible, but within 28 days prior to organ recovery
6. Hepatitis C antibody (anti-HCV) testing as close as possible, but within 28 days prior to organ recovery
7. HCV ribonucleic acid (RNA) by nucleic acid test (NAT) as close as possible, but within 28 days prior to organ recovery
8. Syphilis testing
9. Assessment of tuberculosis risk in living donor and then test for latent infection using either intradermal PPD or Interferon Gamma Release Assay (IGRA)

## Endemic Transmissible Disease Evaluation in Living Donors

Each living donor hospital must develop and follow a written protocol for identifying and testing donors at risk for transmissible seasonal or geographically defined endemic disease as part of its medical evaluation.

## Cancer Screening in Living Donors

Recovery hospitals must develop and comply with protocols consistent with the American Cancer Society (ACS) or the US Preventive Services Task Force to screen for:

(a) Cervical cancer
(b) Breast cancer
(c) Prostate cancer
(d) Colon cancer
(e) Lung cancer

## Imaging Studies

The type of imaging study to be pursued is center specific and may include either CT angiogram or magnetic resonance (MR) angiogram. Anatomic assessment of kidneys by imaging to assess equality of kidney size and evaluate for masses, cysts, stones, or other structural defects to help determine the kidney best suited for donation. Assessment of kidney volume should also be done to assess discrepancy since this information also needs to be factored in while making decisions on which kidney to use for donation.

The minimum exclusion criteria as defined for living kidney donation is defined by OPTN policy number 14 pertaining to living donation.

Living donor recovery hospitals may exclude a donor with any condition that, in the hospital's medical judgment, causes the donor to be unsuitable for organ donation. Living donor recovery hospitals must exclude all donors who meet any of the following exclusion criteria:

(a) Is both less than 18 years old and mentally incapable of making an informed decision
(b) HIV, unless the requirements for a variance are met
(c) Active malignancy or incompletely treated malignancy
(d) High suspicion of donor coercion
(e) High suspicion of illegal financial exchange between donor and recipient
(f) Evidence of acute symptomatic infection (until resolved)
(g) Uncontrolled diagnosable psychiatric conditions requiring treatment before donation, including any evidence of suicidality
(h) Uncontrollable hypertension or history of hypertension with evidence of end-organ damage
(i) Diabetes

Additional center-specific contraindications beyond those specified by OPTN may include:

(a) Proteinuria >300 mg in 24 h. Some centers also exclude microalbuminuria.
(b) Impaired renal function (defined as glomerular filtration rate (GFR) <80 mL/min/1.73 $m^2$ or inappropriately low function for age and sex).
(c) Marked urologic, renal vascular abnormalities, or multiple renal vessels.
(d) Any chronic, active viral infection such as HBV and HCV.
(e) History of malignancy, especially lung, breast, renal or urologic, gastrointestinal, or hematologic cancers and melanoma.
(f) Chronic illness (pulmonary, liver, autoimmune, neurologic, or cardiac disease).
(g) Nephrocalcinosis, bilateral kidney stones, or recurrent nephrolithiasis.
(h) Current pregnancy.
(i) Morbid obesity with BMI >35 kg/$m^2$.
(j) Active illicit substance or alcohol abuse.

## Estimation of Renal Function

The most commonly used measure of evaluating GFR in clinical practice is based on a 24-h creatinine clearance and serum creatinine concentration. It is extremely important to ensure adequacy of 24-h urine collection. An incomplete urine collection leads to an underestimation of creatinine excretion and therefore of the GFR. The completeness of the collection can be estimated from knowledge of the normal rate of creatinine excretion. In adults under the age of 50 years, daily urinary creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women. After age 50, creatinine excretion falls progressively due to a decrease in muscle mass and may be as low as 10 mg/kg. A GFR >80 ml/min corrected to body surface area of 1.73 $m^2$ is generally considered acceptable for kidney donation. The Amsterdam Forum on the Care of the Live Kidney Donor (2005) consensus guidelines state that a GFR <80 mL/min or 2 standard deviations below normal (based on age, gender, and body surface area corrected to

1.73 $m^2$) generally precludes donation. OPTN criteria also states that an individual unsuitable for living donation includes creatinine clearance <80 mL/min per 1.73 $m^2$ or projected GFR with removal of one kidney at 80 years old of <40 mL/min per 1.73 $m^2$. In cases where there is doubt regarding the accuracy of GFR from estimation methods, a direct measurement of GFR is undertaken by exogenous clearance methods. Acceptable methods include a direct evaluation of the GFR by methods such as Cr-EDTA (nuclear GFR), iothalamate, iohexol, or inulin clearance although these methods may not be widely available. Study of practice patterns of US transplant centers by Mandelbrot et al. (2007) has revealed that about 90% of centers rely on measured creatinine clearance to estimate GFR and 10% use an exogenous filtration marker; and approximately 67% used a GFR ≥80 mL/min as cutoff to accept donors, while 25% used a threshold based on age and sex. As some older donors with lower GFR may be used, it is important to keep in mind as shown by Nordén et al. (2000) that cumulative graft survival in the recipient after adjusting for death-censored graft loss was significantly reduced in recipients of grafts from living donors with GFR <80 ml/min. Moreover, implications of letting these low GFR candidates donate do require additional considerations.

## Need for Split Renal Function Testing

For most part, kidney function and size are correlated. As per Wang et al. (2014) and Glodny et al. (2009), the average kidney length and volume in healthy adults are approximately 12 cm and 300 ml, respectively, but vary based on age, sex, and body size. Moreover, the normal right kidney is approximately 5% smaller than the normal left kidney. As specified by KDIGO guidelines, asymmetry in kidney size is generally considered as a difference in kidney size >10% (e.g., a difference in kidney length >1.2 cm or kidney volume >30 ml). An equivalent difference in kidney function would be >10% (>55% vs. <45% of two kidney function on split testing). Radionuclide imaging is desirable before nephrectomy if there is substantial discrepancy in the size of the kidneys or anatomical abnormality is noted. In these situations, most centers would prefer to transplant the kidney with lesser function and leave the donor with the kidney with greater function after all technical considerations for surgical planning have been taken into account.

