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KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors

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Abstract: The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors is intended to assist medical professionals who evaluate living kidney donor candidates and provide care before, during and after donation. The guideline development process followed the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach and guideline recommendations are based on systematic reviews of relevant studies that included critical appraisal of the quality of the evidence and the strength of recommendations. However, many recommendations, for which there was no evidence or no systematic search for evidence was undertaken by the Evidence Review Team, were issued as ungraded expert opinion recommendations. The guideline work group concluded that a comprehensive approach to risk assessment should replace decisions based on assessments of single risk factors in isolation. Original data analyses were undertaken to produce a “proof-in-concept” risk-prediction model for kidney failure to support a framework for quantitative risk assessment in the donor candidate evaluation and defensible shared decision making. This framework is grounded in the simultaneous consideration of each candidate's profile of demographic and health characteristics. The processes and framework for the donor candidate evaluation are presented, along with recommendations for optimal care before, during, and after donation. Limitations of the evidence are discussed, especially regarding the lack of definitive prospective studies and clinical outcome trials. Suggestions for future research, including the need for continued refinement of long-term risk prediction and novel approaches to estimating donation-attributable risks, are also provided.

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This Clinical Practice Guideline is based upon systematic literature searches last conducted in September 2014 supplemented with additional evidence through January 2017. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when considering the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

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Disclosure and funding information can be found in the Appendix on page S106.

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SUMMARY OF RECOMMENDATION STATEMENTS

All recommendation statements are not graded unless specified otherwise.

CHAPTER 1: GOALS OF EVALUATION, FRAMEWORK FOR DECISION-MAKING, AND ROLES AND RESPONSIBILITIES

Goals and Principles of Evaluation

- 1.1: The donor candidate's willingness to donate a kidney voluntarily without undue pressure should be verified.
- 1.2: The benefits and risks of kidney donation should be assessed for each donor candidate.
- 1.3: The decision to accept or exclude a donor candidate should follow transplant program policies.
- 1.4: Donor candidate decision-making should be facilitated through education and counseling on individualized risks and benefits, methods to minimize risks, and the need for postdonation follow-up.
- 1.5: For an accepted donor candidate, a plan for donation care and follow-up should be formulated to minimize risks of donation.
- 1.6: For an excluded donor candidate, a plan for any needed care and support should be formulated.

Framework for Decision-Making

- 1.7: The donor candidate, the intended recipient, and the transplant program must all agree with the decision to proceed with donation in concordance with transplant program policies and informed consent.
- 1.8: Transplant program policies must be defensible based on current understanding of the risks and benefits of kidney donation, and should apply to all donor candidates evaluated at the center.
- 1.9: Each transplant program should establish policies describing psychosocial criteria that are acceptable for donation, including any program constraints on acceptable relationships between the donor candidate and the intended recipient.
- 1.10: All donor candidates should be evaluated using the same criteria, regardless of whether donation is directed towards a designated recipient.
- 1.11: Each transplant program should establish policies describing medical criteria that are acceptable for donation, addressing when possible, numeric thresholds for short-term and long-term postdonation risks above which the transplant program will not proceed with donation. Risks should be expressed as absolute rather than relative risks.
- 1.12: When possible, transplant programs should provide each donor candidate with individualized quantitative estimates of short-term and long-term risks from donation, including recognition of associated uncertainty, in a manner that is easily understood by donor candidates.
- 1.13: Transplant programs should evaluate donor candidate risks in comparison to predetermined thresholds for acceptance. If a donor candidate's postdonation risk is

above the transplant program's acceptable risk threshold, the risk is not acceptable for donation. If a donor candidate's postdonation risk is below the transplant program's acceptance threshold, the candidate makes the decision whether or not to proceed with donation.

- 1.14: If a donor candidate is not acceptable, the transplant program should explain the reason for nonacceptance to the donor candidate.
- 1.15: Transplant programs should protect donor candidate's privacy regarding the evaluation, including all considerations in the decision to donate or not.

Roles and Responsibilities

- 1.16: A multidisciplinary transplant program team knowledgeable in kidney donation and transplantation should evaluate, care for, and formulate a plan for donor care including long-term follow-up.
- 1.17: Transplant programs should minimize conflict of interest by providing at least one key team member not involved in the care or evaluation of the intended recipient who evaluates the donor candidate and participates in the determination of donor acceptance.
- 1.18: Transplant programs should conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and transplant programs.

CHAPTER 2: INFORMED CONSENT

Process of Informed Consent

- 2.1: Informed consent for donation should be obtained from the donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision.

Capacity for Decision Making

- 2.2: The donor candidate's capacity to provide informed consent (ie, ability to understand the risks, benefits and consequences of donation) should be confirmed before proceeding with evaluation and donation.
- 2.3: Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (eg, children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review.

Content of Disclosure

- 2.4: Protocols should be followed to provide each donor candidate with information on:
 - The processes of evaluation, donor acceptance, and follow-up
 - The types of information that may be discovered during the evaluation, and what the transplant program will do with such information
 - Individualized risks, benefits and expected outcomes of the donor evaluation, donation, and postdonation health, including a discussion of the uncertainty in some outcomes

- Treatment alternatives available to transplant candidates, and average expected outcomes
- How personal health information will be handled
- Availability of transplant program personnel for support

Comprehension of Disclosed Information

- 2.5: The donor candidate's understanding of the relevant information on the risks and benefits of donation should be confirmed before proceeding with donation.

Voluntarism

- 2.6: Donor candidates should have adequate time to consider information relevant to deciding whether they wish to donate or not.
- 2.7: A donor candidate's decision to withdraw at any stage of the evaluation process should be respected and supported in a manner that protects confidentiality.
- 2.8: A donor candidate who decides not to donate and has difficulty communicating that decision to the intended recipient should be assisted with this communication by the transplant program.

CHAPTER 3: COMPATIBILITY TESTING, INCOMPATIBLE TRANSPLANTATION, AND PAIRED DONATION

Evaluation

- 3.1: Donor ABO blood typing should be performed twice before donation to reduce the risk of unintended blood type incompatible transplantation.
- 3.2: Donor blood group A subtype testing should be performed when donation is planned to recipients with anti-A antibodies.
- 3.3: Human leukocyte antigen (HLA) typing for major histocompatibility complex (MHC) Class I (A, B, C) and Class II (DP, DQ, DR) should be performed in donor candidates and their intended recipients, and donor-specific anti-HLA antibodies should be assessed in intended recipients.

Counseling

- 3.4: Donor candidates who are ABO blood group or HLA incompatible with their intended recipient should be informed of availability, risks, and benefits of treatment options, including kidney paired donation and incompatibility management strategies.
- 3.5: If a donor candidate and their intended recipient are blood type or crossmatch incompatible, transplantation should be performed only with an effective incompatibility management strategy.
- 3.6: Nondirected donor candidates should be informed of availability, risks and benefits of participating in kidney paired donation.

CHAPTER 4: PREOPERATIVE EVALUATION AND MANAGEMENT

- 4.1: Donor candidates should receive guideline-based evaluation and management used for other noncardiac surgeries to minimize risks of perioperative complications, including a detailed history and examination to assess risks for cardiac, pulmonary, bleeding, anesthesia-related and other perioperative complications.

- 4.2: Donor candidates who smoke should be advised to quit at least 4 weeks before donation to reduce their risk of perioperative complications, and commit to lifelong abstinence to prevent long-term complications.

CHAPTER 5: PREDONATION KIDNEY FUNCTION

Evaluation

- 5.1: Donor kidney function should be expressed as glomerular filtration rate (GFR) and not as serum creatinine concentration.
- 5.2: Donor GFR should be expressed in mL/min per 1.73 m² rather than mL/min.
- 5.3: Donor glomerular filtration rate (GFR) should be estimated from serum creatinine (eGFR_{cr}) for initial assessment, following recommendations from the KDIGO 2012 CKD guideline.
- 5.4: Donor GFR should be confirmed using one or more of the following measurements, depending on availability:
 - Measured GFR (mGFR) using an exogenous filtration marker, preferably urinary or plasma clearance of inulin, urinary or plasma clearance of iothalamate, urinary or plasma clearance of ⁵¹Cr-EDTA, urinary or plasma clearance of iohexol, or urinary clearance of ^{99m}Tc-DTPA
 - Measured creatinine clearance (mCrCl)
 - Estimated GFR from the combination of serum creatinine and cystatin C (eGFR_{cr-cys}) following recommendations from the KDIGO 2012 CKD guideline
 - Repeat estimated GFR from serum creatinine (eGFR_{cr})
- 5.5: If there are parenchymal, vascular or urological abnormalities or asymmetry of kidney size on renal imaging, single kidney GFR should be assessed using radionuclides or contrast agents that are excreted by glomerular filtration (eg, ^{99m}Tc-DTPA).

Selection

- 5.6: GFR of 90 mL/min per 1.73 m² or greater should be considered an acceptable level of kidney function for donation.
- 5.7: The decision to approve donor candidates with GFR 60 to 89 mL/min per 1.73 m² should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 5.8: Donor candidates with GFR less than 60 mL/min per 1.73 m² should not donate.
- 5.9: When asymmetry in GFR, parenchymal abnormalities, vascular abnormalities, or urological abnormalities are present but do not preclude donation, the more severely affected kidney should be used for donation.

Counseling

- 5.10: We suggest that donor candidates be informed that the future risk of developing kidney failure necessitating treatment with dialysis or transplantation is slightly higher because of donation; however, average absolute risk in the 15 years following donation remains low. (2C)

CHAPTER 6: PREDONATION ALBUMINURIA

Evaluation

- 6.1: Donor proteinuria should be measured as albuminuria, not total urine protein.

- 6.2: Initial evaluation of donor albuminuria (screening) should be performed using urine albumin-to-creatinine ratio (ACR) in a random (untimed) urine specimen.
- 6.3: Donor albuminuria should be confirmed using:
- Albumin excretion rate (AER, mg/day [mg/d]) in a timed urine specimen
 - Repeat ACR if AER cannot be obtained

Selection

- 6.4: Urine AER less than 30 mg/d should be considered an acceptable level for donation.
- 6.5: The decision to approve donor candidates with AER 30 to 100 mg/d should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 6.6: Donor candidates with urine AER greater than 100 mg/d should not donate.

CHAPTER 7: PREDONATION HEMATURIA

Evaluation

- 7.1: Donor candidates should be assessed for microscopic hematuria.
- 7.2: Donor candidates with persistent microscopic hematuria should undergo testing to identify possible causes, which may include:
- Urinalysis and urine culture to assess for infection
 - Cystoscopy and imaging to assess for urinary tract malignancy
 - 24-hour urine stone panel to assess for nephrolithiasis and/or microlithiasis
 - Kidney biopsy to assess for glomerular disease (eg, thin basement membrane nephropathy, IgA nephropathy, Alport syndrome)

Selection

- 7.3: Donor candidates with hematuria from a reversible cause that resolves (eg, a treated infection) may be acceptable for donation.
- 7.4: Donor candidates with IgA nephropathy should not donate.

CHAPTER 8: KIDNEY STONES

Evaluation

- 8.1: Donor candidates should be asked about prior kidney stones, and related medical records should be reviewed if available.
- 8.2: The imaging performed to assess anatomy before donor nephrectomy (eg, computed tomography angiogram) should be reviewed for the presence of kidney stones.
- 8.3: Donor candidates with prior or current kidney stones should be assessed for an underlying cause.

Selection

- 8.4: The acceptance of a donor candidate with prior or current kidney stones should be based on an assessment of stone recurrence risk and knowledge of the possible consequences of kidney stones after donation.

Counseling

- 8.5: Donor candidates and donors with current or prior kidney stones should follow general population, evidence-based guidelines for the prevention of recurrent stones.

CHAPTER 9: HYPERURICEMIA, GOUT, AND MINERAL AND BONE DISEASE

Evaluation

- 9.1: Donor candidates should be asked about prior episodes of gout.

Counseling

- 9.2: Donor candidates may be informed that donation is associated with an increase in serum uric acid concentration, which may increase the risk for gout.
- 9.3: Donor candidates and donors with prior episodes of gout should be informed of recommended methods to reduce their risk of future episodes of gout.

CHAPTER 10: PREDONATION BLOOD PRESSURE

Evaluation

- 10.1: Blood pressure should be measured before donation on at least 2 occasions by clinical staff trained in accurate measurement technique, using equipment calibrated for accuracy.
- 10.2: When the presence or absence of hypertension in a donor candidate is indeterminate based on history and clinic measurements (eg, blood pressure is high normal or variable), blood pressure should be further evaluated using ambulatory blood pressure monitoring (ABPM) or repeated using standardized blood pressure measurements.

Selection

- 10.3: Normal blood pressure, as defined by guidelines for the general population in the country or region where donation is planned, is acceptable for donation.
- 10.4: Donor candidates with hypertension that can be controlled to systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg using 1 or 2 antihypertensive agents, who do not have evidence of target organ damage, may be acceptable for donation. The decision to approve donor candidates with hypertension should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

Counseling

- 10.5: Donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for hypertension and cardiovascular disease, including healthy diet, smoking abstinence, achievement of healthy body weight, and regular exercise according to guidelines for the general population. These measures should be initiated before donation and maintained lifelong.
- 10.6: We suggest that donor candidates should be informed that blood pressure may rise with aging, and that donation may accelerate a rise in blood pressure and need for antihypertensive treatment over expectations with normal aging. (2D)

CHAPTER 11: PREDONATION METABOLIC AND LIFESTYLE RISK FACTORS

Identification of Metabolic and Lifestyle Risk Factors

- 11.1: Risk factors for kidney and cardiovascular disease should be identified before donation and addressed by counseling to promote long-term health.

Obesity

- 11.2: Body mass index (BMI) should be computed based on weight and height measured before donation, and classified based on World Health Organization (WHO) criteria for the general population or race-specific categories.
- 11.3: The decision to approve donor candidates with obesity and BMI >30 kg/m² should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 11.4: Donor candidates who have had bariatric surgery should be assessed for risk of nephrolithiasis.

Glucose Intolerance

- 11.5: Donor candidates should be asked about prior diagnosis of diabetes mellitus, gestational diabetes, and family history of diabetes.
- 11.6: Glycemia should be assessed by fasting blood glucose and/or glycated hemoglobin (HbA_{1c}) before donation.
- 11.7: 2-hour glucose tolerance or HbA_{1c} testing should be performed in donor candidates with elevated fasting blood glucose, history of gestational diabetes, or family history of diabetes in a first-degree relative, and results should be used to classify diabetes or prediabetes status using established criteria for the general population.
- 11.8: Donor candidates with type 1 diabetes mellitus should not donate.
- 11.9: The decision to approve donor candidates with prediabetes or type 2 diabetes should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 11.10: Donor candidates with prediabetes or type 2 diabetes should be counseled that their condition may progress over time and may lead to end-organ complications.

Dyslipidemias

- 11.11: Fasting lipid profile (including total cholesterol, LDL-C, HDL-C and triglycerides) should be measured as part of an overall cardiovascular risk assessment before donation.
- 11.12: The decision to approve donor candidates with dyslipidemia should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

Tobacco Use

- 11.13: The use of tobacco products should be assessed before donation.
- 11.14: Donor candidates who use tobacco products should be counseled on the risks of perioperative complications, cancer, cardio-pulmonary disease and kidney failure, should be advised to abstain from use of tobacco products, and should be referred to a tobacco cessation support program if possible.
- 11.15: The decision to approve donor candidates who are active tobacco users should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

CHAPTER 12: PREVENTING INFECTION TRANSMISSION

Evaluation

- 12.1: Risk for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections should be assessed before donation.

- 12.2: Donor candidates should be assessed for factors associated with an increased likelihood of endemic or unexpected infections, including geographic, seasonal, occupational, animal and environmental exposures.
- 12.3: Donor candidates should complete a urinalysis and testing for HIV, HBV, HCV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Treponema pallidum* (syphilis).
- 12.4: If indicated by regional epidemiology or individual history, donor candidates should complete testing for *Mycobacterium tuberculosis*, *Strongyloides*, *Trypanosoma cruzi*, West Nile virus, Histoplasmosis, and/or Coccidiomycosis.
- 12.5: Transplant programs should develop protocols to screen donor candidates for emerging infections in consultation with local public health specialists.
- 12.6: In general, donor infection risk factor and microbiological assessments should be performed or updated as close in time to donation as possible. For HIV, HBV and HCV, screening should be current within 28 days of donation.

Selection

- 12.7: If a donor candidate is found to have a potentially transmissible infection, then the donor candidate, intended recipient and transplant program team should weigh the risks and benefits of proceeding with donation.

CHAPTER 13: CANCER SCREENING

Evaluation

- 13.1: Donor candidates should undergo cancer screening consistent with clinical practice guidelines for the country or region where the donor candidate resides. Transplant programs should ensure that screening is current according to guideline criteria at the time of donation.

Selection

- 13.2: In general, donor candidates with active malignancy should be excluded from donation. In some cases of active malignancy with low transmission risk, a clear management plan and minimal risk to the donor, donation may be considered.
- 13.3: A kidney with a small simple (Bosniak I) cyst can be left in the donor, particularly if there are compelling reasons for donating the contralateral kidney.
- 13.4: Donation of a kidney with a Bosniak II renal cyst should proceed only after assessment for the presence of solid components, septations, and calcifications on the preoperative computed tomography scan (or magnetic resonance imaging) to avoid accidental transplantation of a kidney with cystic renal cell carcinoma.
- 13.5: Donor candidates with high grade Bosniak renal cysts (III or higher) or small (T1a) renal cell carcinoma curable by nephrectomy may be acceptable for donation on a case-by-case basis.
- 13.6: Donor candidates with a history of treated cancer that has a low risk of transmission or recurrence may be acceptable for donation on a case-by-case basis.

CHAPTER 14: EVALUATION OF GENETIC KIDNEY DISEASE

Evaluation

- 14.1: Donor candidates should be asked about their family history of kidney disease, and when present, the type

of disease, time of onset, and extra-renal manifestations associated with the disease.

- 14.2: When the intended recipient is genetically related to the donor candidate, the cause of the intended recipient's kidney failure should be determined whenever possible. The intended recipient should consent to share this medical information with the donor evaluation team, and with the donor candidate if it could affect the decision to donate.

Selection

- 14.3: Donor candidates found to have a genetic kidney disease that can cause kidney failure should not donate.

Counseling

- 14.4: Donor candidates must provide informed consent for genetic testing if indicated as part of their evaluation. Donor candidates should be informed of the possible effects of receiving a diagnosis of a genetic kidney disease, such as any impact on their ability to obtain health or life insurance.
- 14.5: In cases where it remains uncertain whether the donor candidate has a genetic kidney disease and whether the disease can cause kidney failure, donation should proceed only after informing the donor candidate of the risks of donation if the disease manifests later in life.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- 14.6: Donor candidates with ADPKD should not donate.
- 14.7: Donor candidates with a family history of ADPKD in a first-degree relative may be acceptable for donation if they meet age-specific imaging or genetic testing criteria that reliably exclude ADPKD.

Apolipoprotein L1 (APOL1) Risk Alleles

- 14.8: Apolipoprotein L1 (*APOL1*) genotyping may be offered to donor candidates with sub-Saharan African ancestors. Donor candidates should be informed that having 2 *APOL1* risk alleles increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified.

CHAPTER 15: PREGNANCY

Evaluation

- 15.1: Female donor candidates should be asked about future childbearing plans.
- 15.2: Female donor candidates should be asked about prior hypertensive disorders of pregnancy (eg, gestational hypertension, preeclampsia, or eclampsia).
- 15.3: Local guidelines should be followed to confirm the absence of pregnancy before performing radiologic tests, including abdominal computed tomography (with iodinated contrast) or nuclear medicine GFR testing.

Selection

- 15.4: Women should not donate while pregnant.
- 15.5: Women should not be excluded from donation solely because they desire to conceive children after donation.
- 15.6: Women with a prior hypertensive disorder of pregnancy may be acceptable for donation if their long-term postdonation risks are acceptable.
- 15.7: A decision to proceed with donation in the year after childbirth should consider the psychological needs of

mother and child, and should include anesthesia and analgesia planning for nursing mothers.

Counseling

- 15.8: Women with childbearing potential should be informed of the need to avoid becoming pregnant from the time of approval for donation to the time of recovery after nephrectomy; a quantitative human chorionic gonadotropin (β -hCG) pregnancy test should be performed and confirmed as negative immediately before donation.
- 15.9: We suggest that women with childbearing potential be counseled about the effects donation may have on future pregnancies, including the possibility of a greater likelihood of being diagnosed with gestational hypertension or preeclampsia. (2C)
- 15.10: Women with a prior hypertensive disorder of pregnancy should be informed about their long-term risks.
- 15.11: Women with childbearing potential who proceed with donation should be counseled on how to reduce the risk of complications in future pregnancies.

CHAPTER 16: PSYCHOSOCIAL EVALUATION

Evaluation

- 16.1: Donor candidates should receive in-person psychosocial evaluation, education and planning from health professionals experienced in the psychosocial concerns of donor candidates and donors.
- 16.2: To ensure voluntariness, at least a portion of the psychosocial evaluation of the donor candidate should be performed in the absence of the intended recipient, family members and other persons who could influence the donation decision.
- 16.3: Whenever possible, the psychosocial evaluation of the donor candidate should be performed by health professionals not involved in the care of the intended recipient.
- 16.4: Transplant programs should follow protocols for assessing the donor candidate's psychosocial suitability, available support, preparation and concerns for donation.

Selection

- 16.5: Transplant programs should follow protocols defining psychosocial factors that either exclude donation, or prevent further evaluation until resolution.

Disclosures and Support

- 16.6: We suggest that donor candidates be informed that donors usually have good quality of life after donation (2D).
- 16.7: Transplant programs should assist donor candidates and donors in receiving psychosocial or psychiatric support as needed.

CHAPTER 17: ACCEPTABLE SURGICAL APPROACHES FOR DONOR NEPHRECTOMY

- 17.1: Renal imaging (eg, computed tomographic angiography) should be performed in all donor candidates to assess renal anatomy before nephrectomy.
- 17.2: The surgeon should have adequate training and experience for the surgical approach used for the donor nephrectomy.
- 17.3: We suggest that "mini-open" laparoscopy or hand-assisted laparoscopy by trained surgeons should be offered as optimal approaches to donor nephrectomy.

However, in some circumstances, such as for donors with extensive previous surgery and/or adhesions, and at centers where laparoscopy is not routinely performed, open nephrectomy (flank or laparotomy) may be acceptable. (2D)

- 17.4: Robotic, single-port, and natural orifice transluminal nephrectomy should generally not be used for donor nephrectomy.
- 17.5: Nontransfixing clips, (eg, Weck Hem-o-lok) should not be used to ligate the renal artery in donor nephrectomy; instead, renal artery transfixation by suture ligature or anchor staple within the vessel wall should be used.
- 17.6: In the absence of reasons to procure the right kidney (vascular, urological or other abnormalities), the left kidney should be procured in laparoscopic donor nephrectomy because of the relative technical ease associated with a longer venous pedicle.
- 17.7: We suggest laparoscopic procurement of the right rather than the left living donor kidney may be performed if the surgeon has adequate training and experience. (2D)
- 17.8: Procurement of a living donor kidney with 3 or more arteries should only be undertaken by surgeons with adequate experience.
- 17.9: A donor candidate with atherosclerotic renal artery disease or fibromuscular dysplasia involving the orifices of both renal arteries should not donate.

CHAPTER 18: ETHICAL, LEGAL AND POLICY CONSIDERATIONS

Ethical and Legal Framework

- 18.1: Local laws and regulations on living donation should be followed and explained as needed to donor candidates.
- 18.2: Where local laws or policies impede the ethical practice of living donation, avenues to advocate for change should be explored.
- 18.3: Autonomy (self-determination) in the willingness or not to be considered as a living donor should be respected during all phases of the evaluation and donation processes. Transplant programs should support autonomy through a fully informed consent process.

Policies for Donor Candidate Identification

- 18.4: Public awareness of opportunities for living donation should be increased through education, donor advocacy, evaluation efficiencies, and removal of disincentives.
- 18.5: Transplant candidates should be assisted in identifying living donor candidates, as long as these efforts respect donor autonomy and do not exert undue pressure to donate.
- 18.6: Donor candidates should be informed of the dangers of transplant tourism.
- 18.7: Transplant programs should define and disclose their policies for the acceptance of donor candidates identified through public solicitation.

Financial Support

- 18.8: Donor candidates should be informed of the availability of legitimate financial assistance for expenses from evaluation and donation.

Communication of Policies

- 18.9: Nondirected donors and donors participating in paired donation should be informed of the transplant program's

policy on contact with the recipient and other paired donation participants at all stages in the donation process.

- 18.10: Transplant programs should disclose the extent of the expected postdonation program-patient relationship before donation, including whether the donor can seek medical care at the transplant center after donation.
- 18.11: Regional policies should ensure access to kidney replacement therapy (dialysis and/or transplantation) for donors who develop kidney failure.

CHAPTER 19: POSTDONATION FOLLOW-UP CARE

- 19.1: A personalized postdonation care plan should be provided before donation to clearly describe follow-up care recommendations, who will provide the care, and how often.
- 19.2: The following should be performed at least annually postdonation:
 - Blood pressure measurement
 - BMI measurement
 - Serum creatinine measurement with GFR estimation
 - Albuminuria measurement
 - Review and promotion of a healthy lifestyle including regular exercise, healthy diet and abstinence from tobacco
 - Review and support of psychosocial health and well-being
- 19.3: Donors should be monitored for CKD, and those meeting criteria for CKD should be managed according to the 2012 KDIGO CKD Guideline.
- 19.4: Donors should receive age-appropriate healthcare maintenance, and management of clinical conditions and health risk factors according to clinical practice guidelines for the regional population.

METHODS FOR GUIDELINE DEVELOPMENT

AIM

The overall aim of this project was to develop an evidence-based clinical practice guideline on the evaluation and care of living kidney donors. The guideline consists of recommendation statements and supporting rationale, including summaries of systematically generated evidence on relevant predefined clinical topics. The general Kidney Disease: Improving Global Outcomes (KDIGO) guideline development method is described at: <http://www.kdigo.org/home/guidelines/development>, and unique considerations for application to the current guideline are discussed below.

PROCESS

The development of the *KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors* included:

- Appointing work group (WG) members and the Evidence Review Team (ERT)
- Discussing guideline development processes and methods
- Developing guideline scope of work, including submission of proposed topics for public comment, and refining topics based on public feedback
- Identifying populations, interventions, risk factors, and outcomes of interest
- Selecting topics for systematic evidence review and conducting the literature review by:

- Developing and implementing literature search strategies
- Screening abstracts and retrieving full-text articles based on predefined eligibility criteria
- Creating data extraction forms
- Extracting data from individual studies
- Standardizing methodology for evidence quality assessment
- Tabulating data from individual studies into summary tables and performing critical appraisal of the literature
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Where applicable, grading recommendation strength based on the quality of evidence and other considerations for recommendations with available evidence in the systematic review
- Using *de novo* evidence generation, WG consensus and prior KDIGO Guidelines to develop recommendations on topics not assigned to formal systematic review, but deemed important for the guideline
- Developing supporting rationale and finalizing guideline recommendations
- Distributing the guideline draft for public review from November to December 2015
- Editing the guideline based on public feedback, and creating the point-by-point response

The WG coauthors, KDIGO coauthors and ERT met to review the guideline development process, evidence review topics, and systematic review process. After this, 2 in-person meetings were held May 2014 and September 2014 with the WG, ERT, KDIGO coauthors and KDIGO support staff to review the available evidence, formulate recommendation statements and their rationale. Details of each chapter were discussed by teleconference between the WG coauthors, WG members and support staff before each in-person meeting, and by email. The WG coauthors, ERT, and support staff also held regular calls until completion of the evidence review and systematic review report, and the WG coauthors, KDIGO Chair and support staff met by regular teleconferences until guideline completion.

Commissioning of the WG and the ERT

The KDIGO coauthors appointed the WG coauthors, who then assembled the WG to include individuals with expertise in nephrology, organ donation, transplantation, surgery, bioethics, psychology, epidemiology and public policy. The University of Minnesota Veterans Administration Center for Chronic Disease Outcomes Research in Minneapolis, Minnesota was contracted to conduct systematic evidence review and provided expertise in guideline development methodology. The ERT was led by guideline methodologists and clinicians with expertise in nephrology and evidence-based clinical practice guideline development.

Defining the Scope and Topics

The WG coauthors and the ERT defined the scope and goals of the guideline (including a list of critical and important outcomes) and drafted a preliminary list of topics and key clinical questions. The project scope was submitted for public comment in October 2013 and refined based on the feedback. The WG and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms.

Establishing the Process for Guideline Development

The ERT performed a systematic literature search and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. The WG wrote the recommendation statements and supporting rationale, in consultation with the ERT. For recommendations with available evidence in the systematic review, the ERT reviewed draft recommendation statements and their corresponding grades for consistency with the conclusions of the evidence systematic review.

Formulating Questions of Interest

The KDIGO WG developed a scoping document to describe topics to be covered by the guideline. To inform the WG's initial work, the ERT searched for and identified existing clinical practice guidelines related to living kidney donation. The ERT extracted recommendations from prior guidelines on the identified topics of interest for the current guideline and provided a summary table of this information. This document was distributed to the WG in 2013. Certain topics within the scoping document were considered relevant to the systematic review based on importance and feasibility, and the ERT developed key research questions to address these topics (Table 1). The Population, Intervention, Comparator, Outcome, study Design, and Duration of follow-up (PICODDs) criteria for the systematic review (Table 2) are described in detail in an accompanying publication.³ Outcomes were selected and ranked by assessing patient-centeredness. Risk assessment periods were defined as perinephrectomy/postnephrectomy (within 90 days of donation), and longer-term (after 90 days postdonation until the end of available follow-up). Long-term outcomes were based on a mean follow-up of at least 5 years.

Ranking of Outcomes

The WG ranked outcomes of interest based on their importance for informing clinical decision making, as "critical",

TABLE 1.
Key questions defining the evidence review

| |
|--|
| Key Question 1: What is the incidence of perinephrectomy/postnephrectomy outcomes among living kidney donors undergoing different types of nephrectomy procedures? |
| Key Question 2: Does the incidence of perinephrectomy/postnephrectomy outcomes vary by demographic subgroup (age, race, sex)? |
| Key Question 3: Does the incidence of perinephrectomy/postnephrectomy outcomes vary by the presence of donor IMAs (ie, obesity, hypertension, glucose intolerance)? |
| Key Question 4: What is the incidence of long-term health outcomes for living kidney donors compared with healthy nondonors? |
| Key Question 5: Does the incidence of long-term living kidney donor outcomes vary by demographic subgroup (age, race, sex)? |
| Key Question 6: Does the incidence of long-term living kidney donor outcomes vary by the presence of donor IMAs (ie, obesity, hypertension, glucose intolerance)? |
| Key Question 7: What is the incidence of maternal and fetal outcomes among female living kidney donors who become pregnant after donation compared with healthy nondonors? |

IMA, isolated medical abnormality.

TABLE 2.**Systematic review screening criteria****Living kidney donor outcomes**

| | Perinephrectomy/postnephrectomy | Long-term |
|-----------------------|---|--|
| Population | Living kidney donors | Living kidney donors Living kidney donors—demographic subgroup (age, sex, race) Living kidney donors with specific IMAs Donors related to recipient or with known family history of kidney disease Women with postdonation pregnancy Living kidney donation |
| Intervention | Nephrectomy performed post-1994 Nephrectomy in donors with IMAs | Living kidney donation |
| Comparator | Nephrectomy with different types of surgery; Nephrectomy in donors without IMAs | Healthy nondonors ^a (ie, nondonor with medical characteristics suggesting they meet living donor criteria) Living kidney donors—demographic subgroups (age, sex, race) Healthy nondonors ^a —demographic subgroups (age, sex, race) Living kidney donors—without specific IMAs Healthy nondonors ^a —with specific IMAs Donors with unrelated recipient and no family history of kidney disease Donors with predonation pregnancy Healthy nondonors with pregnancy |
| Outcomes | Critical: all-cause mortality High Importance: CVD event Moderate Importance: perinephrectomy/postnephrectomy complications; time to return to usual activities Intermediate Outcomes: blood loss; length of hospital stay | Critical: all-cause mortality, CVD event, kidney failure, fetal death High importance: psychosocial outcomes, major pregnancy complications Moderate importance: fragility fractures, gastrointestinal bleeding, kidney stones, minor pregnancy complications Intermediate outcomes: kidney function, proteinuria, hypertension |
| Study design | Systematic reviews, randomized controlled trials, and observational studies | Systematic reviews, randomized controlled trials, and observational studies Full-text screening identified studies with total sample sizes (donor and comparator combined) more than 50; studies with total sample sizes more than 100 were extracted |
| Duration of follow-up | Systematic reviews with outcomes measured up to 90 d postnephrectomy were extracted Full-text screening identified studies with outcomes measured up to 1 y postdonation for extraction | Full-text screening identified studies with outcomes measured 1 y or later postdonation; studies with a mean duration of 5 y or more postdonation were extracted |

^a “Healthy” nondonor comparison groups must have matched or controlled for demographic and health characteristics. CVD, cardiovascular disease; IMA, isolated medical abnormality.

“high” or “moderate.” The hierarchy of perinephrectomy/postnephrectomy and long-term outcomes is noted in Table 2. “Intermediate outcomes” are defined as events on the pathway to clinical outcomes of interest.

Literature Searches and Article Selection

The ERT searched Ovid Medline, Ovid EMBASE, and the Cochrane Library to identify previous systematic reviews, randomized controlled trials (RCTs), and observational studies published and indexed in bibliographic databases through September 2014. The ERT search strategy included relevant medical subject headings and natural language terms for the concept of living kidney donation (**Supplemental Appendix A, SDC**, <http://links.lww.com/TP/B432>). These terms were combined with filters to select RCTs, systematic reviews, and observational studies. Bibliographic database searches were supplemented with citation searches of highly relevant systematic reviews.

Two independent investigators reviewed titles and abstracts of search results published after 2003 to identify systematic reviews, trials and observational studies relevant to the key questions. The ERT relied on citation searching of relevant systematic reviews to identify relevant studies published before 2004. Citations deemed eligible by either investigator underwent

full text screening. Two investigators independently screened full text to determine if PICODD criteria were met. A third investigator resolved discrepancies. The ERT documented the inclusion and exclusion status of citations undergoing full-text screening. The ERT often revisited the screening process as the WG identified new outcomes or subgroups not included in the original PICODDs. Screening criteria were liberal. The ERT did not extract data from all eligible studies. To capture the highest quality and most relevant and meaningful data as efficiently as possible, the ERT extracted data only from previous systematic reviews for perinephrectomy/postnephrectomy outcomes Key Questions (KQ1-3) and from systematic reviews and select observational studies for long-term outcomes (KQ 4-7). The ERT extracted long-term outcomes data from observational studies with sample sizes over 100 and mean follow-up time of at least 5 years.

Explicit recognition of perspectives of comparison is critical for drawing inferences about donor health outcomes (eg, estimation of predonation risk, absolute postdonation risk, and donation-attributable risk)⁴ (Figure 1), and types of comparison were a critical consideration throughout the development of this guideline, including the design and conduct of the evidence review. Studies reporting long-term outcomes were required to include a nondonor comparison

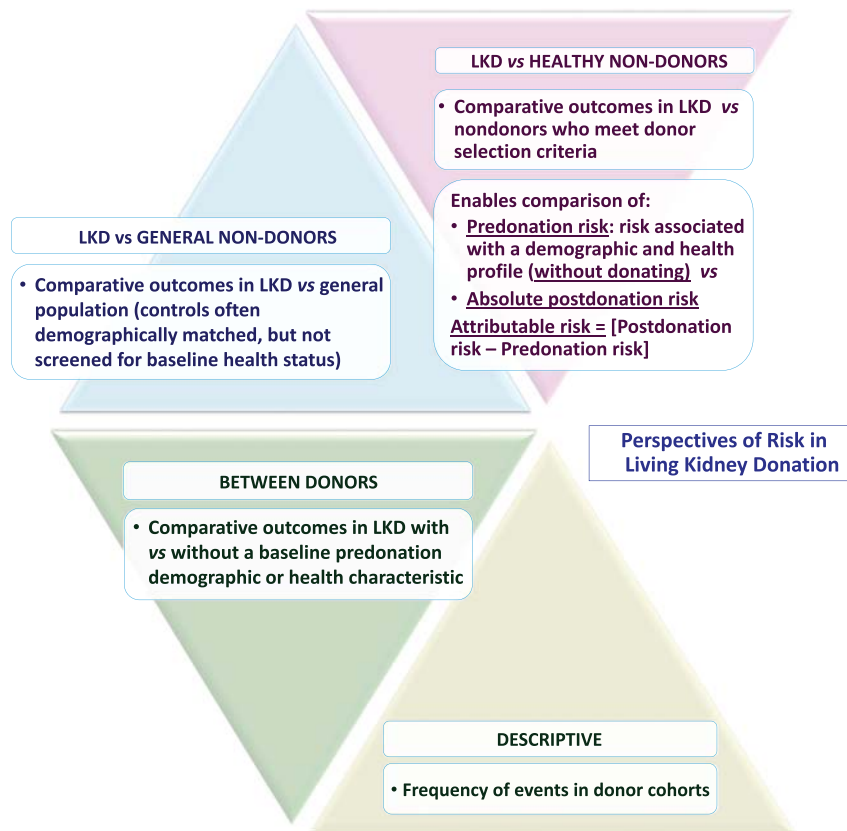


FIGURE 1. Perspectives of risk in living kidney donation. These perspectives provide a framework for assessment of donor outcomes, interpretation of observations, patient communication, and future research design. LKD, living kidney donors. Adapted with permission from Lentine KL, Segev DL. Understanding and communicating medical risks for living kidney donors: a matter of perspective. *J Am Soc Nephrol.* 2017;28:12-24.⁴

group with baseline health characteristics similar to kidney donors. Studies comparing living kidney donors to the general population were not eligible.

Data Extraction and Summary Tables

For perinephrectomy/postnephrectomy outcomes defined in the search criteria, the ERT extracted data from relevant comparisons in recent systematic reviews rather than performing a *de novo* extraction process. The ERT extracted relevant narrative information from systematic reviews that did not provide meta-analyses. For long-term outcomes defined in the search criteria, the ERT extracted data from observational studies and extracted pooled results from previous meta-analyses.

One investigator extracted relevant study, population demographic, and outcomes data from studies eligible for full extraction. Data fields extracted included author, year of publication, setting, donor and comparison populations, inclusion and exclusion criteria, donor and comparison characteristics, follow-up duration, descriptions, and results of outcomes. Relevant data were extracted into tables for descriptive analysis. In several cases, many comparisons were made within the same published study. In these cases, the ERT extracted relevant comparisons but did not extract ineligible comparisons.

Assessment of Prior Systematic Review Quality and Individual Study Risk of Bias

The ERT assessed the quality of eligible systematic reviews using modified A Measurement Tool to Assess Systematic

Reviews (AMSTAR) criteria.⁵ The ERT assessed risk of bias for observational studies using an instrument developed based on the Research Triangle Institute Item Bank for assessing risk of bias and confounding in observational studies of interventions or exposures.⁶ In this instrument, overall summary risk of bias is based upon the collective risk of bias inherent in each domain and confidence that results are believable given study limitations. The ERT used overall summary risk of bias assessments when grading evidence quality as described below.

Evidence Profiles

The structured GRADE approach was used to grade the quality of the overall evidence (Table 3). Evidence profiles consisting of tables examining all relevant outcomes, including a summary of the results and judgments about the certainty and quality of the evidence, were used to facilitate this process. The GRADE approach is prescriptive in how evidence quality is assessed. The study design suggests the initial quality of evidence: high for RCTs and low for observational studies. Of note for the current guideline, most studies of outcomes in living kidney donation are not ethically or practically amenable to randomized controlled designs, limiting the possible quality rating based on the nature of possible study designs. Evidence quality is then lowered by one level if the studies in the evidence base for a comparison have serious risk of bias, and by 2 levels if the evidence base has very serious risk of bias. Evidence quality is also lowered when results across studies are inconsistent or

TABLE 3.
Evidence quality assessment criteria

| Study design | Quality of evidence | Lower if | Higher if |
|---------------------|---------------------|--|--|
| Randomized trial | High | Risk of Bias –1 Serious –2 Very serious | Large effect +1 Large +2 Very Large |
| | Moderate | Inconsistency –1 Serious –2 Very serious | +1 If all plausible confounding would reduce a demonstrated effect or +1 If all plausible confounding would suggest a spurious effect when results show no effect |
| Observational study | Low | Indirectness –1 Serious –2 Very serious | |
| | | Imprecision –1 Serious –2 Very serious | |
| | Very Low | Publication bias –1 Likely | |

very inconsistent, if the relationship between the intervention and the outcome is indirect, or if the outcome does not directly influence patient well-being. Additionally, evidence quality is downgraded when estimates are imprecise and publication bias is likely. Evidence quality improves with a large effect size. A large effect size includes a relative risk (RR) confidence interval (CI) lower limit of at least 2; a very large effect size includes a RR CI lower limit of 5. Evidence quality is also increased when an effect is demonstrated after all plausible confounding has been addressed. Complete evidence profiles for KQs 1-7 can be found in the **Supplemental Evidence Report: Outcomes of Living Kidney Donation: A Systematic Review for a Clinical Practice Guideline by the Kidney Diseases Improving Global Outcomes (KDIGO), SDC**, <http://links.lww.com/TP/B434>. Evidence on long-term outcomes as reviewed and appraised by the ERT has also

been published separately as part of this guideline systematic review.³

Results of the Systematic Review

The ERT's search identified 4530 citations, of which 414 met criteria for full text review after title and abstract screening. The ERT identified an additional 70 references via supplemental citation searching, yielding a total of 484 references for full text review (Figure 2). Studies excluded after full-text review and exclusion reasons are listed in **Supplemental Appendix B, SDC**, <http://links.lww.com/TP/B432>, of the evidence review publication.

The ERT extracted study characteristics, conducted systematic review quality assessments and risk-of-bias assessments, and extracted relevant outcomes into evidence tables for all studies eligible for extraction (**Supplemental Appendix C, SDC**,

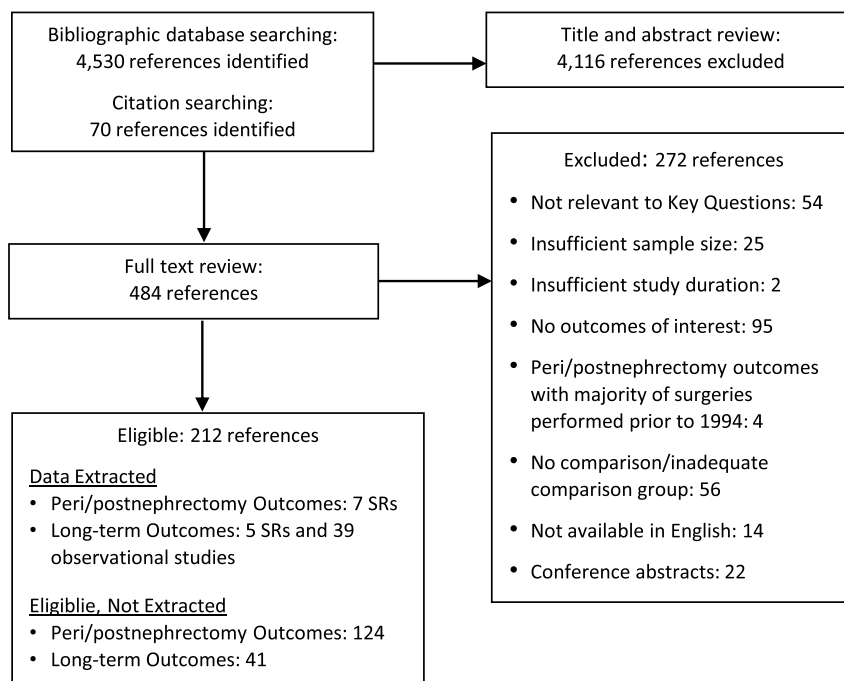


FIGURE 2. Literature flow diagram. SR, systematic review.

<http://links.lww.com/TP/B432> for perioperative/postoperative studies; **Supplemental Appendix D, SDC**, <http://links.lww.com/TP/B432> for long-term outcomes studies of the evidence review publication; **Evidence Report, SDC**, <http://links.lww.com/TP/B434>). Results were grouped by Key Question.

De Novo Evidence Generation

In developing the current guideline, the WG concluded that the framework for assessing the acceptability of candidates for living kidney donation needed to be restructured to include a comprehensive determination of risk to the donor, based on simultaneous consideration of a composite profile of risk factors. No previous guidelines have advocated for this approach to the evaluation of living donor candidates, and there is a paucity of data to demonstrate its feasibility and applicability. The WG therefore collaborated with the Chronic Kidney Disease-Prognosis Consortium (CKD-PC) to conduct a meta-analysis to produce a comprehensive risk-prediction model for end-stage kidney disease (ESKD) applicable to donor candidates. The development and application of this clinical prediction tool are described in chapter 1 (Framework) of this guideline and in a separate publication.⁷

To inform choice of methods for kidney function estimation in the donor candidate evaluation, a web-based calculator was developed to compute posttest probabilities for measured glomerular filtration rate (mGFR) above or below threshold probabilities for decision-making based on estimated glomerular filtration rate (eGFR). The development and application of this clinical tool are described in chapter 5 (Kidney Function) of this guideline and in a separate publication.⁸

Grading the Quality of Evidence and the Strength of Guideline Recommendations

A structured approach, based on GRADE^{1,9,10} and facilitated by the use of evidence profiles, was used to grade the quality of the overall evidence and the strength of recommendations. For each topic with recommendations informed by the systematic review, the discussion of grading evidence quality was led by the ERT, and the discussion regarding the strength of the recommendations was led by the WG coauthors. The “strength of a recommendation” indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The “quality of a body of evidence” refers to the extent to which confidence in an estimate of effect is sufficient to support a recommendation.

Grading the Strength of the Recommendations

The strength of a recommendation is graded as level 1 or level 2. Table 4 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the available evidence and the strength of that recommendation. However, the strength of a recommendation is determined not only by the quality of the evidence, but also by other, often complex judgments regarding the size of the net medical benefit (potential risks vs benefit), values, and preferences, and costs (Table 5). Formal decision analyses including cost analysis were not conducted.

Grading the Overall Quality of Evidence

The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting 4 final categories for the quality of overall evidence were: “A,” “B,” “C,” or “D” (Table 6).

Ungraded Statements

This category was designed to allow the WG to issue advice on topics not explicitly addressed in the systematic review. The current guideline is notable in that many clinically important topics in living donation are not ethically or practically amenable to randomized controlled study designs and have not been addressed in controlled observational studies. Thus, many recommendations were generated on topics deemed important for the care of living donors that were not addressed by eligible studies in the systematic evidence review. These recommendations were developed using other literature and WG consensus, and are therefore ‘ungraded.’

As a result, very few of the guideline recommendations were rated for strength of the recommendation and quality of the evidence. This is not to say that there was no evidence for such “ungraded” guideline recommendations, but the WG and ERT only graded recommendations that were included as part of the ERT’s systematic review and fulfilled the a priori search inclusion criteria. The WG felt that such “good practice statements” were necessary to address important aspects of donor care, and their preponderance may

TABLE 4.
KDIGO nomenclature and description for grading recommendations

| Grade ^a | Implications | | |
|------------------------|---|--|--|
| | Patients | Clinicians | Policy |
| Level 1 ‘We recommend’ | Most people in your situation would want the recommended course of action and only a small proportion would not | Most patients should receive the recommended course of action | The recommendation can be evaluated as a candidate for developing a policy or a performance measure |
| Level 2 ‘We suggest’ | The majority of people in your situation would want the recommended course of action, but many would not | Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences | The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined |

^a The additional category ‘Not Graded’ is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. Ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

TABLE 5.**Determinants of strength of a recommendation**

| Factors | Comments |
|---|---|
| Balance between desirable and undesirable effects | The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted |
| Quality of the evidence | The higher the quality of evidence, the more likely a strong recommendation is warranted |
| Values and preferences | The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature where possible, or were assessed in the judgment of the work group where robust evidence was not identified |
| Costs (resource allocation) | The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted |

be attributed to numerous reasons as stated in Table 7.¹¹ When the WG determined that there was evidence for a recommendation that was outside the scope of the ERT review, this was indicated in the rationale for that recommendation. It is also important to note that when recommendations from other KDIGO WGs were modified for the purpose of this guideline, the prior grading was provided in the rationale but the adapted recommendations were not graded so as to limit grading only to statements derived from the *de novo* systematic review performed for this guideline.

Developing the Recommendations

Draft recommendation statements were developed by the WG coauthors and WG members with input from all WG members. The health risks and benefits associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available. Recommendation statements were revised in a multi-step process during teleconferences and 2 face-to-face meetings, as well as in subsequent emails. All WG members provided feedback on initial and final drafts of the recommendations.

Format for Recommendations

Each chapter contains one or more specific recommendations. When pertinent evidence was available in the systematic review, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C, or D. When the ERT search parameters did not identify evidence from eligible studies pertinent to a recommendation, the statement is ungraded. In all cases, recommendation statements and grades (if applicable) are followed by rationale text summarizing the key points of the evidence base and the judgments supporting the recommendations. Research recommendations for future work to help resolve current uncertainties are also outlined at the conclusion of each chapter.

TABLE 6.**Final grade for overall quality of evidence**

| Grade | Quality of evidence | Meaning |
|-------|---------------------|--|
| A | High | We are confident that the true effect lies close to that of the estimate of the effect |
| B | Moderate | The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| C | Low | The true effect may be substantially different from the estimate of the effect |
| D | Very low | The estimate of effect is very uncertain, and often will be far from the truth |

Limitations of Systematic Review Approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the WG.

Review of Guideline Development Process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE 2) criteria,¹² the Conference on Guideline Standardization (COGS) checklist,¹³ and the Institute of Medicine's recent *Standards for Systematic Reviews*¹⁴ and *Clinical Practice Guidelines We Can Trust*.¹⁵ Table 8 displays the criteria which correspond to the COGS checklist and how each one is addressed in this guideline.

Public Comment and Revision

A draft of the guideline was distributed for open public review in November 2015. The guideline was revised into final form by WG coauthors and members. A point-by-point response to all public comments is available online (**Supplemental Appendix E, SDC**, <http://links.lww.com/TP/B433>). All WG members approved the final version of the guideline.

CHAPTER 1: GOALS OF EVALUATION, FRAMEWORK FOR DECISION-MAKING, AND ROLES AND RESPONSIBILITIES

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 1 and therefore the following recommendations are “Not Graded.”

TABLE 7.**Reasons why many ungraded recommendations are issued in this guideline**

The ERT's inclusion criteria (Table 2) are necessarily stringent given the limited time and resources for collecting and summarizing available evidence. As such, ungraded recommendations are issued:

- For topics that are not part of the ERT's inclusion criteria or when evidence lies outside ERT's search yield
- In areas where the work group does not believe evidence is available (eg, recommendations grounded in ethics) or for which there is no reasonable alternative (ie, based on common sense). Such recommendations may be deemed necessary because the work group considers such "good practice statements" essential especially when net benefit is great and unequivocal.
- In areas for which systematic review is not applicable (eg, monitoring intervals, counseling)
- Based on indirect evidence (eg, extrapolation of evidence from studies in general population)
- When adapted from prior KDIGO guidelines and extrapolated from different populations of interest (eg, general population or CKD population from KDIGO CKD Guideline)

CKD, chronic kidney disease; ERT, evidence review team; KDIGO, Kidney Disease: Improving Global Outcomes.

Goals and Principles of Evaluation

- 1.1: The donor candidate's willingness to donate a kidney voluntarily without undue pressure should be verified.
- 1.2: The benefits and risks of kidney donation should be assessed for each donor candidate.
- 1.3: The decision to accept or exclude a donor candidate should follow transplant program policies.
- 1.4: Donor candidate decision-making should be facilitated through education and counseling on individualized risks and benefits, methods to minimize risks, and the need for postdonation follow-up.
- 1.5: For an accepted donor candidate, a plan for donation care and follow-up should be formulated to minimize risks of donation.
- 1.6: For an excluded donor candidate, a plan for any needed care and support should be formulated.

Framework for Decision-Making

- 1.7: The donor candidate, the intended recipient, and the transplant program must all agree with the decision to proceed with donation in concordance with transplant program policies and informed consent.
- 1.8: Transplant program policies must be defensible based on current understanding of the risks and benefits of kidney donation, and should apply to all donor candidates evaluated at the center.
- 1.9: Each transplant program should establish policies describing psychosocial criteria that are acceptable for donation, including any program constraints on acceptable relationships between the donor candidate and the intended recipient.
- 1.10: All donor candidates should be evaluated using the same criteria, regardless of whether donation is directed towards a designated recipient.
- 1.11: Each transplant program should establish policies describing medical criteria that are acceptable for donation, addressing when possible, numeric thresholds for short-term and long-term postdonation risks above which the transplant program will not proceed with donation. Risks should be expressed as absolute rather than relative risks.
- 1.12: When possible, transplant programs should provide each donor candidate with individualized quantitative estimates of short-term and long-term risks from donation, including recognition of associated uncertainty, in a manner that is easily understood by donor candidates.
- 1.13: Transplant programs should evaluate donor candidate risks in comparison to predetermined thresholds for acceptance. If a donor candidate's postdonation risk is above the transplant program's acceptable risk threshold, the risk is not acceptable for donation. If a donor

candidate's postdonation risk is below the transplant program's acceptable risk threshold, the candidate makes the decision whether or not to proceed with donation.

- 1.14: If a donor candidate is not acceptable, the transplant program should explain the reason for nonacceptance to the donor candidate.
- 1.15: Transplant programs should protect donor candidate's privacy regarding the evaluation, including all considerations in the decision to donate or not.

Roles and Responsibilities

- 1.16: A multidisciplinary transplant program team knowledgeable in kidney donation and transplantation should evaluate, care for, and formulate a plan for donor care including long-term follow-up.
- 1.17: Transplant programs should minimize conflict of interest by providing at least one key team member not involved in the care or evaluation of the intended recipient who evaluates the donor candidate and participates in the determination of donor acceptance.
- 1.18: Transplant programs should conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and transplant programs.

RATIONALE**Goals and Principles of Donor Evaluation**

Evaluation of candidates for living kidney donation requires balancing ethical principles of autonomy, beneficence, nonmaleficence, voluntarism and justice.¹⁶ Determining acceptability or nonacceptability of donor candidates requires an assessment of their potential risks and anticipated benefits of donation, independent of intended recipient issues. Donation must be voluntary (autonomous), and the motivation for donation must be altruistic – to satisfy a well-considered desire to help another person. There must be protection from undue pressure or coercion at every step in the evaluation and donation process, including the option to confidentially withdraw from the evaluation or to decline to donate at any time with the full support of the transplant program.¹⁷ In addition to these ethical principles, protection of patient privacy must be ensured. However, information regarding donor lifestyle, exposures or medical history that increase the risk for transmission of disease may need to be disclosed to the intended recipient for donation and transplantation to proceed; donor candidates should be given the opportunity to withdraw if they do not consent to sharing relevant personal health information in such circumstances.

TABLE 8.**The Conference on Guideline Standardization (COGS)¹³ checklist for reporting clinical practice guidelines**

| Topic | Description | Discussed in KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors |
|---------------------------------------|--|---|
| (1) Overview material | Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources | Abstract and Methods for Guideline Development |
| (2) Focus | Describe the primary disease/condition and intervention/service/technology that the guideline addresses Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development | This guideline seeks to formalize the framework for decision making and evaluation process for living kidney donor candidates and to define the optimal postdonation follow-up care |
| (3) Goal | Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic | This Clinical Practice Guideline is intended to assist the practitioner in evaluating living kidney donor candidates and optimizing the care for donors and their quality of life |
| (4) User/setting | Describe the intended users of the guideline (eg, provider types, patients) and the settings in which the guideline is intended to be used | Target audience is practicing nephrologists, transplant physicians and other allied health professionals who work in the setting of living kidney transplantation |
| (5) Target population | Describe the patient population eligible for guideline recommendations and list any exclusion criteria | Living kidney donors |
| (6) Developer | Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development | Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in the Biographic and Disclosure Information |
| (7) Funding source/sponsor | Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline Disclose potential conflict of interest | This guideline is supported by KDIGO with contributions from Canadian Blood Services, Canadian Society of Nephrology, Minneapolis Medical Research Foundation, and The Transplantation Society |
| (8) Evidence collection | Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence | Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary (eg, prior living kidney donor guidelines), or c) narrative summary. The search was updated through September 2014 and supplemented by articles identified by work group members through January 2017. We also searched for pertinent existing guidelines and systematic reviews |
| (9) Recommendation grading criteria | Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms | Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 4 and 6). The work group could provide general guidance in ungraded statements |
| (10) Method for synthesizing evidence | Describe how evidence was used to create recommendations, eg, evidence tables, meta-analysis, decision analysis | For systematic review topics, summary tables and evidence profiles were generated |
| (11) Prerelease review | Describe how the guideline developer reviewed and/or tested the guidelines before release | The guideline had undergone external public review in November to December 2015. Public review comments were compiled and fed back to the work group, which considered the comments in its revision of the guideline |
| (12) Update plan | State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline | The requirement for an update will be assessed on an ongoing basis from the publication date for potential important new evidence that may lead to changes to the recommendations |
| (13) Definitions | Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation | Abbreviations and Acronyms |
| (14) Recommendations and rationale | State the recommended action precisely and the specific circumstances under which to perform it Justify each recommendation by describing the linkage between the recommendation and its supporting evidence Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9 | This guideline contains recommendations for evaluation of kidney donor candidates and postdonation follow-up care. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation, where applicable |

Continued next page

TABLE 8. (Continued)

| Topic | Description | Discussed in KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors |
|------------------------------------|---|---|
| (15) Potential benefits and harms | Describe anticipated benefits and potential risks associated with implementation of guideline recommendations | The benefits and harm for each recommendation are provided in summary tables and summarized in evidence profiles where applicable. The estimated balance between potential benefits and harm was considered when formulating the recommendations |
| (16) Patient preferences | Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values | The inclusion of patient values and preferences is clearly articulated where appropriate |
| (17) Algorithm | Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline | No overall algorithm |
| (18) Implementation considerations | Describe anticipated barriers to application of the recommendations Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation Suggest review criteria for measuring changes in care when the guideline is implemented | Review criteria were not suggested because implementation with prioritization and development of review criteria must proceed locally. Furthermore, most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria Research recommendations were also outlined to address current gaps in the evidence base |

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes.

Preservation of donor candidate autonomy and minimization of short-term and long-term risks are high priorities in the practice of living donation. The transplant program has the responsibility to disclose anticipated risks and benefits to the donor candidate and intended recipient, tailored when possible for the characteristics of each donor candidate.¹⁸ The donor candidate must have adequate time to make an informed decision and must accept the need for long-term follow-up. The transplant program must offer support for decision-making through education and the informed consent process, and has a responsibility to confirm that the donor candidate understands the likely risks and benefits of donation. The transplant program makes the final determination of acceptance of the donor candidate, based on the program's policies. The transplant program must have a mechanism for resolving disagreement among team members regarding acceptability of donor candidates that avoids conflicts of interest.

A Quantitative Framework for Equitable Decision Making

There will always be risks to living kidney donation. A central objective of donor candidate evaluation and selection is to minimize risks of short-term and long-term adverse outcomes after donation, and to ensure the risks are acceptable. Consistent, transparent and defensible decision-making to accept or decline a living kidney donor candidate has been limited by the lack of an evidence-based means to provide individualized, quantitative estimates of postdonation risk. Prior living kidney donor guidelines describe postdonation risk in relation to single predonation characteristics assessed in isolation, and generally agree on the single predonation characteristics that are associated with higher risks of poor postdonation outcomes. However, prior guidelines often differ on the recommended specific threshold for a characteristic that should be used to accept or decline living donor candidates, and are unclear about how values above or below the threshold alter the risk of postdonation outcomes. There have been several calls to improve the current status quo, and to support better shared

decision making between donor candidates and their transplant professionals.^{16,19-21}

An important advance is quantification of the combined impact of all of a donor candidate's predonation demographic (eg, age, sex, and race) and health characteristics at the time of evaluation (eg, kidney function, blood pressure [BP], body mass index [BMI], and so on) on the risk of serious adverse outcomes after donation. Serious postdonation adverse outcomes can be surgical, medical or psychosocial, and may occur during the perinephrectomy period, in a fixed period of long-term follow-up (eg, 15 years after donation), or for the remaining lifespan of the donor.

As described within this overall framework, a transplant program can use various methods to establish its threshold for acceptable outcomes after kidney donation. For example, if a transplant program decides a lifetime postdonation risk of kidney failure of up to 5% is acceptable, and if a candidate's projected risk is estimated to be above this threshold, the program should decline this candidate as a donor. Donor candidate autonomy does not overrule medical judgment and transplant professionals are ethically justified to decline a donor candidate when they believe the risk of poor postdonation outcomes is too high.²² A poor outcome can have a very negative impact on the donor, on their recipient, and on public opinions about living donation.

Each transplant program should strive to develop and communicate a quantitative threshold of "acceptable risk" for each serious postdonation adverse outcome it wishes to avoid. Thresholds should be both evidence-based and consensus-based, and there are various sources of evidence and processes by which consensus can be achieved. Once established, a threshold should be applied consistently and transparently for all donor candidates evaluated by a program (unless subsequently revised). When a donor candidate's estimated risk is below the acceptable risk threshold, the transplant program should accept a donor candidate, and it should be the candidate's decision whether or not to proceed with living kidney donation after being informed of the risks. When a candidate's estimated risk is above the

acceptable threshold, the transplant program is justified in declining the candidate and can ground its decision in a quantitative framework (Figure 3).

During the development of this guideline we have advanced concepts and analyses to support this framework and approach. Here we discuss certain serious adverse outcomes and their amenability to quantitative risk estimation. We focus particularly on the postdonation development of kidney failure requiring dialysis or transplantation because it is a central outcome of a donor candidate's long-term risk. Finally, we describe the path for future work necessary to strengthen this framework, which includes the need for additional data.

Perinephrectomy Outcomes

The incidence of perioperative death after living kidney donation is low. The 90-day all-cause mortality in a recent United States (US) study of 80 347 donors was reported to be approximately 1 in 3000 (0.03%) based on 25 deaths.²³ Similar rates have also been reported in other studies.^{24,25} Given the low incidence of perioperative mortality, estimates for predonation characteristics that alter the risk of perioperative death are imprecise. For example, in this same study,²³ a predonation history of hypertension was associated with a 1 in 270 risk of 90-day mortality. However, this estimate was based only on 2 observed deaths, and the estimate would have substantially changed if 1 more or less death was observed; the 95% CI for the estimate was also wide, ranging from 1 in 75 to 1 in 2220. Thus, even if a transplant program defines an acceptable risk threshold for perinephrectomy mortality (for example, an incidence less than 1 in 1000), it will be difficult at this time to reliably determine a given donor candidate's estimated risk of this outcome according to their profile of predonation characteristics.

With respect to perioperative complications, the ERT identified 2 systematic reviews that examined perinephrectomy outcomes in relation to demographic and health characteristics of accepted donors. The ERT rated the quality of this evidence as very low (Evidence Report Tables 6 and 7, SDC, <http://links.lww.com/TP/B434>). In one review, a group of selected older donors (mean age, 66 years; range,

60 to 85 years at donation) did not differ statistically from a group of younger donors in their operative time, intraoperative blood loss, and length of hospital stay.²⁶ In both reviews, groups of selected obese donors (mean BMI of 34.5 kg/m²; range 32–39 kg/m²) did not differ statistically from groups of nonobese donors in their rates of perioperative complications, operative time, blood loss and length of hospital stay.^{26,27}

Since then a large US study examined predonation characteristics associated with a higher risk of donor nephrectomy-related complications (as assessed through administrative data rather than adjudication, using a composite outcome of digestive, respiratory, procedural, urinary, hemorrhage, infectious or cardiac complications).²⁸ In this study, where each donor candidate characteristic was considered by itself (rather than as a combination of characteristics), complication rates were higher in men versus women (9.6% vs 7.2%); among African Americans (10.4%) and whites (8.7%) compared with other racial groups (6.3%); among donors without private insurance (8.5%) compared with those who had private insurance (7.3%); and among donors with hypertension (17.7%) compared with those without hypertension (7.9%).

A subsequent study integrated national US donor registry data from 2008 to 2012 with administrative records from a consortium of 98 academic hospitals and found that 16.8% of donors experienced a diagnosis or procedure for a perinephrectomy complication, most commonly gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), and surgical/anesthesia-related injuries (2.4%).²⁹ Major complications, defined as Clavien severity level 4 or 5, were identified in 2.5% of donors. After adjustment for demographic, clinical (including comorbidities), procedure, and center factors, compared with white donors, African Americans had significantly higher risks ($P < 0.05$) of experiencing any complication (18.2% vs 15.5%) and of experiencing major complications (3.7% vs 2.2%). Other significant correlates of major complications included obesity, predonation blood disorders, psychiatric conditions, and robotic nephrectomy, while greater annual hospital volume predicted lower risk.

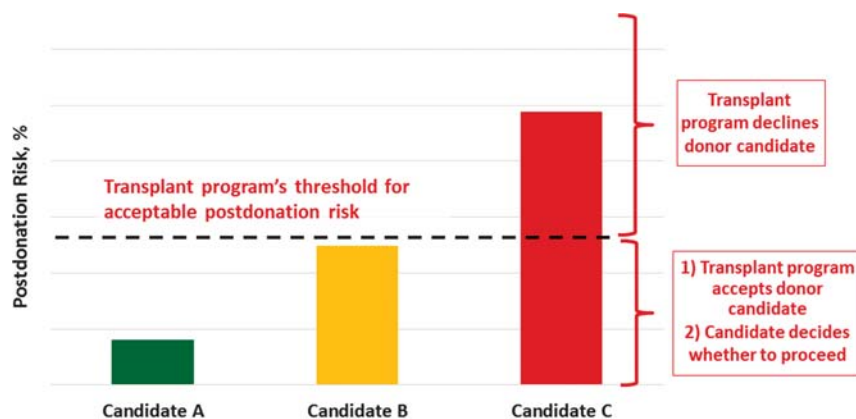


FIGURE 3. Framework to accept or decline donor candidates based on a transplant program's threshold of acceptable postdonation risk. The decision by the transplant program to accept or decline a donor candidate is grounded on whether an individual's estimated postdonation risk is above or below the threshold set (dotted line) by the transplant program. The threshold may vary across transplant programs, but the same threshold should apply to all donor candidates at each program. For example, candidate A (green) would be acceptable because the estimated projected postdonation risk is far below the threshold. Candidate B (yellow) could be accepted with caution because the estimated projected postdonation risk is close but below the threshold, and candidate C (red) would be unacceptable because the estimated postdonation projected risk is far above the threshold.

As future data become available, it may become possible for transplant programs to estimate the risk of well-defined, serious perioperative complications according to a donor candidate's individual profile of baseline characteristics, and to compare these estimates to a threshold of acceptable risk to inform donor acceptance decisions.

Long-term Outcomes

Donating a kidney is a decision with lifetime implications for the donor. While there are many outcomes to consider after kidney donation, a central outcome directly related to having one kidney removed is the long-term risk of developing kidney failure requiring dialysis or transplantation, commonly referred to as ESKD. Donor candidates often have a good understanding of the health effects of kidney failure, as their reason to donate is to treat the kidney failure of their intended recipient. For these reasons, we have grounded a quantitative framework for medical evaluation and acceptance of donor candidates on the long-term risk of postdonation kidney failure.

Each donor candidate has a long-term risk (cumulative incidence) of developing kidney failure that is influenced by the combination of risks conferred by their demographic and health characteristics at the time of evaluation plus risk attributable to donation (Figure 4). Demographic characteristics include age, sex, and race. Health characteristics include glomerular filtration rate (GFR), albuminuria, BMI, BP, diabetes status, smoking history, family history of kidney disease, and other factors. The risk attributable to donation may also vary according to demographic and health characteristics. Minimizing the lifetime risk of kidney failure in accepted donors is important to safeguard the practice, regardless of the degree to which it can be established that donation contributed to the risk of kidney failure.

Challenges to determining the postdonation lifetime risk of kidney failure based on current studies include limitations of study follow-up (the largest studies followed most donors for

less than 2 decades rather than for their lifetime).³⁰ The risk of kidney failure after donation is nonlinear, and is expected to be higher later (≥ 10 years) than earlier (< 10 years) after donation.³¹ When the WG was convened, 2 recent studies reported that the risk of kidney failure is higher in donors compared with risk among nondonors with similar baseline demographics. The ERT assessed the quality of evidence from these 2 studies as moderate (Table 2 of Slinin et al³).^{30,32} Available data suggest that the average donation-attributable risk of kidney failure is approximately 27 per 10 000 (0.3%) at 15 years,³⁰ but there is substantial uncertainty in the estimate, and there are not sufficient data to project lifetime donation-attributable risk. Furthermore, the extent to which donation-attributable risk varies according to individual health characteristics is not known,^{33,34} although available evidence suggests there is higher donation-attributable risks in some subgroups, such as African Americans compared with white donors.³⁰

Existing large population-based studies can help estimate the long-term risk of treated kidney failure in the *absence of donation*, based on a candidate's predonation health characteristics. Furthermore, if the risk of kidney failure attributable to donation becomes more precisely understood in relation to an individual's profile of baseline characteristics, then demographic-related, health status related, and donation-attributable risks can be aggregated to project individualized estimates of long-term risks of postdonation kidney failure.

To help advance this paradigm, we enlisted the help of the CKD-Prognosis Consortium (CKD-PC) to develop a tool to project the 15-year and lifetime incidence of kidney failure in the absence of donation based on demographic and health characteristics at the time of evaluation in low-risk persons from large population cohorts. CKD-PC is a research group composed of investigators who analyze large cohort data and perform collaborative meta-analyses. The methods and results of these analyses are reviewed briefly here and

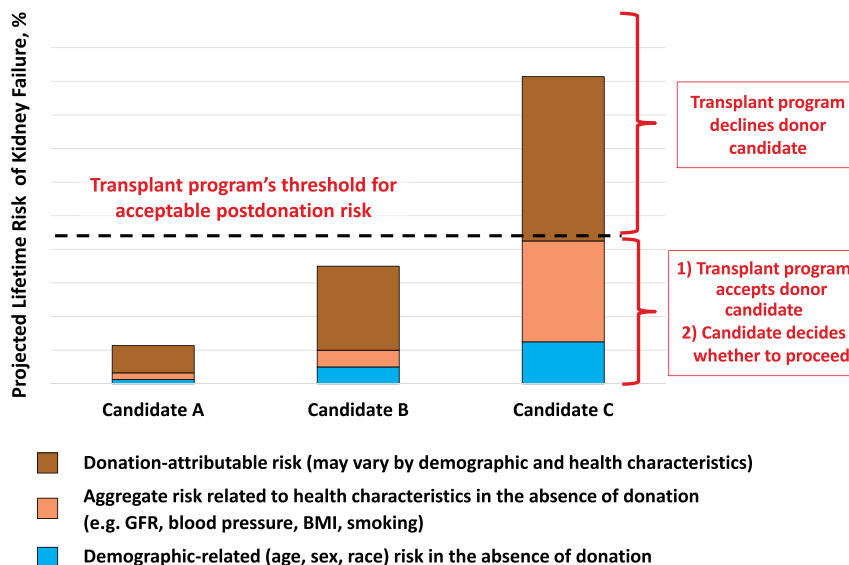


FIGURE 4. Framework to accept or decline donor candidates based on a transplant program's threshold of acceptable projected lifetime risk of kidney failure, quantified as the aggregate of risk related to demographic and health profile and donation-attributable risks. The decision by the transplant program whether to accept or decline a donor candidate is grounded on the candidate's estimated postdonation lifetime risk, including estimated risk in the absence of donation (risk related to demographic and health characteristics as denoted in blue and beige, respectively) and estimated risk attributable to donation (brown). BMI, body mass index; GFR, glomerular filtration rate.

presented in expanded form in a separate publication.⁷ To project the estimated long-term incidence of kidney failure among persons who do not donate a kidney according to 10 demographic and health characteristics, risk associations were derived from a meta-analysis of 7 general population cohorts. Relative risks were calibrated to the population-level annual incidence of ESKD in the United States, derived from actual ESKD incidence and mortality data collected by the US Renal Data System and overall mortality data from the US Census.³⁵ Fifteen-year projections were compared with the observed risk among 52 998 living kidney donors in the United States. For estimation of relative risks related to health characteristics, a total of 4 933 314 participants from 7 cohorts were followed for a median of 4 to 16 years. For a 40-year-old person with health characteristics similar to those of age-matched kidney donors, the 15-year projections of ESKD risk in the absence of donation varied 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. Risk projections were higher in the presence of lower eGFR, higher albuminuria, hypertension, current or former smoking, diabetes, and obesity. In the model-based lifetime projections, the risk of ESKD was highest among persons in the youngest age group, particularly among young black persons. The 15-year observed postdonation risks among kidney donors in the United States were 3.5 to 5.3 times as high as the projected risks in healthy persons in the absence of donation, according to sex and race.

This study has important limitations.³⁶ First, the projections were calibrated to historical incidence rates of ESKD from US population data. Annual incidence was derived with the use of life-table methods, which assume a constant age-, sex-, and race-specific incidence of ESKD over periods of decades and a static population substructure. Second, information on certain health characteristics of interest was not available, including heritable and environmental factors. The estimates reflect population averages for unmeasured characteristics. Donor candidates with a family history of kidney disease (especially younger candidates with such history) would be expected to have a higher risk of ESKD than projected. Third, the relative risk estimates were based on low-risk cohorts followed for a median of 4 to 16 years, based on an assumption of proportional hazards and after testing for nonproportionality. The analysis does not include untreated low GFR as an outcome, a condition that is more common among older persons, nor did it assess the risk of other outcomes, such as hypertension or pre-eclampsia, that have been linked to kidney donation. Finally, the analysis did not estimate the age at which ESKD would be expected to develop in a donor candidate or the duration of ESKD before death.

The resulting risk models were incorporated into an online risk prediction tool for 15-year and lifetime ESKD risk (<http://www.transplantmodels.com/esrdrisk/>). Although the risk tool was developed specifically for the United States, the methods used may be adapted to other countries with the availability of local data sources. The WG endorses use of the online tool as the foundation for a new evaluation framework centered on simultaneous consideration of multiple demographic and health characteristics to predict long-term risk of an important outcome, while recognizing

limitations in precision of risk estimates and uncertainty in donation-attributable risk. These models should be refined through further research to improve the precision and generalizability of predonation risk estimates and to incorporate estimates of individualized risk attributable to donation.

We endorse a quantitative framework for donor candidate evaluation and acceptance centered on lifetime risk of postdonation kidney failure (Table 9). For example, if a transplant program sets the acceptable lifetime postdonation ESKD risk threshold at 5%, and assumes a donation-attributable RR of 3.5 to 5.3 according to sex and race, then the acceptable predonation lifetime ESKD risk threshold would be approximately 1.0-1.5. This strategy enables decision-making based on a more comprehensive and integrated assessment of risk factors than is currently practiced, but application of the currently available online tool at this time requires clinician insight and interpretation.³⁷ Currently, there remains uncertainty in lifetime risk estimates, particularly for younger donor candidates, donors from developing countries, and ethnicities other than black or white race. At this time, transplant programs and donor candidates may consider other factors in their acceptance criteria for living kidney donation in addition to quantitative risk estimates. We see this work as starting point, and advocate strongly for continued efforts to improve the precision, tailoring and generalizability of predonation and postdonation risk estimates. Quantifying donation-attributable risk according to predonation demographic and health profile is a leading priority for future research, and we will update the online tool once estimates are available.

In summary, we advocate for a quantitative paradigm wherein transplant programs accept or decline donor candidates using the strongest evidence-based criteria currently available to simultaneously consider a profile of risk factors (demographic and health characteristics at evaluation and risk attributable to donation) and support consistent, transparent and defensible decisions. Ongoing efforts are needed to strengthen and advance this paradigm, including incorporation of data from cohorts observed for longer periods of time (ideally over the lifetime) and from diverse countries; estimation of risks related to genetic and familial factors; and quantification of donation-attributable risks

TABLE 9.

Approaches to implementation of a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of kidney failure

- (1) Use the online tool (<http://www.transplantmodels.com/esrdrisk/>) to estimate the projected lifetime risk of kidney failure in the absence of donation according to baseline demographic and health characteristics included in the online tool
- (2) Multiply the projected predonation risk by the best available estimate for donation-attributable risk to obtain the projected postdonation risk. For example, Grams et al⁷ report a relative risk of 3.5 to 5.3 for 15-y end-stage kidney disease risk, according to sex and race
- (3) Compare the projected risk estimate to the program's postdonation threshold of acceptable risk
- (4) Exercise caution when there is concern that the individual has risk factors not captured in the online tool (eg, familial or genetic risk) and for younger candidates

TABLE 10.**Roles and responsibilities of participants in donor candidate identification, evaluation, care, and follow-up**

| Entity | Responsibilities |
|---|--|
| General nephrologist/dialysis unit/advanced chronic kidney disease clinic Transplant program | <ul style="list-style-type: none"> • Educate recipient candidates regarding early referral, preemptive and living donor transplantation options and resources for identifying donor candidates • Educate recipient candidates regarding early referral, preemptive and living donor transplantation options |
| Recipient candidate health insurance carrier | <ul style="list-style-type: none"> • Educate donor candidates regarding all phases of the donation process including evaluation, surgery, postdonation follow-up, expected risks and outcomes, and existing uncertainties • Provide coverage for costs related to recipient candidate evaluation and transplantation, including coverage of donor candidate evaluation and treatment costs |
| Donor/donor candidate health insurance carrier | <ul style="list-style-type: none"> • Educate donor candidates regarding any anticipated out-of-pocket expenses related to evaluation and donation processes • Educate donor candidates regarding coverage for postdonation complications, both short-term and long-term after donation |
| Donor/donor candidate primary care physician | <ul style="list-style-type: none"> • Support donor candidates in their desire for information to make informed decisions • Participate in predonation and early postdonation care as needed • Participate in long-term care after donation |
| Donor/donor candidate physician/nephrologist | <ul style="list-style-type: none"> • Evaluate donor candidates without influence from recipient considerations • Oversee evaluation testing • Provide education regarding all phases of the donation process including postdonation follow-up • Participate in donor candidate selection • As needed, participate in care during the surgical hospitalization, in the early postdonation period, and long-term after donation, including serving as resource for primary providers |
| Donor surgeon | <ul style="list-style-type: none"> • Evaluate donor candidates for surgical risks and plan surgical approach • Provide education on the surgical procedure, risks and expected recovery • Participate in donor candidate selection • Provide care during surgery and perioperative period, and as needed postdonation |
| Nurse coordinator | <ul style="list-style-type: none"> • Educate donor candidates on recipient candidate treatment options and phases of the donation process • Facilitate and oversee completion of the evaluation • Assist with arranging surgery and inpatient care |
| Dietitian | <ul style="list-style-type: none"> • Arrange and oversee postoperative care, and coordinate a plan for postdonation follow-up • Review dietary habits and metabolic status including measures of obesity when needed • Provide guidance for nutritional treatment if indicated, including recommendations to address obesity |
| Social worker/psychologist/psychiatrist | <ul style="list-style-type: none"> • Perform donor candidate psychosocial evaluation including assessment of motivation • Educate donor candidates on recipient candidate treatment options • Provide donor candidates with information and support services related to donation, including information on resources that may be available to assist with donation-related expenses • Discuss potential adverse outcomes including loss of income because of donation, donation-related complications, or failure of the transplant. Assess the ability of donor candidates to cope with adverse outcomes • Support informed donation decisions • Assist donors with planning support around the time of donation and creation of a long-term follow-up plan |
| Independent living donor advocate ^a | <ul style="list-style-type: none"> • Verify that donor candidates have information needed to make a voluntary and informed decision on whether or not to donate • Verify consent for donation • Function independently from the recipient candidate's team • Advocate for the rights of donor candidates and donors |
| Regulatory and oversight agencies | <ul style="list-style-type: none"> • Create policies for minimum standards of donor candidate informed consent, evaluation, care and donor follow-up |
| Donor/donor candidate | <ul style="list-style-type: none"> • Agree to required psychosocial and medical evaluation • Agree to disclosure of required personal health information to intended recipient with regard to risk of disease transmission when necessary, or to withdraw from donation • Agree to required lifestyle modifications to reduce risks of donation and promote long-term good health • Agree to participate in postdonation follow-up |

^a The role of the independent donor advocate may be served by another team member as long as criteria for independence and advocacy functions are satisfied.

according to multiple predonation health characteristics. The scope of the current guideline is focused on donor safety, and excludes consideration of recipient outcomes based on donor characteristics. However, we appreciate that a donor candidate's profile of predonation characteristics may also have important impacts on posttransplant recipient outcomes, and that topic also warrants future consideration.

Roles and Responsibilities

Transplant programs bear the primary responsibility for evaluation, care and follow up of living kidney donor candidates and donors. The main responsibilities of the transplant program are to establish and maintain policies and a team of professionals to provide care according to policies. However, many other entities share in these responsibilities (Table 10). The decision to donate should be regarded as a shared responsibility between the donor candidate, the donor candidate's primary physician, and the transplant program. Transplant programs and the organizations that regulate transplant practice should:

- Evaluate and disclose risks to the best of currently available knowledge
- Respect the donor candidate's autonomy, including autonomy to take risk, within a program's/regulators' upper bound of acceptable risk
- Embrace a long-term relationship with the donor, because some risks are uncertain or evolving

RESEARCH RECOMMENDATIONS

- Strengthen and refine estimates of long-term projected predonation and postdonation risks of kidney failure, including incorporation of data from cohorts observed for longer periods of time (ideally over the lifetime), from different countries and regions, and estimates of risk related to familial, genetic (eg, apolipoprotein L1 [*APOLI1*]), and other factors (eg, birth weight).
- Engage in consensus-building activities among transplant professionals, donors and recipients to help establish uniform threshold of unacceptable risk. Strategies that may help inform consensus include:
 - Estimate the long-term risk of kidney failure among previously accepted donors, such as those captured in large national databases.
 - Estimate long-term risk of kidney failure based on donor acceptance criteria specified in prior guidelines.
 - Evaluate implications of racial variation in long-term risk of kidney failure exceeding possible thresholds for acceptable risk on opportunities for living donation. Develop strategies to promote equitable access to kidney transplantation without placing certain donors at unacceptable risk.
- Determine the best methods of communicating individualized risks to donor candidates and their intended recipients so that the information is understood and supports patient decision-making.
- Explore application of individualized risk estimates to guide predonation support and counseling (eg, target predonation BMI levels) to minimize the risk of adverse postdonation outcomes.
- Develop tools to predict risks of adverse short- and long-term psychosocial outcomes and a broader spectrum of medical outcomes according to predonation characteristics.

CHAPTER 2: INFORMED CONSENT

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 2 and therefore the following recommendations are “Not Graded.”

Process of Informed Consent

- 2.1: Informed consent for donation should be obtained from the donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision.

Capacity for Decision Making

- 2.2: The donor candidate's capacity to provide informed consent (ie, ability to understand the risks, benefits and consequences of donation) should be confirmed before proceeding with evaluation and donation.
- 2.3: Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (eg, children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review.

Content of Disclosure

- 2.4: Protocols should be followed to provide each donor candidate with information on:
 - The processes of evaluation, donor acceptance, and follow-up
 - The types of information that may be discovered during the evaluation, and what the transplant program will do with such information
 - Individualized risks, benefits and expected outcomes of the donor evaluation, donation, and postdonation health, including a discussion of the uncertainty in some outcomes
 - Treatment alternatives available to transplant candidates, and average expected outcomes
 - How personal health information will be handled
 - Availability of transplant program personnel for support

Comprehension of Disclosed Information

- 2.5: The donor candidate's understanding of the relevant information on the risks and benefits of donation should be confirmed before proceeding with donation.

Voluntarism

- 2.6: Donor candidates should have adequate time to consider information relevant to deciding whether they wish to donate or not.
- 2.7: A donor candidate's decision to withdraw at any stage of the evaluation process should be respected and supported in a manner that protects confidentiality.
- 2.8: A donor candidate who decides not to donate and has difficulty communicating that decision to the intended recipient should be assisted with this communication by the transplant program.