## Evaluation of Proteinuria in Kidney Donor Candidates

Potential donors with 24-h urine protein >300 mg are usually excluded from donation. Some centers prefer a cutoff of 24-h urine protein >150 mg as a contraindication. Urinary protein comprises of small amounts of high molecular weight proteins (mainly albumin) that does not cross the glomerular filtration barrier and low molecular weight serum proteins that are normally filtered but subsequently undergo tubular reabsorption and finally proteins secreted by the urinary tract. Glomerular proteinuria demonstrated by albuminuria denotes glomerular hyper filtration or damage. Tubular proteinuria can be seen as an overflow proteinuria such as light-chain proteinuria (Bence Jones protein) due to overproduction of light chains as in lymphoproliferative disorders or due to lower urinary tract disease leading to tubular proteinuria. Patients with nephrolithiasis or tumors of the urinary tract may also have proteinuria.

In potential donors <30 years of age with proteinuria outside of acceptable range, orthostatic proteinuria should be ruled out by doing a split 24-h collection. Springberg et al. (1982) published that this entity can cause low-grade proteinuria, has a benign course, and should not be considered a contraindication to donation. In order to diagnose orthostatic proteinuria, it needs to be shown that there is only upright proteinuria with the absence of supine proteinuria. Specifically, the 8-h supine sample should contain <50 mg of protein to make this diagnosis.

Microalbuminuria is considered a sensitive indicator of glomerular pathology and should always be checked in addition to 24-h total protein. An early morning urine sample to measure

albumin excretion is preferred since the effect of diurnal variation is minimized. Furthermore, an albumin/creatinine ratio should be reported in the early morning sample since this overcomes variation due to urine concentration and dilution. An increased 24-h urine protein but normal urine albumin excretion should prompt search for non-glomerular etiology such as tubular or light-chain proteinuria or urinary tract disease. As per KDIGO clinical practice guidelines (2016), specific commercially available assays for α1-microglobulin, β2 macroglobulin, and monoclonal heavy or light chains can be used for this purpose. As recommended by KDIGO-CKD work group (2012), if a 24-h urine albumin excretion rate (AER) is measured, the cutoff usually recommended is AER threshold of <30 mg/day to routinely accept a donor candidate, which corresponds to total protein excretion of <150 mg.

Lastly, it is important to remember that proteinuria can be a result of altered renal physiology in conditions such as fever, exercise, or extreme cold. This is usually transient and can be ruled out on repeat testing.

## Evaluation of Hematuria in Kidney Donor Candidates

All donor candidates should be screened for the presence of microscopic hematuria. If persistent microscopic hematuria is present, additional testing should be pursued to ascertain the cause. Microscopic hematuria can be from benign entities such as menstruation, endometriosis, benign prostatic hypertrophy, as well as strenuous exercise. Urinary tract infection can also cause hematuria and is not a contraindication to donation provided it is addressed prior to donation. Other conditions such as nephrolithiasis can be picked up on CT imaging, and donor suitability with this diagnosis is covered in detail under stone discussion. Finally, microscopic hematuria can be associated with conditions that preclude donation such as genitourinary or renal malignancy, polycystic kidneys, sickle cell disease, or glomerular disease. A urinary tract malignancy picked up during hematuria work-up will be a contraindication due to transmission risk. Further work-up usually involves CT urography and completion of cystoscopy along with focused clinical history for risk factors. Some glomerular diseases can also present with persistent isolated hematuria such as Ig A nephropathy, thin basement membrane disease, and Alport syndrome. A renal biopsy is usually needed in cases of unexplained persistent hematuria. Donor candidates with additional features such as low GFR, proteinuria, or hypertension are generally excluded from donation. Donors with isolated hematuria with a negative urologic evaluation and normal renal biopsy are generally acceptable for donation.

As per Cohen and Brown (2003), estimated prevalence of microscopic hematuria varies widely from 0.18% to 16%. The American Urological Association (AUA) states that a positive dipstick alone does not define micro hematuria, and evaluation should be based solely on findings of microscopic examination of urinary sediment as suggested by Davis et al. (2012). A commonly accepted definition is microscopic evidence of >2–5 red blood cells per high-power field of urinary sediment on 2–3 separate occasions in the absence of exercise, trauma, sexual activity, or menstruation (Cohen and Brown (2003), Davis et al. (2012), Sutton (1990), Vivante et al. (2011). This is because urine dipstick can give false positive results in the presence of contaminants, myoglobin, or hemoglobin.

As recommended by the AUA, micro hematuria work-up includes assessment of risk factors for urinary tract malignancies (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures); radiological evaluation (CT) urography, without and with intravenous (IV) contrast, or magnetic resonance urography; and cystoscopy in patients age 35 or older regardless of history of the use of anticoagulation therapy (Davis et al. 2012). Urine cytology and urine markers are not included in routine evaluation but may be considered in patients with persistent micro hematuria following a negative work-up or in those with other risk factors for urinary tract malignancies.