RATIONALE

Obtaining informed consent to be evaluated as a living kidney donor candidate, and informed consent to undergo living kidney donation, are processes rather than a discreet

event. The transplant program has a responsibility to establish that the donor candidate is capable of understanding the relevant information (*capacity*), is adequately informed of the likely risks and benefits of the donation, and of the alternative treatment options available to the recipient (*disclosure*), understands this information (*understanding*), and is acting voluntarily (*voluntarism*). This chapter provides recommendations to ensure satisfaction of the informed consent requirements for the living kidney donor candidate. The reader should also refer to chapter 1 for related discussions on the framework for decision-making and chapter 18 on the ethical, legal, and policy framework of living donation. Details of specific donation-related surgical, medical, and psychosocial risks are provided in other chapters (3-17) of the guideline.

Process of Informed Consent

Transplant programs must establish a defensible process to ensure that the requirements of informed consent are met.^{18,38-41} To date, donor candidate informed consent processes have been shown to vary widely across transplant programs worldwide, with discrepancies noted in standards, consistency and implementation.^{39,40,42-45} It has been recommended that the informed consent structure and process be the same for donor candidates regardless of relationship (or lack thereof for nondirected donation) between the donor candidate and their intended recipient.^{39,46,47}

Transplant programs must assure a donor candidate is acting voluntarily and not yielding to pressure or coercion. It is best if evaluations of the donor candidate and the intended recipient are performed by separate teams to mitigate potential conflict of interest. A recommendation that the donor candidate be evaluated by a team that is independent of the evaluation of the intended recipient is also recommended in several past guidelines.⁴⁷⁻⁵¹ The process of informed consent with a living kidney donor candidate should include discussions with a healthcare professional skilled and knowledgeable in organ donation and in evaluating a person's comprehension of the information. In the United States, to minimize conflict of interest, living donor recovery hospitals must designate and provide each donor candidate with an Independent Living Donor Advocate who is independent of the intended recipient's evaluation and the decision to transplant the intended recipient. This person seeks to ensure that the rights of the donor candidate are protected, that all the requirements of informed consent are met, and that the donation decision is made voluntarily.⁵¹ Other countries may use other strategies such as an external review of planned donations to ensure that independence, advocacy for the donor's rights, and voluntarism are respected.⁵² While avoidance of conflict of interest is a central principle, it also remains important that healthcare professionals in the teams evaluating the donor candidate and intended recipient work together to ensure effective communication and coordination of the donation and transplant processes. For example, it would be inefficient to fully evaluate a donor candidate if their intended recipient does not meet eligibility criteria for transplantation.

Capacity for Decision Making

The transplant team has a duty to confirm that the donor candidate has the capacity to provide informed consent,

and is able to communicate their decisions based on accurate comprehension of the information disclosed to them.^{2,18} Local laws and guidelines should be followed regarding minimum age criteria to become a living kidney donor.⁵³ For example, prior guidelines indicate that persons who are younger than 18 years or who lack the mental capacity to provide informed consent should not become living kidney donors with the assistance of substitute decision-makers, and that donation in such a setting only be considered in highly exceptional circumstances (eg, young parent to child) after ethical and legal review.^{18,38,47,48,51,54,55}

Content of Disclosure

Transplant programs must have a process to communicate relevant information to donor candidates that enables informed decision making.¹⁸ Some prior guidelines have suggested use of a standardized checklist to ensure that all items are disclosed.⁵⁰ For US programs, the Organ Procurement and Transplantation Network (OPTN) has developed an informed consent checklist for programs to support compliance with policy requirements⁵⁶ and a patient resource (English and Spanish translations) to explain the process in lay language for donor candidates.⁵⁷

The donor candidate needs to be informed from the onset of what is involved in the donor evaluation, including the required assessments and anticipated timelines. In general, education about the process and potential outcomes of living donation should be introduced in a manner conducive to learning and understanding. Prior guidelines and policy statements have recommended that discussions be provided in a language that enables meaningful dialogue between the donor candidate and transplant program staff, using communication strategies and materials that are culturally sensitive.^{47,49} The information should also be presented in a sympathetic environment, using simple language, allowing time for questions, with information that is appropriate to a candidate's understanding and experience, at a pace determined by their needs.⁴⁹ Repetition of key information, and use of approaches that foster adult learning, are prudent.⁵⁸ The information to be disclosed to the donor candidate is described in many prior guidelines and policy statements.^{47,48,51,54,59} Some regulations require minimum content elements that must be disclosed in the informed consent process,⁵¹ and these requirements should be respected when locally applicable. The donor candidate must also provide consent for some tests performed during the evaluation, such as consent to receive intravenous contrast for renal imaging. In this guideline, we present a list of the content of recommended disclosures during the donor candidate evaluation, considering these prior guidelines and policies (Table 11). Candidates should also be reminded that they can only donate a kidney as a living person once, even though they may know someone else who may need a kidney transplant in the future.

Treatment alternatives available to transplant candidates (in general terms, not with specific recipient medical information) should be disclosed to the donor candidate (Table 11). Donor candidates who are biologically incompatible with an intended recipient should be informed of the availability desensitization protocols and kidney paired donation (KPD), and the considerations related to pursuit of these treatment options. Logistics, outcomes and risks specific to KPD and planned incompatible transplantation are discussed in chapter 3 of this guideline. Participation in KPD and incompatible

TABLE 11.
Recommended content of disclosure during the evaluation of living donor candidates

| Type of disclosure | Information disclosed to the donor candidate |
|--|--|
| Handling of donor candidate's personal health information | <ul style="list-style-type: none"> • Personal health information collected during the donor candidate evaluation is confidential and protected under privacy law, similar to other personal health information • The transplant program will only disclose a donor candidate's personal health information to the intended recipient or other parties with the donor candidate's permission • The donor candidate may be asked for permission to disclose certain personal health information to their intended recipient. This information may include the donor candidate's identity, immunological compatibility, and medical history affecting the risk of disease transmission |
| Risks of discovery of donor health information | <ul style="list-style-type: none"> • The program's policy for disclosing information and arranging follow-up care for each of the following: <ul style="list-style-type: none"> ◦ A health condition that may require further medical intervention ◦ A health condition that could affect the donor candidate's ability to obtain insurance (eg, life, medical, disability), or the cost of insurance ◦ An infectious disease that must be reported to public health authorities ◦ A misattributed biological relationship between the donor candidate and intended recipient (such as misattributed paternity in a father-child relationship) discovered through blood group and immune compatibility testing |
| Risk and expected outcomes of donation | <ul style="list-style-type: none"> • The anticipated medical, surgical, psychosocial, and economic risks and outcomes of donation (for specific details see other chapters of this guideline), and the uncertainty in estimating risk and outcomes |
| Treatment alternatives available to transplant candidates | <ul style="list-style-type: none"> • Treatment options for kidney failure, including dialysis and deceased donor kidney transplantation, and their average expected outcomes compared with living kidney donor transplantation |
| Process of transplant candidate selection and when the intended recipient's personal health information is shared with the donor candidate | <ul style="list-style-type: none"> • Transplant candidate evaluation teams determine eligibility to receive a kidney transplant based on program criteria and clinical judgment • Personal health information collected during the transplant candidate's evaluation is confidential, protected under privacy law, and is not generally shared with the donor candidate unless: 1) the transplant program determines the donor candidate requires such information to make an informed decision about proceeding with donation, and 2) the intended recipient gives permission for this information to be shared with the donor candidate |
| Processes of donor candidate evaluation, candidacy determination, and follow-up | <ul style="list-style-type: none"> • Separate consents may be needed for some tests • Programs and personnel available to help donors with the financial burden of donation • It may be a crime to receive any valuable consideration (money, property) for donation • A description of what will happen if the candidate decides not to donate, emphasizing the right of the candidate to decline to donate at any time with the full support of the transplant program • The transplant program decides if the donor candidate is eligible for donation based on the results of their evaluation • If excluded from donation, information on why the donor candidate does not meet the program's criteria for donation and how the transplant program will support the candidate • The program's recommendations for follow-up care, including the timing and financial impacts of care and the need for regular, ongoing healthcare maintenance and healthy lifestyle choices • The program's need to collect ongoing personal health information after donation to inform the care of the recipient, and to guide the care of the donor • The program's policy about providing care to the donor after evaluation and donation • The availability of national and regional policies to assure prompt access to dialysis and transplantation for living donors who develop kidney failure |

transplantation requires specific informed consent, and minimum content elements may be specified by paired donation programs.^{60,61} The transplant program should inform the donor candidate of policies regarding confidentiality and anonymity in KPD and nondirected donation, and should ensure donor acceptance of these policies before donation.⁶² Some programs now permit biologically compatible pairs to participate in KPD; when this option is discussed, donor candidates who are biologically compatible with their intended recipient should voluntarily decide whether or not to pursue this option.⁶³⁻⁶⁵

Participating in donor evaluation includes risks of discovery. These risks include possible discovery of a health condition

that requires referral for further care, discovery of a health condition that could affect the donor candidate's insurability or cost of insurance, or discovery of an infectious disease for which there is a reporting requirement to public health authorities. Transplant programs should establish policies for managing such discoveries, and share these policies with the donor candidate as part of the informed consent process for evaluation. Testing a donor candidate and intended recipient in a family for the purpose of assessing immune compatibility may identify misattributed biological relationships as an incidental finding. For example, misattributed paternity is estimated to occur in approximately 1 to 3% of father-child living kidney donor-recipient pairs, or approximately

0.25% to 0.5% of all living kidney donation evaluations.⁶⁶ Transplant programs should establish a policy on how or whether this information is disclosed.^{67,68}

The donor candidate should be informed of donation-related surgical, medical, and psychosocial outcomes and risks as provided in other chapters of this guideline, individualized whenever possible for donor characteristics, and including the uncertainty of estimates. As described in chapter 1, 90-day all-cause mortality after donation in a US study of 80 347 donors (1994-2009) based on registry data and national death records was approximately 1 in 3000 (0.03%).²³ Similar rates have also been reported in other studies.^{24,25} Given the low incidence of perinephrectomy mortality, estimates for predonation characteristics that alter the risk of perioperative death are imprecise.

The donor candidate should be informed of anticipated recipient outcomes associated with living donor transplantation (such as 1-year, 5-year and median recipient graft and patient survival), and with available treatment alternatives including deceased kidney donor transplantation and different types of dialysis. US policy requires that donor candidates are provided with current national and program-specific 1-year transplant recipient patient and allograft survival statistics, and that donor candidates are also informed that any transplant candidate may have risk factors for increased likelihood of adverse outcomes (including graft failure, complications, mortality) that exceed local or national averages.⁵¹

Many regions have legislation that protects the confidentiality of personal health information, and the same protections apply to information collected during the donor candidate evaluation. The donor candidate should know that their personal health information will only be disclosed to their intended recipient or other parties if they provide permission to do so. The donor candidate should also know that it is likely they will be asked for permission to disclose certain personal health information to their intended recipient so that the intended recipient can provide informed consent for the transplant to occur.^{69,70} For example, in directed donation, while a donor candidate may wish to keep their act of donor evaluation initially confidential, if the transplant program does not permit anonymous directed donation, or if the intended recipient does not wish to proceed with anonymous directed donation, there may be a need for the donor candidate to provide permission for their identity to be disclosed to the intended recipient so that the intended recipient can make an informed decision about proceeding with the transplant. Similarly, donor candidates and intended recipients need to provide permission to make each other aware whether they are biologically compatible or not. During the donor evaluation process, it may be recognized that a donor candidate has additional health information that could impact the transplant outcome. For example, despite negative serological testing, a donor candidate may have a higher risk of specific infectious diseases based on his/her behavioral history. Some jurisdictions require standardized behavioral screening⁷¹ during the evaluation and consent from the donor candidate to inform the intended recipient of behavior associated with increased risk of certain infections, so that the intended recipient can provide informed consent for the transplant to proceed.⁵¹ Before donation the transplant program should also inform the donor candidate of requirements to share certain personal health information

with the recipient after donation, such as in the rare circumstance where soon after transplant (ie, within 1-2 years) it is discovered the donor has evidence of a serious infectious disease or malignancy.⁵¹

It is possible that the intended recipient has health information that could impact transplant outcomes, and which the transplant team believes could affect the donor candidate's decision making. For example, some donor candidates may want to know if the recipient lost a previously transplanted kidney due to medication nonadherence.⁷² Knowledge of a genetic kidney disease in an intended recipient may be important for the evaluation and care of a genetically related donor candidate. As for the health information of donor candidates, personal health information collected during the transplant candidate's evaluation is protected under privacy law, and can only be shared with permission of the intended recipient. Prior guidelines, such as those of the British Transplantation Society and policy of the US OPTN, recommend disclosure of relevant information about the intended recipient to the donor candidate if the intended recipient has given consent^{48,51}; the British Transplantation Society also recommends that donation and transplant not proceed unless the relevant information is shared.⁴⁸ The criteria for relevant information beyond the determination that the intended recipient is approved as a suitable transplant candidate by their evaluation team are currently undefined. Ongoing efforts are warranted to develop standardized criteria for the identification and disclosure of recipient risk factors for adverse transplant outcomes that may be relevant to donor decision making, and when donation and transplant should not proceed in the absence of disclosure, weighing considerations of privacy law, ethics, and the concerns of donor and recipient candidates (see Research Recommendations).

Donor candidates should be informed of transplant program resources and personnel available to offer support. Such support can include psychological support in the setting of a poor recipient outcome after transplantation or donor complications, or financial reimbursement programs for out-of-pocket expenses incurred during the evaluation and donation process. The donor candidate should understand what is required of them after donation, including the likely timing and financial impacts of donation-related recommended lifelong healthcare. The donor candidate should also understand how this care will be provided after donation, and the transplant program's policy for providing any healthcare (and what types of healthcare) after donation. In the US transplant programs are required to collect and report follow-up data on donors for 2 years after donation.⁷³

In nearly all places in the world it is a crime to knowingly acquire or obtain any human organ for valuable consideration (ie, for anything of value such as money or property). Some prior guidelines recommend the donor candidate sign a statement attesting that they are not donating a kidney for monetary gain^{46,74}; in the United States, such attestation is required for donation to proceed.⁵¹ The donor candidate should understand the withdrawal process from evaluation, and their right to withdraw at any time before donation with the full support of the transplant program (described further below in this guideline chapter). Finally, while transplant programs respect the autonomy of a donor candidate to proceed with donation based on their preferences, needs and values, programs remain ethically justified to decline a donor

candidate who does not meet their eligibility criteria for donation (ie, when the donation is deemed to incur unacceptable risks).²² A donor candidate should understand the transplant program makes the final determination of whether the donor candidate is eligible for donation or not based on the results of their evaluation. If the donor candidate does not meet the transplant program's criteria for donation, the program should inform the donor candidate of the decision and reason. Being told they do not meet a transplant program's acceptance criteria is distressing for some donor candidates.⁷⁵ The donor candidate should be informed how the transplant program will support them if they do not meet criteria for donation. Such support may include assistance in communicating the decision to the intended recipient; ongoing follow-up communication with the evaluation team; counseling related to the outcome of the evaluation; alternative ways of helping the intended recipient; and the possibility of referral to another program for a second opinion if the donor candidate does not accept the noneligibility decision.

Comprehension of Disclosed Information

Donor candidates should have adequate time to consider the information they are provided during the evaluation process, as this is required for informed consent. The duration of adequate time is not well defined, and may vary according to donor characteristics. Some, but not all transplant programs, require all donor candidates to exercise a minimal period for this adequate consideration, referred to as a 'cooling-off' period.⁴⁴

In current routine care, an assessment of a donor candidate's knowledge and comprehension of the possible outcomes of donation is typically done through discussions with healthcare professionals. Optimal methods to assess understanding in living donor candidates are not well defined,^{39,58} but general techniques for comprehension assessment may include use of "teach-back," in which patients are asked to "teach back" what they have learned during their visit.⁷⁶ An instrument for assessing comprehension during informed consent for living liver donation has been pilot tested,⁷⁷ and provides a model for developing similar instruments for comprehension assessment in living kidney donor candidates. It is common for many donor candidates to voice no concerns during the evaluation process about the donation, as they are using an emotional rather than deliberative decision-making process. Some donors have an exaggerated sense of the true benefit of donation to their intended recipient, while others underappreciate the amount of postoperative physical pain they may experience or the time needed to fully recover after surgery.⁷⁸

The Voluntary Nature of Kidney Donation

Voluntarism is established when a transplant program ensures the donor candidate is free from undue pressure or coercion in deciding whether or not to donate.⁷⁹ Voluntarism should be respected by all members of the transplant team; as discussed above, additional safeguards may include use of Independent Living Donor Advocates or external reviews of planned donations.^{51,52} Special groups such as prisoners have unique considerations.⁸⁰ Interviewing the donor candidate without the intended recipient, family members and other persons who could influence the donation decision is important in the assessment of voluntarism. Trust is maintained when the transplant program assures a donor candidate that

their participation in evaluation and personal health information is confidential, to be shared with the intended recipient only with their approval. This enables the donor candidate to speak openly about their health and donation choices.

For the purposes of donor candidacy, 'not deciding' about donation should be considered the same as 'deciding not to' proceed, as may occur in cases of ambivalent donor candidates who have not decided to proceed, but who also have not elected to formally withdraw from the donation process.³⁹

Transplant programs should support donor candidates who decide to withdraw from the evaluation process or decline to donate in a way that is respectful and confidential.⁸¹ So-called 'medical alibis,' provision of a false medical reason to justify unsuitability as a living donor, are discouraged as untruthful statements may undermine trust in the transplant program and the patient/physician relationship.⁸¹ Thiessen et al recommend that all donor candidates be offered a general statement regarding 'unsuitability to donate' at any time; there is controversy about whether the transplant program should assist the donor candidate with wording that includes factual medical findings which may or may not preclude donation (such as mildly elevated BP or risk factors for metabolic syndrome).⁸² Understandably, a donor candidate who decides not to donate may have difficulty communicating this decision to the intended recipient or others; in such circumstances the transplant program should assist with this communication, which may involve communication through the recipient evaluation team to the transplant candidate.

RESEARCH RECOMMENDATIONS

- Determine the best methods to achieve informed consent from living kidney donor candidates, including what methods are most useful to impart information including risks and outcomes and what methods are most useful to assess comprehension.⁴²
- Through focus groups and/or surveys, develop standardized criteria for circumstances under which intended recipients should be asked for permission to disclose certain personal health information to the living kidney donor candidate (such as loss of a prior graft due to medication nonadherence), so that donor candidates can make an informed decision about whether to proceed with donation or not.
 - Develop standardized criteria for when donation and transplant should not proceed in the absence of disclosure, weighing considerations of privacy law, ethics, and the concerns of donor and recipient candidates.
- Perform postdonation surveys to measure donors' assessments of the quality of standardized informed consent processes, including if the information provided before donation met the donor's needs and prepared them for the donation.⁸³
- Compare experiences of donors who donated before and after the implementation of country-specific regulations for better informed consent processes for the practice of living donation.
- Evaluate appropriate circumstances for and approaches to substitute decision making and use of surrogate consent, including definition of the necessary supporting ethical framework for particular scenarios.
- Develop ethically-grounded, practical strategies to consider and manage evaluation of living kidney donor candidates identified by the intended recipient or their representatives through mass advertising and social media.⁸⁴

CHAPTER 3: COMPATIBILITY TESTING, INCOMPATIBLE TRANSPLANTATION, AND PAIRED DONATION

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 3 and therefore the following recommendations are “Not Graded.”

Evaluation

- 3.1: Donor ABO blood typing should be performed twice before donation to reduce the risk of unintended blood type incompatible transplantation.
- 3.2: Donor blood group A subtype testing should be performed when donation is planned to recipients with anti-A antibodies.
- 3.3: Human leukocyte antigen (HLA) typing for major histocompatibility complex (MHC) Class I (A, B, C) and Class II (DP, DQ, DR) should be performed in donor candidates and their intended recipients, and donor-specific anti-HLA antibodies should be assessed in intended recipients.

Counseling

- 3.4: Donor candidates who are ABO blood group or HLA incompatible with their intended recipient should be informed of availability, risks, and benefits of treatment options, including kidney paired donation and incompatibility management strategies.
- 3.5: If a donor candidate and their intended recipient are blood type or crossmatch incompatible, transplantation should be performed only with an effective incompatibility management strategy.
- 3.6: Nondirected donor candidates should be informed of availability, risks and benefits of participating in kidney paired donation.

RATIONALE

Evaluation: Blood Type and Histocompatibility Testing

ABO blood typing should be performed in living donor candidates before donation, including routine duplicate testing, to reduce the risk of unintended blood type-incompatible transplantation. Unintended ABO-incompatible (ABOi) transplantation should be avoidable with ABO typing of the donor and the recipient; however, human errors have led to cases of accidental ABOi organ transplantation in contemporary practice.⁸⁵ ABO-subtype testing should be performed when donation is planned to recipients with anti-A antibodies.⁸⁶ Human leukocyte antigen (HLA) typing for major histocompatibility complex (MHC) class I (A, B, C) and class II (DP, DQ, DR) should be obtained in living donor candidates for recipient candidates with anti-HLA antibodies, as part of the assessment of compatibility during preoperative planning; there is an association between the presence of HLA-C and/or HLA-DP and DQ and a higher incidence of graft rejection.^{87,88} While recipient care is out of the scope of this guideline, it is important to emphasize that recipient candidates should undergo antidonor antibody examinations, including complement-dependent cytotoxicity or flow cytometry crossmatching and Luminex (Bio-Rad Laboratories, Inc., Hercules, CA) assays to determine the history of sensitization,⁸⁹ and this testing should be current before proceeding with donor nephrectomy and living donor transplantation.

Counseling Regarding Transplant Options and Expected Outcomes

Biological incompatibility remains a significant barrier to living donor kidney transplantation. Estimates based on blood group prevalence in the United States suggest that more than 35% of willing, healthy potential living donors are blood group incompatible with their intended recipients.⁹⁰ Options for transplant candidates whose only willing, healthy donor is ABO or HLA incompatible include: KPD, planned incompatible transplantation (with preconditioning/desensitization treatment of the intended recipient as needed), attempting to find a different living donor, or waiting for a compatible deceased donor organ.⁹¹⁻⁹³ While evaluation and management of the transplant recipient is not within the scope of this project, outcomes of recipients after various forms of transplant or waiting are relevant to living kidney donor candidate education. Perspectives of risk and benefit for counseling of the intended recipient and donor candidate include outcomes after compatible versus incompatible transplantation, outcomes after incompatible transplantation versus dialysis, and the likelihood of transplantation with options including KPD programs. Donor candidates who are ABO or HLA incompatible with their intended recipient should be informed of expected patient and graft survival for KPD and incompatible transplantation, as compared with compatible living donor transplantation and deceased donor transplantation, as well as expected patient survival on dialysis, based on best available information.

Kidney Paired Donation

KPD has emerged as a successful approach to address ABO blood group and HLA incompatibilities for those who have a willing, but incompatible living donor candidate. The fastest growing modality for living donor transplantation is KPD, rising from 2 cases in 2000 to approximately 700 cases reported to the US OPTN in 2013.⁹⁴ In 2004, the Netherlands instituted a paired exchange system in all their transplant centers, which may explain the recent increase in living kidney donation in that country.⁹⁵

Donor candidates who are ABO or HLA incompatible with their intended recipient should be informed of the availability of KPD, and the considerations related to pursuit of this treatment option. Participation in KPD requires KPD program-specific informed consent^{60,61} (Please see also chapter 2: Informed Consent for details). The transplant program should inform the donor candidate of policies regarding confidentiality and anonymity in KPD and nondirected donation, and should ensure donor acceptance of these policies before donation.⁶² Some programs now permit biologically compatible pairs to participate in KPD; when this option is discussed, donor candidates who are biologically compatible with their intended recipient should voluntarily decide whether or not to pursue this option.⁶³⁻⁶⁵

Donor candidates participating in KPD should be informed of the risks and benefits of kidney transport, possible organ redirection due to unforeseen circumstances, the inability to provide information on the ultimate recipient of their organ, as well as nonexchange donation options.⁶⁰ Living donors participating in exchanges should have the option to travel to the recipient center; however, experience from countries with well-developed KPD programs suggests that

transport of living donor kidneys can be accomplished safely without adversely impacting transplant outcomes, obviating the need for donor travel. In a survey of 30 US programs transporting 56 living donor kidneys (2007-2010), the creatinine nadir was less than 2.0 mg/dL (<177 $\mu\text{mol/L}$) in all recipients but one, and there were no cases of delayed graft function as defined by the need for dialysis in the first week.⁹⁶ Continued feasible and safe transport of living donor kidneys in the United States has been reported.⁹⁷

Nondirected donors (donor without an identified recipient) have the unique potential to expand the donor pool through chains of kidney exchanges.⁹⁸ Nondirected donor candidates should be informed of opportunities for donating into a chain or KPD program, if available.

Participation in KPD should be considered preferable to incompatible transplantation if participation is deemed to have “reasonable” likelihood of yielding a compatible or lower-immunologic risk match for the donor candidate’s intended recipient. Despite the expansion of KPD, blood group O candidates continue to have much lower rates of success on KPD lists than their non-O counterparts, particularly in circumstances of broad HLA sensitization.⁸⁶ Thus, for some transplant candidates, incompatible transplantation may offer their best option for transplantation without prolonged waiting times.

Blood Type-Incompatible Living Donor Transplantation

While incompatible transplantation without preconditioning/desensitization treatment of the recipient may lead to hyperacute rejection and allograft loss, predetermined incompatibility management protocols have been developed in recent decades. In 1987, successful ABOi living donor transplantation was introduced in Japan using pretransplant antibody depletion, to expand access to transplantation in the absence of legal recognition of brain death.⁹⁹⁻¹⁰¹ Since that time, ABOi transplantation evolved into routine practice and constituted nearly 14% of living donor transplant procedures performed in Japan in 2011.

Recipient and donor candidates interested in ABOi living donor transplantation should be informed of possible complications and expected outcomes. US studies have reported higher rates of perioperative complications including hemorrhage, infections, and early graft loss compared with ABO-compatible (ABOc) transplantation.^{91,102} In contrast, some European and Asian studies have found no increases in early or longer-term complications after ABOi transplantation,¹⁰³⁻¹⁰⁶ possibly reflecting differences in preconditioning management protocols. Even in the US experience, after an early reduction in graft survival relative to blood ABOc living donor kidney transplant recipients,⁹¹ the average long-term graft survival in ABOi living donor transplant recipients is not inferior to, and often exceeds, that of ABOc deceased donor transplant recipients.^{91,107} In the United States, recipients of ABOi living donor kidney transplants also appear to incur higher costs of care before, during, and after transplant, although these costs increases are offset by avoiding long-term dialysis and its associated morbidity and costs.¹⁰⁸

HLA-Incompatible Living Donor Transplantation

HLA-incompatible transplantation remains the most difficult hurdle in achieving successful transplant outcomes. Flow cytometry crossmatching + or Luminex +/-complement dependent cytotoxicity- incompatibility may be acceptable with

management including B-cell-depleting treatments (eg, anti-CD 20 antibody, rituximab) and/or splenectomy and/or intravenous immunoglobulin, but increased risk of early rejection remains, requiring additional immunosuppression and attendant risks to the recipient. Nonetheless, while allograft survival after HLA-incompatible living donor kidney transplantation is inferior to compatible transplantation, incompatible transplantation after desensitization may offer a substantial survival benefit compared with dialysis or waiting for a deceased donor kidney; however, there are few high-quality studies testing this hypothesis. A recent study compared 1025 recipients of HLA-incompatible living donor kidney transplants at 22 US medical centers with matched controls who remained on waiting lists or waited and received a transplant from a compatible deceased donor. After 8 years, 76.5% of those who received an incompatible living donor transplant were still alive, compared with 62.9% who remained on the waiting list or received a deceased donor transplant and only 43.9% who remained on the waiting list but were never transplanted.¹⁰⁹ HLA-incompatible transplantation does confer additional costs compared with compatible transplantation, but may be cost-effective compared with dialysis; formal cost effectiveness evaluations are needed.¹¹⁰

What Prior Guidelines Recommend

In contrast with our recommendations, the European Renal Best Practice (ERBP) guideline for kidney donor and recipient evaluation recommends performing HLA-DQ, HLA-DP and HLA-C typing of the donor only when the intended recipient has HLA antibodies against those antigens.⁵⁰ The ERBP does not recommend routine typing for MHC Class I-related chain-A and other non-HLA antigens in either recipient or donor. Similar to our recommendations, the ERBP recommends establishing programs to select a donor towards whom the recipient does not produce antibodies through KPD, and recommends transplanting patients with donor-specific antibodies only if this cannot be accomplished by KPD.⁵⁰ Details of testing and clinical management associated with HLA and non-HLA antibodies in transplantation are out of the scope of the current guideline, but consensus-based recommendations from a 2012 Transplantation Society work group are available.⁸⁹

In 2012, the American Society of Transplantation (AST)/American Society of Transplant Surgeons (ASTS) held a consensus conference directed at overcoming barriers to the adoption of KPD that produced recommendations related to KPD donor evaluation and care, guidelines for KPD histocompatibility testing, and recommended policies to overcoming geographic barriers to KPD.⁶⁰

RESEARCH RECOMMENDATIONS

- Define mediators of clinical outcomes and optimal management of ABO and HLA incompatible living donor transplantation to support donor and recipient selection, understanding of transplant utility and informed consent, including:
 - Standardized, controlled comparisons of preconditioning/desensitization and posttransplant immunosuppressive protocols for incompatible transplantation
 - Elucidation of the mechanisms of antibody production and long-term impact on the allograft
- Develop a long-term, appropriately powered RCT to compare the outcomes and cost effectiveness of options for highly sensitized candidates including participation in KPD with varying

waiting times versus living donor transplantation after various desensitization protocols.

CHAPTER 4: PREOPERATIVE EVALUATION AND MANAGEMENT

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 4 and therefore the following recommendations are “Not Graded.”

- 4.1: Donor candidates should receive guideline-based evaluation and management used for other noncardiac surgeries to minimize risks of perioperative complications, including a detailed history and examination to assess risks for cardiac, pulmonary, bleeding, anesthesia-related and other perioperative complications.
- 4.2: Donor candidates who smoke should be advised to quit at least 4 weeks before donation to reduce their risk of perioperative complications, and commit to lifelong abstinence to prevent long-term complications.

RATIONALE

Evaluation

The goals of the general preoperative evaluation are to assess a donor candidate's risk of perioperative complications according to their profile of predonation characteristics assessed through a careful medical history, physical examination and testing; to determine if this risk is acceptable to proceed with donation; and to counsel the donor candidate on how to minimize their risk of perioperative complications (eg, stop smoking, lose weight if obese). The donor then receives care during the perioperative period to minimize their risk of complications, so that they can return to their level of presurgical function as quickly as possible. Recommendations on how to achieve these outcomes with good preoperative evaluation and management are sparse in prior living kidney donor guidelines, other than a description of elements of the detailed history required before donation (eg, prior surgeries, anesthesia-related reactions and bleeding disorders).⁵¹ Associations of donation-specific surgical techniques with perioperative outcomes are described elsewhere (see chapter 17).

Risks of Perinephrectomy Complications

Living kidney donor nephrectomy is an elective surgical procedure that carries a low risk for complications as compared with other types of surgical procedures. As described in chapter 1, the 90-day all-cause mortality in a US study of integrated donor registry data and national death records (80 347 donors, 1994-2009) was approximately 1 in 3000 (0.03%) based on 25 deaths.²³ Similar rates have also been reported in other studies.^{24,25} Given the low incidence of perioperative mortality, estimates for predonation characteristics that alter the risk of perioperative death are imprecise.

A US study recently described the incidence of perioperative complications in a large sample of living kidney donors from 1998 to 2010.²⁸ Outcomes were assessed through administrative data, using a composite outcome of digestive, respiratory, procedural, urinary, hemorrhage, infectious or cardiac complications. The incidence of perioperative complications was 7.9% and decreased from 1998 to 2010 (from 10.1% to 7.6%). Limitations of this study include the lack of confirmation of donor status through patient level-linkages

to the national registry, and use of weighting schemes to draw inferences for a “represented” sample of all US donors based on a stratified sample of 20% of acute care hospitalizations. A subsequent study integrated national US donor registry data as a source of verified living donor status with administrative records from a consortium of 98 academic hospitals (2008 to 2012, n = 14 964), and found that 16.8% of donors experienced any perioperative complication, most commonly gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), and surgical/anesthesia-related injuries (2.4%).²⁹ Major complications, defined as Clavien grading system for surgical complications level 4 or 5,¹¹¹ affected 2.5% of donors. The limitations of administrative database studies, including possible coding biases, highlight the need for prospective collection of granular clinical data on living donor perioperative outcomes. A Norwegian registry-based study of 1022 living kidney donations performed between 1997 and 2008 recorded 30 (2.9%) major complications and 184 (18%) minor complications by Clavien grading.¹¹²

Readmission after surgery is commonly used as a measure of care quality and healthcare utilization. A recent study examined postnephrectomy readmission using integrated US living donor registry data, records from a nationwide pharmacy claims warehouse, and administrative records from an academic hospital consortium (N = 14 959 donors, 2008-2012).¹¹³ Overall, 2.9% of donors were readmitted to hospital within 90 days of donation. 11.3% donors filled 1 or greater opioid prescription in the year before donation, and those with the highest level predonation opioid use were more than twice as likely as nonusers to be readmitted within 90 days postdonation (6.8% vs 2.6%; adjusted odds ratio [OR]; 95% lower CI [OR] 95% upper CI 1.74-2.49_{3.58}). Adjusted readmission risk was also significantly (*P* < 0.05) higher for women (adjusted OR = 1.25), African Americans (adjusted OR = 1.45), spouses (adjusted OR = 1.42), exchange participants (adjusted OR = 1.46), uninsured donors (adjusted OR = 1.40), donors with predonation eGFR <60 mL/min per 1.73 m² (adjusted OR = 2.68), donors with predonation pulmonary disease (adjusted OR = 1.54), and after robotic nephrectomy (adjusted OR = 1.68). Continued efforts to identify and prevent modifiable causes of postoperative complications in all donors are warranted to maximize safety of the donation procedure.

Readers are encouraged to refer to chapter 17 for discussion of acceptable surgical approaches to donor nephrectomy and anticipated outcomes. As discussed in the Framework for this guideline (chapter 1), the transplant program team should provide the donor candidate with individualized quantitative estimates of short-term and long-term risks from kidney donation to the extent possible, including recognition of associated uncertainty, in a manner that is easily understood by donor candidates.

Preoperative and Perioperative Management to Minimize the Risk of Perinephrectomy Complications

Guidelines for evaluation and management before noncardiac surgery in the general population have been thoroughly reviewed and summarized.¹¹⁴ There is no evidence to suggest that additional preoperative testing beyond guideline-based evaluation and management strategies used for other noncardiac surgeries results in a reduced incidence of perioperative complications in kidney donors.

Some transplant programs routinely perform preoperative noninvasive cardiac testing in older living kidney donor candidates (eg, stress electrocardiogram, nuclear stress test), but this practice is not supported by existing evidence. Recent US guidelines for the general population do not recommend cardiac testing for those undergoing noncardiac surgery with no active symptoms of heart disease who have reasonable functional capacity (defined as at least 4 metabolic energy equivalents, which represents the ability to walk 2 blocks on ground level or carry 2 bags of groceries up one flight of stairs without symptoms).¹¹⁵ Outside the context of perioperative evaluation, other guidelines recommended against noninvasive cardiac testing for asymptomatic coronary artery disease, or conclude that there is insufficient evidence to warrant such testing.¹¹⁶

Recent guidelines on the assessment of bleeding risk before surgery or invasive procedures describe the following¹¹⁷: (i) Routine coagulation screening before surgery to predict postoperative bleeding in unselected patients is not recommended; (ii) bleeding history assessment should include details of a family history of bleeding, previous excessive posttraumatic or postsurgical bleeding, and current use of antithrombotic drugs; (iii) if the bleeding history is negative, no further coagulation testing is indicated; (iv) comprehensive coagulation testing is warranted if the bleeding history is positive. Although evidence in the context of donor nephrectomy is lacking, current OPTN policy for living donor evaluation in the United States requires assessment of bleeding and clotting disorders in the medical history, and performance of coagulation testing,⁵¹ and other prior living donor evaluation guidelines have recommended blood coagulation testing.^{54,118}

In a recent multicenter randomized trial of 10 010 patients undergoing noncardiac surgery, the use of aspirin before surgery and throughout the early postsurgical period had no significant effect on the risk of death or nonfatal myocardial infarction but increased the risk of major bleeding.¹¹⁹ The trial authors recommend aspirin not be started before surgery, and for those chronically taking aspirin to hold it at least 3 days before surgery.

Recent guidelines for the prevention of perioperative venous thromboembolism (ie, deep vein thrombosis and pulmonary embolism) describe the use of a risk score (Rogers or Caprini score) to determine which of early ambulation, mechanical prophylaxis or perioperative unfractionated heparin (or low-molecular-weight heparin) is warranted to reduce risk.¹²⁰ Factors associated with a higher risk of perioperative venous thromboembolism include older age, obesity, and the use of oral contraceptive or hormone replacement therapy. Many donors will be at low risk (<2%) of perioperative venous thromboembolism, and some guidelines suggest early ambulation is all that is required in individuals at low risk of such events.

Guidelines to reduce the risk of perioperative pulmonary complications recommend a careful assessment of risk factors for postoperative pulmonary complications (conditions such as chronic obstructive pulmonary disease or congestive heart failure which will be absent in almost all donors).¹²¹ Preoperative spirometry and chest radiography are not recommended as routine tests to predict the risk for postoperative pulmonary complications. Patients at higher risk for postoperative pulmonary complications may benefit from deep breathing exercises or incentive

spirometry, or selective use of a nasogastric tube (as needed for postoperative nausea or vomiting, inability to tolerate oral intake, or symptomatic abdominal distention). The utility and difficulties of the preoperative evaluation for the potential identification of obstructive sleep apnea is described elsewhere.¹²²

There have been 6 RCTs that enrolled smokers (ranging from 47 to 213 patients) to receive a smoking cessation intervention or not before surgery (procedures other than donor nephrectomy)¹²³ and found that smoking cessation reduced the risk of perioperative complications.

RESEARCH RECOMMENDATIONS

- Develop contemporary estimates of 5.10, the risk of perinephrectomy complications according to an individualized profile of predonation characteristics, accounting for changes in baseline comorbidity burdens.
- Assess the predictive value of novel risk factors for perioperative complications and readmission after donor nephrectomy, including use of opioids and other pharmaceuticals.¹¹³
- Perform RCTs to formally assess the efficacy of evaluation and perioperative management techniques to minimize the risk of perioperative complications after living donor nephrectomy.

CHAPTER 5: PREDONATION KIDNEY FUNCTION

Except in the case of Recommendation 5.10, the ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 5 and therefore the following recommendations are “Not Graded.” Some of the recommendations extrapolated from the 2012 KDIGO CKD Guideline (Section 1.4.3)¹²⁴ were not part of the ERT review for this guideline and as such they are also “Not Graded.”

Evaluation

- 5.1: Donor kidney function should be expressed as glomerular filtration rate (GFR) and not as serum creatinine concentration.
- 5.2: Donor GFR should be expressed in mL/min per 1.73 m² rather than mL/min.
- 5.3: Donor glomerular filtration rate (GFR) should be estimated from serum creatinine (eGFR_{cr}) for initial assessment, following recommendations from the KDIGO 2012 CKD guideline.
- 5.4: Donor GFR should be confirmed using one or more of the following measurements, depending on availability:
 - Measured GFR (mGFR) using an exogenous filtration marker, preferably urinary or plasma clearance of inulin, urinary or plasma clearance of iohalamate, urinary or plasma clearance of ⁵¹Cr-EDTA, urinary or plasma clearance of iohexol, or urinary clearance of ^{99m}Tc-DTPA
 - Measured creatinine clearance (mCrCl)
 - Estimated GFR from the combination of serum creatinine and cystatin C (eGFR_{cr-cys}) following recommendations from the KDIGO 2012 CKD guideline
 - Repeat estimated GFR from serum creatinine (eGFR_{cr})
- 5.5: If there are parenchymal, vascular or urological abnormalities or asymmetry of kidney size on renal imaging, single kidney GFR should be assessed using radionuclides or contrast agents that are excreted by glomerular filtration (eg, ^{99m}Tc-DTPA).

Selection

- 5.6: GFR of 90 mL/min per 1.73 m² or greater should be considered an acceptable level of kidney function for donation.
- 5.7: The decision to approve donor candidates with GFR 60 to 89 mL/min per 1.73 m² should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 5.8: Donor candidates with GFR less than 60 mL/min per 1.73 m² should not donate.
- 5.9: When asymmetry in GFR, parenchymal abnormalities, vascular abnormalities, or urological abnormalities are present but do not preclude donation, the more severely affected kidney should be used for donation.

Counseling

- 5.10: We suggest that donor candidates be informed that the future risk of developing kidney failure necessitating treatment with dialysis or transplantation is slightly higher because of donation; however, average absolute risk in the 15 years following donation remains low. (2C)

RATIONALE

Evaluation

The goals of the evaluation of kidney function in living donor candidates are to:

- Provide accurate assessment of level of GFR and prediction of long-term risk of ESKD (in the absence of and after donation) based on level of predonation GFR and other factors.
- Allow identification and exclusion of donor candidates whose postdonation risks are expected to exceed the acceptable risk threshold established by the transplant program.
- Provide counseling regarding level of risk for donor candidates whose long-term risks for ESKD are expected to be below the acceptable risk established by the transplant program.
- Provide counseling regarding the need for follow-up of decreased GFR after donation.

For this section, recommendations related to measurement of kidney function are based on physiological principles and recommendations for general clinical practice from the KDIGO 2012 CKD guideline.¹²⁴ These recommendations were based on a systematic review of the literature, which included some studies of donors before and after kidney donation.¹²⁵ There is no evidence to suggest that living kidney donor candidates or kidney donors differ from other populations regarding these recommendations.

Box 1. Key recommendations from the KDIGO 2012 CKD guideline regarding GFR estimation.¹²⁴

- We recommend using serum creatinine and a GFR estimating equation for initial assessment (Recommendation 1.4.3.1, Grade 1A).
- We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate (Recommendation 1.4.3.2: Grade 2B).

- We recommend that clinicians (Recommendation 1.4.3.3, Grade 1B):
 - Use a GFR estimating equation to derive GFR from serum creatinine (eGFR_{cr}) rather than relying on the serum creatinine concentration alone.
 - Understand clinical settings in which eGFR_{cr} is less accurate.
- We recommend that clinical laboratories should (Recommendation 1.4.3.4, Grade 1B):
 - Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.
 - Report eGFR_{cr} in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFR_{cr}.
 - Report eGFR_{cr} in adults using the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.
- When reporting serum creatinine:
 - We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (μmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL).
- When reporting eGFR_{cr}:
 - We recommend that eGFR_{cr} should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m² in adults using the units mL/min per 1.73 m².
 - We recommend eGFR_{cr} levels less than 60 mL/min per 1.73 m² should be reported as “decreased.”
- If cystatin C is measured, we suggest that health professionals (Recommendation 1.4.3.6, Grade 2C):
 - Use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.
 - Understand clinical settings in which eGFR_{cys} and eGFR_{cr-cys} are less accurate.
- We recommend that clinical laboratories that measure cystatin C should (Recommendation 1.4.3.7, Grade 1B):
 - Measure serum cystatin C using an assay with calibration traceable to the international standard reference material.
 - Report eGFR from serum cystatin C in addition to the serum cystatin C concentration in adults and specify the equation used whenever reporting eGFR_{cys} and eGFR_{cr-cys}.
 - Report eGFR_{cys} and eGFR_{cr-cys} in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively, or alternative cystatin C-based GFR estimating equations if they have been shown to improve accuracy of GFR estimates compared to the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.
- When reporting serum cystatin C:
 - We recommend reporting serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/L).
- When reporting eGFR_{cys} and eGFR_{cr-cys}:
 - We recommend that eGFR_{cys} and eGFR_{cr-cys} be reported and rounded to the nearest whole number and

relative to a body surface area of 1.73 m^2 in adults using the units mL/min per 1.73 m^2 .

- We recommend eGFR_{cys} and $\text{eGFR}_{\text{cr-cys}}$ levels less than $60 \text{ mL}/\text{min}$ per 1.73 m^2 should be reported as “decreased.”
- We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions (Recommendation 1.4.3.8, Grade 2B).

GFR as an Index of Kidney Function

The level of GFR is widely accepted as the best overall index of kidney function in health and disease. The foundations for this acceptance are the well-known relationships of alterations in kidney structure and GFR in kidney disease, and well known pathophysiologic relationships of kidney disease complications to decreased GFR. Normative levels of GFR are expressed per 1.73 m^2 because GFR is proportional to kidney size, which is proportional to body size. Adjusting GFR to body surface area (BSA) reduces the variability in GFR in healthy individuals, allowing communication of GFR threshold for decision-making that can be applied to most donors across the usual distribution of body size.

Based on a large body of evidence, mean GFR in healthy young adult white individuals is approximately $125 \text{ mL}/\text{min}$ per 1.73 m^2 , with a wide range.¹²⁶ There is some evidence that the normal level of GFR varies among ethnic groups.¹²⁷ GFR is affected by numerous physiologic and pathologic conditions and varies with time of day, dietary protein intake, exercise, age, pregnancy, obesity, hyperglycemia, use of antihypertensive drugs, surfeit or deficit of extracellular fluid, and acute and chronic kidney disease. Despite these limitations, no other measure has been proposed as an overall index of kidney function in the general population or in kidney donor candidates. Thus, it is important that the evaluation of kidney function in kidney donor candidates take into account factors that can affect GFR.

Measurement Methods

It is not possible to directly measure GFR in humans; thus, the “true” GFR cannot be known with certainty. GFR can be measured indirectly as the clearance of exogenous filtration markers or estimated from serum levels of endogenous filtration markers, but both measured GFR (mGFR) and estimated GFR (eGFR) are associated with error in their determination. We recommend that the transplant program use the best available method to assess GFR in donor candidates, recognizing that at many centers, more than one method may be available. The accuracy of various methods for measuring and estimating GFR is not known with sufficient certainty to define specific threshold for each method.

The KDIGO 2012 CKD guidelines for GFR evaluation in the general population recommend expressing kidney function as GFR and not as serum creatinine concentration, and recommend expressing GFR in mL/min per 1.73 m^2 rather than mL/min .¹²⁴ The guidelines recommend 2-stage testing (initial testing followed by confirmatory testing as necessary). The WG concluded that these general recommendations were applicable to living kidney donor candidates.

The eGFR based on serum creatinine (eGFR_{cr}) is the recommended initial test. Serum creatinine assays should be traceable to the international reference standard. In North America, Europe, and Australia, the 2009 CKD CKD-EPI creatinine equation should be used unless other equations have been shown to be more accurate. eGFR_{cr} using the 2009 CKD-EPI creatinine equation has minimal bias at normal GFR; however, it is imprecise (Figure 5), thus it is most useful for an initial evaluation.¹²⁸ In regions other than North America, Europe, and Australia, the 2009 CKD-EPI creatinine equation is less accurate. In these regions, other equations are recommended if they are more accurate than the 2009 CKD-EPI creatinine equation.

GFR estimating equations are developed using regression methodologies to relate the mGFR to steady state serum creatinine concentration and a combination of demographic and clinical variables as surrogates of the non-GFR determinants of serum creatinine. By definition, GFR estimates using serum creatinine concentration are more accurate in estimating mGFR than the serum creatinine concentration alone in the study population in which they were developed. Sources of error in GFR estimation from serum creatinine concentration include nonsteady-state conditions, non-GFR determinants of serum creatinine, measurement error at higher GFR, and interferences with the creatinine assays (Table 12). GFR estimates are less precise at higher GFR levels than at lower levels. The clinician should remain aware of caveats for any creatinine-based estimating equation which may influence the accuracy in a given individual.

A variety of confirmatory tests for GFR are available. In the general population, the 2012 KDIGO guideline suggests confirmation of GFR with either GFR estimation using cystatin C or a clearance measurement in specific circumstances when eGFR based on serum creatinine is less accurate (Box 1, 2012 CKD Recommendation 1.4.3.2). KDIGO further

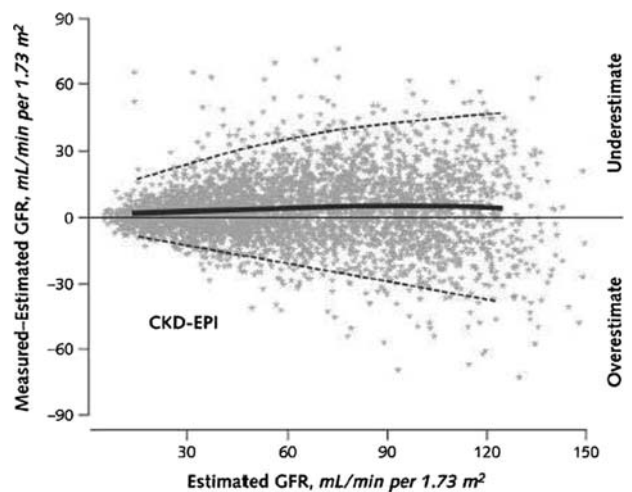


FIGURE 5. Performance of the CKD-EPI equation in estimating measured GFR. The figure shows the difference between measured and estimated GFR (bias) versus estimated GFR in an external validation dataset ($N = 3896$). A smoothed regression line is shown with the 95% CI. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate. Copyright © 2009 American College of Physicians and reprinted with permission from Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.¹²⁸

TABLE 12.**Sources of error in GFR estimation using creatinine**

| Source of error | Example |
|---|---|
| Non-steady state | AKI |
| Non-GFR determinants of SCr that differ from study populations in which equations were developed | Race/ethnicity other than United States and European black and white |
| <ul style="list-style-type: none"> • Factors affecting creatinine generation | Extremes of muscle mass |
| | Extremes of body size |
| | Diet and nutritional status |
| | <ul style="list-style-type: none"> • High protein diet • Creatinine supplements |
| | Muscle wasting diseases |
| | Ingestion of cooked meat |
| <ul style="list-style-type: none"> • Factors affecting tubular secretion of creatinine | Decrease by drug-induced inhibition |
| | <ul style="list-style-type: none"> • Trimethoprim • Cimetidine • Fenofibrate |
| <ul style="list-style-type: none"> • Factors affecting extra-renal elimination of creatinine | Dialysis |
| | Decrease by inhibition of gut creatininase by antibiotics |
| | Increased by large volume losses of extracellular fluid |
| Higher GFR | Higher biological variability in non-GFR determinants relative to GFR |
| | <ul style="list-style-type: none"> • Higher measurement error in SCr and GFR |
| Interference with creatinine assay | Spectral interferences (eg, bilirubin, some drugs) |
| | Chemical interferences (eg, glucose, ketones, bilirubin, some drugs) |

AKI, acute kidney injury; GFR, glomerular filtration rate; SCr, serum creatinine.

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;1–150.¹²⁴

suggests measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions (Box 1, 2012 CKD Recommendation 1.4.3.8), including the evaluation of living organ donors). Based on these recommendations, the WG concluded that confirmation of GFR using the most accurate method available at the transplant center. In the United States, OPTN policy requires a clearance measurement (measured creatinine clearance [mCrCl] or mGFR) for confirmation of GFR.

Many methods for mGFR determination using exogenous filtration markers and clearance calculations are available, with variable accuracy. Recommendations for specific methods are based on a recent systematic review.¹²⁹ mGFR is not available at all centers, so other alternatives are acceptable. mCrCl is less accurate than mGFR,¹²⁹ but it is acceptable if mGFR is not available. mCrCl overestimates mGFR due to creatinine secretion.¹³⁰ The magnitude of overestimation is 15% or more at normal GFR, based on older data using nonstandardized serum creatinine assays. The magnitude of overestimation may be higher using standardized assays. In principle, mCrCl is available worldwide, however, in some donor candidates, mCrCl may not be available due to logistical difficulties in collecting or transporting a timed urine collection.

A recent study suggests that eGFR may be sufficiently accurate for decision-making without the need for mGFR in many cases.⁸ A web-based calculator is available to compute posttest probabilities for mGFR above or below threshold probabilities for decision-making: <http://ckdepi.org/equations/donor-candidate-gfr-calculator/>. Post-test probabilities are computed from pretest probabilities for mGFR and test

performance for eGFR using serum creatinine (eGFR_{cr}) or the combination of creatinine and cystatin C (eGFR_{cr-cys}). Very high posttest probabilities provide reassurance that mGFR is above the threshold level for decision-making, while very low posttest probabilities provide reassurance that mGFR is below the threshold levels for decision-making. Transplant programs can determine what posttest probabilities are sufficient for clinical decision-making in the absence of mGFR and mCrCl. One study validating these computations in donor candidates has been reported.¹³¹ Future studies should address prediction accuracy among racial and ethnic groups for whom the accuracy of eGFR is less certain (eg, nonblack, nonwhite persons).

In general eGFR_{cys} is not more accurate than eGFR_{cr}; however using 2 filtration markers improves precision of GFR estimates compared with using either marker alone; thus eGFR_{cr-cys} is generally recommended over eGFR_{cr} or eGFR_{cys}.^{132,133} Advantages of cystatin C compared with creatinine are that cystatin C is not affected by muscle mass and current equations do not require specification of race. Therefore, eGFR_{cys} maybe more accurate than eGFR_{cr-cys} in people with very large or very small muscle mass, very high or very low meat intake, or race-ethnicity other than black (African American or African European) or white. If cystatin C is measured, cystatin C assays should be traceable to international reference standard (which is in the early stages of implementation) and the 2012 CKD-EPI eGFR_{cys} equation or eGFR_{cr-cys} equation should be used unless other equations have been shown to be more accurate. If cystatin C is not available, eGFR_{cr} can be used for decision-making. As with creatinine, sources of error in GFR estimation from serum cystatin C concentration include non-steady-state conditions, nonGFR determinants of serum cystatin C, measurement

TABLE 13.
Sources of error in GFR estimation using cystatin C

| Source of error | Example |
|--|--|
| Non-steady state | AKI |
| Non-GFR determinants of SCysC that differ from study populations in which equations were developed | Race/ethnicity other than United States and European black and white Disorders of thyroid function Administration of corticosteroids Other hypothesized factors based on epidemiologic associations (diabetes, adiposity) |
| <ul style="list-style-type: none"> • Factors affecting cystatin C generation • Factors affecting tubular reabsorption of cystatin C • Factors affecting extra-renal elimination of cystatin C | None identified Increased by severe decrease in GFR |
| Higher GFR | Higher biological variability in non-GFR determinants relative to GFR Higher measurement error in SCysC and GFR |
| Interference with cystatin C assay | Heterophilic antibodies |

AKI, acute kidney injury; GFR, glomerular filtration rate; SCysC, serum cystatin C.

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;1–150.¹²⁴

error at higher GFR, and interferences with the cystatin C assays (Table 13).

Single (“divided” or “split”) kidney GFR can be assessed by radionuclide imaging, but is not required in all kidney donor candidates. However, all kidney donor candidates undergo kidney imaging to detect parenchymal, vascular or urologic abnormalities, and asymmetry in kidney size suggests asymmetry in kidney function.

Selection: Criteria for Acceptable Predonation GFR

GFR in the General Population

GFR in young men and women of 90 mL/min per 1.73 m² or greater is generally considered normal.¹²⁴ GFR between 60 and 89 mL/min per 1.73 m² is considered to be decreased

compared with the usual level for young adults, but does not meet the KDIGO criterion for CKD.

GFR declines with age, although the cause of decline is not known and the rate of decline appears widely variable. Most data are based on cross-sectional studies, in which mean GFR is lower in older populations than in young populations. Other kidney functions are also lower in older populations (eg, renal plasma flow, maximal urinary concentration) and kidney structure is altered in older populations (eg, cortical atrophy, global glomerulosclerosis, nephrosclerosis). There is debate about whether abnormalities in kidney function and structure in older people represents normal aging or disease.

Decreased GFR in the general population is associated with a higher risk of complications of CKD, including ESKD,

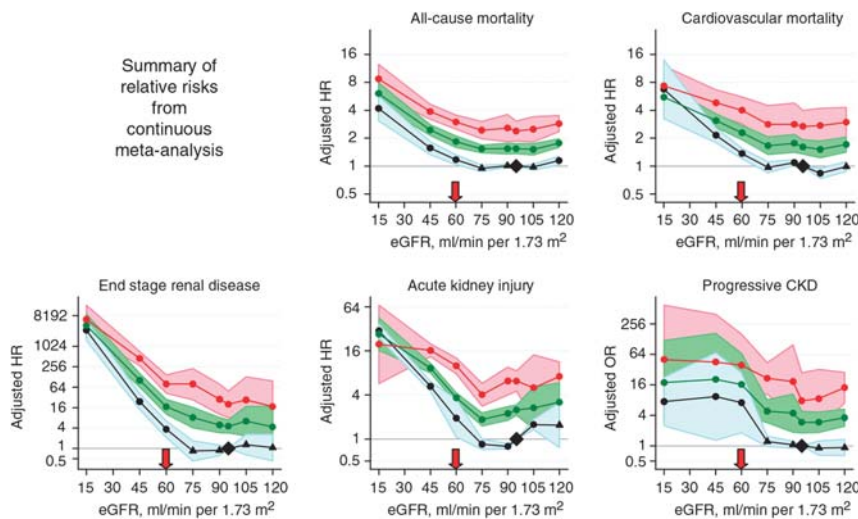


FIGURE 6. Complications of CKD according to baseline eGFR and albuminuria. The data above were derived using creatinine-based eGFR (eGFR_{cr}) estimated with the MDRD Study equation.¹³⁵ Comparable data are not available for mGFR. However, studies using more accurate GFR estimates confirm these results. For the outcomes of ESKD, all-cause mortality and cardiovascular mortality, any given reduced level of eGFR is associated with a greater increase in the risk of these outcomes if the 2009 CKD-EPI equation is used to estimate eGFR_{cr}.¹³⁶ The increase in risk is even greater if cystatin C is used to estimate GFR, either with or without creatinine (eGFR_{cr-cys} or eGFR_{cys}), compared with eGFR_{cr}.¹³⁷ The 3 lines represent severe, moderate, and normal/mild albuminuria (top to bottom, respectively). CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate. MDRD, Modification of Diet in Renal Disease. Reprinted with permission from Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17-28.¹³⁵

cardiovascular disease (CVD) and death. In general populations, compared with a reference eGFR of 95 mL/min per 1.73 m², the RR for complications related to decreased eGFR is apparent between 60 and 75 mL/min per 1.73 m² and is exponentially higher at lower eGFR.¹³⁴ Similar relationships of lower eGFR with adverse outcomes have been observed in subgroups including patients with known CKD (Figure 6).¹³⁴⁻¹³⁷ KDIGO 2012 guideline defines GFR less than 60 mL/min per 1.73 m² for 3 months or more as satisfying the criteria for CKD. GFR 15 to 30 mL/min per 1.73 m² is defined as severely reduced, and GFR less than 15 mL/min per 1.73 m² is defined as kidney failure. However, the association of lower eGFR with a higher risk of adverse outcomes may be related to other conditions that co-occur with low GFR, such as hypertension, diabetes and CVD. Lower GFR in older people is associated with increased risk for CKD outcomes, including ESKD, CVD and death. The RR for these outcomes in older people with lower eGFR compared with the reference eGFR is less than the RR in younger people, however the increment in absolute risk is higher in older people than in younger people.¹³⁸

A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 general population cohorts who are similar to kidney donor candidates found that lower GFR (in the absence of donation) is associated with an increased risk for ESKD over median cohort follow-up of 4 to 16 years.⁷ After calibration to annual ESKD incidence in the US healthy population, variations in the projected 15-year and lifetime risks of ESKD based on level of eGFR were generated according to age, sex, and race for healthy persons (assuming systolic BP (SBP) 120 mm Hg, urine albumin-to-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus) (Figures 7

and 8). This analysis demonstrates that lower eGFR is associated with increased lifetime risk for ESKD in all demographic subgroups. For eGFR of 90 mL/min per 1.73 m² or greater and other optimal characteristics (see above), lifetime risk for white men and white women was less than 1% at all ages, but was higher among young black men and women (Figure 8). Lifetime risk for eGFR 60 to 89 mL/min per 1.73 m² was less than 1% at ages older than 60 years. While these displays are useful for visualizing the impact of baseline eGFR on ESKD risk, we endorse consideration of eGFR as part of the assessment of predicted long-term ESKD risk based on a donor candidate's complete demographic and health profile (as opposed to consideration of single risk factors in isolation).

GFR after Kidney Donation

GFR declines after kidney donation. A person with a predonation GFR of at least 90 mL/min per 1.73 m² would be expected to have a 1-year postdonation GFR of at least 60 mL/min per 1.73 m². In general, a donor immediately loses approximately 50% of renal mass, but there is rapid compensatory hyperfiltration leading to a net reduction in GFR of approximately 30% (25% to 40%) after donation (decrement in GFR of 25 to 40 mL/min per 1.73 m²).¹³⁹⁻¹⁴¹

In prior guidelines a GFR level of 80 mL/min is frequently cited as the minimal threshold for an acceptable level of kidney function for donation.^{38,142} Limited data show a higher risk for lower GFR after donation among kidney donors with lower predonation GFR.³ (Evidence Report Table 16, SDC, <http://links.lww.com/TP/B434>, and Supplemental Appendix Table D13, SDC, <http://links.lww.com/TP/B432>).

There is theoretical justification for concern about development of kidney disease after nephrectomy. In experimental animals, hemodynamic alterations associated with

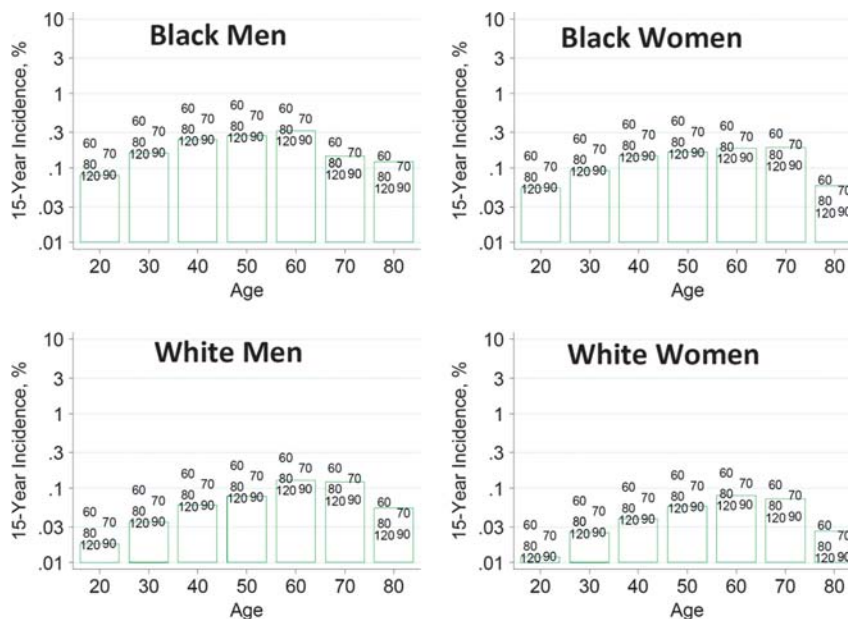


FIGURE 7. Estimated 15-year incidence (%) of ESKD in the United States according to baseline eGFR and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

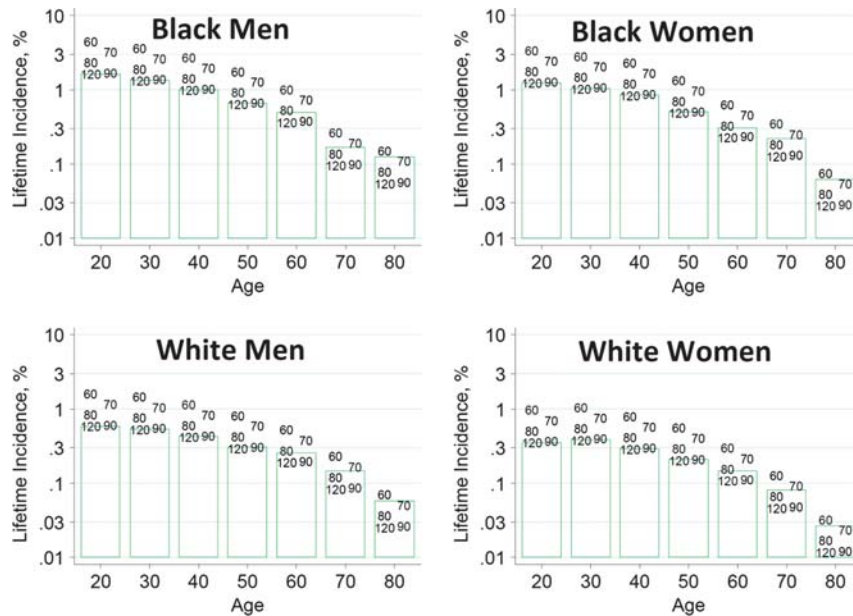


FIGURE 8. Estimated lifetime incidence (%) of ESKD in the United States according to baseline eGFR and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

hyperfiltration after reduction in renal mass are followed by development of structural and functional abnormalities associated with kidney disease. In general, the severity of reduction in renal mass is directly associated with the rate of development of subsequent kidney disease. A recent study in humans documents similar hemodynamic alterations associated with hyperfiltration after kidney donation.^{143,144}

The risk of ESKD after kidney donation does not exceed ESKD risk in the general population.^{140,145,146} An analysis of living kidney donors in the United States between 1994 and 2003 quantified a postdonation ESKD rate of 0.134 per 1000 person-years over an average follow-up of 9.8 years, which was not higher than the ESKD rate in the general population, even though GFR is lower.¹⁴⁷ However, the general population is a limited comparison group given that donors undergo careful medical evaluation and selection.⁴ The ERT identified 2 recent studies suggesting that donation is associated with an increase in the risk of ESKD compared to risk in nondonors selected for baseline good health, although the risk increase is small and the absolute postdonation risk remains low (Supplemental Appendix Table D5, SDC, <http://links.lww.com/TP/B432>). The quality of this evidence was rated as moderate. In comparing 1901 kidney donors with 32 621 healthy, demographically matched controls, Mjølven et al reported that 0.47% of donors (n=9) developed ESKD versus 0.07% of healthy nondonors (n=22) over a median 15.2-year follow-up.³² Based on linking 96 217 donors from the US donor registry and healthy participants drawn from the National Health and Nutrition Examination Survey III to national ESKD reporting forms, Muzzale et al estimated that the cumulative incidence of ESKD at 15 years was 30.8 per 10 000 in donors compared with 3.9 per 10 000 in

matched donors (risk attributable to donation of 26.9 per 10 000).³⁰ In this study, the incidence of ESKD was higher in individuals who are older versus younger at the time of donation, in men versus women, in blacks versus whites, and in biologically related versus unrelated donors, but risk based on predonation eGFR was not reported. Based on these findings, the likelihood of a small increase in ESKD risk should be discussed with donor candidates; such counseling is endorsed by a 2015 AST *Live Donor Community of Practice* consensus statement,¹⁴⁸ and is required in the US by the OPTN Informed Consent Policy beginning in 2017.⁵¹

Single Kidney GFR

Many factors determine the preferred kidney to remove for transplantation. If GFR is acceptable, but there are parenchymal, vascular or urological abnormalities or asymmetry in kidney function, it is preferable to transplant the more severely affected kidney or the kidney with lesser function (see also chapter 16).

On average, kidney function and size are correlated. The average length and volume of a single kidney in healthy adults are approximately 11 cm and 150 mL, respectively, but vary based on age, sex, and body size.¹⁴⁹⁻¹⁵¹ On average the normal right kidney is approximately 5% smaller than the normal left kidney. Asymmetry in kidney size is generally considered as a difference in kidney size greater than 10% (for example, a difference in kidney length > 1.1 cm or kidney volume > 15 mL). An equivalent difference in kidney function would be greater than 10% (>55% vs <45% in split kidney function). Based on low quality evidence, 1 prior guideline suggested considering a radionuclide imaging study if the difference between kidney lengths is greater

than 2 cm, and that a difference in function of 10% or greater between the kidneys may be considered significant.⁴⁸ No studies were found meeting criteria for review by the ERT.

What Prior Guidelines Recommend

Some guidelines recommend that GFR of 80 mL/min or greater is acceptable for donation, based on the level of GFR in the donor (not adjusted for BSA) that was associated with acceptable outcomes in the recipient, not the donor.¹⁵² Alternatively, some guidelines recommend a GFR level within 2 standard deviations of normal for age and sex. In general, the guidelines do not specify the GFR measurement method to be used, whether the threshold value should be adjusted for BSA, or provide standardized reference values based on sex, race, and age.¹⁵³

A 2007 survey of practices by transplant programs in the United States revealed that approximately 90% of programs used mCrCl to measure kidney function, while the other 10% of programs used the clearance of an exogenous filtration marker, and that approximately 67% of transplant programs used a threshold of 80 mL/min or more to accept donors, while 25% used a threshold based on age and sex.¹⁵⁴

In our view, there is not sufficient evidence to justify a single threshold value of 80 mL/min not adjusted for BSA, nor age-specific thresholds. In contrast, our recommendations are more consistent with accepted measurement methods and thresholds in general clinical practice, and acknowledge that there is variation in GFR measurement methods and uncertainty in the appropriate threshold to accept or decline donor candidates. For this reason, we recommend GFR measurement by urinary or plasma clearance of specific exogenous filtration markers, which are known to be more accurate than mCrCl, but allow other methods. We recommend a higher threshold value of GFR (≥ 90 mL/min per 1.73 m^2) to routinely accept a donor candidate, and lower threshold value of GFR (< 60 mL/min per 1.73 m^2) to routinely decline a donor candidate, and a wide intermediate range of GFR (60-89 mL/min per 1.73 m^2) in which transplant programs can individualize decisions based on other risk factors. Of note, this intermediate range would generally include a mCrCl of 80 mL/min as well as previously recommended age and sex thresholds for mGFR.

RESEARCH RECOMMENDATIONS

- Evaluate the accuracy of $e\text{GFR}_{\text{cr}}$, $e\text{GFR}_{\text{cys}}$ and $e\text{GFR}_{\text{cr-cys}}$ for the prediction of mGFR in the evaluation and selection of living donor candidates.
- Evaluate long-term risks, including lifetime risk of ESKD, in living donor candidates and living donors according to predonation GFR.

CHAPTER 6: PREDONATION ALBUMINURIA

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 6 and therefore the following recommendations are “Not Graded.” Some of the recommendations extrapolated from the 2012 KDIGO CKD Guideline¹²⁴ were not part of the ERT review for this guideline and as such they are also “Not Graded.”

Evaluation

- 6.1: Donor proteinuria should be measured as albuminuria, not total urine protein.
- 6.2: Initial evaluation of donor albuminuria (screening) should be performed using urine albumin-to-creatinine ratio (ACR) in a random (untimed) urine specimen.
- 6.3: Donor albuminuria should be confirmed using:
 - Albumin excretion rate (AER, mg/day [mg/d]) in a timed urine specimen
 - Repeat ACR if AER cannot be obtained.

Selection

- 6.4: Urine AER less than 30 mg/d should be considered an acceptable level for donation.
- 6.5: The decision to approve donor candidates with AER 30 to 100 mg/d should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 6.6: Donor candidates with urine AER greater than 100 mg/d should not donate.

RATIONALE

Evaluation

The goals of the evaluation of albuminuria in living donor candidates are to:

- Provide an accurate assessment of the amount of albuminuria and long-term risk of ESKD based on albuminuria and other factors.
- Exclude donor candidates whose postdonation risk is expected to exceed the acceptable risk threshold for ESKD established by the transplant program.
- Provide counseling regarding level of risk for donor candidates whose long-term risk for ESKD is expected to be below the acceptable risk threshold established by the transplant program.
- Provide counseling regarding follow-up of albuminuria after donation.

In this section, recommendations are based on physiological principles and recommendations for general clinical practice from the 2012 KDIGO CKD guideline.¹²⁴ There is no evidence to suggest or a reason to think that kidney donors differ from the general population regarding these recommendations.

Proteinuria as a Marker of Kidney Damage

Urine protein is composed of small amounts of high molecular weight proteins (principally albumin) that are not normally filtered, low molecular weight serum proteins that are normally filtered by the glomeruli and reabsorbed by the tubules, and proteins secreted by the urinary tract.

Increased urinary protein is generally considered a marker of kidney damage: albuminuria reflects increased permeability of the glomeruli (glomerular proteinuria), and low molecular weight proteinuria reflects decreased tubular reabsorption (tubular proteinuria). CKD due to either glomerular or tubulointerstitial diseases is generally associated with both glomerular and tubular proteinuria (albuminuria and low molecular weight proteinuria). Some tubulointerstitial diseases may cause predominantly tubular proteinuria, including Dent disease, toxicity due to heavy metals (eg, cadmium and lead) or aristolochic acid (Balkan and Chinese herb) nephropathy, Sjogren syndrome, multiple myeloma or hereditary diseases

associated with Fanconi syndrome, and acute tubular necrosis. Conditions other than kidney disease can also cause proteinuria: low molecular weight proteinuria may also reflect overproduction (eg, light chain proteinuria in lymphoproliferative disorders) and high and low molecular weight proteins may arise from increased secretion of urinary tract proteins (due to lower urinary tract diseases).

Urine albumin is the preferred measure of urine protein for assessment of kidney damage. Tests for total urine protein cannot be standardized because they are not traceable to a standard reference material due to the varying composition of urine protein. Current efforts to standardize albuminuria assessment are directed to establishing traceability of tests for urine albumin to standardized reference material for serum albumin. Other urine proteins are less well standardized than albumin.

The albumin loss rate (hereafter referred to as albumin excretion rate, AER) is not regulated in health and is widely accepted as a marker of kidney damage. Increased AER is associated with a wide range of complications and increased AER is one of the criteria for the definition of CKD. In diabetic kidney disease and other glomerular diseases, increased AER generally occurs before the decline in GFR.

Measurement Methods

The KDIGO 2012 CKD guideline for the evaluation of albuminuria in the general population recommends 2-stage testing (initial testing followed by confirmatory testing).¹²⁴ The current living donor guideline WG concluded that these general recommendations were applicable to kidney donor candidates.

Initial tests, in order of preference, and the rationale are described below. In all cases an early morning urine sample is preferred as it minimizes variation due to diurnal variation in albumin excretion and urine concentration.

Urine Albumin-to-Creatinine Ratio (ACR)

The rationale for preferring ACR to albumin concentration is that urine concentration and dilution can vary by more than

10-fold among individuals and during the day. The KDIGO CKD guideline therefore recommends that clinical laboratories measure creatinine when albumin is requested, and express the results as ACR in addition to albumin concentration. Indexing urine albumin by urine creatinine concentration overcomes variation due to urine concentration and dilution, but introduces variation by creatinine generation.

Recently, some investigators have proposed estimating creatinine excretion rate and multiplying this quantity by ACR to estimate AER.¹⁵⁵ The lower limit of detection for urine albumin in the clinical laboratory where the test is performed can be used for computation of urine ACR if the clinical laboratory reports “below the detectable limit.” Factors affecting urine ACR in addition to kidney disease are shown in Table 14.

One study reported excellent performance of ACR to detect AER of 30 mg/d. The area under the receiver operator curve was 0.93.¹⁵⁶ An ACR threshold of ≥ 10 mg/g was associated with sensitivity and specificity of 88% each for detecting AER ≥ 30 mg/d. There was minor variation in area under the receiver operator curve based on age, sex, race, and body weight.

Urine Protein-to-Creatinine Ratio (PCR)

Tests for total urine protein cannot substitute for tests for urine albumin. PCR is less sensitive than ACR, so even negative tests must be confirmed by tests for albumin. Increased PCR suggests increased ACR, but nonalbumin protein can cause a positive test, so positive tests should be confirmed by tests for albumin. Patients with elevated PCR and negative tests for albumin may have tubular proteinuria, light chain proteinuria or urinary tract disease. Specific assays are available for $\alpha 1$ -microglobulin, $\beta 2$ microglobulin, monoclonal heavy or light chains.

Reagent Strip Urinalysis for Total Protein with Automated Reading

Reagent strips allow point-of-care, semi-quantitative assessment of total urine protein concentration. Reagent strips

TABLE 14.
Factors affecting urinary ACR

| Factor | Examples of effect |
|--|---|
| Preanalytical factors | |
| • Transient elevation in albuminuria | Menstrual blood contamination Symptomatic UTI Exercise Upright posture (orthostatic proteinuria) Other conditions increasing vascular permeability (eg, septicemia) |
| • Intraindividual variability | Intrinsic biological variability Genetic variability |
| • Preanalytical storage conditions | Degradation of albumin before analysis |
| • Nonrenal causes of variability in creatinine excretion | Age (lower in children and older people) Race (lower in white than black people) Muscle mass (eg, lower in people with amputations, paraplegia, muscular dystrophy) Gender (lower in women) Non-steady state for creatinine (AKI) |
| • Changes in creatinine excretion | |
| Analytical factors | |
| • Antigen excess (“prozone”) effect | Samples with very high albumin concentrations may be falsely reported as low or normal using some assays |

ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; UTI, urinary tract infection.

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;1–150.¹²⁴

(“dipsticks”) are more sensitive to albumin than other proteins, but lack specificity. Automated readers are more accurate than manual reading of reagent strips.

Reagent Strip Urinalysis for Total Protein with Manual Reading, if the Above Measures are not Available

Because of variability in urine ACR and its relationship to urine AER, the WG recommends confirmation in all cases. The preferred confirmatory test is urine AER, expressed as mg/d. If urine AER is not available, a repeat ACR is acceptable. Consistent with the 2012 KDIGO CKD guideline, testing for specific urine proteins such as α 1-microglobulin, β 2 microglobulin, monoclonal heavy or light chains (also known as “Bence Jones” proteins) can be undertaken if significant nonalbumin proteinuria is suspected. These assays can be performed at the same time as tests for albuminuria.

Selection: Criteria for Acceptable Predonation Albuminuria

AER in the General Population

The normal level of AER in healthy young men and women is less than 10 mg/d. The coefficient of variation for repeated measurements is approximately 30%.¹⁵⁷ Because of the high coefficient of variation, repeated measurements are preferred for assessment of albuminuria.

AER rises with age, although the cause of rise is not known and the rate of rise appears widely variable. Most data are based on cross-sectional studies and mean AER is higher in older populations than in young populations. As discussed in chapter 5, there are often abnormalities in kidney function and structure in the elderly and there is debate about whether higher AER in older people represents normal aging or disease.

Higher albuminuria in the general population is associated with a higher risk of complications of CKD, including ESKD, CVD and death. In general populations, compared with a reference ACR of 5 mg/g (0.5 mg/mmol), the RR for complications related to increased ACR rises at higher ACR, without an apparent threshold when expressed on the log scale.¹³⁴ The risk of higher ACR is independent of the eGFR. Similar

relationships of high albuminuria with adverse outcomes have been observed in subgroups including patients with known CKD (Figure 6).¹³⁴⁻¹³⁷ KDIGO 2012 CKD guideline defines AER >30 mg/d for 3 months or more as satisfying the criteria for CKD. AER less than 30 mg/d in young men and women is considered normal to mildly increased, with 10 to 29 mg/d considered as “high normal”; AER 30 to 300 mg/d is defined as moderately increased compared with the young adult level; and AER greater than 300 mg/d is defined as severely increased compared with the young adult level. Approximate ranges for other measures of urine protein are as shown in Table 15. The association of higher albuminuria with higher risk of adverse outcomes may be related to other conditions that co-occur with high albuminuria, such as hypertension, diabetes and CVD. The RR for these adverse CKD outcomes (ESKD, CVD, death) in older people with higher urine ACR compared with the reference urine ACR is less than the RR in younger people; however the increment in absolute risk in older people is higher in older people than in younger people.¹³⁸

A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 general population cohorts found that each 10-fold increase in urinary ACR was associated with 3 times the risk of ESKD over median cohort follow-up of 4 to 16 years, although the finding was not statistically significant (95% Lower Confidence Limit adjusted hazard ratio [aHR] 95% Upper Confidence Limit; 0.992, 94.8, 75).⁷ After calibration to annual ESKD incidence in the US healthy population, variations in the projected 15-year and lifetime risks of ESKD based on urine ACR were generated according to age, sex, and race for healthy persons (assuming age-specific eGFR, SBP 120 mm Hg, BMI 26 kg/m², and absence of diabetes mellitus; Figures 9 and 10). This analysis demonstrates that higher albuminuria is associated with higher lifetime risk of ESKD in all subgroups, with higher risk in men than women and blacks than whites. For urine ACR less than 10 mg/g and other optimal risk factors (see above), lifetime risk for white men and white women was less than 1% at all ages, but exceeded 2% for black men younger than 40 (Figure 10). For urine ACR less than 30 mg/g, the lifetime

TABLE 15.
Relationship among categories for albuminuria and proteinuria

| Measure | Categories | | |
|-----------------------|---------------------------------|---------------------------|-------------------------|
| | Normal to mildly increased (A1) | Moderately increased (A2) | Severely increased (A3) |
| AER (mg/24 h) | <30 | 30-300 | >300 |
| PER (mg/24 h) | <150 | 150-500 | >500 |
| ACR | | | |
| (mg/mmol) | <3 | 3-30 | >30 |
| (mg/g) | <30 | 30-300 | >300 |
| PCR | | | |
| (mg/mmol) | <15 | 15-50 | >50 |
| (mg/g) | <150 | 150-500 | >500 |
| Protein reagent strip | Negative to trace | Trace to + | + or greater |

Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore the relationship among these categories is approximate only. ACR less than 10 mg/g (<1 mg/mmol) is considered normal; ACR 10 to 30 mg/g (1-3 mg/mmol) is considered “high normal.” ACR greater than 2200 mg/g (>220 mg/mmol) is considered “nephrotic range.” The relationship between urine reagent strip results and other measures depends on urine concentration. ACR, albumin-to-creatinine ratio; AER albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate. Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;1-150.¹²⁴

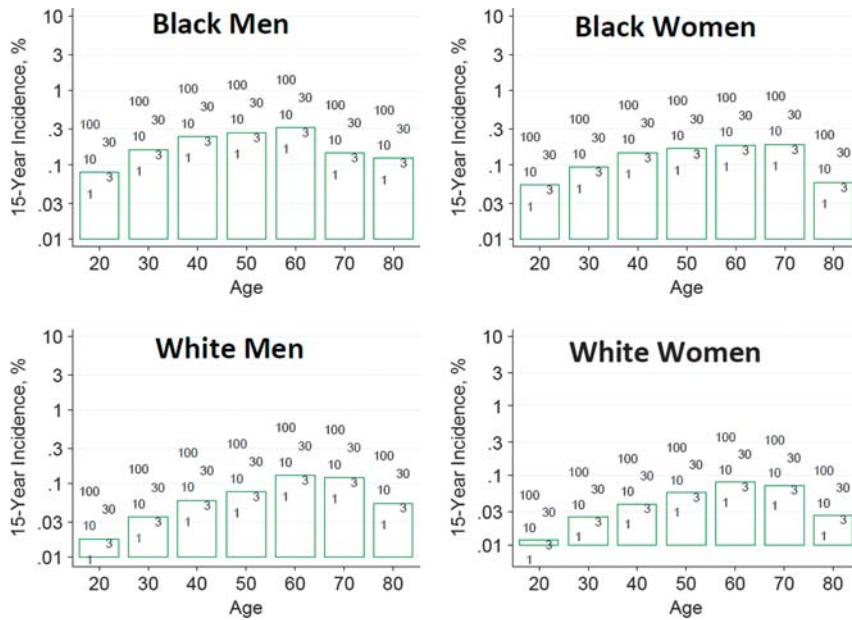


FIGURE 9. Estimated 15-year incidence (%) of ESKD in the United States according to baseline albumin-to-creatinine ratio (ACR, mg/g) and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

risk was less than 1% in white men at age >50 years, black men at age >70, and black women at age >60. While these displays are useful for visualizing the associations of baseline ACR with ESKD risk, we endorse consideration of ACR

as part of the assessment of predicted long-term ESKD risk based on a donor candidate’s complete demographic and health profile (as opposed to consideration of single risk factors in isolation).