This section will cover relevant glomerular diseases in reference to hematuria-like thin basement membrane nephropathy (TBMN), Alport,

and Ig A nephropathy. Savige et al. (2013) have published expert guidelines for the management of Alport syndrome and TBMN and also cover living kidney donation. According to these guidelines: (A) "Individuals with TBMN may be kidney donors if they have normal blood pressure (BP), proteinuria, and renal function" and if a biopsy is done and Alport syndrome is excluded. Close monitoring and use of nephroprotective strategies are advised. (B) "Individuals from families with autosomal recessive Alport syndrome who have only one of the causative mutations (parents, offspring, some siblings) may be renal donors if they have normal BP, proteinuria levels, and renal function; if coincidental renal disease has been excluded by renal biopsy; and if X-linked Alport syndrome has been excluded by genetic testing." These guidelines recommended "discouraging affected mothers of males with X-linked Alport syndrome from renal donation because of their own risk of kidney failure." It is important to recall that carrier states for Alport mutations may present clinically as TBMN, and therefore it is important to confirm by doing genetic testing. High frequencies of eventual proteinuria (75%) and ESRD (8–30%) have been reported in female carriers of X-linked Alport syndrome mutations as per Jais et al. (2003). Glomerular pathology like Ig A nephropathy precludes kidney donation.

## Evaluation of Kidney Stones in Donor Candidates

In a report from the National Health and Nutritional Examination Survey, the prevalence of kidney stones has increased in the United States from 3.8% in the period from 1976 to 1980 to 8.4% in the period from 2007 to 2010 (Scales et al. 2012, Stamatelou et al. 2003). Up to 16% of men and 8% of women will have at least one symptomatic stone by the age of 70 years (Scales et al. 2012). Over 80% of these stones will contain calcium, usually as calcium oxalate. Almost half of symptomatic stone formers will develop a recurrent stone in their lifetime. There are some factors which are associated with higher recurrence probability such as age at first stone detection $<40$ years, bilateral stones, deranged urinary biochemical profile, and presence of nephrocalcinosis. Sometimes, small 1–2 mm foci of calcification may be picked up on donor CT scan in the renal papillae which are known as Randall's plaque and are of undetermined prognosis.

Personal and family history of kidney stones should be queried in all live kidney donors. About 5–10% of potential donors will be diagnosed with asymptomatic kidney stones. These donors should have a detailed stone specific history and testing. A urine metabolic profile should be obtained to determine the cause and suggest corrective measures. Generally, donors with small unilateral kidney stone $<15$ mm with no history of recurrence may be accepted to donate. In most cases, the kidney with the stone is utilized for transplantation with ureteroscopy pursued in the operative field to remove the kidney stone from the explanted kidney. Such donors are encouraged to follow evidence-based dietary recommendations to minimize the risk of stone recurrence after donation. These recommendations include maintaining a urine output of 2.5 liters/day and low-salt and low-oxalate diet, cutting down on animal protein, and consuming average recommended calcium intake with avoidance of calcium supplements.

## Evaluation of Obesity in Kidney Donors

All donors routinely should have a body mass index (BMI) assessment at their evaluation. However, there are inherent limitations on solely relying on BMI to convey body composition, and therefore additional measurement such as abdominal circumference may be used to convey body fat distribution and assess for metabolic syndrome. Donor candidates with morbid obesity (BMI $\geq 40$ kg/m$^2$) should be excluded from donation. Obesity is a known risk factor for diabetes mellitus and may also cause direct kidney injury in the form of obesity-related focal segmental glomerulosclerosis. It is difficult to directly quantify the risk of kidney disease from obesity in isolation due to associated CKD risk factors such

as hypertension, diabetes, obstructive sleep apnea, and cardiovascular disease which may be also present. Per SRTR 2014 Annual report, most transplant programs have been accepting living donors with increasing donor body mass index (BMI); percentages of donors with BMI 25 to <30 and 30 to <35 kg/m$^2$ increased from 35.3% and 15.9% in 2004 to 41.2% and 19.7% in 2014. Gracida et al. (2003) and Ibrahim et al. (2009) examined associations of pre-donation BMI with post-donation renal function and found that BMI increase was correlated with modest reductions in estimated glomerular filtration rate (eGFR) at follow-up. They also examined pre-donation BMI with post-donation hypertension and found increased odds of hypertension requiring medication (OR per BMI unit: 1.12, 95% CI 1.02–1.23) or modest increases in mean arterial pressure (91.2 vs. 88.2 mmHg), respectively. Some other studies have looked at ESRD and mortality risk in obese donors. Mjoen et al. (2014) have reported that cardiovascular death is increased in donors with increasing BMI, but not risk of ESRD and all-cause mortality over a 15-year follow-up in a study involving a large cohort of 1900 living donors. Segev et al. (2010) have reported on over 4000 obese live donors with BMI ≥30 mg/m$^2$ at the time of donation compared to matched healthy controls and found no associations of BMI at donation with perioperative mortality or death over 12 years. Heimbach et al. (2005) have published their experience with obese donors and have shown that major surgical complications such as conversion to open or reoperation and length of stay are not different in comparison to ideal BMI donors. However, overall 9–10% wound complication rate for obese donors in comparison to 2–4% rate in nonobese donors was observed, and this should be disclosed to potential obese donors prior to surgery. Most centers use a threshold of BMI ≥35 kg/m$^2$ as an absolute or relative contraindication to live donation.

History of bariatric surgery in potential donors is usually not a contraindication to donation provided risk assessment for kidney stones and urine biochemical profile has been done. Most centers will not accept these donors if they have hyperoxaluria and or the presence of kidney stones. Most centers will also turn down obese donors who demonstrate metabolic syndrome, hypertension, obstructive sleep apnea, microalbuminuria, and/or hyperlipidemia. It is reasonable to set weight-loss goals in obese living donor candidates prior to donation. Finally, long-term risks of obesity and counseling to maintain a healthy body weight after donation should be stressed.

## Evaluation of Diabetes in Kidney Donor Candidates

Potential donors with history of diabetes are generally excluded from living donation. Per UNOS/OPTN criteria, diabetes is an absolute contraindication to living donation. However, the British guidelines (2011) do not list this as an absolute contraindication but instead mentions "diabetics can be considered for kidney donation after a thorough assessment of the lifetime risk of cardiovascular and progressive renal disease in the presence of a single kidney." European best practices by Pascual et al. (2014) mention that certain donors with diabetes may be allowed to donate under "exceptional circumstances."