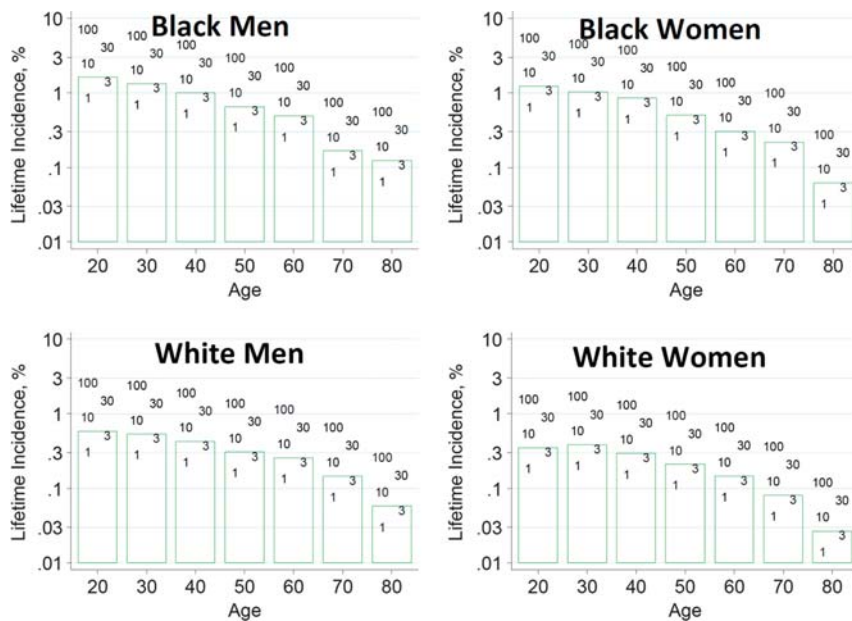


FIGURE 10. Estimated lifetime incidence (%) of ESKD in the United States according to baseline albumin-to-creatinine ratio (ACR, mg/g) and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

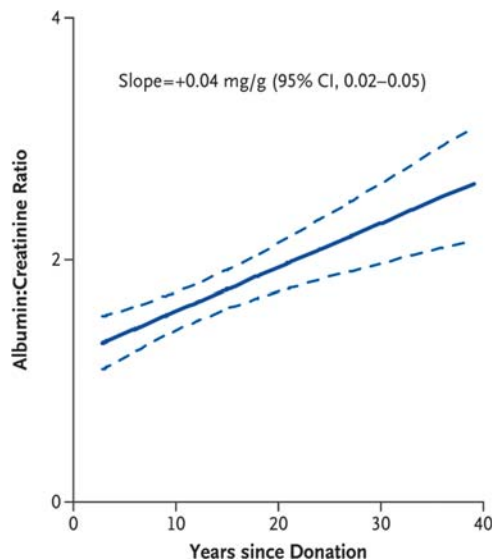


FIGURE 11. Proteinuria after kidney donation. Solid line, regression line; dotted line: 95% confidence interval. Reprinted with permission of the Massachusetts Medical Society from Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med.* 2009;360:459-469.¹⁴⁰

Proteinuria after Kidney Donation

Some but not all studies demonstrate donors have an increase in proteinuria compared with nondonor control groups (Figures 11 to 12).¹³⁹⁻¹⁴¹ In prior guidelines a protein excretion rate (PER) <150 mg/d was frequently cited as acceptable for donation.^{48,50,158,159} This level corresponds roughly to AER less than 30 mg/d, which includes normal and mildly increased (Table 15).¹²⁴ However, the risk associated with albuminuria in kidney donors is uncertain.

There is theoretical justification for concern about development of kidney disease after nephrectomy. First, in experimental animals, reduction in renal mass is associated with increased glomerular permeability to albumin followed by other structural and functional abnormalities associated with kidney disease. Second, given that GFR declines after kidney donation, the filtered load of albumin would be expected to decline. Unchanged or higher albuminuria after donation suggests increased albumin filtration per nephron.

In a prior systematic review, the incidence of clinical proteinuria after donation was quantified in 42 studies, that followed 4793 living donors for an average of 7 years (range, 2-25 years).¹⁴¹ There was significant heterogeneity between the studies ($P < 0.0001$). Some studies reported an incidence of proteinuria over 20%, whereas in others the incidence was less than 5%. The pooled incidence of proteinuria was 12% (95% CI, 8-16%). These results were similar in a supplementary analysis limited to 9 studies which consistently defined proteinuria as greater than 300 mg/d based on 24-hour urine. The pooled incidence of proteinuria among these 9 studies, which followed a total of 1799 donors for 7 years, was 10% (95% CI, 7-12%).

What Prior Guidelines Recommend

Some guidelines recommend that accepted living donor candidates have a PER less than 150 to 300 mg per day, based on the usually accepted normal range, generally without reference to measurement methods. A survey of practices by transplant programs in the United States reported in 2007

found that approximately 76% of programs used a PER in a 24-hour urine collection for donor evaluation, and that 36% used PER > 150 mg/d as a threshold for donor exclusion (unless proteinuria is postural), while 44% reported higher exclusion thresholds of 300-1000 mg/d.¹⁵⁴

By comparison, our recommendations are more consistent with the recently accepted criterion standard, measurement methods and thresholds in general clinical practice, but acknowledge that there is variation in ascertainment of albuminuria for screening and uncertainty in the appropriate threshold to accept or decline donor candidates. For these reasons, we recommend measurement of albumin rather than total protein, and AER in a timed urine collection rather than ACR in a spot urine specimen if possible. We recommend an AER threshold of less than 30 mg/d to routinely accept a donor candidate, which corresponds to normal to mildly increased. We recommend an intermediate range of AER 30 to 100 mg/d corresponding to the lower range for moderately increased AER, in which to individualize decisions based on other risk factors. We acknowledge that AER of 30 to 100 mg/d meets the criteria for CKD, and past recommendations have strived to exclude donor candidates with CKD. We have not excluded candidates solely on the basis of AER 30 to 100 mg/d because estimated projected predonation lifetime risk of ESKD in older persons with ACR in this range is very low in the absence of decreased GFR and other health risk factors.⁷ Thus, we concluded that universal exclusion would not be consistent with a Framework that would allow donation from other candidates with similar risk due to other clinical risk factors.

We do not require tests of total urine protein in addition to albumin because there are no accepted normal ranges for urine nonalbumin protein excretion; disorders associated with predominant tubular proteinuria (tubulointerstitial kidney disease) and overproduction proteinuria (plasma cell or B-lymphocyte disorders) are uncommon, and patients with these disorders usually have other clinical abnormalities that would be discovered during the donor evaluation.

RESEARCH RECOMMENDATIONS

- Assess the accuracy of urine ACR compared with AER for evaluation and selection of living donor candidates.
- Evaluate the association of urine albumin with other kidney measures (eg, GFR and kidney size) at the time of donor evaluation and with kidney measures and outcomes (eg, GFR change, ESKD, survival) after donation.

CHAPTER 7: PREDONATION HEMATURIA

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 7 and therefore the following recommendations are “Not Graded.”

Evaluation

- 7.1: Donor candidates should be assessed for microscopic hematuria.
- 7.2: Donor candidates with persistent microscopic hematuria should undergo testing to identify possible causes, which may include:
 - Urinalysis and urine culture to assess for infection

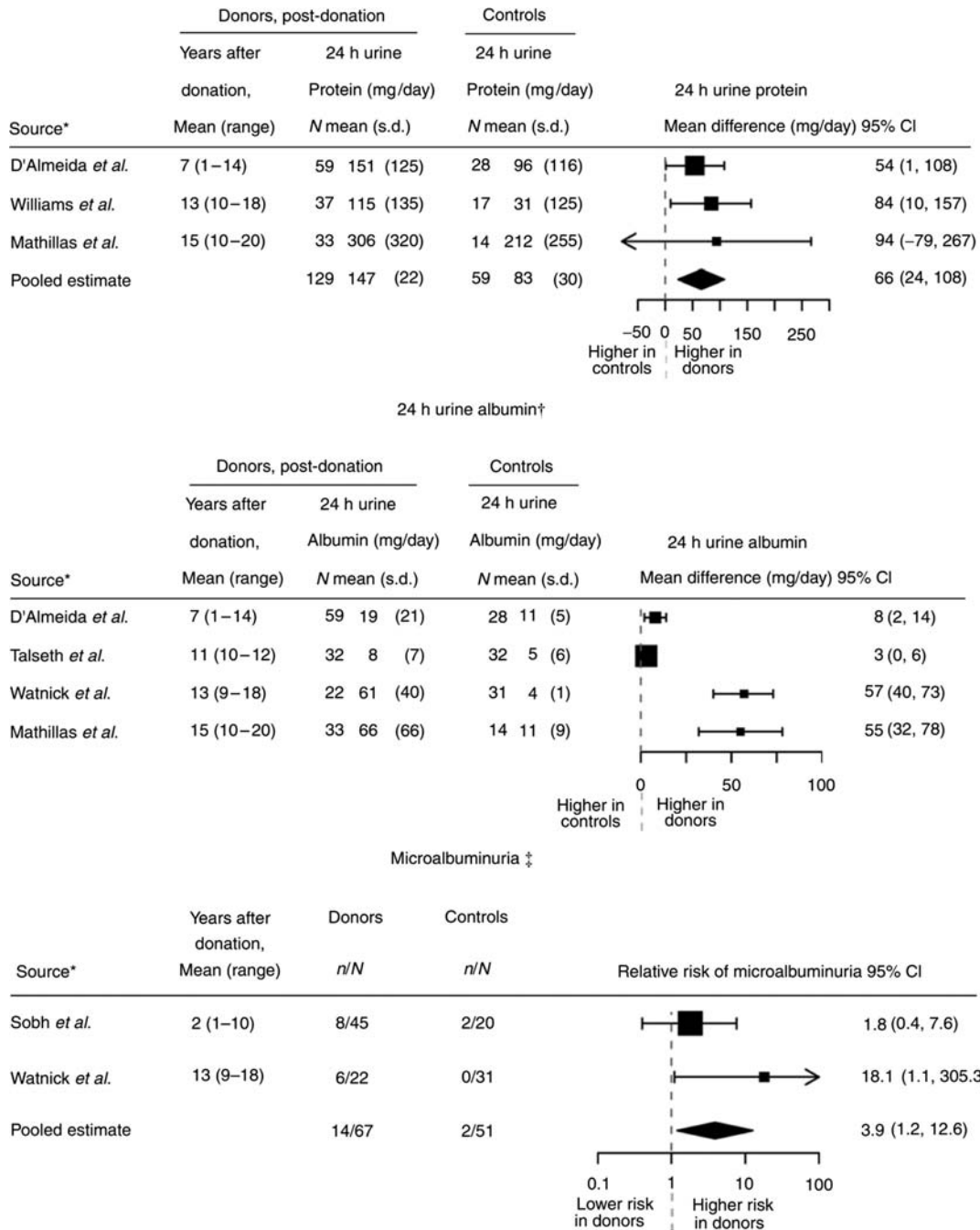


FIGURE 12. Meta-analysis of proteinuria after kidney donation. Controlled studies of proteinuria after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. ‡Microalbuminuria was assessed by 24-hour urine. †Mathematically pooled results are not presented graphically because of statistical heterogeneity between studies. CI, confidence interval. Reprinted with permission from Garg AX, Muirhead N, Knoll G, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. *Kidney Int.* 2006;70:1801-1810.¹⁴¹

- Cystoscopy and imaging to assess for urinary tract malignancy
- 24-hour urine stone panel to assess for nephrolithiasis and/or microlithiasis
- Kidney biopsy to assess for glomerular disease (eg, thin basement membrane nephropathy, IgA nephropathy, Alport syndrome)

Selection

7.3: Donor candidates with hematuria from a reversible cause that resolves (eg, a treated infection) may be acceptable for donation.

7.4: Donor candidates with IgA nephropathy should not donate.

RATIONALE

Evaluation and Definitions

Persistent microscopic hematuria is most often defined as 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.¹⁶⁰⁻¹⁶³ Consensus-based guidelines of the American Urological

Association state that while a positive dipstick reading warrants microscopic examination to confirm the diagnosis of asymptomatic microhematuria, a positive dipstick alone does not define microhematuria, and evaluation should be based solely on findings from microscopic examination of urinary sediment.¹⁶¹ Causes of a positive dipstick reading in the absence of red blood cells in the urine include hemoglobinuria, myoglobinuria, a dilute urine sample, or simply a false-positive test.

The estimated prevalence of microscopic hematuria varies widely from 0.18% to 16%.¹⁶⁰ A recent population study of 1.2 million persons aged 16 to 25 years in Israel identified prevalent asymptomatic persistent microscopic hematuria in 0.3% of individuals.¹⁶³ Persistent microscopic hematuria may be associated with urologic abnormalities (eg, stones, tumors) or glomerular disease. The most common glomerular causes of persistent isolated microscopic hematuria are IgA nephropathy, thin basement membrane nephropathy (TBMN) and Alport syndrome.¹⁶⁴⁻¹⁶⁷

There are consensus-based guidelines for the evaluation of asymptomatic microhematuria in the general population. For example, the 2012 recommendations from the American Urological Association¹⁶¹ include assessment of risk factors for urinary tract malignancies (eg, irritative voiding symptoms, current or past tobacco use, chemical exposures), radiological evaluation (eg, multiphasic computed tomography urography, without and with intravenous contrast, or magnetic resonance urography), and cystoscopy in patients age 35 years or older regardless of history of use of anticoagulation therapy. Urine cytology and urine biomarkers are not recommended as a part of the routine evaluation of asymptomatic microhematuria.

The presence of dysmorphic urinary red blood cells detected by conventional microscopy, phase-contrast microscopy, or

automated analyzer has a broad a range of sensitivities (32% to 100%) and specificities (from 33% to 100%) for glomerular causes of microhematuria.¹⁶¹ The presence of dysmorphic red blood cells or cellular urinary casts and other clinical information can be used to prioritize the evaluation for glomerular causes of hematuria. However, the presence of dysmorphic red blood cells does not exclude underlying urologic disease.¹⁶¹

Although isolated microscopic hematuria in young persons is often considered “benign,” a recent population-based study of 1.2 million Israeli persons aged 16 to 25 years with up to 35 years of follow-up identified small but significant increase in long-term renal risk associated with persistent asymptomatic isolated microscopic hematuria, with ESKD rates of 34.0 versus 2.05 per 100 000 person-years among those with versus without persistent microscopic hematuria (adjusted HR, 12.418.527.6).¹⁶³ While participants were required to have serum creatinine values “within the normal range” and 24-hour urine protein less than 200 mg, this study does not provide information on ESKD risk after comprehensive evaluation and selection including measured kidney function.

Selection

The sequence of the evaluation for microscopic hematuria, like other testing in this guideline, is designed to perform less invasive/expensive tests before more invasive/expensive tests, and only if the less invasive/expensive tests do not preclude donation (Figure 13).¹⁶⁸ Reversible causes of microscopic hematuria, for example, treatable urinary tract infection, should generally not preclude donation. In the absence of a family history suggesting possible TBMN or Alport disease, additional testing to rule out these causes is generally not

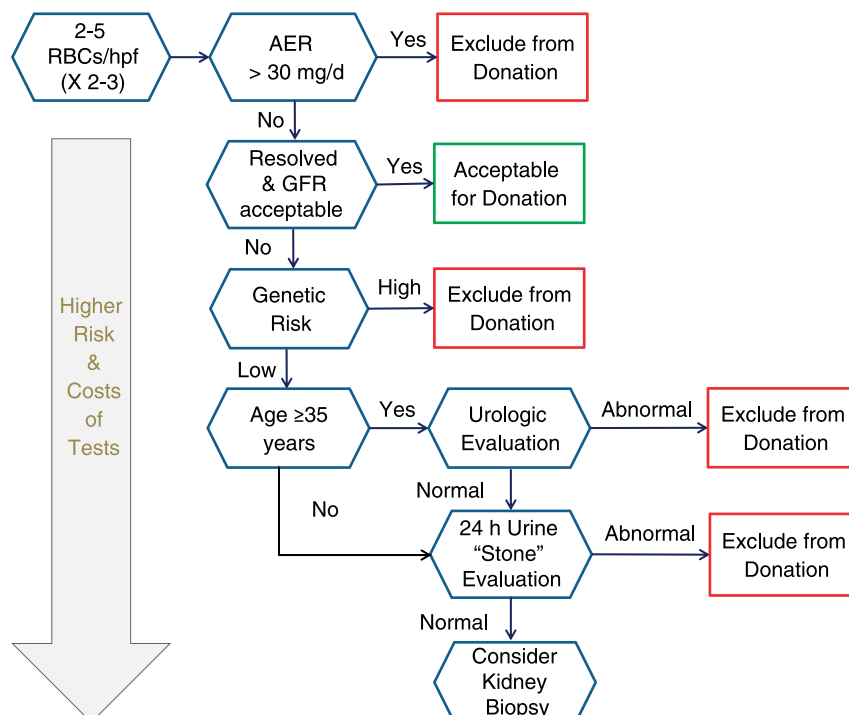


FIGURE 13. Sequential evaluation of microscopic hematuria in living kidney donor candidates. In general, lower risk and less expensive tests should be performed first, and at each step additional testing should only be performed if necessary. Boxes indicate stopping points in the donor candidate hematuria evaluation. AER, albumin excretion rate; GFR, glomerular filtration rate; hpf, high-power field; RBC, red blood cell.

necessary. Please refer to chapter 14 for a related discussion on genetic testing in the donor candidate.

Epidemiological studies of TBMN suggest increased risks of hypertension and proteinuria compared with the general population over time, but progression to ESKD is rare and thought to require an additional insult.¹⁶⁹ Data on outcomes of living kidney donor evaluation and donation in persons with TBMN are limited to small series with short-term follow-up.^{170,171} A series of 512 consecutive donors at a US center identified asymptomatic, microscopic hematuria for at least 1 month in 2.7% (n = 14). Hematuria resolved after treatment for urinary tract infection in 2. Kidney biopsy was performed in 10/12, and showed: TBMN (5/12); normal (2/12); nonhomogeneous basement membrane abnormalities (1/12); IgA nephropathy (1/12); and greater than 20% glomerulosclerosis in a patient with a family history of Schimke's syndrome (immune-osseous dysplasia). Two of the 4 with TBMN, aged 44 and 53 years, proceeded with donation; after 15 months follow-up, donors were free of hypertension, proteinuria, and recipients had "excellent" graft function.¹⁷⁰ A Korean series including 5 living donors with TBMN defined by predonation biopsy reported favorable short-term outcomes, including mean serum creatinine 0.94 ± 0.32 mg/dL (83 ± 28.3 μ mol/L) and no cases of new-onset hypertension or proteinuria over mean follow-up period of 34.7 ± 42.5 months.¹⁷¹

Notably, TBMN is often defined based on pathological description rather than as a distinct clinical entity. Carrier states for Alport mutations may present as TBMN. High rates of proteinuria (75%) and ESKD (8-30%) have been reported in female carriers of X-linked Alport syndrome mutations.¹⁷² A recent study identified adverse outcomes in 234 Alport carriers (including 29 autosomal recessive and 205 X-linked mutation carriers): ESKD developed in 17.5% at a median age of 49 years, and outcomes including ESKD, proteinuria and impaired kidney function were similar in X-linked and autosomal recessive carriers,¹⁷³ although the number of autosomal recessive carriers was small. Among 6 female Alport carriers (5 X-linked, 1 autosomal recessive) who donated to their children at several European centers and were followed for an average 6.7 years, 3 developed new-onset hypertension and 2 developed new-onset proteinuria.¹⁷⁴ Creatinine clearance remained greater than 40 mL/min in all donors after up to 14 years. Thus, while data are limited, female carriers of X-linked Alport syndrome (ie, *COL4A5* mutation) should be discouraged from kidney donation because of their own increased risk of hypertension and adverse kidney outcomes even in the absence of donation.

IgA nephropathy that presents with hematuria and minimal proteinuria is often a progressive disease.¹⁷⁵ In one series in Hong Kong, 72 consecutive patients with IgA nephropathy presenting as hematuria and minimal proteinuria (0.4 g/day or less) were followed for a median of 84 months; 33% developed proteinuria, 26% became hypertensive, and 7% developed impaired kidney function.¹⁷⁶ The presence of hematuria and glomerular IgA deposition is associated with increased risk of progressive kidney disease even in the absence of other clinical findings.¹⁷⁵ For this reason, there is broad consensus that people with known IgA nephropathy should not donate a kidney. Examination of a series of 510 implantation biopsies at a large center in Tokyo (including 446 living donors) found latent mesangial IgA

deposition to be relatively common in healthy Japanese living donors, present in 16.1% of living donor allograft biopsies.¹⁷⁷ Mesangial IgA deposition was associated with a mild degree of microhematuria, mesangial proliferation and glomerular macrophage infiltration in some of the affected individuals, especially with C3 deposition.

Persistent hematuria without defined renal histopathology has been associated with proteinuria after kidney donation. In a series of 242 living kidney donors at one center in Japan, persistent predonation hematuria was identified in 8.3% (18.6% vs 6% in those with vs without family history of IgA nephropathy or Alport syndrome).¹⁷⁸ 95% of those with persistent predonation hematuria continued to have persistent hematuria after donation over median 27 month follow-up (compared with 28% of those with predonation occasional hematuria and 5% without predonation hematuria). Predonation hematuria was associated with increased likelihood of persistent proteinuria (dipstick $\geq 1+$) after donation (without dysmorphic red blood cells: adjusted OR 3.8; with dysmorphic red blood cells: adjusted OR 12.3). Predonation hematuria was not associated with postdonation GFR, but persistent postdonation hematuria with dysmorphic red blood cells was associated with significant GFR decline over the study period.

What Prior Guidelines Recommend

Previous guidelines recommend that evaluation of donor candidates for causes of hematuria include urine culture and imaging,⁴⁸ cystoscopy if older than 40 years,⁴⁸ urine cytology and "complete" urological evaluation.⁵⁴ A recent Canadian protocol recommends tests of urine culture, urine cytology, 24-hour urine calcium, metabolic stone workup, and then if the cause of hematuria is undetermined, cystoscopy and a native kidney biopsy.¹⁷⁹ In the absence of an identified cause, evaluation by kidney biopsy has been advised if hematuria is $>1+$ ⁴⁸ or possibly caused by glomerular disease.^{38,54}

While a number of prior living donor guidelines recommend kidney biopsy as part of the evaluation of persistent microhematuria before donation,^{48,180} few articulate criteria for donor selection. The 2011 British Transplantation Society guidelines offer a "moderate quality" recommendation that "glomerular pathology precludes donation, with the possible exception of thin basement membrane disease."⁴⁸ Canadian Blood Service's protocol for KPD defines IgA nephropathy and Alport syndrome (including carrier status) as exclusions to donation.¹⁷⁹

The 2013 "Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy" include several consensus-based recommendations related to living donation selection¹⁸¹: A) "Individuals with TBMN may be kidney donors if they have normal 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 kidney donors if they have normal BP, proteinuria levels, and renal function; if coincidental kidney disease has been excluded by kidney biopsy; and if X-linked Alport syndrome has been excluded by genetic testing." The document recommends "discouraging affected mothers of males with X-linked

Alport syndrome from renal donation because of their own risk of kidney failure.”

RESEARCH RECOMMENDATIONS

- Perform long-term follow-up studies of living donors with infrequent clinical conditions including:
 - Alport female “carrier” state
 - TBMN
 - Incidental IgA deposition in glomeruli and isolated hematuria
 - Nephrolithiasis
- These studies should include appropriate controls and examine endpoints including CKD and kidney failure, premature death, and health-related quality of life.

CHAPTER 8: KIDNEY STONES

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 8 and therefore the following recommendations are “Not Graded.”

Evaluation

- 8.1: Donor candidates should be asked about prior kidney stones, and related medical records should be reviewed if available.
- 8.2: The imaging performed to assess anatomy before donor nephrectomy (eg, computed tomography angiogram) should be reviewed for the presence of kidney stones.
- 8.3: Donor candidates with prior or current kidney stones should be assessed for an underlying cause.

Selection

- 8.4: The acceptance of a donor candidate with prior or current kidney stones should be based on an assessment of stone recurrence risk and knowledge of the possible consequences of kidney stones after donation.

Counseling

- 8.5: Donor candidates and donors with current or prior kidney stones should follow general population, evidence-based guidelines for the prevention of recurrent stones.

RATIONALE

Evaluation

Transplant programs typically assess donor candidates with past or present, symptomatic or asymptomatic kidney stones. In a cohort of approximately 2000 living kidney donor candidates who underwent computed tomography (CT) angiograms/urograms at a large US center (mean age, 43 years; 92% white; 58% women), 3% of candidates had past symptomatic kidney stones, and 11% had evidence of stones on renal imaging.¹⁸²

A kidney stone in an individual with a solitary kidney can potentially obstruct the ureter, leading to acute kidney injury, and may result in urgent hospital attention and even surgical intervention. Donor candidates should have a detailed evaluation including a careful history and medical record review of any prior or current kidney stones. In the case of a prior history of stones, additional details that should be assessed include the time and location of prior episodes,

and any prior investigations or treatments. The frequency of kidney stones varies by sex, race and climate. The overall prevalence of kidney stones is approximately 6 to 9% in men, and 3 to 4% in women, and most stones are composed of calcium oxalate.¹⁸³ Living kidney donors without a predonation history of kidney stones have no difference in the risk of developing kidney stones after donation, or in receiving a urologic procedure for kidney stones after donation, compared with selected nondonors matched for similar baseline health.¹⁸⁴

Asymptomatic Kidney Stones Seen on Imaging

Approximately 5% of individuals have evidence of an asymptomatic kidney stone on CT angiography performed as part of the donor evaluation.¹⁸⁵ Such CT scans may detect very small calcifications in the kidneys in patients who are asymptomatic and have no history of a clinically recognized kidney stone; very small 1 to 2 mm calcifications in the renal papillae found on CT scans are referred to as Randall’s plaques. These plaques have uncertain prognostic significance.

Evaluation of Donor Candidates and Donors with Prior or Current Kidney Stones

Donor candidates and donors with current or prior kidney stones should have an evidence-based evaluation of nephrolithiasis. For example, the 2014 American Urological Association Guideline provides comprehensive consensus and evidence-based recommendations for the evaluation of adult patients with kidney stones¹⁸⁶:

1. A clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries and urinalysis on a patient newly diagnosed with kidney or ureteral stones. (clinical principle)
2. Serum intact parathyroid hormone (PTH) concentration should be obtained as part of the screening evaluation if primary hyperparathyroidism is suspected. (clinical principle)
3. When a stone is available, a stone analysis should be performed at least once. (clinical principle)
4. Clinicians should obtain or review available imaging studies to quantify stone burden. (clinical principle)
5. Additional metabolic testing should be performed in high-risk or interested first-time stone formers and recurrent stone formers. (moderate evidence)
6. Metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. (expert opinion)

Similarly, the 2016 European Association of Urology guideline also provides comprehensive expert and evidence-based recommendations on the evaluation of adults with kidney stones,¹⁸⁷ as do the Caring for Australians with Renal Impairment (CARI) guidelines.¹⁸³

Risk Factors for Recurrent Stones

Prospective studies have shown the median recurrence rate of kidney stones is 15 per 100 person-years.¹⁸⁸ However, the risk of recurrence after a single stone is difficult to predict in an individual. Compared with older adults, younger adults

have more remaining years to live, and so have a higher lifetime chance of kidney stone recurrence.

Characteristics associated with a higher lifetime risk of stone recurrence include¹⁸³:

- Younger age (<40 years)
- A family history of kidney stones
- Frequent, recurrent kidney stones

Characteristics associated with a lower lifetime risk of stone recurrence include:

- Older age (≥40 years)
- No prior symptoms of kidney stones
- A kidney stone that is less than 15 mm, solitary and unilateral

Selection and Management

The acceptance of a donor candidate with prior or current kidney stones should be based on an assessment of stone recurrence risk and knowledge of the possible consequences of kidney stones after donation.

As recommended in chapter 5 (Predonation Kidney Function), when asymmetry in GFR, parenchymal abnormalities (including stones), vascular abnormalities, or urological abnormalities are present but do not preclude donation, the more affected kidney should be used for donation.

Possible Consequences of Kidney Stones

Kidney stones may be associated with a higher risk of CKD and ESKD, with possible mechanisms including obstructive uropathy or pyelonephritis, crystal plugs at tips of the renal papilla and parenchymal injury from treatments such as shockwave lithotripsy.^{183,189} One or more episodes of kidney stones were associated with a 2-fold higher risk of ESKD in one population-based study from Alberta, Canada.¹⁹⁰ The association was stronger in patients with 2 or more episodes of kidney stones versus a single episode of kidney stones. A National Health and Nutrition Examination Survey also reported that a history of kidney stones was associated with CKD and ESKD, however the effect was largely confined to women.¹⁹¹ Among 10 678 patients in the Atherosclerosis Risk in Communities study, nephrolithiasis history was associated with a 29% (HR, 1.071.29_{1.54}) higher risk of CKD in demographic-adjusted analyses, but the association was no longer statistically significant after multivariable adjustment (HR, 0.901.09_{1.32}).¹⁹² To inform this guideline, CKD-PC analyzed multiple cohorts (see chapter 1).⁷ They found the association between a prior history of kidney stones and ESKD was not significant in the meta-analysis; for this reason a history of kidney stones does not appear as a characteristic in the online tool to predict the 15-year and lifetime chance of kidney failure in the absence of donation.⁷

Ex-vivo Removal of Kidney Stones

There are reports of nephrolithiasis-related adverse events for recipients of an allograft with a stone left in situ.¹⁹³ There are also reports on the safety and success of ex vivo ureteroscopy to remove stones from explanted donor kidneys before transplantation.¹⁸⁵

Counseling

Donors and donor candidates who develop kidney stones should follow general population evidence-based guidelines for dietary and pharmacologic-based strategies to prevent

recurrent kidney stones. Recent systematic reviews and clinical practice guidelines summarize this evidence.^{194,195} For example, there is low-strength evidence that increased fluid intake to achieve a urine output of at least 2 liters per day (vs normal fluid intake) and reduced soft-drink consumption lowers the risk of recurrent stones. In patients with multiple past calcium stones, most of whom increased their fluid intake, there is moderate-strength evidence that thiazide diuretics, citrate supplements, and allopurinol each further reduce the risk of future stones compared with placebo or control, although the benefit from allopurinol seemed limited to patients with baseline hyperuricemia or hyperuricosuria.

What Prior Guidelines Recommend

Several prior guidelines and US policy requirements describe evaluation methods and/or acceptance criteria for donor candidates with prior or current kidney stones.^{38,48,51,55,179} Generally, most prior guidelines recommend complete metabolic testing (serum PTH, 24-urine collection for calcium, phosphate, oxalate, citrate, urate, creatinine and sodium), and one guideline recommends all such candidates be assessed by a urologist.¹⁷⁹ Several prior guidelines recommend the current presence of bilateral kidney stones, multiple stones, or nephrocalcinosis precludes donation, while a current small single stone may be eligible to proceed with donation.^{38,54,55,179,196}

RESEARCH RECOMMENDATIONS

- Perform follow-up studies of approved donors with current stones, risk factors for recurrent stones, or small calcifications discovered on imaging to determine impact of these factors on long-term outcomes compared to donors without these characteristics, and also compared to nondonors with similar risk factors.
- Develop a tool to estimate the risk of postdonation kidney stones according to predonation clinical and demographic factors.

CHAPTER 9: HYPERURICEMIA, GOUT, AND MINERAL AND BONE DISEASE

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 9 and therefore the following recommendations are “Not Graded.”

Evaluation

- 9.1: Donor candidates should be asked about prior episodes of gout.

Counseling

- 9.2: Donor candidates may be informed that donation is associated with an increase in serum uric acid concentration, which may increase the risk for gout.
- 9.3: Donor candidates and donors with prior episodes of gout should be informed of recommended methods to reduce their risk of future episodes of gout.

RATIONALE

Hyperuricemia and Gout

High serum uric acid concentration is a potent risk factor for gout, for which the 10-year incidence is estimated to be

1%, 5%, and 49% for uric acid levels of < 7.0, 7.0-8.9, and ≥ 9.0 mg/L respectively.^{197,198} A decline in GFR results in less uric acid excretion and a higher serum uric acid concentration.^{199,200} These changes are evident with the 25% to 40% reduction in GFR that occurs after living kidney donation.^{139,201,202} For example, one prospective US cohort study found that at 6 months after nephrectomy, donors versus healthy nondonor controls had 8.2% higher serum uric acid level [mean values of 5.3 ± 1.1 mg/dL (315.2 ± 65.4 μ mol/L; standard deviation) vs 4.9 ± 1.2 mg/dL (291.5 ± 71.4 μ mol/L); $P < 0.001$], that persisted over 36 months of follow-up.^{139,201} Another study found donors to have 20% higher serum uric acid concentrations at a mean of 7 years after nephrectomy compared with predonation.²⁰³

In a study of 1988 living kidney donors from Ontario, Canada, who were followed for a median of 8.8 years (maximum, 20.8 years), living kidney donors were more likely to be diagnosed with gout compared to matched nondonors with similar baseline health, although the absolute risk remained low (3.5 vs 2.1 events per 1000 person-years; HR 1.21, 62.1%).²⁰³ At 8 years, the cumulative incidence of gout was 1.4% higher in donors compared to nondonors (3.4% vs 2.0%).²⁰³ This report was not reviewed by the ERT but would be expected to have a moderate risk of bias similar to other reported outcomes from this cohort. Based on this report, some transplant teams may decide to inform donor candidates that donation is associated with an increase in serum uric acid concentration, which may increase the risk of gout. However, the authors of the primary report suggested the finding first be corroborated in other studies. In this guideline we endorse that donor candidates be asked about prior gout episodes, but given the limitations of existing information, we did not propose measuring uric acid as a standard part of evaluation or follow-up processes at this time. The risk of gout after kidney donation may vary based on demographic characteristics. A study of 4650 kidney donors from the US including 13.1% African Americans, found that, by 7 years, African Americans were almost twice as likely to develop gout as white donors (4.4% vs 2.4%; adjusted HR, 1.01, 83.2).²⁰⁴ Postdonation gout risk also increased with older age at donation and was nearly 3-times higher in men compared with women.²⁰⁴

In nondonor populations hyperuricemia is associated with a higher risk of CVD and new-onset CKD.^{203,205} However, the prognostic significance of hyperuricemia in living kidney donors is currently uncertain and warrants additional study. In the US cohort study mentioned above, compared with matched donors without gout, donors with gout had more frequent diagnoses of acute kidney injury, CKD, and other disorders of the kidney.

Donor candidates and donors with prior episodes of gout should be informed of recommended methods to reduce their risk of future episodes of gout. Previous clinical practice guidelines cite modest to low evidence for certain diet and lifestyle measures (eg, avoiding excessive alcohol, and avoiding ingestion of organ meats high in purine content) and possibly pharmacological therapies.²⁰⁶ The prevention and treatment of hyperuricemia and gout may be complicated by decreased kidney function. The dose of allopurinol, which is frequently used to treat increased serum uric acid and prevent gout, should be adjusted in patients with decreased kidney function. Dose reductions may not be necessary with newer uricosuric agents.²⁰⁷ Nonsteroidal anti-inflammatory drugs

should probably be used cautiously in patients with decreased kidney function including living kidney donors. The treatment of choice for acute gout is colchicine, however the dose of colchicine should be reduced in patients with decreased kidney function.

Metabolic Bone Disease

The effect of the modest decrease in GFR on the development of metabolic bone disease among kidney donors is not clear. Several recent studies describe changes in measures of bone mineral metabolism in kidney donors. These changes include a decline in the serum concentration of 1, 25-dihydroxyvitamin D and phosphate, a decline in tubular phosphate reabsorption, and a rise in the concentration of serum PTH.^{139,201,202,208} For example, one study showed that kidney donors had higher serum concentrations of fibroblast growth factor-23 and greater fractional excretion of inorganic phosphate compared with nondonor controls.²⁰⁹ The Assessing Long Term Outcomes of Living Donation prospective cohort study found a 23% higher PTH concentration among 206 donors assessed at 6 months postdonation compared with concentrations among 198 healthy controls (52.7 vs 42.8 pg/mL, respectively)²⁰¹ that persisted at 36-month follow-up.¹³⁹ Similarly, the Chronic Renal Impairment in Birmingham study of 68 donors at 2 United Kingdom centers reported larger increases in serum fibroblast growth factor-23 and parathyroid hormone concentrations compared with prospective changes in these parameters among healthy nondonors.²⁰²

The long-term effects of these changes on the risk of fractures, CVD, or other outcomes important to donors is uncertain, therefore the WG made no recommendations for managing mineral and bone disorders that would differ from guidelines for the general population. The ERT identified a single study of fractures in kidney donors (moderate risk of bias, with only a single study the quality of evidence was deemed very low; Evidence Report Table 8, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table D5 SDC, <http://links.lww.com/TP/B432>). In this study, 2015 kidney donors in Ontario, Canada, experienced no increase in the risk of non-trauma-related upper- or lower-extremity fractures compared with healthy nondonors.²¹⁰

What Prior Guidelines Recommend

As many of the studies on hyperuricemia, gout and mineral and bone disease in living kidney donors are recent, these issues have generally not been addressed in prior donor guidelines. The British Transplantation Society describes the importance assessing a history of gout as part of the candidate evaluation.⁴⁸ Amsterdam Forum and Spanish Society of Nephrology and Spanish National Transplant Organisation guidelines describe serum uric acid as a standard test in the evaluation of all living kidney donor candidates.^{38,54}

RESEARCH RECOMMENDATIONS

- Determine the effects of hyperuricemia in living kidney donor candidates and donors on the incidence of gout and CVD.
- Perform long-term follow-up of donors and healthy nondonor controls to determine the impact of kidney donation on gout recurrence.
- Perform long-term follow-up of donors and healthy nondonor controls to determine the impact of kidney donation (if any) on fracture risk.

CHAPTER 10: PREDONATION BLOOD PRESSURE

Except in the case of Recommendation 10.6, the ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 10 and therefore the following recommendations are “Not Graded.”

Evaluation

- 10.1: Blood pressure should be measured before donation on at least 2 occasions by clinical staff trained in accurate measurement technique, using equipment calibrated for accuracy.
- 10.2: When the presence or absence of hypertension in a donor candidate is indeterminate based on history and clinic measurements (eg, blood pressure is high normal or variable), blood pressure should be further evaluated using ambulatory blood pressure monitoring (ABPM) or repeated using standardized blood pressure measurements.

Selection

- 10.3: Normal blood pressure, as defined by guidelines for the general population in the country or region where donation is planned, is acceptable for donation.
- 10.4: Donor candidates with hypertension that can be controlled to systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg using 1 or 2 antihypertensive agents, who do not have evidence of target organ damage, may be acceptable for donation. The decision to approve donor candidates with hypertension should be individualized based on demographic and health profile in relation to the transplant program’s acceptable risk threshold.

Counseling

- 10.5: Donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for hypertension and cardiovascular disease, including healthy diet, smoking abstinence, achievement of healthy body weight, and regular exercise according to guidelines for the general population. These measures should be initiated before donation and maintained lifelong.
- 10.6: We suggest that donor candidates should be informed that blood pressure may rise with aging, and that donation may accelerate a rise in blood pressure and need for antihypertensive treatment over expectations with normal aging. (2D)

RATIONALE

Evaluation and Definitions

BP Measurement and Classification

It is important to use an accurate, well-calibrated device and an appropriately sized BP cuff based on arm length and circumference. An overly small cuff will overestimate and an excessively large cuff will underestimate true BP levels. The donor candidate should be seated quietly with back supported, feet on the floor and arm supported at heart level for the measurements. It is advisable to measure BP on at least 2 separate occasions by trained staff, or on one occasion plus ambulatory BP monitoring (ABPM) to minimize anxiety effects in donor candidates.²¹¹ Automated serial BP measurements can also eliminate a “white coat” effect.²¹² Multiple prior guidelines and policies for the evaluation and care of living kidney donor candidates recommend assessment of

predonation BP on several occasions,^{212,213} and/or consideration of ABPM in donor candidates with elevated office readings, receiving antihypertensive therapy, or who are older at evaluation.^{38,50,51,196,214,215}

Hypertension is defined by office readings of systolic SBP of 140 mm Hg or greater or diastolic BP (DBP) of 90 mm Hg or greater, out-of-office daytime mean ABPM or home measurements of SBP of 135 mm Hg or greater or DBP of 85 mm Hg or greater,²¹³ or the need for medication to control BP. Note that some antihypertensive agents may be used for indications other than BP treatment (eg, diuretics for edema or beta-blockers for migraine headache prevention), and that the indication for the prescribed medications should be determined as part of the evaluation.

White coat hypertension is defined as hypertension by office BP measurements with normal out of office measurements by ABPM or home readings. Individuals with white coat hypertension have lower cardiovascular risk than persons with hypertension, but may carry increased risk for future hypertension.^{212,216} Population-based studies suggest that 20-25% of adults may have white coat hypertension.²¹⁶ Individuals with treated hypertension may also have a “white coat effect,” such that elevated BP is recorded in the medical environment even when treated BP is controlled by ABPM or home readings.

Masked hypertension is defined as normal BP by office measurements with hypertension by ABPM or home readings. Like sustained hypertension, masked hypertension is accompanied by increased risk for hypertensive target organ damage, and thus treatment is warranted if identified. Population-based studies suggest that 10-30% of adults may have masked hypertension.^{216,217} Masked hypertension cannot be identified in donor candidates in whom BP is measured by office readings alone, but the implications of requiring ABPM or home readings to screen for masked hypertension in donor candidates (eg, outcomes, cost, efficiency) are not defined.

Hypertension Risk Factors and Counseling

Potentially modifiable risk factors for hypertension include use of certain medications (eg, nonsteroidal anti-inflammatory agents, decongestants, stimulants) and presence of certain lifestyle factors (eg, excess alcohol intake, high sodium diet, use of dietary supplements, or smoking).²¹⁸⁻²²⁰ Nonmodifiable hypertension risk factors include a family history of hypertension, race, and age. Additional considerations include women with a history of preeclampsia or gestational hypertension. In this setting we suggest predonation counseling on the potential for increased cardiovascular risk and emphasis on healthy behaviors to reduce cardiovascular risk. Risk factors for hypertension by themselves do not constitute contraindications to donation in a normotensive person. Consistent with recommendations for the general population,²²¹ British Transplantation Society and Renal Association guidelines⁴⁸ recommend lifestyle measures in kidney donors to reduce the risk of hypertension and its consequences, including frequent exercise, smoking cessation, and weight loss where appropriate.