The World Health Organization (WHO) defines diabetes mellitus as fasting plasma glucose ≥126 mg/dl, random plasma glucose ≥200 mg/dl, or plasma glucose concentration >200 mg/dl 2 h after a 75 g anhydrous glucose load in an oral glucose tolerance test (OGTT) or a HbA1c ≥6.5% on standardized assays. Both WHO and American Diabetes Association (ADA) define impaired glucose tolerance as 2-h glucose levels of 140–199 mg/dl on the 75 g oral glucose tolerance test. However, they differ on the criteria for impaired fasting glucose with WHO defining it is 110–125 mg/dl for fasting plasma glucose (FPG), and ADA defines this as 100–125 mg/dl.

It is important to obtain family history of diabetes, personal history of gestational diabetes, or polycystic ovarian syndrome in all donors. In potential donors, the first step is to obtain a fasting blood glucose level. Additionally, 2-h glucose tolerance test and/or glycated A1c should be obtained in case of impaired fasting blood glucose, first-degree

relative with diabetes, history of gestational diabetes, or history of polycystic ovarian syndrome.

Some patients with prediabetes may be allowed to donate based on their predicted lifetime incidence of ESRD. Such candidates should be extensively counseled regarding their increased lifetime risk for developing diabetes and consequent end-organ complications and the importance of recognizing modifiable risk factors to reduce risks.

## Evaluation of Blood Pressure in Kidney Donor Candidates

Hypertension is defined by office BP readings of systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg, or as per Chobanian et al. (2003) daytime mean ambulatory blood pressure monitoring (ABPM) or home measurements of SBP $\geq$135 mmHg or DBP $\geq$85 mmHg or the need to use drugs to control hypertension. Accurate blood pressure measurement with properly calibrated equipment is an integral part of living donor work-up. Blood pressure measurement should be done on at least two occasions. There should be low threshold to use ABPM for those potential donors who manifest high readings or known hypertensive donors to assess adequate control.

Potential donors with hypertension and end-organ damage such as myocardial infarction or stroke, microalbuminuria, hypertensive retinopathy, and/or evidence of left ventricular hypertrophy are universally excluded per most transplant center donor protocols. Moreover, donor candidates with hypertension requiring >1 or 2 drugs for adequate control are also generally excluded. Some centers only allow hypertensive donor candidates >50 years of age to proceed with donation with the rationale that kidney damage from hypertension likely would have manifested by this age. Mandelbrot et al. (2007) studied the practice of using hypertensive living donors across the United States and reported that 47% of transplant programs will not accept a hypertensive living donor. Another 41% will exclude donors if they are taking more than one drug to control hypertension, and 8% will exclude donors if they are on more than two drugs. A very recently published paper by Lentine et al. (2016) concluded that donor history of hypertension is not associated with increased perioperative complications which is in contrast to an earlier paper published by Segev et al. (2010) where donors with hypertension had a statistically significantly higher surgical mortality than did donors without hypertension (36.7 per 10,000 donors; 95% CI, 4.4–132.6; vs. 1.3 per 10,000 donors; 95% CI, 0.4–3.4). However, Segev et al. also concluded that the magnitude of the excess surgical risk was considered to be uncertain as indicated by the wide CI.

In normal healthy individuals, blood pressure tends to rise with aging. Kidney donation may accelerate the risk or progression of hypertension over time to a greater degree as a result of interplay between reduced GFR from donation, aging process, and compensatory hyperfiltration. Boudville et al. (2006) have published an estimated 6 and 4 mmHg higher systolic and diastolic BP in about 5000 primarily Caucasian donors in comparison to controls after an average of 7 years. Another study involving African-American donors by Doshi et al. (2013) reported higher rates of post-donation hypertension in comparison to race-matched healthy nondonor controls about 6 years post-donation. In general, all donor candidates should undergo extensive counseling on modifiable risk factors such as healthy diet, smoking cessation, weight reduction strategies, exercise, and salt restriction. They should also be counseled that blood pressure rises with aging and that donation may accelerate this process above and beyond what is expected with normal aging. This process may be more prominent in African-American donors which may result in need for antihypertensive treatment.

Finally, the Amsterdam guidelines (2005) provide some recommendations in using hypertensive living kidney donors and are similar to recommendations outlined in this section. According to them, BP >140/90 by ABPM are generally not acceptable as donors. BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings. Some patients with easily controlled hypertension who meet other

defined criteria (e.g., >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/ day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors. It should be stressed to these donors that long-term follow-up with a physician to monitor blood pressure control and renal function is important.

## Assessment of Infection Transmission from Living Donors to Recipients

Living donor candidates should be rigorously screened for infections. This ensures that disease transmission risk is reduced, and health of the donor is protected. The risk of donor-derived disease transmission can be alleviated by obtaining detailed clinical, social, and travel history of the donor and pursuing blood testing. Some transmissions such as CMV and EBV are considered acceptable in the realm of both living and deceased organ donation and can be managed by adequate prophylaxis and center-specific monitoring protocol. Unanticipated and unacceptable infectious disease transmissions such as HIV and Hepatitis B and C through organ transplantation are rare in the era of current testing but may result in serious adverse outcomes and are a crucial focus of donor testing. The updated 2013 US Public Health Service (PHS) Guidelines by Seem et al. (2013) as outlined in Table 2 provide an evidence-based tool for this assessment. HIV transmission has occurred in living donor transplantation in 2009 in New York, and this case was confirmed to be donor derived based on testing of frozen specimens, tight phylogenetic clustering of HIV sequences from the donor and recipient, and lack of another HIV exposure risk in the recipient. The donor in this case was a high-risk male homosexual donor and was tested for HIV more than 2 months prior to donation with a negative result. After this case, transplant centers have started to screen living donors for HIV as well as Hepatitis B and C as close to the time of donation surgery and also provide counseling to potential living donors to reduce their risk of HIV and Hepatitis B and C exposure and acquisition. In the nutshell, the updated PHS 2013 Guidelines by Seem et al. (2013) recommend testing potential living donors for HIV and hepatitis B and C by both nucleic acid testing (NAT) and serological testing as close as possible to donation surgery. The window period by NAT testing as adapted from Humar et al. (2010) is highlighted in Table 3.

Per OPTN guidelines, microbiological testing as highlighted under transmissible disease screening previously is required on all donors. In addition,

**Table 2** US Public Health Service (PHS) 2013 screening to assess increased likelihood of recent HIV, HBV, or HCV infection (Adapted from Seem et al. 2013)

| | |
|---|---|
| 1. Have you had sex with a person known or suspected to have human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections in the preceding 12 months? | 2. If female: Have you had sex with a man with a history of male-sex-with-male (MSM) behavior in the preceding 12 months? |
| 3. If male: Have you had sex with another man in the preceding 12 months? | 4. Have you had sex in exchange for money or drugs in the preceding 12 months? |
| 5. Have you had sex with a person that has injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months? | 6. Have you injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months? |
| 7. Have you been in lockup, jail, prison, or a juvenile correctional facility for more than 72 h in the preceding 12 months? | 8. Have you been newly diagnosed with or have been treated for syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 months? |
| **Donors who meet the following criterion should be identified as being at increased risk for recent HCV infection only:**<br>9. Have you been on hemodialysis in the preceding 12 months? | **US PHS risk factors also include:** A child who is ≤18 months of age and born to a mother known to be infected with or at increased risk for HIV, HBV, or HCV infection. A child who has been breastfed within the preceding 12 months, and the mother is known to be infected with, or at increased risk for, HIV infection |

**Table 3** Estimates of window period length for HIV and Hepatitis B and C by different testing methods (Adapted from Humar et al. 2010)

| Pathogen | Standard serology | Enhanced serology (fourth-generation or combined antibody-antigen tests) | Nucleic acid testing |
|---|---|---|---|
| HIV | 17–22 days | ~7–16 days | 5–6 days |
| HCV | ~70 days | ~40–50 days | 3–5 days |
| HBV | 35–44 days | Not applicable | 20–22 days |

**Table 4** Screening tool to assess geographically endemic infections and infections related to specific exposures (Adapted from OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee report 2014)

| | |
|---|---|
| Geographic risks (including duration of time spent in a location) | Where was the potential living donor born (outside vs. inside the United States)?<br>Home country/region? Prolonged residence outside home region, recent or distant?<br>Close family members countries of origin<br>Living donor recovery hospital region?<br>Occupational or recreational travel to other countries and/or regions? |
| Occupational risks | Healthcare workers, vets/animal care workers<br>Landscapers, park rangers, and other outdoor workers<br>Peace Corps workers, international journalists<br>Current or previous military service, particularly outside the United States<br>Medical mission trips (consider a 3-month washout period prior to donation to allow identification of subclinical disease) |
| Seasonal risks | Particularly with warm weather and insect exposure – local West Nile virus, dengue, chikungunya virus transmission, local rickettsial infections, Lyme disease |
| Hobbies | Hunting/dressing game, taxidermy<br>Time living outdoors including camping, swimming in lakes, drinking stream water, insect exposures<br>Adventure sports<br>Gardening |
| Significant animal exposure (wild and/or domestic) | Large numbers of cats or dogs or any unusual pets<br>Laboratory/research animals<br>Veterinarian/vet assistant |
| Family members and close contacts with potential risk factors | Geographic or seasonal infections previously diagnosed in close family members or other contacts may predict risk for subclinical infection in potential donor |

urinary tract infection evaluation is typically pursued at donor evaluation and again close to actual donation surgery. UTI should always be treated prior to donation in the donor. Presence of UTI in a male donor candidate should prompt additional detailed urologic evaluation to rule out prostatitis, urethral stricture and seek history for predisposing conditions such as anal intercourse or family history of reflux nephropathy. Sometimes, female donors may have asymptomatic bacteriuria. Urinary tract infection in a living donor should be treated prior to donation.

Transplant centers are also required to evaluate and maintain a written policy for geographic, environmental, and occupational exposures in potential living donor candidates as per OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee (DTAC) guidance published in 2014 as highlighted in Table 4. Microbiological screening for additional infections to assess seasonal or geographic and endemic infections, implications of results, and strategies to prevent recipient infection as suggested by KDIGO and DTAC are highlighted in Table 5.

**Table 5** Common seasonal and geographically endemic infections in organ donors (Adapted from OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee report 2014)

| Pathogen | Target population for testing | Screening tests | Confirmatory/ additional tests | Implications of positive test for donation and management |
|---|---|---|---|---|
| **West Nile virus (WNV)** | Persons with history of mosquito exposure or blood transfusions; risk varies by geography and season | Anti-WNV Ab IgM is available, but NAT advised in initial screening | WNV NAT typically within 7–14 days of donation | Donation should be delayed for 28d when NAT screening is positive, followed by repeat NAT and IgM testing, with further decisions based on combined results |
| **Mycobacterium Tuberculosis (MTB)** | Born outside or prolonged residence outside the United States, homeless, alcohol or other substance abuse, prison time, healthcare worker, known TB exposure | Chest radiograph Histo Tuberculin skin testing (TST) or Interferon gamma release assay (IGRA) | Acid-fast bacilli (AFB) staining, culture and/or NAT testing for active infection | Donation is contraindicated from persons with active MTB infection. Consideration of donation after treatment of active MTB should be individualized Donation may be considered from persons with latent MTB infection after initiation of chemoprophylaxis in the donor before donation, informed consent of the recipient, and recipient monitoring after transplant |
| ***Strongyloides cruzi*** | Born or lived in tropical/ subtropical countries with substandard sanitation. Significant exposure to soil in the Appalachia or the southeastern United States including walking barefoot. Unexplained eosinophilia and travel to an endemic area. Prior history of *Strongyloides* infection | Anti-*Strongyloides* Ab (IgG) | | Donation may proceed after treatment of the donor with an appropriate antiparasitic agent such as ivermectin |
| ***Trypanosoma cruzi* (Chagas)** | Born or lived in endemic areas of Mexico, Central and South America. Children of woman who lived in endemic area. Recipients of blood transfusion in endemic areas. Prior history of Chagas | Anti-*T. cruzi* Ab (EIA or IFA test) NAT insensitive for chronic phase disease due to low levels of parasitemia | | Donation may be considered from persons with chronic Chagas disease after treatment of the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant |

(*continued*)

**Table 5** (continued)

| Pathogen | Target population for testing | Screening tests | Confirmatory/ additional tests | Implications of positive test for donation and management |
|---|---|---|---|---|
| **Histoplasmosis** | Born or lived in Midwestern US Mississippi or Ohio River valleys | Chest radiograph (may be suggestive but not diagnostic) Anti-histoplasmosis Ab (complement fixation, immunodiffusion or EIA) | Urine or serum antigen testing | Donation may be considered from persons with pulmonary-limited histoplasmosis after treatment of the donor candidate before donation, resolution of clinical signs/symptoms and of antigenuria/ antigenemia (if present at diagnosis), informed consent of the recipient, and recipient monitoring after transplant |
| **Coccidioidomycosis** | Born or lived in desert areas of Southwestern United States | Chest radiograph (may be suggestive but not diagnostic) Anti-*Coccidioides* Ab (complement fixation, immunodiffusion, or EIA) | Urine or serum antigen testing | Donation may be considered from persons with coccidioidomycosis after treatment of the donor candidate before donation, resolution of clinical signs/symptoms and of antigenuria/ antigenemia (if present at diagnosis), informed consent of the recipient, and recipient monitoring after transplant |

## Cancer Screening in the Donor

All living donors undergo routine age-appropriate cancer screening. These include screening recommendations for colon, breast, cervical, prostate, and lung cancer. This is done to protect donor health and to prevent malignancy transmission to the recipient. In general, any active malignancy except for some low-grade nonmelanoma skin cancers is considered an absolute contraindication to organ donation. Any history of choriocarcinoma, melanoma, lymphoma, and leukemia is also considered an absolute contraindication to donation as well. The malignancy subcommittee of DTAC was established to monitor probable transmissions and provide guidance to maximize organ usage in a safe manner. Nalesnik et al. (2011) summarized their report to minimize donor malignancy transmission as outlined in Table 6. In general, live kidney donation from candidates in minimal- and low-risk categories may be considered but with the caveat that recipient informed consent must be obtained as per OPTN policy 4.2.

Renal cancer, melanoma, lymphoma, and lung cancer are the most commonly transmitted donor cancers among kidney transplant recipients. In general, all donors with melanoma are categorized as high malignancy transmission risk donors, irrespective of stage or active versus past disease with the possible exception of in situ melanoma, where metastatic risk is low as per DTAC report by Nalesnik et al. (2011). The Israel Penn International Transplant Tumor Registry has previously reported a 75% transmission rate resulting in 62%

**Table 6** Risk categories for donor tumor transmission risk (Adapted from Nalesnik et al. 2011)

| No significant risk | Benign tumors in which malignancy is excluded |
|---|---|
| Minimal risk (<0.1% transmission) | Basal cell carcinoma, skin<br>Squamous cell carcinoma, skin without metastases<br>Carcinoma in situ, skin (nonmelanoma)<br>In situ cervical carcinoma<br>In situ vocal cord carcinoma<br>Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage) (nonrenal transplant only)[a]<br>Solitary papillary thyroid carcinoma ≤0.5 cm<br>Minimally invasive follicular carcinoma, thyroid ≤1.0 cm<br>(Resected) solitary renal cell carcinoma ≤1.0 cm, well differentiated (Fuhrman 1–2) |
| Low risk (0.1–1% transmission) | (Resected) solitary renal cell carcinoma, >1.0 cm ≤2.5 cm, well differentiated (Fuhrman 1–2)[b]<br>Low-grade CNS tumor (WHO grade I or II)<br>Primary CNS mature teratoma<br>Solitary papillary thyroid carcinoma, 0.5–2.0 cm<br>Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm<br>History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure |
| Intermediate risk (1–10% transmission) | Breast carcinoma (stage 0, i.e., carcinoma in situ)<br>Colon carcinoma (stage 0, i.e., carcinoma in situ)<br>(Resected) Solitary renal cell carcinoma T1b (4–7 cm) well-differentiated (Fuhrman 1–2) stage I[b]<br>History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90 and 99% |
| High risk (>10% transmission) | Malignant melanoma<br>Breast carcinoma >stage 0 (active)<br>Colon carcinoma >stage 0 (active)<br>Choriocarcinoma<br>CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation, or extra-CNS metastasis<br>CNS tumor WHO grade III or IV<br>Leukemia or lymphoma<br>History of melanoma, leukemia or lymphoma, small cell lung/neuroendocrine carcinoma<br>Any other history of treated non-CNS malignancy either (a) insufficient follow-up to predict behavior, (b) considered incurable, or (c) with probability of cure <90%<br>Metastatic carcinoma<br>Sarcoma<br>Lung cancer (stages I–IV)<br>Renal cell carcinoma >7 cm or stage II–IV<br>Small cell/neuroendocrine carcinoma, any site of origin<br>Active cancer not listed elsewhere |

[a]Does not apply to renal transplant, as lesions may be multicentric
[b]Assumes complete resection of tumor prior to transplant

recipient mortality in 28 recipients who were transplanted with organs provided by 13 donors. These 13 donors were deemed free of melanoma at donation (Penn 1996; Buell et al. 2004). Some donors with completely resected small renal cell cancers prior to implantation have minimal risk of transmission (Table 6) and may be considered as living donors after informed consent has been obtained.