Target organ damage may be manifest as prior occurrence of a cardiovascular event such as myocardial infarction or stroke, urine AER greater than 30 mg/d (ACR > 30 mg/g or

3 mg/dL), reduced kidney function (eg, GFR < 60 mL/min per 1.73 m²), hypertensive retinopathy, and/or evidence of left ventricular hypertrophy.²¹³

Lifestyle modification can effectively treat hypertension without medication or with fewer medications and lower dosages required to achieve BP control.²²¹ Lifestyle modifications include healthy diet, smoking cessation, weight loss if overweight, regular exercise, and discontinuation of potential contributing medications according to guidelines for the general population. *Follow-up* of patients with hypertension is critical for monitoring of control in relation to targets and for monitoring and management of complications. The importance of access to healthcare and regular follow-up have also been emphasized in the selection and care of hypertensive donor candidates in 2 prior guidelines,^{38,54} whereas the Spanish Society of Nephrology and Spanish National Transplant Organisation guidelines specify “reasonable guarantee that the donor will follow the check-up period and treatment indefinitely” among the criteria for acceptance of a hypertensive donor candidate.⁵⁴

Selection

Impact of Reduced GFR on BP in the General Population and After Donation

Reduced kidney function may cause or worsen hypertension in the general population.²²² While it is documented that BP often rises with aging,²²³ GFR reduction from kidney donation may accelerate the risk or progression of hypertension over time to a greater extent than expected from normal aging, possibly due to physiological alterations (eg, hyperfiltration in the remaining kidney, changes in vascular tone and renin-angiotensin-aldosterone regulation) and/or heightened detection at donor follow-up.^{224,225} Existing retrospective studies examining the impact of kidney donation on hypertension risk have been limited by short follow-up times, high rates of loss to follow-up, lack of controls and/or comparisons to unselected general rather than healthy populations. Use of antihypertensive medications was lower in a cohort of privately-insured donors compared with age- and sex-matched unscreened beneficiaries in the same insurance plan.²²⁶ In contrast, a systematic review including data for 5145 predominantly white donors estimated 6 mm Hg higher weighted mean SBP and 4 mm Hg higher weighted mean DBP in donors compared with controls after an average of 7 years²²⁴ (Supplemental Appendix Tables D1 and D2, SDC, <http://links.lww.com/TP/B432>). An administrative claims linkage study of 1278 (primarily white race) living donors in Ontario, Canada followed for a mean of 6 years (range, 1-16 years) found a higher incidence of claims-based hypertension diagnoses (16.3% vs 11.9%; HR, 1.21.4_{1.7}) among living donors compared with matched controls who were also screened for the absence of baseline comorbidities through administrative claims.²²⁵

Among more recent donor cohorts, higher rates of postdonation hypertension and antihypertensive medication use in African American compared with white donors have been reported.²²⁶⁻²²⁸ While these patterns parallel hypertension prevalence differences in the general population,²²⁸ one small study found higher rates of postdonation hypertension among 103 African American donors compared with race-matched “healthy” nondonor controls (41% vs 18% at an average of 6.8 years postdonation)²²⁹ (Supplemental Appendix

Table D10, SDC, <http://links.lww.com/TP/B432>). Furthermore, many donors in this study were unaware of their hypertension. Associations of age at donation and sex with postdonation hypertension have been inconsistent (Supplemental Appendix Tables D7 and D9, SDC, <http://links.lww.com/TP/B432>).

Based on these data, we suggest that donor candidates should be informed that BP may rise with aging, and that donation may accelerate the rise in BP and the need for antihypertensive treatment over that expected with normal aging, especially if BP is high-normal before donation and among African American donor candidates. Furthermore, antihypertensive medication is more likely to be prescribed after donation.

Hypertension as a Cause of CKD in the General Population

Hypertension is a contributing cause of CKD in the general population, although in many cases, CKD may be the cause of hypertension. A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 general population cohorts found that every 20 mm Hg increase in SBP was associated with a 42% increase (adjusted HR, 1.271.42_{1.58}) in the risk of ESKD over median cohort follow-up of 4 to 16 years. Use of antihypertensive medications was also associated with increased ESKD risk (adjusted HR, 1.011.35_{1.82} over cohort follow-up).⁷ After calibration to annual ESKD incidence in the US healthy population, variations in the projected 15-year and lifetime risks of ESKD based on level of SBP from this analysis were generated according to age, sex, and race for healthy persons (assuming age-specific GFR, urine ACR 4 mg/g [0.4 mg/dL], BMI 26 kg/m², and absence of diabetes mellitus; (Figures 14 and 15). While these figures are useful for visualizing the impact of higher SBP on increased ESKD risk, we endorse consideration of BP as part of the assessment of predicted long-term ESKD risk based on a donor candidate’s complete demographic and health profile (as opposed to consideration of single risk factors in isolation).

Clinical consequences of hypertension vary by race in the general population. Treating mild-to-moderate primary hypertension may not halt kidney disease progression in non-diabetic African Americans, whereas hypertension control appears to slow kidney disease progression in European Americans.²³⁰⁻²³⁴ Recent literature supports that at least a portion of kidney failure previously attributed to hypertensive nephrosclerosis in persons of African descent may be genetically mediated by coding variants in the gene for *APOL1* and not modifiable by antihypertensive therapy (see chapter 14).²³⁵⁻²³⁸

Predonation Hypertension as a Risk Factor for Adverse Outcomes after Kidney Donation

Living donor candidates undergo a rigorous evaluation process which includes measurement of kidney function and urine protein, but subtle scarring of the kidney from hypertensive nephrosclerosis may not be detected by these tests.²³⁹ Compensatory hyperfiltration in the remaining kidney is normal after nephrectomy^{240,241}; however, subclinical pathology or aging processes may impair compensation and reduce postdonation GFR.^{240,242}

The ERT identified 3 studies, rated as very low quality in reporting postdonation outcomes according to predonation BP or hypertension status (Evidence Report Table 19, SDC,

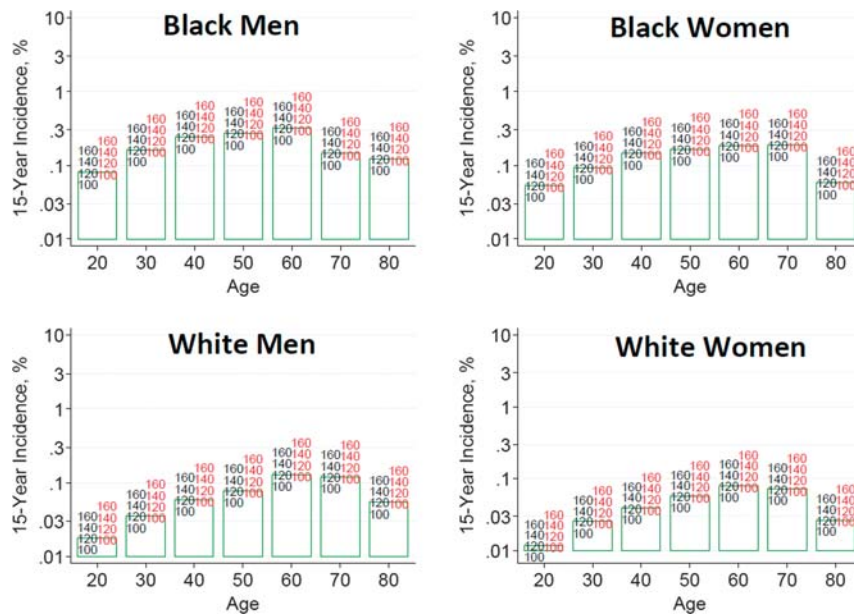


FIGURE 14. Estimated 15-year incidence (%) of ESKD in the United States according to baseline systolic blood pressure (SBP) and demographic profile from the CKD-PC. SBP mm Hg without (black) and with (red) antihypertension medication. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

<http://links.lww.com/TP/B434>, and **Supplemental Appendix Table D16, SDC**, <http://links.lww.com/TP/B432>). In a combined cohort of donors and matched healthy nondonors in

Norway, each 1 mm Hg increase in SBP was associated with a small increase in cardiovascular death and ESKD during up to 25 years of follow-up.³² A study of only 6 hypertensive donors

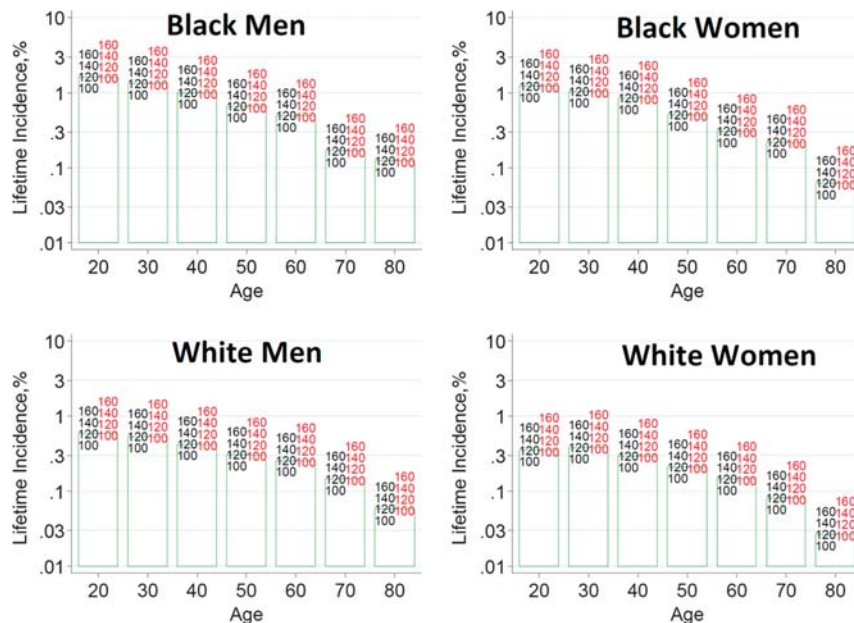


FIGURE 15. Estimated lifetime incidence (%) of ESKD in the United States according to baseline systolic blood pressure (SBP) and demographic profile from the CKD-PC. SBP mm Hg without (black) and with (red) antihypertension medication. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

reported CKD in 4 (67%) compared with 22% of non-hypertensive donors during an average of 5.4 years follow-up.²⁴³ A third study of 16 hypertensive donors was deemed at high risk of bias.²⁴⁴ A systematic review by Young et al concluded that results from this and 2 additional studies were substantially heterogeneous and thus results were not pooled.²⁶

Additional studies that did not meet criteria for the ERT evidence review include a large study based on linkage of the US Transplant Registry with national death records that found higher perioperative mortality among donors with versus without predonation hypertension (36.7 vs 1.3 per 10 000).²³ While reported baseline hypertension was not associated with long-term mortality, SBP of 140 mm Hg or greater at donor registration was associated with 3-times the adjusted RR of death over 12 years compared to SBP less than 120 mm Hg (adjusted HR 1.13, 3.9, 7). A single-center study of 24 white, older (mean age, 53 years) donors with predonation hypertension (awake ABPM > 135/85 mm Hg and clinic/nurse-measured BP > 140/90 mm Hg) that was not included in the evidence review based on sample size found similar postdonation GFR reduction and urine protein excretion as in normotensive donors, and no increase in urinary protein excretion compared with predonation values over a mean 282 days of follow-up.²⁴⁵ A recent US registry study found that ESKD among donors was more likely to be attributed to hypertension if the duration of follow-up was more than 10 years compared with less than 10 years.³¹

The WG concluded that the decision to approve donation in candidates with hypertension should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold. Donor candidates with hypertension should be treated according to guidelines for the general population in the country or region where donation will occur. BP control should be confirmed by standardized BP measurements over at least several weeks before donation. Donor candidates with hypertension should be informed that donation may accelerate the rise in BP and the need for antihypertensive treatment over expectations with normal aging, and that uncontrolled hypertension may cause target organ damage to their remaining kidney, and be counseled on the importance of maintaining a healthy lifestyle and BP control before and after donation.

What Prior Guidelines Recommend

Multiple prior guidelines for the evaluation and care of living kidney donor candidates identify hypertensive end-organ damage (eg, proteinuria, microalbuminuria, left ventricular hypertrophy, and hypertensive retinopathy), as relative contraindications or exclusion criteria for kidney donation.^{38,48,50,54,55,196,214,215} Other relative contraindications or exclusion criteria for donation defined in prior guidelines include uncontrolled hypertension^{48,55,196,214}; need for more than 1,⁵⁴ or more than 2 antihypertensive agents^{214,215} for adequate control; hypertension and age younger than 50 years at evaluation¹⁹⁶; non-white or African American race^{54,196}; or the presence of several comorbidities or cardiovascular risk factors.^{50,196,214} We concur that uncontrolled hypertension or hypertension with target organ damage should be exclusions to kidney donation. However, based on our evidence review, we also conclude that

there is limited evidence from the donor population to make recommendations for donor acceptance based on hypertension status alone. Rather we endorse adherence to the general framework that compares predicted individual long-term ESKD risk according to baseline profile of demographic and health characteristics including BP to the transplant program's acceptable risk threshold.

RESEARCH RECOMMENDATIONS

- Define optimal strategies for measuring BP during the donor candidate evaluation.
- Determine optimal strategies for treatment of hypertension in kidney donor candidates before donation, and in accepted donors after donation.
- Quantify the impact of living kidney donation on hypertension risk, as well as the impact of hypertension before and after donation on clinical outcomes including CVD and lifetime ESKD risk.
- Evaluate possible variation in the risk and consequences of hypertension at donation according to other characteristics, including baseline demographic and other clinical factors.

CHAPTER 11: PREDONATION METABOLIC AND LIFESTYLE RISK FACTORS

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 11 and therefore the following recommendations are "Not Graded."

Identification of Metabolic and Lifestyle Risk Factors

- 11.1: Risk factors for kidney and cardiovascular disease should be identified before donation and addressed by counseling to promote long-term health.

Obesity

- 11.2: Body mass index (BMI) should be computed based on weight and height measured before donation, and classified based on World Health Organization (WHO) criteria for the general population or race-specific categories.
- 11.3: The decision to approve donor candidates with obesity and BMI >30 kg/m² should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 11.4: Donor candidates who have had bariatric surgery should be assessed for risk of nephrolithiasis.

Glucose Intolerance

- 11.5: Donor candidates should be asked about prior diagnosis of diabetes mellitus, gestational diabetes, and family history of diabetes.
- 11.6: Glycemia should be assessed by fasting blood glucose and/or glycated hemoglobin (HbA_{1c}) before donation.
- 11.7: 2-hour glucose tolerance testing or HbA_{1c} testing should be performed in donor candidates with elevated fasting blood glucose, history of gestational diabetes, or family history of diabetes in a first-degree relative, and results should be used to classify diabetes or prediabetes status using established criteria for the general population.
- 11.8: Donor candidates with type 1 diabetes mellitus should not donate.

- 11.9: The decision to approve donor candidates with prediabetes or type 2 diabetes should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
- 11.10: Donor candidates with prediabetes or type 2 diabetes should be counseled that their condition may progress over time and may lead to end-organ complications.

Dyslipidemias

- 11.11: Fasting lipid profile (including total cholesterol, LDL-C, HDL-C and triglycerides) should be measured as part of an overall cardiovascular risk assessment before donation.
- 11.12: The decision to approve donor candidates with dyslipidemia should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

Tobacco Use

- 11.13: The use of tobacco products should be assessed before donation.
- 11.14: Donor candidates who use tobacco products should be counseled on the risks of perioperative complications, cancer, cardio-pulmonary disease and kidney failure, should be advised to abstain from use of tobacco products, and should be referred to a tobacco cessation support program if possible.
- 11.15: The decision to approve donor candidates who are active tobacco users should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.

RATIONALE

Goals of Evaluation and Definitions

This section addresses the evaluation and management of metabolic and lifestyle risk factors associated with ESKD, CVD and/or all-cause mortality, as applicable to the care of donor candidates. Some of the factors considered do not have currently known associations with ESKD risk, but are relevant to a comprehensive predonation health assessment. Even if donation does not increase the risk, traditional CVD risk factors are expected to have at least the same effect in donors as in the general population. Attention to these risk factors is intended to prevent or delay the onset and progression of comorbid diseases, kidney disease, and CVD. All risk factors considered in this section are potentially modifiable by lifestyle and/or medical care.

According to World Health Organization (WHO), the prevalence of diabetes mellitus increased from 108 million people worldwide in 1980 to 422 million in 2014.²⁴⁶ The rising prevalence of diabetes is linked with the obesity epidemic and 2.1 billion adults worldwide were estimated to be overweight or obese in 2013.²⁴⁷ Underlying causes of the obesity epidemic may be modifiable, and include sedentary lifestyles, high-fat and energy-dense diets, and increased urbanization.²⁴⁸⁻²⁵⁰ The WHO defines obesity based on thresholds of BMI, a measure of weight scaled for height, as: underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), obese (30-34.9 kg/m²), and morbidly obese (>35 kg/m²).²⁴⁸ While BMI is recognized to be an imperfect measure of body composition, the components of BMI are easily measured, recorded, and followed over time, and have prognostic implications. Optimal BMI-based thresholds for

obesity may differ from WHO standards in non-whites, and race-specific thresholds have been proposed. Measurement of waist circumference and/or waist-to-hip ratios may also be considered to characterize the distribution of adiposity in obese persons.²⁵¹

Multiple prior guidelines and policies for the evaluation and care of living donors recommend measurement of fasting plasma glucose and consideration of oral glucose tolerance testing and/or glycated hemoglobin (HbA_{1c}) as part of the donor evaluation.^{38,48,51,196,252} The WHO defines diabetes mellitus as: fasting plasma glucose of 7.0 mmol/L or greater (≥ 126 mg/dL), random plasma glucose of 11.1 mmol/L or greater (≥ 200 mg/dL), or plasma glucose concentration of 11.1 mmol/L or greater (≥ 200 mg/dL) 2 hours after a 75-g anhydrous glucose load in an oral glucose tolerance test. A 2011 addendum included recognition of HbA_{1c} of 48 mmol/mol or greater (6.5%) as an additional criterion for diagnosing diabetes if assays are standardized to criteria aligned with international reference values, but also indicated that HbA_{1c} less than 48 mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests.²⁴⁶

The WHO defines Impaired Glucose Tolerance as fasting plasma glucose less than 7.0 mmol/L (<126 mg/dL) or 2-hour post-load plasma glucose of 7.8 or greater and less than 11.1 mmol/L (≥ 140 and < 200 mg/dL), while Impaired Fasting Glucose is defined as fasting plasma glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL) or 2-hour post-load plasma glucose less than 7.8 mmol (<140 mg/dL).²⁵³ Currently there are various definitions of prediabetes and the equivalent term used by WHO, intermediate hyperglycemia, is defined by fasting plasma glucose of 6.1 to 6.9 mmol/L (110-125 mg/dL) and 1-hour post-load plasma glucose of 7.8-11.0 mmol/L (140-199 mg/dL).²⁵⁴

Dyslipidemias are classified based on elevations in total cholesterol and low-density lipoprotein cholesterol (LDL-C), and low concentrations of high-density lipoprotein cholesterol (HDL-C). Hypertriglyceridemia is an independent CVD risk factor.²⁵⁵

Obesity

Increased risk of perioperative complications including wound and surgical site infections in obese patients is well established in the general surgical literature.²⁵⁶ The ERT report identified 2 systematic reviews that examined perioperative outcomes after donor nephrectomy according to BMI, with quality of source studies rated as low. Among 8 studies reporting operative time, all but one found a modest increase in operative time (mean difference of 16.9 minutes) among donors with BMI of 30 or greater compared to those with BMI less than 30 kg/m² (**Supplemental Appendix Table C7, SDC**, <http://links.lww.com/TP/B432>). While warm ischemia times were reported to be longer for obese donors in all but one study, this difference was not significant on meta-analysis. Pooled results showed no differences in blood loss or length of stay among obese compared with normal weight donors.

In the general population, obesity has been identified as a risk factor for diabetes mellitus and it may also be a risk factor for kidney disease, particularly obesity-related glomerulopathy.²⁵⁷ The ERT identified 5 studies comparing long-term outcomes among donors by predonation BMI, rated as low quality, with follow-up ranging from 6.7 to 15.1 years (**Supplemental Appendix Table D12, SDC**, <http://links.lww.com/TP/B432>).

com/TP/B432). One study found that BMI was associated with cardiovascular mortality but not all-cause mortality.³² In contrast, another registry study found no association between BMI and death over 12 years.²³ A few studies of variable quality examined associations between BMI and intermediate outcomes.^{140,244,258}

Multiple prior guidelines for the evaluation and care of living kidney donor candidates recommend BMI greater than 35 kg/m² as an absolute or relative contraindication to donation.^{38,48,50,54,196,215,259} and other guidelines recommend careful evaluation for other comorbidities in donor candidates with BMI greater than 30 kg/m².^{48,54} With regard to other metrics of obesity aside from BMI, the Spanish Society of Nephrology and Spanish National Transplant Organisation guidelines define waistline greater than 82 cm in women or greater than 102 cm in men as additional relative contraindications to donation.⁵⁴ CARI guidelines advise measurement of waist circumference within the assessment of overweight and obese donor candidates,²⁵⁹ and a US Joint Societies work group consensus statement includes abdominal circumference as part of the definition of metabolic syndrome.¹⁹⁶ In contrast, the ERT concluded that there is limited evidence from the donor population to make recommendations for donor acceptance based on BMI alone among obese donor candidates.

A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 general population cohorts found a modest association of BMI greater than 30 kg/m² with increased risk of ESKD over median cohort follow-up of 4 to 16 years (adjusted HR, 1.041.16_{1.29}).⁷ Projected 15-year and lifetime risks of ESKD for healthy persons varied according to BMI and age, sex, and race (Figures 16 and 17). A recent study of 119 769 US donors published after the ERT

systemic review found a stronger association of higher BMI at donation with postdonation ESKD risk over 20 years than the predonation risk relationship observed in the general population cohorts.²⁶⁰ We endorse consideration of BMI as part of the assessment of predicted long-term risk based on a donor candidate's complete demographic and health profile (as opposed to consideration of single risk factors in isolation). Findings from the recent US study²⁶⁰ suggests more uncertainty when drawing inferences about long-term postdonation risk in obese donor candidates, and the need to develop individualized postdonation risk estimates according to demographic and health profile. Acceptance thresholds for donor candidate BMI can incorporate perinephrectomy complications along with long-term risks of ESKD and other complications as data become available.

We agree with prior recommendations that obese donor candidate should be counseled about the long-term risks of obesity, advised to pursue weight loss before donation, and to maintain a healthy body weight after donation.^{38,48,50,215}

Glucose Intolerance

Type 2 diabetes is a leading cause of CKD worldwide and accounts for approximately 50% of acquired, adult-onset ESKD.^{261,262} Patients with diabetes mellitus are commonly excluded from living kidney donation. One report of 71 donors with baseline glucose intolerance including 27 older patients (mean age, 58 years) with diabetes defined by 2-hour glucose tolerance testing found no ESKD events and similar survival compared to donors without glucose intolerance over a mean follow-up of 88 months (Supplemental Appendix Table D14, SDC, <http://links.lww.com/TP/B432>).²⁶³

A recent meta-analysis based on data from nearly 5 million persons identified from 7 general population cohorts found

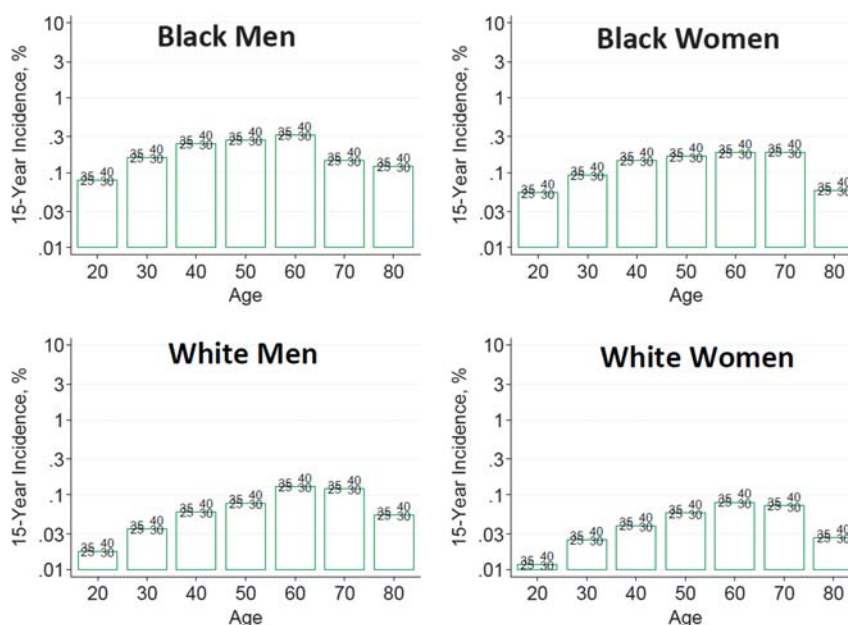


FIGURE 16. Estimated 15-year incidence (%) of ESKD in the United States according to baseline body mass index (BMI) and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. ACR, albumin-to-creatinine ratio; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

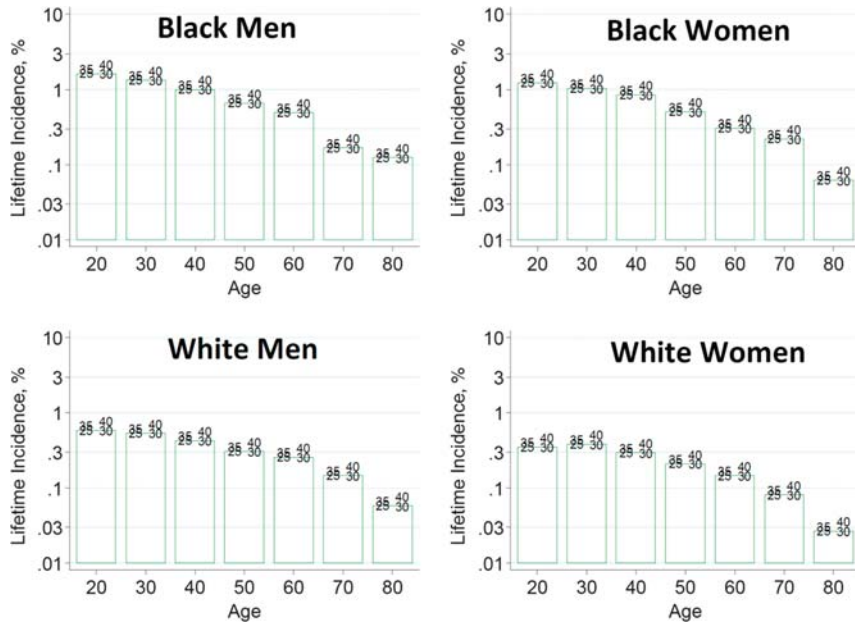


FIGURE 17. Estimated lifetime incidence (%) of ESKD in the United States according to baseline body mass index (BMI) and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. ACR, albumin-to-creatinine ratio; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

that, compared with nondiabetic persons, those with type 2 diabetes but otherwise good health had 3-times the risk of ESKD over median cohort follow-up of 4 to 16 years

(adjusted HR, 1.91^{3.01}_{4.74}).⁷ The 15-year and lifetime risks of ESKD for healthy persons varied by type 2 diabetes and age, sex, and race (Figures 18 and 19). Multiple prior

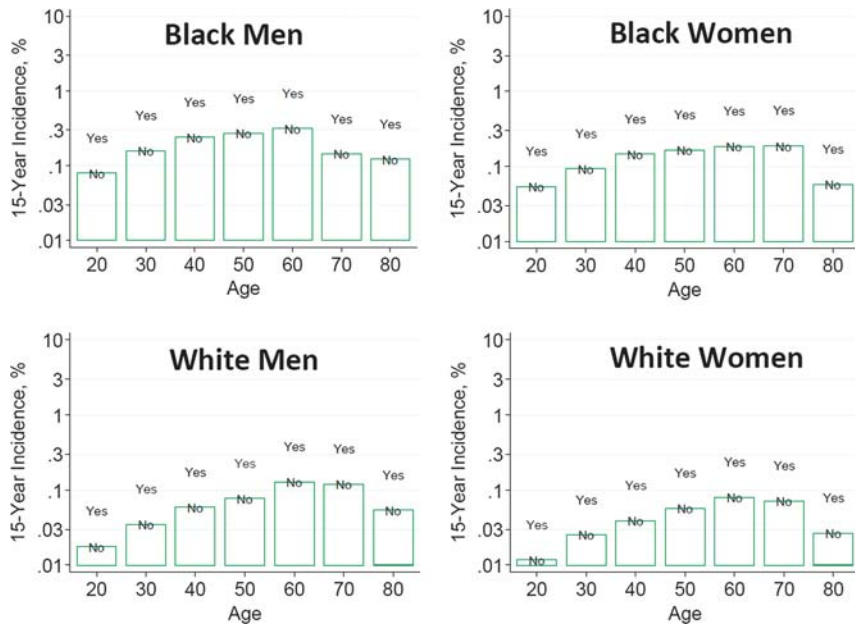


FIGURE 18. Estimated 15-year incidence (%) of ESKD in the United States according to non-insulin-dependent diabetes mellitus status and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

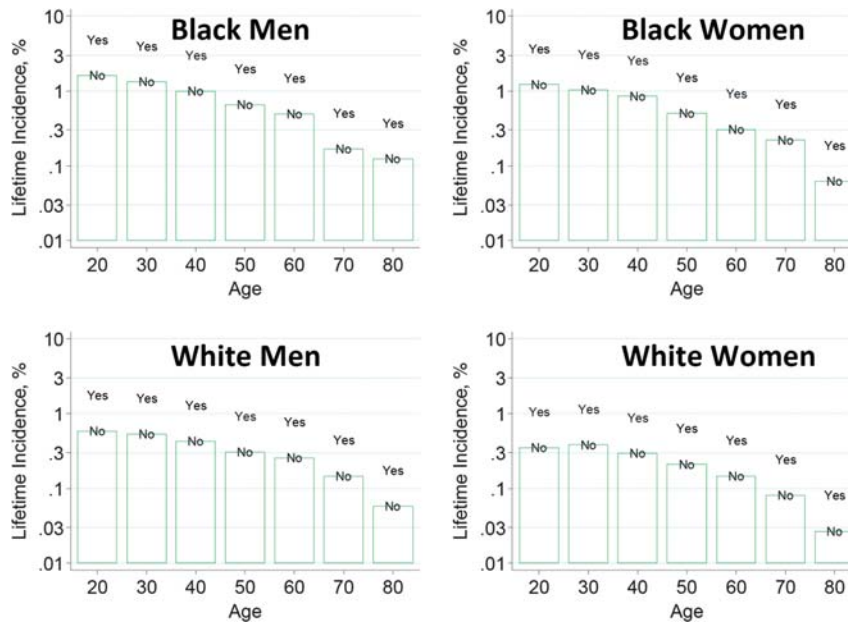


FIGURE 19. Estimated lifetime incidence (%) of ESKD in the United States according to non-insulin-dependent diabetes mellitus status and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

guidelines for the evaluation and care of kidney donors recommend that diabetic persons be excluded from kidney donation.^{38,54,179,196,215,252} However, the European Best Practice Guideline qualifies an exception of “exceptional circumstances”²¹⁵ and the British Transplantation Society recommends that “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.”⁴⁸ The WG concluded that persons with type 1 diabetes should be excluded from kidney donation. However, consistent with the framework of integrated risk assessment, we endorse individualizing the decision to approve donation in persons with prediabetes or type 2 diabetes based on the severity of illness and predicted long-term risk (considering complete demographic and health profile) in relation to the transplant program’s acceptable risk threshold. The WG considers that older candidates with type 2 diabetes with well-controlled glycemia, not requiring insulin and without end-organ damage, might be considered for donation.

Prediabetes represents an intermediate category of hyperglycemia, which poses increased risks for future type 2 diabetes mellitus and CVD.²⁶¹ Important risk factors for diabetes and prediabetes in the general population include increasing age, high-risk ethnicity or race, obesity, and history of diabetes in a first degree relative. Approximately 5-10% of individuals with prediabetes progress to diabetes per year²⁶⁴ but the risk of progression can be reduced with lifestyle changes and weight loss.²⁶⁵ The younger the individual with risk factors for prediabetes, the higher the likelihood that diabetes and subsequent kidney disease will develop in that person’s remaining lifetime.²⁶⁶

A small cohort study found that carefully screened prediabetic living kidney donors may revert to normal fasting glucose and did not have an increased risk of impaired kidney function in the short term²⁶⁷ (Evidence Report Table 17, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table D14, SDC, <http://links.lww.com/TP/B432>). However, quality of this study was very low. A recent study linking US national donor registry data to ESKD registry data for 125 427 living donors examined causes of ESKD after donation.³¹ The finding that early postdonation ESKD was predominantly reported as due to glomerulonephritis while late postdonation ESKD was more frequently reported as diabetic-ESKD and hypertensive-ESKD could be consistent with an effect of donation on diabetes and hypertension as causes for ESKD. These findings emphasize the importance of counseling donor candidates with prediabetes regarding their increased lifetime risk for progression to diabetes and subsequent end-organ complications, and the importance of healthy lifestyle behaviors to reduce risks. Those who are approved to donate should be counseled on the importance of regular medical follow-up after donation including surveillance for hyperglycemia and kidney function for many decades after donation, and prompt institution of appropriate management.

Prior recommendations regarding candidacy of persons with prediabetes for kidney donation are conflicting. The European Best Practice Guideline states that impaired glucose tolerance is not an absolute contraindication to donation^{50,215}; other guidelines consider prediabetes a relative contraindication^{54,196} or a condition warranting careful consideration,⁴⁸ while CARI considers prediabetes as well as past history of gestational diabetes to be absolute contraindications.²⁵² Given the lack of current data specific to the donor population, we endorse individualizing the decision to approve donation in persons with

prediabetes based on their predicted long-term risk in relation to the transplant program's acceptable risk threshold.

Dyslipidemias

Dyslipidemia is a modifiable risk factor for CVD, and hypertriglyceridemia and low HDL-C are components of the metabolic syndrome. With regard to associations of lipid levels with outcomes after donation, one study identified by the ERT compared kidney function and albuminuria at 5 years among donors with versus without predonation metabolic syndrome (Evidence Report Table 18, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table D15, SDC, <http://links.lww.com/TP/B432>). Although small differences in the outcomes were suggested, statistical comparisons were not performed. No studies were identified comparing postdonation outcomes based on lipid status alone. A recent meta-analysis based on data from nearly 5 million persons identified from 7 general population cohorts found no associations of total cholesterol or LDL-C with ESKD risk over median cohort follow-up of 4 to 16 years.⁷

Several prior guidelines recommend fasting lipid profiling as part of the donor evaluation,^{51,54,59,196} but do not define donor selection criteria based on lipid levels alone. A US Joint Societies work group consensus statement recognizes hypertriglyceridemia and low HDL-C as components of the metabolic syndrome, and considers impaired fasting glucose and other components of metabolic syndrome to be relative contraindications to donation in persons younger than age 50 years.¹⁹⁶ We endorse individualizing the decision to approve donation in persons with dyslipidemia based on their predicted long-term risk (considering complete demographic and health profile) in relation to the transplant program's acceptance threshold.

Tobacco Use

Cigarette smoking is a strong, modifiable risk factor for CVD (as well as other adverse health outcomes such as lung disease and cancer); smoking may also cause direct renal damage through microvascular injury and promotion of atherosclerosis, and has been associated with CKD in the general population.^{268,269} A recent meta-analysis based on data from nearly 5 million persons identified from 7 general population cohorts found that, compared with nonsmokers over median cohort follow-up of 4 to 16 years, current smokers had a 76% increase in the risk of ESKD (adjusted HR, 1.29^{1.76}_{2.41}) and past smokers had a 45% increase in risk (adjusted HR, 1.23^{1.45}_{1.71}).⁷ After calibration to annual ESKD incidence in the US healthy population, variations in the projected 15-year and lifetime risks of ESKD based on smoking status were generated according to age, sex, and race for healthy persons (assuming age-specific GFR, urine ACR 4 mg/g [0.4 mg/mmol], SBP 120 mmHg, BMI 26 kg/m², and absence of diabetes mellitus; Figures 20 and 21).

Although data on the outcomes associated with smoking among living kidney donors are limited, an analysis of linked US transplant registry and national death records found that while smoking was not significantly associated with perinephrectomy mortality, donors who smoked had approximately 5-times the adjusted mortality over 12 years compared with nonsmoking donors.²³ See chapter 4 (Preoperative Evaluation) for a discussion of the smoking-related risks before general surgery.

Some prior guidelines for the evaluation and care of living donors advise assessment of smoking, but make no recommendations concerning smoking in the selection of donors.^{51,196} Others advise encouraging smoking cessation

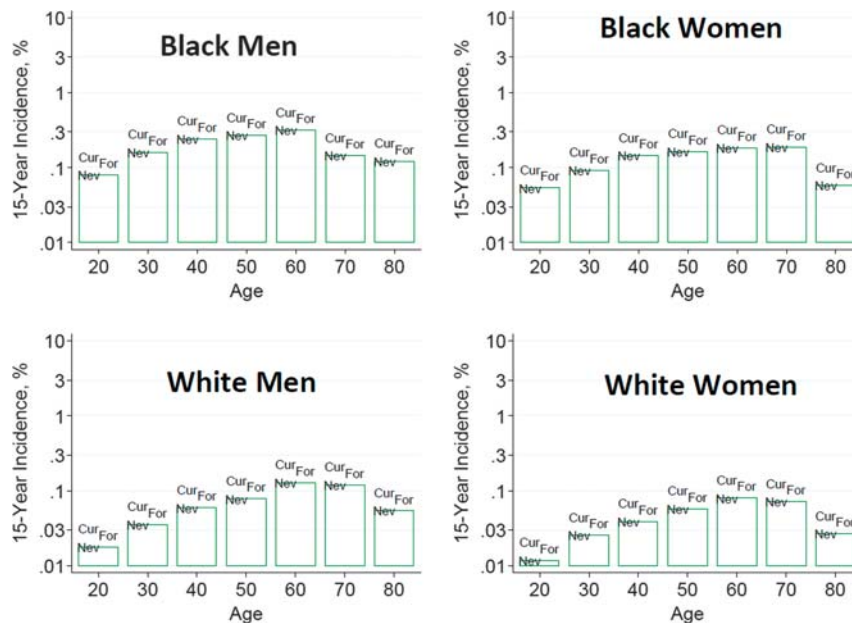


FIGURE 20. Estimated 15-year incidence (%) of ESKD in the United States according to baseline smoking status and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI, 26 kg/m²; and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Smoking status, current (Cur), former (For), and Never (Nev). ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

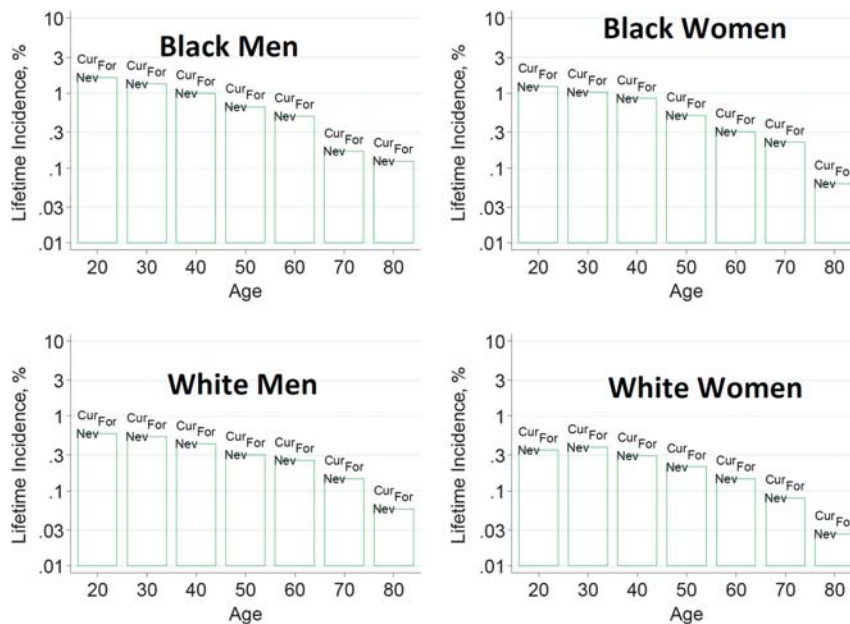


FIGURE 21. Estimated lifetime incidence (%) of ESKD in the United States according to baseline smoking status and demographic profile from the CKD-PC. *The base-case scenario is defined as: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 mL/min per 1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), SBP 120 mm Hg, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESKD in the low-risk population, and thus are likely imprecise. Smoking status, current (Cur), former (For), and Never (Nev). ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD-PC, Chronic Kidney Disease-Prognosis Consortium, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SBP, systolic blood pressure. Reprinted from Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411-421.⁷

without defining an exclusion criterion.^{48,50,215} Two guidelines recommend smoking cessation 4 weeks before donor nephrectomy,^{38,54} and guidelines from the Spanish Society of Nephrology and Spanish National Transplant Organisation emphasize long-term abstinence.⁵⁴ The 2000 National Kidney Foundation (NKF)/AST guidelines recommend considering acceptance of donor candidates who smoke only if they abstain from use of tobacco products for 6 months and have normal pulmonary studies.¹⁸ We endorse individualizing the decision to approve donation in active smokers based on their predicted long-term risk (considering complete demographic and health profile) in relation to the transplant program's acceptance threshold.

Impact of Donation on Cardiac Risk

The ERT identified 2 studies comparing cardiovascular events in donors versus healthy nondonors (very low quality of evidence; Evidence Report Table 8, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table D5, SDC, <http://links.lww.com/TP/B432>). In a study comparing 2028 living kidney donors in Ontario, Canada (1992 to 2009) with 20280 healthy, demographically matched nondonors, the risk of death or major cardiovascular events over a median 7 years follow-up (maximum, 18 years) was lower in donors than in healthy nondonors (2.8 vs 4.1 events per 1000 person-years, adjusted HR, 0.48 [0.66, 0.90]).²⁷⁰ The risk of death-censored major cardiovascular events was similar among donors and nondonors (1.7 vs 2.0 events per 1000 person-years).

A study with longer follow-up compared cardiovascular and all-cause mortality in 1901 kidney donors with a group of 32621 healthy, matched controls selected from a population-based survey in Norway (Nord-Trøndelag Health

Study [HUNT] I).³² Mortality was similar in donors versus nondonors over the first 15 years, but at 25 years after donation, cumulative all-cause mortality was approximately 18% among donors versus 13% among healthy nondonors (adjusted HR 1.1 [1.3, 1.5]). Limitations of this study include differences in accrual periods and in baseline characteristics (including age) between the donors and nondonors.^{271,272} Continued study is needed to assess the impact of donation on long-term survival in large, representative cohorts.