## Evaluation of Genetic Diseases in the Donor

It is important to ascertain the cause of ESRD in a transplant candidate not only to assess risk of recurrence but also to stratify the risk of renal disease in a biologically related donor.

*Autosomal dominant polycystic kidney disease (ADPKD)* results from mutations in one of two genes, PKD1 on chromosome 16 or PKD2 on 4. PKD1 mutations accounted for 85% of cases and PKD2 for 15% (Rossetti et al. 2007). PKD 1 mutations are associated with a faster progression to ESRD by the fifth decade of life versus individuals with PKD2 mutations that often do not develop ESRD until seventh decade. Based on the work of Ravine and Pei et al. (2009), updated ADPKD criteria are available for use in clinical scenarios in at-risk population in whom molecular testing is not available. Accordingly, ADPKD can be confidently excluded in the absence of cysts for at-risk individuals between ages 30 and 39 (negative predictive value [NPV] 98.3%) and in the presence of fewer than two cysts for patients ≥40 years (NPV 100.0%). Clearly, ultrasonography is limited in excluding ADPKD in at-risk individuals <30 years, even in the absence of cysts (NPV 90.8%), and a negative ultrasound does not exclude disease between the ages of 30 and 39 years in about 1.7% of those at risk. In a more recent study by Pei et al. (2014), the presence of fewer than five cysts on non-contrast MRI in both kidneys combined where all the cysts are also less than 1.0 cm in length excluded the disease in at-risk individuals aged between 16 and 40 years.

In individuals aged <40 years who are being considered as living related kidney donors, who have no cysts on renal ultrasound or five to ten cysts by MRI, genetic testing is a valuable additional tool to exclude ADPKD with certainty. Linkage-based genetic diagnoses of ADPKD using sequencing of microsatellite regions flanking ADPKD1 and ADPKD2 genes are now rarely performed except in cases of preimplantation diagnostics for pregnancy planning. Rather, direct mutation testing which involves sequencing of the entire coding regions of both *PKD1* and *PKD2*, including intron/exon boundaries, is the current method of choice for molecular diagnosis of ADPKD (Audrezet et al. 2012). The recipient is first screened for PKD1 and PKD2 mutations, and if a causal mutation is identified, then focused mutation detection can be carried out on the prospective donor. Up to 15% of patients with suspected ADPKD have a negative comprehensive mutation screen. In such cases where the mutation screening in the first-degree relative with ADPKD is negative, DNA testing is unhelpful in determining whether the donor candidate does or does not have ADPKD.

*APOL1 genotype:* The American Society of Transplantation (AST) held an APOL1 Consensus Building Meeting in December 2015 to bring experts in the field together to address the potential impact of the APOL1 gene variants on organ donation and transplantation. It is accepted that homozygosity or compound heterozygosity for the G1 and G2 alleles causes autosomal recessive predisposition to myriad manifestations of CKD such as focal segmental glomerulosclerosis and HIV-associated nephropathy, proteinuria, reduced GFR, and younger age at dialysis in African-Americans of sub-Saharan descent (Parsa et al. 2013). Having at least one *APOL1* allele risk variant confers resistance to lethal *Trypanosoma brucei* infections. Kidneys from African-American deceased donors that harbored two APOL1 risk variants have failed far more rapidly after transplantation than those with zero or one risk variant (Reeves-Daniel et al. 2011). The probability that an African-American in the general population carries two risk alleles is 12% and increases to about 72% in an African-American with FSGS. The offspring of two individuals, one without kidney disease and one with FSGS, has a 28% risk of carrying two risk alleles and a seven- to tenfold higher risk of developing FSGS or hypertensive CKD, even without donation (Kuppachi et al. 2015). However, at this time the utility of *APOL1* testing for living donation has not been described in current or prior living donor guidelines but is an intense area of intense interest.

*Hereditary interstitial kidney disease:* Autosomal dominant interstitial kidney disease is rare. Mutations in at least four genes are implicated: *MUC1* gene which encodes mucin1 (*MCKD1*), *REN* gene which encodes renin, *UMOD* gene which encodes uromodulin (*MCKD2*), and the *HNF1B* gene which encodes hepatocyte nuclear factor-1β (Hart et al. 2002; Kirby et al. 2013). HNF1B is implicated in causing the RCAD

(renal cysts and diabetes) syndrome which manifests as renal cysts and diabetes (MODY5). According to Thomas et al. (2008), mutations in HNF1B can have variable manifestations such as renal hypoplasia or agenesis, multicystic renal dysplasia, horseshoe kidney, and glomerulocystic kidney disease. Disease resulting from mutations in the UMOD gene has been called familial juvenile hyperuricemic nephropathy. MCKD1 is characterized by features of a chronic tubulointerstitial disease with occasional cortical cysts on renal imaging, minimal proteinuria, bland urinary sediment, and no other associated features other than progressive CKD. Potential biologically related living donors should undergo mutational testing if the intended recipient with kidney failure is confirmed to have the pathogenic mutation.

*Atypical HUS:* Current genetic testing is deficient in ruling out the presence of atypical HUS in a potential donor even when the mutation is known in the recipient. Although mutations in complement regulatory genes such as complement factor H (CFH), membrane cofactor protein (MCP), factor I (CFI), factor B (CFB), and complement C3 were initially identified in aHUS, the list of genes associated with aHUS has grown to include proteins in the coagulation pathway such as thrombomodulin and others according to Bu et al. (2014). Inheritance of an abnormal allele increases susceptibility to aHUS, and an environmental trigger such as pregnancy, infection, surgery, or drugs appears to be necessary for the disease to manifest. Given that as many as 30% of aHUS transplant candidate patients do not have an identifiable genetic mutation, a negative genetic screen cannot eliminate the risk for aHUS in a screened related living donor. Based on the known genetic risk of aHUS and the false-negative rate, it is wise to discourage at-risk candidates from donating.