Limited data are available on the impact of donation on the pathophysiology of CVD. The Chronic Renal Impairment in Birmingham (CRIB)-Donor study included 68 donors at 2 United Kingdom centers (2011 to 2014), of whom 90% were white, and prospectively examined changes in left ventricular mass and other CVD surrogate markers at 12 months postdonation versus predonation, compared with changes in these parameters in healthy nondonors.²⁰² Donors had a greater increase in left ventricular mass (+7 ± 10 vs -3 ± 8 g; *P* < 0.001) and mass:volume ratio (+0.06 ± 0.12 vs -0.01 ± 0.09 g/mL; *P* < 0.01), but decreased aortic distensibility; donors were also more likely than controls to develop detectable highly sensitive troponin T levels. The increase in left ventricular mass among donors was independently associated with the magnitude of decrease in mGFR. These pilot observations warrant replication efforts in larger cohorts with longer follow-up to better define the impacts of donation on CVD surrogates and clinical events.

RESEARCH RECOMMENDATIONS

- Evaluate the outcomes of donors with metabolic and lifestyle risk factors for CVD, including perinephrectomy complications,

long-term mortality, CVD events, CKD/proteinuria and ESKD. Develop integrated risk assessment tools tailored for demographic and health profiles.

- Quantify the direct effects of donation on CVD risk.
- Assess effectiveness of predonation interventions including counseling and weight or lifestyle changes on long-term donor outcomes.
- Assess the impact of the duration and durability of predonation weight loss on donor acceptance and postdonation outcomes in those who proceed to donation.

CHAPTER 12: PREVENTING INFECTION TRANSMISSION

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 12 and therefore the following recommendations are “Not Graded.”

Evaluation

- 12.1: Risk for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections should be assessed before donation.
- 12.2: Donor candidates should be assessed for factors associated with an increased likelihood of endemic or unexpected infections, including geographic, seasonal, occupational, animal and environmental exposures.
- 12.3: Donor candidates should complete a urinalysis and testing for HIV, HBV, HCV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Treponema pallidum* (syphilis).
- 12.4: If indicated by regional epidemiology or individual history, donor candidates should complete testing for *Mycobacterium tuberculosis*, *Strongyloides*, *Trypanosoma cruzi*, West Nile virus, Histoplasmosis, and/or Coccidiomycosis.
- 12.5: Transplant programs should develop protocols to screen donor candidates for emerging infections in consultation with local public health specialists.
- 12.6: In general, donor infection risk factor and microbiological assessments should be performed or updated

as close in time to donation as possible. For HIV, HBV and HCV, screening should be current within 28 days of donation.

Selection

- 12.7: If a donor candidate is found to have a potentially transmissible infection, then the donor candidate, intended recipient and transplant program team should weigh the risks and benefits of proceeding with donation.

RATIONALE

Goals of Evaluation and Definitions

The goals of infection screening in donor candidates are to identify illnesses that may affect the donor candidate or the intended recipient.²⁷³⁻²⁷⁶ Evaluation of donor candidates to reduce the risk of transmissible infections should include assessment of the individual’s history of past infections and infectious disease risk factors (eg, risk of local endemic infections or travel to endemic areas), awareness of current patterns of geographically endemic infections, and focused microbiological screening.

Donor-derived infections can be classified as “expected” versus “unexpected.”^{274,276} The risks of “expected” donor-derived infection transmission are defined by donor and recipient screening, such as in high-risk scenarios for transmission of cytomegalovirus (CMV), Epstein-Barr virus (EBV) or toxoplasmosis from a seropositive donor to a seronegative recipient. “Expected” transmissions occur frequently and are managed by surveillance and/or prophylaxis strategies in the recipient after transplantation.²⁷⁷⁻²⁸² “Unexpected” donor-derived infections arise despite routine donor screening, such as human immunodeficiency virus (HIV) or hepatitis C virus (HCV) transmission due to false negative serologic testing or infection in a “window period.” The 2013 US Public Health Service (PHS) Guideline provides an evidence-based instrument to screen for behavioral factors associated with recent HIV, hepatitis B virus (HBV), or HCV infection (Table 16).⁷¹

TABLE 16.

US Public Health Service (PHS) 2013 Screening for factors associated with increased likelihood of recent HIV, HBV, or HCV infection

- Donors who meet one or more of the following criteria should be identified as being at increased risk for recent HIV, HBV, and HCV infections.
- Each factor listed reflects increased risk of all 3 pathogens as an aggregate, as there is overlap of associated risk, even though each factor does not convey risk from all pathogens equally.
- The first 6 factors address sexual contact; the definition of “had sex” refers to any method of sexual contact, including vaginal, anal and oral contact.

1. Have you had sex with a person known or suspected to have HIV, HBV, or HCV infections in the preceding 12 mo?
2. If male: Have you had sex with another man in the preceding 12 mo?
3. If female: Have you had sex with a man with a history of male-sex-with-male behavior in the preceding 12 mo?
4. Have you had sex in exchange for money or drugs in the preceding 12 mo?
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 mo?
6. Have you injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 mo?
7. Have you been in lockup, jail, prison, or a juvenile correctional facility for more than 72 h in the preceding 12 mo?
8. Have you been newly diagnosed with or have been treated for syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 mo?

- Donors who meet the following criterion should be identified as being at increased risk for recent HCV infection only:

9. Have you been on hemodialysis in the preceding 12 mo?

US PHS risk factors also include: 10. 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. 11. 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. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PHS, Public Health Service. Adapted with permission from Seem DL, Lee I, Umscheid CA, et al. Excerpt from PHS guideline for reducing HIV, HBV and HCV transmission through organ transplantation. *Am J Transplant*. 2013;13:1953-1962.⁷¹

“Unexpected” infectious disease transmissions through organ transplantation are rare, but may result in serious morbidity and mortality.^{274,283} Although most “unexpected” disease transmissions have involved deceased donors, cases of HIV and HCV transmissions from living donors have been reported.^{283,284} Notably, while reporting of suspected or documented donor-derived infection transmissions is required in the United States, reporting is voluntary in many other countries, and thus true incidence may be underestimated.

Infection transmission events may also be categorized according to the certainty that the donor is the origin of the infection, as opposed to reactivation or *de novo* infection in the recipient.²⁸⁵ Consensus-based definitions have been offered to standardize categorization as: “proven,” “probable,” “possible,” “unlikely,” “excluded,” “intervened upon without documented transmission,” and “positive assay without apparent disease transmission” events.²⁸⁵ “Proven” denotes clear evidence of the same infectious disease in the donor and at least one of the recipients, while “probable” is based on strong evidence suggesting but not proving a disease transmission. Use of standardized nomenclature may facilitate global tracking and study of such infectious disease transmissions as well as the comparison of data between published studies and reports collected globally.²⁸⁵

The risk of donor-derived disease transmission can be mitigated by the donor evaluation, including history taking (clinical, social/behavioral, travel) and microbiological testing. While microbiological testing should be performed in all donors for some pathogens [HIV, HBV, HCV, CMV, EBV, syphilis], focusing testing for other pathogens based on regional epidemiology and individual clinical, social or geographic risk factors should reduce the likelihood of procuring an organ that could transmit infection, while preserving opportunities for donation (avoiding false-positive test results) (Table 17). Approaches to screening should consider the virulence of a particular pathogen, available testing assays, and residual window periods for transmission despite screening^{283,286} as discussed according to specific pathogen below.^{71,273,275,276,286-291} Risks versus benefit must be balanced in the decision to use organs from infected donors, incorporating predonation treatment and recipient prophylaxis where appropriate. It is also necessary to inform the recipient and their care team of any known risks from the potential donated kidney.

Hepatitis B Virus

Evaluation of donor candidates should include US PHS risk factor screening for increased risk of HBV infection.⁷¹ All donor candidates should undergo testing for IgG hepatitis B core antibody (anti-HBcAb) and hepatitis B surface antigen (HBsAg).^{71,273,275} HBV DNA nucleic acid testing (NAT) can further stratify transmission risk in donor candidates from HBV endemic areas who are anti-HBcAb+, those with possible mutant HBV infections, and those with abnormal liver function tests or a past history of liver disease of unknown etiology. Testing for HBV should be performed as close as possible to the date of the organ recovery, but within no longer than 28 days before donation.⁷¹

Transplantation of kidneys from HBsAg+ donors is contraindicated for HBV- recipients, but may be considered for HBsAg+ recipients or recipients with HBV protective immunity,²⁷⁵ with informed consent of the recipient, possible

antiviral HBV treatment of the recipient and posttransplant monitoring. Kidney transplant recipients from anti-HBcAb+/HBsAg-/HBV DNA- donors appear to have little risk of acquiring active HBV infection.^{275,292} HBV NAT testing should be performed in donor candidates with isolated HBcAb+ status to further define risk of transmission. If the donor is anti-HBc+ and HBV DNA-, the risk of transmission is negligible,²⁹³ especially if the recipient is anti-HBcAb+ or has been effectively immunized against HBV. Still, the recipient should be informed of the small potential risk of disease transmission, and posttransplant monitoring should be performed.

Hepatitis C Virus

Evaluation of donor candidates should include US PHS risk factor screening for increased risk of HCV infection.⁷¹ Additional HCV risk factors identified by the US Centers for Disease Control for the general public (not specific to organ donation) include: persistently abnormal alanine aminotransferase concentrations, receipt of blood transfusion or blood components before 1992, receipt of clotting factor concentrates produced before 1987, recognized exposure among healthcare workers, and children born from HCV+ mothers.²⁹⁴ Regardless of past risk factors, all donor candidates should undergo testing for HCV infection as close as possible to the date of the organ recovery, but within no longer than 28 days before donation.⁷¹ Thus, behavioral risk factor assessment is used to inform pretest probability for interpretation of microbiological test results and to guide counseling to avoid infection after testing, not to determine which donor candidates should be tested. Approximately 15% of people with anti-HCV antibodies will not have detectable HCV-RNA in the serum. The 2013 US PHS guideline recommends that all living donor candidates should be tested for both anti-HCV antibody and for HCV RNA by NAT.⁷¹

Before the advent of new direct-acting antiviral agents, active HCV infection in a donor candidate was considered a contraindication to living donation, not only because of the risk of transmitting HCV to the recipient but also because of the risk of glomerular disease in the donor.²⁹⁵ HCV has been transmitted to naïve organ recipients from infected living and deceased donors.²⁹⁶ Organ transplantation from an HCV+ donor is associated with significant risk of HCV transmission, especially to HCV- recipients.²⁹⁷ However, how to handle the situation when an otherwise suitable living kidney donor is HCV+ may evolve in the era of effective treatment with direct-acting antiviral agents. It is of course best to use a living donor who is not HCV+. However, if research protocols are developed to assess living kidney donation from HCV+ persons, then regardless of the HCV status of the recipient it would make sense that protocols require donor treatment with direct-antiviral agents for at least 12 weeks, the treatment duration when most studies show sustained virologic response, before donating a kidney.²⁹⁸

Human Immunodeficiency Virus

Evaluation of donor candidates should include US PHS risk factor screening for increased risk of HIV infection.⁷¹ All donor candidates should undergo microbiological testing for HIV infection as close as possible to the date of the organ recovery, but within no longer than 28 days before donation.^{71,275} HIV infection is a contraindication to organ donation to HIV- recipients as the transmission of HIV by organ

TABLE 17.**Microbiological screening to reduce the risk of living donor-derived infection transmission**

| Pathogens | Target population for testing | Screening tests | Confirmatory/ additional tests | Timing of testing | Implications of positive test for donation and management |
|--|--|---|---|---|--|
| HIV (1/2) | All donor candidates | Anti-HIV-1/2 Ab or Ag/Ab combination assay | HIV NAT or HIV Ag/Ab combination assay | At initial screening and within no longer than 28 d before donation | <ul style="list-style-type: none"> Donation from HIV+ persons contraindicated unless as part of an approved research protocol for HIV+ recipients |
| HBV | All donor candidates | Anti-HBcAb and HBsAg | HBV NAT | At initial screening and within no longer than 28 d before donation | <ul style="list-style-type: none"> Donation from HBsAg + persons contraindicated for HBV– recipients, but may be considered for HBsAg+ recipients or recipients with HBV protective immunity,²⁷⁵ with informed consent of the recipient, possible antiviral HBV treatment of the recipient and posttransplant monitoring Donation from isolated HBcAb+ persons may be considered with informed consent of the recipient and posttransplant monitoring; consider HBV immunoglobulin and anti-HBV antiviral treatment in nonimmune recipients Donation from HCV+ persons contraindicated unless as part of an approved research protocol for HCV+ recipients |
| HCV | All donor candidates | Anti-HCV Ab HCV NAT also recommended in all donors ⁷¹ | | At initial screening and within no longer than 28 d before donation | <ul style="list-style-type: none"> Donation from HCV+ persons contraindicated unless as part of an approved research protocol for HCV+ recipients |
| CMV | All donor candidates | Anti-CMV IgG Ab | | At initial screening | <ul style="list-style-type: none"> Use to guide posttransplant antiviral prophylaxis and monitoring in the recipient, based on recipient serology and program protocol |
| EBV | All donor candidates | Anti-EBV IgG Ab (antiviral capsid antigen and/or antinuclear antigen) | | At initial screening | <ul style="list-style-type: none"> Use to guide assessment for and monitoring of risk of posttransplant lymphoproliferative disorder, especially in EBV-negative pediatric recipients |
| <i>Treponema pallidum</i> (Syphilis) | All donor candidates | Rapid plasma reagin (RPR) | Anti- <i>T. pallidum</i> Ab | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> Donation from persons with latent syphilis may be considered after treatment of the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant |
| <i>Mycobacterium tuberculosis</i> (TB) | Persons with any of the following risk factors: <ul style="list-style-type: none"> Lived in endemic regions Social or environmental risk factors such as: working in healthcare, jail/prison exposure, known TB exposure, homelessness, alcohol or other substance abuse | Chest radiograph (may be suggestive but not diagnostic) Tuberculin skin testing (TST) or interferon gamma release assay (IGRA) | Acid-fast bacilli staining, culture and/or NAT testing for active infection | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> Donation contraindicated from persons with active TB infection. Consideration of donation after treatment of active TB should be individualized Donation may be considered from persons with latent TB infection after initiation of chemoprophylaxis in the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant |

Continued next page

TABLE 17. (Continued)

| Pathogens | Target population for testing | Screening tests | Confirmatory/ additional tests | Timing of testing | Implications of positive test for donation and management |
|-----------------------------------|--|--|---|--|--|
| <i>Strongyloides</i> | Persons with any of the following risk factors: <ul style="list-style-type: none"> Born in 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 IgG Ab Serologic Ab testing preferred to stool examination, as stool screening tests may be negative in asymptomatic chronic infection. ²⁸⁶ | | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> Donation may proceed after treatment of the donor with an appropriate antiparasitic agent such as ivermectin |
| <i>Trypanosoma cruzi</i> (Chagas) | Persons with any of the following risk factors: <ul style="list-style-type: none"> Born or lived in endemic areas of Mexico, Central and South America Children of women who lived in endemic area Recipients of blood transfusion in endemic areas Prior history of Chagas | Anti- <i>T. cruzi</i> Ab (EIA or IFA test) | <i>T. cruzi</i> NAT is insensitive for chronic phase disease due to low levels of parasitemia | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> 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 |
| WNV | Persons with history of mosquito exposure or blood transfusions <ul style="list-style-type: none"> Risk varies by geography and season | Anti-WNV IgM Ab is available, but WNV NAT advised in initial screening | WNV NAT | Within 7-14 d of donation when testing is indicated | <ul style="list-style-type: none"> Donation should be delayed for 28 d when WNV NAT screening is positive, followed by repeat NAT and WNV IgM Ab testing, with further decisions based on combined results |
| Histoplasmosis | Persons who were born or lived in endemic regions (eg, Midwestern United States, Mississippi or Ohio River valleys, St. Lawrence River Valley in Canada, Gangetic West Bengal in India) | Chest radiograph (may be suggestive but not diagnostic) Anti-Histoplasmosis Ab (complement fixation, immunodiffusion or EIA) | Urine or serum antigen testing | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> 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 |
| Coccidiomycosis | Persons who were born or lived in desert areas of the Southwestern United States | Chest radiograph (may be suggestive but not diagnostic) Anti-Coccidioides Ab (complement fixation, immunodiffusion or EIA) | Urine or serum antigen testing | Perform or update as close in time to donation as possible | <ul style="list-style-type: none"> Donation may be considered from persons with Coccidiomycosis 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 |

Source: References^{71,273,275,276,286-291}
 Ab, antibody; Ag, antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EIA, enzyme immunoassay; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IFA, immunofluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; NAT, nucleic acid testing; WNV, West Nile Virus.

transplantation is well documented. Tests to detect HIV include antibodies generated against HIV antigens, direct detection of viral nucleic acid (NAT testing) or HIV antigen p24. Currently, antibodies against HIV antigens remain the most commonly used method for detection of HIV. The period from HIV exposure to the development of HIV antibodies is approximately 22 days, but can be up to 6 months. Thus the donor may be seronegative while potentially infectious.²⁸³ NAT testing can reduce the window period for HIV to between 5.6 and 10.2 days.²⁹⁹

In contrast to undetected donor disease transmission, medical advancements in HIV antiviral therapy have led to consideration of planned kidney transplantation from HIV+ donors to HIV+ recipients, such as recent experience described in South Africa.³⁰⁰ In the United States, the National Organ Transplant Act (NOTA) of 1984 prohibited the knowing procurement or transplantation of organs from an HIV infected donor, but in 2013 the HIV Organ Policy Equity (HOPE) Act repealed this prohibition and authorized the OPTN to develop standards for use of organs from known HIV infected individuals in HIV infected recipients. At this time, such donations and transplantation should occur only within the context of research protocols; protocols in the United States were developed by the National Institutes of Health (NIH).³⁰¹

Increased Risk Donors and Window Periods for HBV, HCV and HIV

Serological testing for infections has been highly effective in reducing the risks of donor-derived disease transmission. However, seroconversion requires the elaboration of antibodies against a specific pathogen and could be delayed for several weeks after infectious exposure. Testing during the window period for seroconversion may generate false-negative test results and could lead to inadvertent infection transmissions. Cases of donor-derived infection transmissions related to window period infections missed by serologic screening of donors have been reported.^{274,283} The period from HIV exposure to the development of HIV antibodies is 22 days on average, but can be up to 6 months.²⁷⁴ HBsAg enzyme-linked immunosorbent assays (ELISAs) have a window period of 38.3 to 49.7 days, while the time from HBV exposure to positive NAT testing ranges from 20.4 to 25.7 days. The window period for detection of HCV infection by ELISA is 38 to 94 days, but the duration of the window is substantially reduced to 6.1 to 8.7 days by the use of NAT.²⁷⁴

In 2007 in the United States, a previously uninfected deceased donor kidney transplant recipient tested positive for HIV and HCV infection. Routine donor serologic screening for HIV and HCV infection was negative; the donor's only known risk factor for HIV was having sex with another man. Four organs (2 kidneys, liver and heart) were transplanted to 4 recipients. NAT of donor sera and posttransplant sera from all recipients were positive for HIV and HCV.³⁰² This case highlighted the potential for donors to harbor HIV and HCV infection during the window period, when infection cannot be detected by antibody screening.

In 2009, a case of unexpected HIV transmission from a living organ donor in New York City was also reported.²⁸⁴ Based on this case, it was suggested that to reduce the risk for transmission of HIV through living donor organ transplantation, transplant programs should screen living donors

for HIV as close to the time of organ recovery as possible, using sensitive tests for both chronic and acute infections, namely, antibody and NAT testing.²⁸⁴

In 2013, the US PHS updated their "Guideline for Reducing HIV, HBV and HCV Transmission through Organ Transplantation," including recommended risk factor assessment in all donor candidates (Table 16).⁷¹ Living donor candidates with behaviors associated with increased risk of acquiring HIV, HBV or HCV identified during evaluation should receive individualized counseling on specific strategies to prevent exposure to these viruses during the period before donation surgery. Recommendations regarding microbiological testing include:

- All potential organ donors (living or deceased) should be tested for antibodies to HIV (ie, anti-HIV 1/2 Ab or HIV antigen/antibody [Ag/Ab] combination assay). All potential organ donors identified as being at increased risk for HIV infection should also be tested for HIV RNA by NAT or HIV antigen (eg, HIV Ag/Ab combination assay). Donor blood specimens should be obtained before procurement. Ab or Ag/Ab test results should be made available before transplantation.
- All potential organ donors (living or deceased) should be tested for both anti-HCV Ab and for HCV RNA by NAT. Donor blood specimens should be obtained before procurement. Antibody test results should be made available before transplantation.
- All potential organ donors (living or deceased) should be tested for anti-HBcAb and for HBsAg. Donor blood specimens should be obtained before procurement. Ag/Ab test results should be made available before transplantation.
- As noted above, the guideline recommends that all living donor candidates should be tested for HIV, HBV and HCV as close as possible to the date of the organ recovery operation, but within no longer than 28 days before surgery.

Whether retesting closer to the time of transplantation (eg, within 7 to 10 days before donation) is warranted to detect new infections and reduce the window period, overall or among high-risk donor candidates, remains controversial.^{303,304} A survey of living donor transplant programs in New York State in 2012 found that most responding programs had policies to retest living donors within 14 days of donation and while there were rare cases of delays in donation associated with repeat testing, no cancellations occurred.³⁰⁵

Epstein Barr Virus

The presence of anti-EBV antibodies signifies prior donor infection, with potential for reactivation of the latent virus and subsequent infection of the immunosuppressed recipient. While detection of the EBV in the living donor generally will not preclude donation, knowing that the kidney comes with latent EBV infection may be important in posttransplant recipient care.³⁰⁶ Infection with EBV manifests as a spectrum of diseases ranging from asymptomatic viremia to infectious mononucleosis to posttransplant lymphoproliferative disorder (PTLD).³⁰⁷ EBV disease and associated PTLD are more frequently seen when primary EBV infection occurs after transplant, a common scenario in EBV- pediatric solid organ transplant recipients who receive a kidney from an EBV+ donor. In the United States, the cumulative 1- and 5-year incidence of PTLD in 2010 was reported to be 1.3% and 2.4%, respectively, for pediatric kidney recipients but less

than 0.2% and 0.6% respectively, for adult recipients.³⁰⁷ When the donor is EBV+ and the recipient is EBV-, particularly in pediatric recipients, clinical vigilance is required after transplantation to detect PTLD.³⁰⁸ Intensity of EBV viral load and immunosuppressive therapies influence the risk for PTLD.³⁰⁷

Cytomegalovirus

Cytomegalovirus disease may result from reactivation of latent infection or primary infection transmitted by a kidney from a CMV+ donor. The laboratory methods for CMV diagnosis are serology, culture, antigenemia, and molecular methods such as CMV NAT, which is most commonly performed using real-time polymerase chain reaction.³⁰⁹ The main clinical utility of CMV serology is stratification of a transplant recipient's risk of CMV disease based on donor and recipient status.^{279,280,310}

The presence of anti-CMV antibodies in a donor candidate indicates prior infection, with the potential that the latent virus will reactivate and cause infection, particularly in the CMV- recipient. The detection of anti-CMV antibodies does not preclude donation, and infection risk can be anticipated and managed. Primary CMV infection is generally more severe than reactivation and recipients at highest risk are those who are CMV seronegative and receive a kidney transplant from a CMV seropositive donor. Matching CMV seronegative recipients with CMV seronegative donors is an effective strategy for reducing the risk of CMV infection but is rarely practical in the context of living donor kidney transplantation. CMV seropositive recipients may develop disease reactivation or donor-related infection. Thus organ donors and recipients should be tested for prior (latent) CMV infection using anti-CMV antibody for risk stratification and guidance of appropriate surveillance and/or antiviral prophylaxis after transplantation.³¹¹

Syphilis

Transmission of syphilis by organ transplantation has been documented.³¹² In the United States, all assays currently FDA-approved for detecting evidence of *T. pallidum* infection in organ and tissue donors are serologic assays.³¹³ There are 2 types of serologic assays: nontreponemal and treponemal. Nontreponemal assays use a combination of cardiolipin, cholesterol, and other lipid substances released from damaged cells as the antigenic source to detect antibodies against cardiolipin, which circulates in the sera of individuals infected with syphilis and may also be present in individuals with a variety of other conditions. Reactivity to cardiolipin generally disappears within a year or 2 after successful treatment of syphilis.³¹³ Treponemal assays detect *T. pallidum* antibodies, which tend to remain elevated for life. Therefore, treponemal assays cannot distinguish between recent, remote, and previously treated infection. Donors are screened for serological evidence of syphilis with a nontreponemal assay such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) test, which should be confirmed later with a treponemal Ab immunoassay. A recent study found that current screening of deceased organ donors by RPR yields a significant number of false-positive results. Use of alternative tests or the routine use of confirmatory tests may reduce the frequency of false-positive syphilis results in potential deceased and living organ donors.³¹⁴

As there are multiple available syphilis assays providing different types of information, no single blood assay can conclusively define an individual's disease status. For donor candidate testing, specimen collection and the time available to perform testing must be considered in choosing an appropriate donor screening assay.³¹³ Living donor candidate evaluation is less time constrained than the screening of deceased donors, and thus screening with nontreponemal assays followed by confirmation with treponemal assays is preferred if feasible.

Transmission of syphilis has been reported in the United Kingdom to 2 recipients from a deceased donor with a past history of treated disease, supporting recommendations of penicillin for treatment of recipients of deceased donor organs from serologically reactive donors.³¹² Donation from living persons with latent syphilis may be considered after treatment of the donor candidate before donation (eg, with penicillin), informed consent of the recipient, and recipient monitoring after transplant.

Tuberculosis (TB)

The incidence of posttransplant TB varies substantially depending on the local prevalence of TB infection, which ranges from 1% in Germany to nearly 14% in India.²⁹⁰ Studies in the United States and Europe have estimated that 0.35% to 6.6% of transplant recipients develop TB (across organ and donor types), and that 4% posttransplant TB cases are donor-derived.^{290,315} TB is one of the more common bacterial causes of donor-derived infection in the United States.³¹⁶

Consensus-based recommendations for the diagnosis and management of TB in organ donors include:^{288,290,317}

- Risk stratification of all donor candidates, according to:
 - Place of birth, residence or travel to a geographically endemic region, with increased risk defined by residence greater than 3 months or relief work in a high prevalence region
 - Social risk factors including working in healthcare, prison exposure/incarceration, known TB contact, homelessness, alcohol or other substance abuse
 - Medical risk factors including history of untreated TB or radiographic evidence of prior TB; underweight BMI and diabetes have also been correlated with increased TB risk
- Chest radiograph in all donor candidates
- Consideration of urinalysis with microscopy, genitourinary imaging, urine acid-fast bacilli smear and culture in living donor candidates from countries with intermediate to high TB prevalence
- Consideration of immune-based diagnostic testing by tuberculin skin testing (TST) or the interferon-gamma release assay (IGRA)
 - Diagnostic tests for latent TB infection are limited in sensitivity and have a relatively low predictive value for development of active TB.³¹⁸ The specificity of TST is related to the burden of TB in that region or country, and IGRA has superior specificity in populations where use of Bacillus Calmette-Guérin vaccination is common based on use of specific antigens absent in Bacillus Calmette-Guérin strains
 - Immune testing of all donor candidates or selective testing based on risk profile are considered acceptable options
 - Persons with positive immune-based TB testing who are asymptomatic and do not have signs of active TB are considered to have latent TB infection
- Donation from persons with active TB is contraindicated. Risk of transmission from donors with prior appropriately

treated active TB appears to decline with longer time from treatment. Donation may be considered with informed consent of the recipient, consideration of recipient chemoprophylaxis under the guidance of an infectious disease specialist, and recipient monitoring after transplant.

- Living donor candidates with latent TB infection should be offered chemoprophylaxis according to local or national guidelines. Donation may be considered from persons with latent TB infection with informed consent of the recipient and recipient monitoring after transplant. As there are no data on optimal duration of treatment before donation, individualization of the timing of donation in relation to start of donor chemoprophylaxis is recommended. Chemoprophylaxis of recipients from donors with latent TB infection should also be considered, especially if the donor did not complete chemoprophylaxis before donation.³¹⁷

A recent study in Korea, a country with an intermediate prevalence of TB, prospectively evaluated living donors using the TST and *Mycobacterium tuberculosis*-specific enzyme-linked immunosorbent spot (ELISPOT) IGRA.³¹⁹ Among the 205 living donors, 31% had a positive TST and 47% had a positive ELISPOT. Based on the high rate of suspected latent TB infection detected by screening living donors using TST and ELISPOT in a country with a TB intermediate prevalence, the authors recommended further study of the cost effectiveness of recipient TB chemoprophylaxis.³¹⁹

Urine Culture

Urine should be sent for culture from all donor candidates at evaluation, and ideally repeated close to the time of donation (eg, within the preceding 2 weeks). Acute symptomatic urinary tract infection is a reason to postpone donation. However, detection of asymptomatic bacteriuria is not infrequent, especially in female donors. A history of urinary tract infection in a donor candidate, particularly if there is a family history of reflux nephropathy, or in a male, requires detailed imaging of the kidneys (eg, assessment for cortical scarring). Any active bacterial or fungal infection in the donor should be treated and, ideally, resolved before donation and transplantation.²⁸³ Antibiotic prophylaxis should be given to the recipient if resolution of infection is not confirmed before donation, as a positive urine culture early after transplantation, even when asymptomatic, may be associated with increased risk of acute rejection in the recipient.^{320,321}

Seasonal and Geographically Endemic Infections

The donor candidate evaluation should include assessment of place of residence, travel, seasonal, occupational, and recreational risks, as well as prior infections in the donor candidate and family members (Table 17). A number of geographically endemic and seasonal diseases have been transmitted through organ donors including: *Strongyloides*, *Trypanosoma cruzi* (Chagas disease), West Nile virus, histoplasmosis, coccidiomycosis, *Aspergillus*, toxoplasmosis, malaria, Creutzfeldt–Jacob disease, human T-cell lymphotropic virus infection, and schistosomiasis.^{273,275,286} Other viral, fungal, bacterial and parasitic pathogens recognized as sources of organ donor-derived infection transmissions are listed in Table 18. Living donation affords sufficient time for microbiological testing, donor treatment and deferral of donation and transplantation until resolution of infection. Organ donation may be possible after treatment of the donor candidate before donation,

TABLE 18.

Social and clinical factors associated with increased likelihood of geographically endemic infections and infections related to specific exposures

| | |
|---|--|
| Geographic risks (including duration of time spent in a location) | <ul style="list-style-type: none"> • Home country/region • Place of birth (outside vs inside home region) • Prolonged residence outside home region (recent or distant) • Occupational or recreational travel to other countries and/or regions • Countries of origin for close family members • Ingestion of well water |
| Occupational risks | <ul style="list-style-type: none"> • Healthcare workers • Veterinarians, animal care workers • Landscapers, park rangers, and other outdoor workers • Occupations with international travel, such as Peace Corps, international journalists • Medical mission trips (consider a 3-mo washout period before donation to allow identification of subclinical disease) |
| Seasonal risks | <ul style="list-style-type: none"> • Warm weather and insect exposure—eg, local West Nile Virus, dengue, Chikungunya virus, local rickettsial infections, Lyme disease |
| Hobbies | <ul style="list-style-type: none"> • Hunting/dressing game, taxidermy • Time living outdoors including camping, swimming in lakes, drinking stream water, insect exposures • Adventure sports • Gardening |
| Significant animal exposure (wild and/or domestic) | <ul style="list-style-type: none"> • Large numbers of cats or dogs or any unusual pets, including whether pets reside mainly indoors or outdoors • Laboratory/research animals • Veterinarian/veterinarian assistant |
| Family members and close contacts with potential risk factors | <ul style="list-style-type: none"> • Geographic or seasonal infections previously diagnosed in close family members or other contacts may predict risk for subclinical infection in donor candidate |
| Personal history of seasonal or geographic infection in donor candidate, even if remote | |

Adapted from OPTN *Ad Hoc* Disease Transmission Advisory Committee²⁸⁷

informed consent of the recipient, as well as recipient monitoring and possible prophylaxis after transplant (Table 19).

Strongyloidiasis typically occurs only in the setting of specific environmental exposures. Donor-derived *Strongyloides* hyperinfection cases with high associated mortality have been reported, including from kidney transplantation.^{322–324} Consensus-based recommendations of the 2013 *AST Infectious Diseases Community of Practice* work group and the OPTN *Ad Hoc* Disease Transmission Advisory Committee (DTAC) support screening for *Strongyloides* in the following potential organ donors^{286,287}:

- Persons who were born in or lived in tropical or subtropical countries where sanitation conditions are substandard, including candidates with prior military service in endemic areas. The WHO emphasizes a correlation between improved sanitation and human waste disposal with the disappearance of *Strongyloidiasis*.³²⁵ *Strongyloidiasis* has occurred in most countries with the exception of Canada, Japan and Northern Europe.

TABLE 19.**Recognized organ donor-derived infection transmissions**

| Viruses | Bacteria |
|---|---|
| Adenovirus | <i>Mycobacterium tuberculosis</i> |
| BK polyoma virus | <i>Nocardia</i> spp. |
| Cytomegalovirus | <i>Rickettsia rickettsii</i> (Rocky Mountain Spotted Fever) |
| Epstein-Barr virus | <i>Treponema pallidum</i> (syphilis) |
| Herpes simplex virus | <i>Borrelia</i> (Lyme disease) |
| HIV | |
| HBV | |
| HCV | |
| Hepatitis E virus | |
| Human T-cell lymphotropic virus 1 and 2 | |
| Influenza A/B | |
| Lymphocytic choriomeningitis virus | |
| Parvovirus B19 | |
| Rabies | |
| West Nile virus | |
| Fungi | Parasites |
| <i>Aspergillus</i> spp. | <i>Babesia microti</i> |
| <i>Candida</i> spp. | <i>Balamuthia mandrillaris</i> |
| <i>Coccidioides immitis</i> | <i>Malaria</i> spp. |
| <i>Cryptococcus neoformans</i> | <i>Naegleria fowleri</i> |
| <i>Histoplasma capsulatum</i> | <i>Toxoplasma gondii</i> |
| <i>Scopulariopsis brevicaulis</i> | <i>Trypanosoma cruzi</i> |
| Zygomycetes (Mucor) | <i>Schistosoma</i> spp. |
| | <i>Strongyloides stercoralis</i> |

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus. Adapted by permission from Macmillan Publishers Ltd: Fishman JA, Grossi PA. Donor-derived infection—the challenge for transplant safety. *Nat Rev Nephrol.* 2014;10:663–672.²⁷⁴

- Persons with significant exposure to soil in Appalachia or the Southeastern United States, including walking barefoot.
- Persons with unexplained eosinophilia and travel to endemic area.
- Persons reporting a prior history of *Strongyloides* infection.

Serologic Ab testing is the preferred screening test for *Strongyloides* infection, as the sensitivity of stool testing is limited and multiple stool screening tests may be negative in asymptomatic chronic infection.²⁸⁶ *Strongyloides* IgG antibody testing (ELISA-based) is available in many reference labs.

Infected donor candidates should be treated with a minimum of 2 doses of ivermectin before donation (200 µg/kg orally daily on 2 consecutive days)^{286,287} Because of the potential for persistence of migrating larvae and eggs in the tissues, some experts recommend repeating this treatment 2 weeks later to cover an autoinfection cycle. After treatment, follow-up laboratory testing of the donor candidate before donation to confirm cure has been deemed unnecessary, unless reexposure has occurred.^{286,287}

Chagas disease is transmitted through contact with infected triatomine “kissing” bugs, and residents of poorly constructed housing where these insects reside are at greatest risk of acquiring infection. Transmission has also been reported from mother to infant, through blood transfusion, and through organ transplantation. Consensus-based recommendations of the 2011 Chagas in Transplant Working Group, the 2013 AST Infectious Diseases Community of Practice work group, and OPTN DTAC support screening in the following potential organ donors^{286,287,289}:

- Those who were born in or lived in an endemic region in Mexico, Central or South America
- Children of women who lived in endemic regions and whose *T. cruzi* infection status is positive or unknown
- Persons who received a blood transfusion in endemic regions
- Persons reporting a prior history of Chagas disease

Assessment of outcomes of 32 transplant recipients who received organs from 14 *T. cruzi* seropositive donors in the United States from 2001 to 2011 confirmed transmission in 9 recipients from 6 donors, including 2 of 15 (13%) kidney recipients, 2 of 10 (20%) liver recipients and 3 of 4 (75%) heart recipients.³²⁶ Recommended monitoring posttransplant comprised regular testing by polymerase chain reaction, hemoculture, and serologic testing. Thirteen recipients had no or incomplete monitoring; transmission was confirmed in 5 of these recipients; 4 of the 5 recipients had symptomatic disease and all 4 died, although death was directly related to Chagas disease in only one. Nineteen recipients had partial or complete monitoring for *T. cruzi* infection with weekly testing by polymerase chain reaction, hemoculture and serologic testing; transmission was confirmed in 4 of the 19 recipients with no cases of symptomatic disease. Based on such evidence, recent guidelines support consideration of kidney donation from donors with *T. cruzi* infection on an individual basis with consent of the recipient.^{286,287,289} Recipients must be informed of the need for participation in close monitoring and the available therapeutic interventions in the event of infection, as the medications available for treatment are not FDA-approved and are generally only available through specific protocols. Consideration of the recipient’s access to testing and monitoring is imperative, as geographic concerns may impact the ability to follow the recipient closely.

West Nile Virus is a flavivirus that is transmitted by mosquitoes in an enzootic cycle with birds. When testing is indicated, screening living donor candidates by West Nile virus NAT within 7 to 14 days of donation has been recommended.^{273,291} Proposed strategies for when to begin testing living donor candidates for West Nile virus include when regional blood banks start performing NAT screening or testing during a defined period of time that reflects the peak of local West Nile virus infection.²⁹¹ The 2013 AST Infectious Diseases Community of Practice work group recommended delaying donation for 28 days when NAT screening is positive, followed by repeat NAT and immunoglobulin M (IgM) Ab testing with the following management pathways based on the results²⁷³:

- NAT+: Defer donation for at least 120 days. Donation deemed likely to be safe if clearance of viremia demonstrated by NAT testing after 120 days
- NAT-/IgM Ab-: Consider initial NAT testing to reflect a false positive result. Donation may be considered after infectious disease consult
- NAT-/IgM Ab+: Suggests infection with clearance of viremia. Donation may be considered after infectious disease consult

Emerging Infections

Transplant programs must maintain awareness of new and emerging infections that may be transmissible through organ donation. Availability of microbiological testing for new infections may be limited or available only at specialized laboratories, emphasizing the importance of careful assessment of exposure history in the donor candidate evaluation.

For example, during the Ebola virus outbreak of 2014, the OPTN DTAC recommended that evaluation of candidates for organ donation should include screening for travel and epidemiologic risk factors for Ebola exposure, including³²⁷:

- Travel to a country where an Ebola outbreak occurred within the past 21 days
- Contact with blood, other body fluids, or human remains of a patient known or suspected to have Ebola
- Exposure as a healthcare worker to patients known to have Ebola
- Direct handling of bats or nonhuman primates from disease-endemic areas

If risk factors for Ebola are identified, the OPTN DTAC recommends aborting the evaluation process and excluding donation.

Zika virus is a mosquito-borne pathogen that gained attention in association with an outbreak of primary microcephaly among children born to infected mothers in Brazil in 2015, followed by rapid geographic spread across the Americas, prompting recognition as a global health emergency.³²⁸ Other complications of Zika virus infection include acute autoimmune neuropathies such as Guillain-Barré syndrome. Guidance from the OPTN DTAC, the AST, and the ASTS recommend considering donor deferral if there is history of travel to Zika-endemic areas in the 28 days before donation.³²⁹ In the case of potential living donors with Zika infection, donation should be deferred where possible.

Transplant programs should develop and maintain screening protocols to address emerging infections, including awareness of evolving geographic exposure patterns in consultation with local public health specialists. Current information on global health outbreaks are reported by organizations such as the US Centers for Disease Control.³³⁰

What Prior Guidelines Recommend

US OPTN Policy for Medical Evaluation Requirements for Living Donors mandates similar screening tests as recommended in our current guideline: anti-CMV Ab, anti-EBV Ab, anti-HIV 1,2 Ag/Ab, HBsAg, anti-HBcAb, anti-HCV Ab, and syphilis testing.⁵¹ US transplant programs are required to determine whether the donor has TB exposure risk factors and to test accordingly. US programs are also required to develop protocols to determine who to screen for geographically endemic and seasonal infections such as *Strongyloides*, *Trypanosoma cruzi* and West Nile virus.

The British Transplantation Society has also recommended testing for HBV, HCV, EBV, CMV and HIV as part of donor candidate evaluation.⁴⁸ The Spanish Society of Nephrology and Spanish National Transplant Organization recommendations for living donor kidney transplantation included the following as routine tests in the donor candidate evaluation: HIV [a], Hepatitis B: HBsAg [a], anti-HBcAb IgM/IgG [b], HBsAb, HBV DNA in plasma if anti-HBcAb+, Hepatitis C (ELISA and polymerase chain reaction) [a], CMV IgG/IgM [b], EBV IgG/IgM [b], *Toxoplasma* test, Syphilis (RPR- fluorescent treponemal antibody) [b], *Brucella* [b]. Here, [a] stands for 'Donation is contraindicated with positive results' and [b] stands for 'Donors and/or recipients have to undergo treatment with positive results'.⁵⁴

In contrast to this recommendation, we believe that testing for *Toxoplasma* and *Brucella* should be guided by geography

and risk factors for possible exposure. Also, since the Spanish Society of Nephrology and Spanish National Transplant Organization guidelines were published in 2010,⁵⁴ new research published above supports revision of some categories of [a] 'Donation is contraindicated with positive results.'

RESEARCH RECOMMENDATIONS

- Define the incidence of donor-derived disease transmission through improved monitoring and reporting. This is critical since determining the relative importance of specific pathogens and risk mitigation strategies requires collection of global data.
- Develop and validate risk assessment questionnaires and protocols for living donor-derived infections, taking into consideration behavioral, occupational, hobby-related, geographic and seasonal exposures.
- Optimize and standardize methods of microbiological assays for donor infection screening and diagnosis.
- Assess results of planned US NIH studies of transplantation from HIV+ donors to HIV+ recipients to develop guidance on appropriate consideration of such transplants in clinical practice.
- Determine, through clinical trials or observational protocols with informed consent, whether kidney donation and transplantation can be performed with acceptable safety and outcomes for the donor and recipient in the following scenarios:
 - Donation from HCV+ living donors to HCV+ recipients after antiviral treatment of the donor
 - Donation from HBsAg + living donors to HBsAg + recipients or recipients with HBV

CHAPTER 13: CANCER SCREENING

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 13 and therefore the following recommendations are "Not Graded."