*Alport and Fabry Disease:* Alport syndrome is most often an X-linked disorder (~80% of families), but can also be inherited in an autosomal recessive (~15% of families) and autosomal dominant fashion (very rare). There is little information on the outcomes of heterozygous women who proceeded with kidney donation (after confirming an absence of proteinuria, hypertension, low GFR, and other manifestations of the disease such as sensorineural hearing loss). If donation is entertained, it should only be done so in older women who have time to manifest kidney disease and after a careful deliberation and consideration of all other alternatives (including other living donors). In the evaluation of male potential living kidney donors, those >20 years of age without hematuria are very unlikely to have X-linked Alport syndrome.

Fabry disease is an X-linked lysosomal storage disease caused by deficiency of the lysosomal hydrolase, α-galactosidase A (α-Gal A), which results in systemic accumulation of trihexosylceramide (globotriaosylceramide [GL-3]) in the lysosomes of the vascular endothelium in multiple organs. ESRD is reached in the third or fourth decade of life in most affected males. Heterozygous females have variable clinical manifestations owing to lyonization (random X chromosome inactivation). Fabry disease is confirmed by biochemical and genetic testing. If the transplant candidate is known to have Fabry disease, all donor candidates at 50% or greater risk of disease, which includes siblings, mothers of affected children, fathers of affected daughters, and all children of an affected mother, should be screened for Fabry disease. All daughters of an affected father are at 100% risk and are not suitable living kidney donors. As with heterozygotes with Alport syndrome, if donation is entertained, it may only be acceptable in older women who have time to manifest any kidney disease and after a careful deliberation and consideration of all other alternatives.

## Psychosocial Assessment of Living Donor

According to OPTN living donor policy 14, it is mandatory for all living donors to undergo psychosocial evaluation by a psychiatrist, psychologist, Masters-prepared social worker, or licensed clinical social worker prior to donation, including documentation of the following:

(a) Mental health issues that might complicate the living donor's recovery and could be identified as risks for poor psychosocial outcome.
(b) Assessment of behaviors that may increase risk for disease transmission as defined by the US Public Health Service (PHS) Guideline.
(c) Living donor's history of smoking, alcohol, and drug use, abuse, and dependency.
(d) The identification of factors that warrant educational or therapeutic intervention prior to the final donation decision.
(e) Determine that the living donor understands the short- and long-term medical and psychosocial risks for both the living donor and recipient associated with living donation.
(f) Assess whether the decision to donate is free of inducement, coercion, and other undue pressure by exploring the reasons for donating and the nature of the relationship, if any, to the transplant candidate.
(g) Assess living donor's ability to make an informed decision and the ability to cope with the major surgery and related stress. This includes evaluating whether the donor has a realistic plan for donation and recovery, with social, emotional, and financial support available as recommended.
(h) Review living donor's occupation, employment status, health insurance status, living arrangements, and social support.
(i) Determine that the living donor understands the potential financial implications of living donation.

**Independent Living Donor Advocate (ILDA)**: Per OPTN requirements, living donor recovery hospitals must designate and provide each living donor candidate with an ILDA (one person or a team with a key contact) who is not involved with the potential recipient evaluation and is independent of the decision to transplant the potential recipient. Detailed role description of the ILDA is covered in the chapter Essential Components of the Living Donor Team.

**Living Donor Follow-Up Requirements**: OPTN policy 18.5A outlines the living donor follow-up requirements and policy 18.6A details reporting of living donor adverse events. This follow-up is needed for up to 2 years post-donation but certainly would be wise to perform this for lifetime. Failure to comply with these reporting requirements can lead to citation of the transplant program. Required kidney donor status and clinical information includes all of the following:

1. Patient status
2. Working for income and, if not working, reason for not working
3. Loss of medical (health, life) insurance due to donation
4. Has the donor been readmitted since last contact?
5. Kidney complications
6. Maintenance dialysis
7. Donor developed hypertension requiring medication
8. Diabetes
9. Cause of death, if applicable and known

Required kidney laboratory and other objective data includes *all* of the following:

1. Serum creatinine
2. Urine protein
3. BP reading

## Conclusions

Potential living kidney donors are required to undergo a detailed medical, surgical, and psychosocial evaluation to ensure that their health status is optimal and their renal function and anatomy are suitable for donation. This evaluation also identifies and assesses infection and malignancy transmission risks from donor to recipient. It is also mandatory for all donors to meet with an ILDA who ensures that the donor is making an informed decision to donate, and all relevant information has been provided to the donor. OPTN has defined the minimum criteria for the medical and psychosocial evaluation of living donor candidates. All transplant centers are required to maintain a written living donor

inclusion and exclusion criteria which may have requirements above and beyond those defined by the OPTN minimum requirements. Based on this evaluation, the donor may be accepted, rejected, or need additional work-up to assess candidacy. This additional work-up may include ABPM, genetic testing to assess risk for inherited renal diseases, geographic and endemic diseases risk, and others. In general, all living kidney donors should be advised regarding modifiable risks of developing chronic kidney disease and should be counseled to adopt healthy lifestyles including weight reduction, smoking cessation, healthy diet, and regular exercise. Finally, it is difficult to quantify the short- and long-term risks of developing renal disease in a medically complex living donor post-donation. This decision-making process is quite intricate, and the final decision to accept or decline a donor depends on a composite of estimated post-donation ESRD risk based on demographic, clinical factors in addition to directly attributable risk from donation itself.

## Cross-References


- A History of Kidney Transplantation
- Ethical Issues in Organ Transplantation
- Live Donor Nephrectomy
- Necessary Components of a Living Donor Team
- Organ Procurement Organization and New Kidney Allocation


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