Evaluation

- 13.1: Donor candidates should undergo cancer screening consistent with clinical practice guidelines for the country or region where the donor candidate resides. Transplant programs should ensure that screening is current according to guideline criteria at the time of donation.

Selection

- 13.2: In general, donor candidates with active malignancy should be excluded from donation. In some cases of active malignancy with low transmission risk, a clear management plan and minimal risk to the donor, donation may be considered.
- 13.3: A kidney with a small simple (Bosniak I) cyst can be left in the donor, particularly if there are compelling reasons for donating the contralateral kidney.
- 13.4: Donation of a kidney with a Bosniak II renal cyst should proceed only after assessment for the presence of solid components, septations, and calcifications on the preoperative computed tomography scan (or magnetic resonance imaging) to avoid accidental transplantation of a kidney with cystic renal cell carcinoma.
- 13.5: Donor candidates with high grade Bosniak renal cysts (III or higher) or small (T1a) renal cell carcinoma curable by nephrectomy may be acceptable for donation on a case-by-case basis.

13.6: Donor candidates with a history of treated cancer that has a low risk of transmission or recurrence may be acceptable for donation on a case-by-case basis.

RATIONALE

Goals of Evaluation

The goals of malignancy screening are two-fold. First, it is necessary to identify cancers to protect the health of the donor candidate. Reduced kidney function may compromise long-term health outcomes in individuals requiring cancer treatments with nephrotoxic or cardiovascular side effects (eg, some chemotherapies or radiation treatments). Potential psychosocial stresses of living donation may also be prohibitive in individuals faced with stress of an active cancer diagnosis and treatment. Second, the evaluation must mitigate risks of donor-derived malignancy transmission to the transplant recipient.

General Population Cancer Screening and Incidence

Most jurisdictions have regional recommendations for which members of the general population should be screened for common cancers, including frequency of screening and acceptable testing modalities. These include screening recommendations for colon, breast, cervical, prostate, and lung cancer.³³¹⁻³³³ There are potential harms associated with cancer screening, as with any form of screening, if additional testing and procedures are undertaken in patients who ultimately do not have cancer. These risks should be included in the consent for evaluation of the living donor candidate. Transplant programs in countries without local clinical practices guidelines can refer to guidelines from countries or regions most similar to their population.³³¹⁻³³³

The limited available data on cancer diagnoses after living kidney donation support that donor evaluation and selection practices reduce the incidence of postdonation cancer below that of general population controls, although risk reduction may dissipate with time after donation.³³⁴ However, cases of cancer diagnoses including melanoma and uterine cancer within less than 1 year of donation have been reported,³³⁴ emphasizing the need for up-to-date assessment for malignancy before donation.

Recurrence Risk after Treated Cancer

Recurrence rates after treated cancer from the general population may be used to guide observation periods after cancer treatment before considering organ donation. Average times to recurrence vary by cancer type. Consideration of living donation from a person with a history of treated cancer should include consultation with the donor candidate's oncologist to confirm that individual case factors are associated with "low" (eg, less than 1%) risks of both lifetime recurrence and disease transmission, and that long-term surveillance will not require frequent imaging that may be restricted by reduced GFR (eg, CT scans with iodinated contrast or magnetic resonance imaging (MRI) scans requiring gadolinium).

Donor-Derived Malignancy Transmission

Cases of malignancy transmission from deceased or living organ donors to recipients have been reported. A recent systematic review examined all case reports, case series and

registry studies describing the outcomes of kidney transplant recipients with donor-derived cancer transmission published through December 2012.³³⁵ Among 104 donor-transmitted cancer cases identified from 69 studies, the most common transmitted cancer types were renal cancer (n = 20, 19%), followed by melanoma (n = 18, 17%), lymphoma (n = 15, 14%) and lung cancer (n = 9, 9%). Recipients with transmitted renal cancers had the best outcomes, with more than 70% of recipients surviving for at least 24 months after transplantation. Patients with melanoma and lung cancers had the worst prognosis, with less than 50% of recipients surviving beyond 24 months from transplantation. While these data support that donor-derived cancer transmission is uncommon, potential reporting-bias prevents accurate incidence estimates. This report highlights the high mortality associated with donor-derived melanoma and lung cancer transmission.

A history of melanoma is particularly concerning when evaluating a living donor candidate. Aside from the potential for late recurrence and subsequent complications in the donor, melanoma transmission to transplant recipients has been reported after apparent dormancy in the donor for decades, supporting the ability of melanoma cells to remain dormant at distant sites for decades and then reactivate upon exposure to immunosuppression,^{336,337} and transmission can be fatal. The Israel Penn International Transplant Tumor Registry, a voluntary registry of more than 250 cases of organs transplanted from donors with a history of malignancy that captures tumor histology, donor risk factors, method of tumor presentation and recipient outcome, described 13 donors with a history of melanoma (but deemed free of the disease at donation) who provided organs to 28 recipients.^{338,339} Melanoma transmission occurred in 21 recipients (75%), of whom 13 (62%) died from metastatic disease. The time to diagnosis ranged from 2.5 to 42 months (median, 10.5 months), and the only patients who survived were those who underwent nephrectomy and cessation of immunosuppression. While some prior general population guidelines such as the US Preventative Services Task Force state that there is insufficient evidence to recommend routine whole body skin exam screening among general adults,³⁴⁰ skin examinations for donor candidates with increased recreational or occupational exposure to sunlight, family or personal history of skin cancer, or clinical evidence of precursor lesions may be warranted. Pathology reports of living donor candidates with a prior history of skin cancer resection should be reviewed to ensure that the cancer was not a melanoma before approving donation.

Selection

In 2011, the OPTN DTAC Malignancy Subcommittee published a classification of 6 risk categories for donor-derived malignancy transmission and suitability of organ donation from persons with active or prior malignancy histories³⁴¹; this was also recently reviewed in Kirchner et al.²⁷³ Classification was based on review of cancer registry reports, published literature, and data submitted to the OPTN. This article did not differentiate between cancer transmissions from living compared with deceased donors due to limited data.

- "No significant risk" was defined as benign tumors where malignancy has been excluded.

- “Minimal risk” was defined as tumors with 0% to 0.1% transmission events per organ transplanted from donors with the specific tumor, and includes nonmelanoma skin cancers, noninvasive carcinoma of the bladder (for nonrenal transplants only), small papillary or follicular carcinoma of the thyroid and solitary, well-differentiated (≤ 1 cm) renal cell carcinoma.
- “Low risk” (0.1-1% transmission events per organ transplanted from affected donors) includes small renal cell carcinoma (1-2.5 cm), low grade central nervous system (CNS) tumors, primary CNS mature teratoma, solitary papillary thyroid carcinoma (0.5-2.0 cm), minimally invasive follicular carcinoma (1.0-2.0 cm), and history of treated non-CNS malignancy (≥ 5 years prior) with greater than 99% probability of cure.
- “Intermediate risk” (1-10% transmission events per organ transplanted from affected donors) includes breast and colon carcinoma *in situ*, resected well differentiated renal cell carcinoma (4-7 cm) and history of treated non-CNS malignancy (≥ 5 years prior) with probability of cure between 90-99%.
- “High risk” ($>10\%$ transmission events per organ transplanted from affected donors) includes current or past history of melanoma, leukemia/lymphoma or neuroendocrine tumors, breast or colon cancer stage 1 or higher, choriocarcinoma, any CNS tumor with ventriculoperitoneal or ventriculoarterial shunt, metastasis or high grade (III/IV) histology, metastatic carcinoma, sarcoma, lung cancer Stage I-IV, and renal cell carcinoma greater than 7 cm. The high risk category also included any treated non-CNS malignancy with insufficient follow-up to predict behavior, incurable or with $<90\%$ probability of cure, or any other active cancer not previously classified.
- Tumors of “unknown risk” were defined as a final category.

The authors suggested that donors in the “no significant risk” category are standard, and that organs from donors with “minimal risk” malignancies may be used for transplantation based on clinical judgment with informed consent of the recipient. The authors also proposed that organs from donors with “intermediate risk” malignancies could be considered for transplantation with informed consent for recipients who face substantial mortality without transplantation. This classification scheme should be updated with new information as data become available.

Considerations Related to Renal Cysts and Renal Cell Carcinoma

The development of kidney cancer in a patient with a single kidney is very concerning because the surgical treatment of renal tumors may result in loss of function of the remaining kidney. The age-stratified lifetime cumulative incidence of kidney cancer is low. In a matched cohort study of 2119 donors in Ontario Canada (1992-2010) and 21 190 nondonors from the general population with similar baseline health, no living kidney donor in the cohort received a partial or total nephrectomy of their remaining kidney during follow-up.³⁴²

The decision to approve donation in a person with kidney cysts depends on radiographic characteristics (Tables 20 and 21). Because simple (Bosniak I) renal cysts are not associated with increased risk of complications, organ dysfunction, or cancer, simple cysts are not contraindications to kidney donation. Cases of back table excision of small renal cell carcinomas after donor nephrectomy, followed by use of the kidney for transplantation have been reported.³⁴⁵⁻³⁴⁸ Based on review of cancer registry reports, published literature and disease transmission cases reported to the OPTN, a 2011 OPTN DTAC Malignancy Subcommittee

TABLE 20.

Bosniak renal cyst classification system

| Category | Description |
|-----------------------|---|
| I | A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance |
| II | A benign cyst that may contain a few hairline thin septa in which “perceived” enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high attenuation lesions < 3 cm (so-called high-density cysts) that are well marginated and do not enhance are included in this group. Cysts in this category do not require further evaluation |
| III (F for follow-up) | Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions > 3 cm are also included in this category. These lesions require follow-up studies to prove benignity |
| III | “Indeterminate” cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (eg, hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma), some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma |
| IV | These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft-tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal |

Reprinted with permission from Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. *Urology*. 2005;66:484-488.³⁴³

TABLE 21.**International TNM staging system for renal cell carcinoma****T: Primary tumor**

| | | | |
|-------------------------|---|-------|----|
| TX | Primary tumor cannot be assessed | | |
| T0 | No evidence of primary tumor | | |
| T1a | Tumor ≤ 4.0 cm and confined to the kidney | | |
| T1b | Tumor > 4.0 cm and ≤ 7.0 cm and confined to the kidney | | |
| T2a | Tumor > 7.0 cm and ≤ 10.0 cm and confined to the kidney | | |
| T2b | Tumor > 10.0 cm and confined to the kidney | | |
| T3a | Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia | | |
| T3b | Tumor grossly extends into the vena cava below the diaphragm | | |
| T3c | Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava | | |
| T4 | Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland) | | |
| N: Regional lymph nodes | | | |
| NX | Regional lymph nodes cannot be assessed | | |
| N0 | No regional lymph nodes metastasis | | |
| N1 | Metastasis in regional lymph node(s) | | |
| M: Distant metastases | | | |
| MX | Distant metastasis cannot be assessed | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis present | | |
| Stage grouping | | | |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T1 or T2 | N1 | M0 |
| | T3 | Any N | M0 |
| Stage IV | T4 | Any N | M0 |
| | Any T | Any N | M1 |

Reprinted from Campbell SC, Lane BR. Chapter 57: Malignant renal tumors. In: *Campbell-Walsh Urology*, 11th Edn. Wein AJ, Kavoussi LR, Partin AW, et al. (eds). Elsevier, pp. 1314–1364, 2016.³⁴⁴

concluded, from a disease-transmission perspective, that "... kidneys with small, solitary, well differentiated renal cell carcinoma may be usable for transplantation provided the lesion itself is completely resected."³⁴¹ While partial (rather than complete) nephrectomy is often the treatment choice for small renal cell carcinomas for the purpose of nephron-sparing with comparable cure rates in affected individuals, persons planning kidney donation intend to undergo complete nephrectomy. Thus, the decision to proceed with donor nephrectomy in an individual with a high grade Bosniak cysts or suspected kidney cancer based on pre-donation imaging should incorporate considerations of the anticipated risk of future carcinoma in the donor's contralateral kidney, risk of disease transmission to the recipient (including whether the lesion is amenable to complete back table excision), chances of possible discard without transplantation after nephrectomy. Donation of a kidney with a Bosniak II renal cyst should proceed only after assessment for the presence of solid components, septations, and calcifications on the preoperative computed tomography scan (or magnetic resonance imaging) to avoid accidental transplantation of a kidney with cystic renal cell carcinoma. Procurement and transplantation of living donor kidneys with Bosniak (III or higher) renal cysts or small (T1a) renal cell carcinoma curable in the donor by nephrectomy and amenable to complete excision before implantation should proceed only after detailed informed consent of donor and recipient, and donor and recipient understanding and acceptance of these risks. In most circumstances, Bosniak IIF

or higher cysts should not be left in the donor but such decision should be individualized.

What Prior Guidelines Recommend

Prior guidelines and policies for the evaluation and care of living donors recommend history, clinical examination, and investigation to exclude occult malignancy before donation, especially in those older than 50 years or with risk factors including family history.^{38,48,51} The Amsterdam Forum recognized that risks of specific cancers may vary across countries.³⁸ "Active malignancy" is commonly cited as a contraindication to living kidney donation,^{38,48,51} although exceptions were noted for low-grade nonmelanoma skin cancer.³⁸ Renal cell carcinoma was considered a contraindication to donation in some prior guidelines,^{38,48} but is currently permissible under US policy in selected cases.⁵¹

Past cancers considered to be an absolute contraindication to donation in prior guidelines include melanoma, testicular cancer, choriocarcinoma, hematological malignancy, monoclonal gammopathy, bronchial cancer, and metastatic cancer.^{38,48} Breast cancer is included, although the European Association of Urology qualifies the restriction to "advanced" disease.⁵⁵ Criteria for which donation may be acceptable despite a prior history of malignancy articulated in prior guidelines include that the specific cancer is curable and the potential transmission of the cancer can reasonably be excluded (eg, colon cancer (Dukes A, > 5 years ago), nonmelanoma skin cancer, or carcinoma in situ of the cervix).^{38,48} The Amsterdam Forum defined additional criteria

for approving donation in a person with prior cancer to include that prior treatment of the malignancy did not decrease renal reserve, place the donor at increased risk for ESKD, or increase the operative risk of nephrectomy.³⁸

RESEARCH RECOMMENDATIONS

- Improve quantification of the incidence of donor-derived disease transmission according to cancer type, clinical features and duration since treatment, through improved monitoring and reporting. Support and expand efforts such as the “Notify Project,”³⁴⁹ a consortium of global experts who gather didactic information on documented types of adverse outcomes in transplantation to identify general principles for detection and investigation.
- Develop systematic monitoring of long-term donor and recipient outcomes in the case of kidney transplantation from living donors with small (T1a) renal cell carcinoma to better inform guidance for when donation and transplantation may or may not be acceptable.

CHAPTER 14: EVALUATION OF GENETIC KIDNEY DISEASE

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 14 and therefore the following recommendations are “Not Graded.”

Evaluation

- 14.1: Donor candidates should be asked about their family history of kidney disease, and when present, the type of disease, time of onset, and extra-renal manifestations associated with the disease.
- 14.2: When the intended recipient is genetically related to the donor candidate, the cause of the intended recipient’s kidney failure should be determined whenever possible. The intended recipient should consent to share this medical information with the donor evaluation team, and with the donor candidate if it could affect the decision to donate.

Selection

- 14.3: Donor candidates found to have a genetic kidney disease that can cause kidney failure should not donate.

Counseling

- 14.4: Donor candidates must provide informed consent for genetic testing if indicated as part of their evaluation. Donor candidates should be informed of the possible effects of receiving a diagnosis of a genetic kidney disease, such as any impact on their ability to obtain health or life insurance.
- 14.5: In cases where it remains uncertain whether the donor candidate has a genetic kidney disease and whether the disease can cause kidney failure, donation should proceed only after informing the donor candidate of the risks of donation if the disease manifests later in life.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- 14.6: Donor candidates with ADPKD should not donate.
- 14.7: Donor candidates with a family history of ADPKD in a first-degree relative may be acceptable for donation if

they meet age-specific imaging or genetic testing criteria that reliably exclude ADPKD.

Apolipoprotein L1 (APOL1) Risk Alleles

- 14.8: Apolipoprotein L1 (*APOL1*) genotyping may be offered to donor candidates with sub-Saharan African ancestors. Donor candidates should be informed that having 2 *APOL1* risk alleles increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified.

RATIONALE

Goals of Evaluation

Genetic kidney diseases include autosomal dominant polycystic kidney disease (ADPKD), *APOL1*-related kidney disease, atypical hemolytic uremic syndrome (aHUS), Alport syndrome, Fabry disease, familial focal segmental glomerulosclerosis (FSGS), and autosomal dominant tubulointerstitial kidney disease (ADTKD). A family history of a genetic kidney disease with an autosomal recessive mode of inheritance (such as cystinosis or some forms of familial FSGS) is usually not a contraindication for living kidney donation, although long-term follow-up data are not available in the literature.

All donor candidates should be asked detailed questions about a possible family history of hereditary kidney disease, and all reasonable measures should be taken by health professionals caring for the intended recipient to determine the cause of kidney failure in the setting of possible hereditary kidney disease. With permission of the intended recipient, information about the intended recipient’s cause of kidney failure should be reviewed carefully by the donor evaluation team and shared with the donor candidate if it could affect the decision to donate.

Some donor candidates have a family history of genetic kidney disease.³⁵⁰ Some of these diseases first manifest later in life and are not identified when donor evaluation occurs at a younger age. Donation could increase the lifetime risk of kidney failure in such a candidate. For this reason, it is important that transplant programs have a strategy for evaluating for inherited kidney disease in donor candidates when there is a family history of kidney failure and the recipient’s cause of kidney failure is uncertain.

Many of the standard tests done as part of the donor evaluation should be interpreted with special consideration in the setting of a family history of genetic kidney disease. Examples include renal imaging in the setting of family history of ADPKD, or hematuria testing in the setting of a family history of Alport syndrome (see also chapter 7).

Ideally, the estimation of long-term postdonation risk in a donor candidate should account for their family history of genetic kidney disease, but there are currently no tools that incorporate family history of genetic kidney disease with a donor candidate’s other demographic and health characteristics to estimate long-term risk. Living donors who are biologically related versus unrelated to a recipient may have a higher incidence of ESKD. In a large study from the United States, the 15-year cumulative incidence of ESKD was 0.34% in living donors who were biologically related to a recipient versus 0.15% in unrelated donors (a two-fold increase in relative terms, although difference was not statistically significant ($P = 0.15$)).³⁰

Donor candidates must provide informed consent to have genetic testing if indicated as part of their evaluation. Donor

candidates should be informed of the possible effects of receiving a diagnosis of a genetic kidney disease, such as any effects on their ability to obtain health or life insurance. In cases where despite a normal evaluation at the time of donor candidate evaluation it remains uncertain whether the candidate has a genetic kidney disease, donation should proceed only after a full discussion with the donor candidate of the risks of donation if the disease manifests later in life.

With advances in genetic medicine and the implications of new risk alleles such as *APOL1*, there is likely to be rapidly evolving knowledge that may influence future donor candidate evaluations. However, at this time the testing for several genetic conditions is imperfect. This uncertainty should prompt a discussion with all relevant stakeholders to achieve consensus on proceeding with donation or not.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Recent studies and a KDIGO Controversies Conference summarize diagnostic criteria for ADPKD.^{351,352} Simple cysts occur more frequently with increasing age in the general population. Kidney disease from *PKD2* presents later in life than *PKD1*. Age-dependent imaging criteria for diagnosis and disease exclusion have been established for at-risk adults with unknown ADPKD gene type (*PKD1* or *PKD2*).³⁵³ For example, for candidates 40 years or older with a first degree relative with ADPKD, the finding of normal kidneys or a single cyst seen in one kidney with no cysts seen in the other kidney reliably rules out the presence of ADPKD.³⁵⁴ However, the utility of ultrasound to rule out ADPKD in younger donor candidates is more limited, where an absent or limited number of cysts on CT or MRI can be considered to rule out ADPKD.³⁵² DNA testing can also sometimes help diagnose or exclude the condition.³⁵⁵ Linkage-based genetic diagnoses of ADPKD using polymorphic markers flanking the 2 disease genes is now rarely performed. Rather, direct mutation screening (by Sanger or next-generation sequencing) is now commonly used for molecular diagnosis of ADPKD.^{356,357} Up to 15% of patients with suspected ADPKD have a negative comprehensive mutation screen. The first-degree relative with ADPKD should undergo *PKD1* and *PKD2* mutation screening (using an acceptable technique), and if a pathogenic mutation is successfully identified, the donor candidate can be tested for this same mutation. However, when mutation screening in the first-degree relative with ADPKD is negative, DNA testing including molecular diagnostics is unhelpful in determining whether the donor candidate does or does not have ADPKD.

The criteria to diagnose ADPKD in patients with no family history of ADPKD is less certain (a family history is absent in 10-15% of patients with ADPKD). A patient with bilaterally enlarged kidneys with innumerable cysts most likely has ADPKD, although the presence of other cystic kidney diseases should also be considered.³⁵¹

Apolipoprotein L1 (*APOL1*) Risk Alleles

The use of *APOL1* genotyping in the donor evaluation is currently grounded primarily in evidence extrapolated from nondonor populations. Recent literature supports that at least a portion of kidney failure previously attributed to hypertensive nephrosclerosis or other diseases (eg, FSGS, lupus nephritis, HIV nephropathy, sickle cell disease) in persons of

African descent may be genetically mediated or accelerated by coding variants in the *APOL1* gene. Having at least one *APOL1* risk allele confers resistance to lethal *Trypanosoma brucei* infections, and these variant alleles are observed in populations of African descent but essentially absent among white persons. Regionally, *APOL1* risk variants are common in persons from West Africa and South Africa (sub-Saharan African descent), and uncommon in North Africa. Approximately 13% of African Americans carry 2 *APOL1* risk alleles.³⁵⁸ Among African Americans in the general population, carrying 2 *APOL1* risk alleles has been associated with FSGS³⁵⁹ and HIV-associated nephropathy histopathologies, proteinuria, reduced GFR, younger age at dialysis and more rapid progression of kidney disease.²³⁵⁻²³⁸ The presence of 2 *APOL1* risk alleles in a deceased donor associates with 2-to-4-times higher RR of graft loss in the recipient, compared with 0 or 1 risk alleles.^{360,361} Case reports of possible *APOL1*-mediated adverse donor and recipient outcomes after living kidney donation among siblings of African ancestry were recently described.^{359,362}

Routine use of *APOL1* genotyping and related counseling within evaluation protocols has been advocated by some,^{358,363-365} while others raise concerns.³⁶⁶ The utility of *APOL1* testing has not been addressed in prior living donor guidelines. The impact of *APOL1* screening on donor candidate exclusion, and the impact of test results on postdonation outcomes and graft outcomes in living donor transplant recipients are yet to be defined.³⁶⁷ Nevertheless, given *APOL1*-related risks identified in the general population and among deceased donor transplant recipients, as well as known higher risk of renal complications among African American compared with white donors,³⁶⁸ we recommend considering *APOL1* genotyping in donor candidates with sub-Saharan African ancestors. The implications of having 2 *APOL1* risk alleles likely differ in younger versus older donor candidates, and whether the genetically related intended recipient has the same alleles. The implications of having 2 *APOL1* risk alleles may also be influenced by the results of kidney function testing done at the time of donor candidate evaluation.

A 2016 *AST Expert Conference* opined that pending more evidence, at this time all African American living donor candidates should be informed about the associations of *APOL1* risk alleles with CKD/ESKD risk in the general population and offer genetic testing as part of the evaluation (including coverage of testing costs) to candidates who wish to know their *APOL1* status.³⁶⁹ The WG also recommended counseling donor candidates that precise ESKD risk for an affected individual cannot currently be quantified, and that genetic testing may post psychological stress. Finally, the authors advised that use of *APOL1* risk allele status should be integrated with the donor candidate's full profile of demographic and health characteristics in determining donor candidacy.

Alport Syndrome (See also Chapter 7)

Alport syndrome is a genetic disease that alters collagen biosynthesis. Collagen is an important structural component of the basement membranes in the kidney, inner ear and eye, and the clinical manifestations of Alport syndrome include persistent microscopic hematuria, early onset bilateral sensorineural hearing loss, and ocular anterior lenticonus and

retinal flecks. The combination of a detailed family history assessment and a kidney biopsy helps establish the diagnosis, where electron microscopy demonstrates areas of irregular glomerular basement membrane thickness with lamellation, splitting and sometimes characteristic “basket-weave appearances.”³⁷⁰ The presence of Alport syndrome can be confirmed by genetic testing, and next-generation sequence panels provide opportunities to genetically screen for collagen mutations.³⁷¹ Alport syndrome is primarily an X-linked disorder (approximately 80% of families), but can also be inherited in an autosomal recessive (approximately 15% of families) and autosomal dominant fashion (very rare).^{372,373} Most women who are heterozygotes for X-linked Alport syndrome exhibit hematuria (95% of women in one European cohort). Of note, collagen (*COL4A*) mutations are present in families with Alport syndrome (85% of Alport syndrome is caused by mutations of *COL4A5*), and are also present in some families with familial FSGS, sporadic FSGS, and thin basement membrane disease.^{374,375} Overall, the severity of nephropathy in Alport syndrome is variable. Many males with X-linked Alport syndrome will develop ESKD before the age of 40 years. Most female carriers of X-linked Alport syndrome will not develop kidney failure in their lifetime although cases of ESKD do occur.^{370,373}

There is little information on the outcomes of such heterozygotes who proceeded with kidney donation (after confirming the absence of proteinuria, hypertension, low GFR and other manifestations of the disease such as sensorineural hearing loss). Gross et al¹⁷⁴ described 6 mothers with Alport syndrome (across several European centers) who donated kidneys to their children with the disease. Five mothers with X-linked Alport syndrome donated to their sons and one mother who was a carrier of autosomal recessive Alport syndrome donated to her daughter; kidney function declined 25% to 60% in 4 of the 6 donors over the observed 2 to 14 years after nephrectomy, although no donor's creatinine clearance was less than 40 mL/min at the time of follow-up evaluation; 4 of the 6 developed microalbuminuria or proteinuria, and hypertension was diagnosed in 4 of 6 donors. There are often several considerations in evaluating a mother with X-linked Alport syndrome for donation to a son with kidney failure, including her desire to care for her child and the possible guilt associated with passing on a genetic kidney disease.³⁷⁶ Alternative treatment options should be considered (including other living donors), as should the age of the woman (older women have had more time to manifest kidney disease, so normal testing at the time of their evaluation is more reassuring than similar results in a younger woman).

Fabry Disease

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. Clinical features include neuropathic pain and angiokeratoma, proteinuria, CKD, left ventricular hypertrophy, arrhythmia and stroke. Symptoms generally appear in childhood, although some go unrecognized until adulthood. Many affected males develop ESKD by the time they are 35 to 45 years of age. Heterozygous females have a different

clinical course with variable clinical manifestations owing to random X chromosome inactivation. Renal manifestations include microscopic hematuria and the presence of white blood cells in the urine; less than 1% of heterozygous females develop kidney failure in their lifetime. A presumptive clinical diagnosis of Fabry disease can be made on the basis of a family history and signs and symptoms, with confirmatory testing for deficient α -galactosidase A enzyme activity in plasma and leukocytes (this deficiency is evident in males with the disease), and genetic testing.³⁷⁷

There is very little information on the outcomes of heterozygous females with Fabry disease who proceeded with kidney donation.³⁷⁸ As with heterozygous Alport syndrome carriers, if donation is entertained, considerations should include the age of the woman and careful deliberation of all other treatment options for the intended recipient.

Familial Focal Segmental Glomerulosclerosis (FSGS)

In recent years, many inheritable genetic forms of FSGS have been described, caused by mutations in a number of genes for proteins that are important for podocyte function or glomerular basement membrane assembly.^{374,379} FSGS can follow both recessive and dominant inheritance patterns.³⁸⁰ Of note, other clinical terms are used to describe the same or similar diseases based on age of onset or response to therapy (eg, congenital nephrotic syndrome, steroid resistant nephrotic syndrome).³⁸¹

There are case reports of individuals who have developed FSGS, proteinuria and kidney failure after donating a kidney to a sibling with kidney failure from FSGS.³⁸² The role of genetic testing in relatives with a family history of kidney failure from FSGS is yet to be determined.

Atypical Hemolytic Uremic Syndrome (aHUS)

There are case reports of individuals who donated a kidney to a relative with kidney failure from Atypical Hemolytic Uremic Syndrome (aHUS), where the donor developed aHUS in the year after donation.³⁸³ A high chance of graft failure from aHUS reoccurrence in the recipient has also been described (>80% with some aHUS mutations). Current genetic testing is imperfect in excluding the presence of aHUS in a donor candidate even when the mutation is known in the recipient. For these reasons some suggest never to proceed with living kidney donation in the setting of a related recipient with aHUS. Others suggest assessing whether a donor candidate shares a genetic susceptibility factor to aHUS to determine whether or not they may be an acceptable donor.³⁸⁴

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)

ADTKD is a heterogeneous genetic disorder. Individual families may have a large number of affected individuals. Mutations in at least 4 genes are implicated: *MUC1* gene which encodes mucin 1 (*MCKD1*), *REN* gene which encodes renin, *UMOD* gene which encodes uromodulin (*MCKD2*) and the *HNF1B* gene which encodes hepatocyte nuclear factor-1 β .^{385,386} Similar to other autosomal dominant diseases, there is 50% probability that each child will inherit the disease from their affected parent. Both *HNF1B* and *MUC1* mutations can arise *de novo* without a prior family history of disease. Donor candidates may be offered target mutation screening to assess whether the disease is present,

if they are biologically related to a patient with kidney failure who has evidence of the pathogenic mutation.

Sickle Cell Trait

Approximately 8% of black Americans have sickle trait, and the trait is also common among patients with Mediterranean or Indian subcontinent heritage.^{387,388} Many affected persons may be unaware that they carry the trait. The prevalence of sickle trait among potential and actual kidney donors is not known. Renal abnormalities in the presence of sickle cell trait range from isosthenuria to hematuria, to rare presentations with acute kidney injury in the context of severe physical stress, such as military training or pregnancy.³⁸⁹ The manifestations of sickle cell trait depend on the individual's overall hemoglobin genotype and exposure to environmental stressors.^{389,390} An increased incidence of medullary renal carcinoma has also been reported among persons with sickle cell trait. A prior survey of US transplant programs (2005, 54% response rate) demonstrated substantial variation in screening and exclusion practices, such that 83% (113/137) of responding programs did not have a policy to screen donors for sickle cell trait.³⁹¹ Among the programs reporting related exclusion practices, 18% (19/105) reported always excluding donor candidates with sickle cell trait whereas 16% (17/105) indicated they never exclude.

What Prior Guidelines Recommend

Prior guidelines and policies for the practice of living kidney donation discuss genetic considerations in the evaluation, although not to the extent presented in the current guideline. Current OPTN policy requires that US transplant programs establish and follow a protocol for screening for ADPKD and other inherited kidney diseases as guided by family history.⁵¹ Several guidelines including those from the British Transplantation Society describe imaging criteria used to exclude the presence of ADPKD.⁴⁸

RESEARCH RECOMMENDATIONS

- Determine how a genetic predisposition to various kidney diseases relates to outcomes after donation. Use genetic information along with other candidate characteristics to estimate the long-term risk of ESKD in the absence and presence of donation.⁷
- Develop better strategies and tools to screen donor candidates for genetic kidney diseases that consider the accuracy, efficiency and costs of testing, including assessment of targeted gene panels for known mutations implicated in kidney diseases.³⁹²
- Develop reliable imaging criteria to exclude ADPKD in donor candidates based on the results of the CT angiogram, which is frequently used to assess the renal vasculature as a routine part of the donor evaluation.
- Define the role *APOL1* genotyping in the evaluation of donor candidates of sub-Saharan African ancestry.³⁶⁹ Acquire adequate data to assess rare outcomes such as ESKD in donors from national registries incorporating biospecimens and long-term outcomes information.
 - For example, in December 2016 the NIH announced 2 requests for applications to form the *APOL1* Long-term Kidney Transplantation Outcomes (APOLLO) Network consortium directed at designing and conducting multicenter, prospective, longitudinal studies to determine the impact of *APOL1* genetic variants on outcomes after living kidney donation/transplantation and deceased donor kidney transplantation.^{393,394}

- Better define the implications of sickle cell trait on long-term kidney function and implications for donor selection.

CHAPTER 15: PREGNANCY

Except in the case of Recommendation 15.9, the ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 15 and therefore the following recommendations are “Not Graded.”

Evaluation

- 15.1: Female donor candidates should be asked about future childbearing plans.
- 15.2: Female donor candidates should be asked about prior hypertensive disorders of pregnancy (eg, gestational hypertension, preeclampsia, or eclampsia).
- 15.3: Local guidelines should be followed to confirm the absence of pregnancy before performing radiologic tests, including abdominal computed tomography (with iodinated contrast) or nuclear medicine GFR testing.

Selection

- 15.4: Women should not donate while pregnant.
- 15.5: Women should not be excluded from donation solely because they desire to conceive children after donation.
- 15.6: Women with a prior hypertensive disorder of pregnancy may be acceptable for donation if their long-term postdonation risks are acceptable.
- 15.7: A decision to proceed with donation in the year after childbirth should consider the psychological needs of mother and child, and should include anesthesia and analgesia planning for nursing mothers.

Counseling

- 15.8: Women with childbearing potential should be informed of the need to avoid becoming pregnant from the time of approval for donation to the time of recovery after nephrectomy; a quantitative human chorionic gonadotropin (β -hCG) pregnancy test should be performed and confirmed as negative immediately before donation.
- 15.9: We suggest that women with childbearing potential be counseled about the effects donation may have on future pregnancies, including the possibility of a greater likelihood of being diagnosed with gestational hypertension or preeclampsia. (2C)
- 15.10: Women with a prior hypertensive disorder of pregnancy should be informed about their long-term risks.
- 15.11: Women with childbearing potential who proceed with donation should be counseled on how to reduce the risk of complications in future pregnancies.

RATIONALE

Evaluation and Selection

Female donor candidates should be asked about their future childbearing plans and potential, which is determined by the candidate's age, history of menopause, and any prior history of sterilization. This information has implications for counseling and the need to confirm the absence of pregnancy at the time of donor nephrectomy.

When evaluating donor candidates, knowledge about a prior history of hypertensive disorder during pregnancy and its severity is important, as when such a history is present

(vs absent) it is associated with a higher risk of ESKD.³⁹⁵ One meta-analysis concluded that women were at greater risk of albuminuria after a preeclamptic pregnancy compared with a normal pregnancy (5- to 10-year incidence of 31% vs 7%).³⁹⁶ This meta-analysis was, however, restricted by small studies of variable quality that focused often on women with severe preeclampsia or underlying diseases such as diabetes mellitus. A population-based study from Norway suggested that women were at greater risk of ESKD if they developed preeclampsia during pregnancy than if they did not (approximate 30-year cumulative incidence after a woman's first pregnancy of 0.4% vs 0.1%)³⁹⁷ The risk remained evident after excluding women with a prepregnancy history of known kidney disease, diabetes or hypertension. A study from Taiwan also described a greater risk of ESKD in pregnant women who developed a hypertensive disorder during pregnancy compared with a normal pregnancy (approximate 12-year cumulative incidence after pregnancy of 0.6% vs < 0.1%)³⁹⁸ In general, characteristics associated with a lower long-term risk of ESKD after a history of hypertension in pregnancy include: i) a mild (vs severe) hypertensive event during pregnancy; ii) more than 10 years since last hypertension event in pregnancy; iii) no evidence of hypertension, albuminuria or low GFR in the current donor evaluation; and iv) no wish for future pregnancies.

Gestational diabetes is a strong risk factor for subsequent diabetes mellitus. A history of gestational diabetes mellitus is also associated with a higher risk of ESKD.³⁹⁹ For recommendations related to gestational diabetes see Recommendations 11.5 and 11.7.

Because a fetus may be harmed by radiation and/or radiocontrast, local guidelines should be followed to confirm the absence of pregnancy before performing certain tests as part of the donor candidate evaluation, such as an abdominal CT (with iodinated contrast) or a nuclear GFR test. Some guidelines suggest that it may be reasonable to proceed without a quantitative human chorionic gonadotropin (β -hCG) pregnancy test if a woman's menstrual period is not overdue and there is an absence of pregnancy symptoms.⁴⁰⁰

A woman should not donate while pregnant. Women with childbearing potential should be informed about the need to avoid becoming pregnant from the time she is approved for donation to the time she has recovered after nephrectomy. Approximately 1% of patients develop postoperative venous thromboembolism after donor nephrectomy and the risk of using estrogen-based oral contraceptive medications before surgery should be balanced against harms. Barrier birth control can be an appropriate option in the weeks before surgery.

Women with childbearing potential should be supported by transplant programs to make a well-informed donation decision. Transplant programs should enable donation when they estimate a candidate's long-term postdonation risks are acceptable. In other words, motivated well-informed women should not be excluded from donation solely on the basis of a desire to conceive children after donation. Most women with access to recommended pregnancy care have good maternal and fetal outcomes in their postdonation pregnancies.⁴⁰¹ We advocate that recommended postdonation pregnancy care be available to all women worldwide, including any treatments needed for pregnancy complications. A decision to proceed with donation in the year after delivery should carefully consider the needs of the mother and her baby.

With regard to prior guidelines, the 2004 Amsterdam Forum concluded that donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies. At the time, the participants concluded there were no data to suggest that hyperfiltration associated with the combination of unilateral nephrectomy and pregnancy leads to significant hypertension, proteinuria, change in GFR, or abnormalities of the urinary sediment.³⁸ Some transplant programs have historically not disclosed any potential postdonation pregnancy risks as part of the informed consent process. However, 3 recent studies provided new information on this risk. Two retrospective cohort studies, one from the United States and the other from Norway, reported an increased risk of gestational hypertension and preeclampsia after kidney donation, based on comparisons of pregnancies before and after donation within donors (**Evidence Report Table 21, SDC**, <http://links.lww.com/TP/B434>, and **Supplemental Appendix Table D18, SDC**, <http://links.lww.com/TP/B432>).^{402,403} Another recent retrospective cohort study from Canada demonstrated gestational hypertension or preeclampsia was more likely to be diagnosed in kidney donors than matched nondonors with similar indicators of baseline health (11% vs 5%).⁴⁰¹ The 2 groups did not differ significantly with respect to other maternal or fetal outcomes (Caesarean section, postpartum hemorrhage, preterm birth with gestation less than 37 weeks, low birth weight < 2500 g), and there were no maternal deaths, stillbirths, or neonatal deaths in either group (however, the CIs for the estimates were wide, meaning that a clinically important risk among donors was not excluded). Most women in these cohorts were white (Table 22).

Counseling

Based on the new information, our guideline suggests that women who are capable of conceiving children after donation be counseled about the possible impact donation may have on future pregnancies. This suggestion agrees with a 2015 AST *Live Donor Community of Practice* consensus conference conclusion that information on postdonation pregnancy risk should be shared in the informed consent process for donor candidates with reproductive potential.¹⁴⁸ Beginning in 2017, OPTN Informed Consent Policy requires that US transplant programs inform donor candidates that the risks of preeclampsia or gestational hypertension are increased in pregnancies after donation.⁵¹ The ERT found the evidence for a higher likelihood of being diagnosed with gestational hypertension or preeclampsia after donation to be consistent across the 3 studies, but of low quality.³

Women with childbearing potential who proceed with donation should be educated on recommended evidence-based methods to reduce the risk of complications in postdonation pregnancies. For example, in the nondonor population, several dietary and lifestyle interventions including interventions to reduce or prevent obesity have the potential to reduce the risk of preeclampsia.^{404,405}

RESEARCH RECOMMENDATIONS

- Investigate the precision of estimated, individualized pregnancy outcomes among donors through expanded monitoring and reporting, including capture of more detailed clinical information such as BP and kidney function.

TABLE 22.**Donor characteristics and maternal and fetal outcomes in postdonation pregnancies from 3 studies: Norway, Minnesota (United States), and Ontario (Canada)**

| | Norway | Minnesota, United States | Ontario, Canada |
|--|--------------|--------------------------|-----------------|
| Donor characteristics | | | |
| No. women | 69 | 239 | 85 |
| Years of donation | 1967 to 2002 | 1963 to 2007 | 1992 to 2009 |
| Family history of kidney failure (%) | NR | 96% | 65% |
| Mean predonation GFR, mL/min per 1.73 m ² | NR | 91 | 114 |
| White race (%) | 98% | 97% | 70% |
| Number of postdonation pregnancies | 106 | 490 | 131 |
| Mean age at donation, y | 27 | 26 | 29 |
| Mean age at pregnancy, y | 32 | 29 | 32 |
| No. women with at least one predonation pregnancy (%) | NR | 98 (41%) | 25 (29%) |
| Mean or median time from donation to postdonation pregnancies, y | 5 | 5 | 4 |
| Outcomes after donation | | | |
| Postdonation maternal outcomes | | | |
| Gestational hypertension or preeclampsia | 9/106 (8%) | 55/490 (11%) | 15/131 (11%) |
| Gestational hypertension | 3/106 (3%) | 28/490 (6%) | 7/131 (5%) |
| Preeclampsia | 6/106 (6%) | 27/490 (6%) | 8/131 (6%) |
| Maternal death | NR | NR | 0 |
| Postdonation fetal outcomes | | | |
| Preterm birth (<37 wk gestation) | 10/106 (9%) | 35/490 (7%) | 10/131 (8%) |
| Low birth weight (<2500 g) | 9/106 (8%) | NR | 8/131 (6%) |
| Stillbirth | 3/106 (3%) | 2/490 (<1%) | 0 |
| Neonatal death (<28 days after birth) | 0 (0.0%) | NR | 0 |

GFR, glomerular filtration rate; NR, not reported. Modified with permission from Garg AX et al.⁴⁰¹

- Develop individualized estimates for women who differ in race/ethnicity, family history of kidney disease, and their healthcare system.
- Determine whether the risks of complications in postdonation pregnancies vary according to the side of nephrectomy. Pregnancy may be associated with ureteral obstruction and dilation, particularly of the right kidney.^{37,406,407}
- Define the clinical sequelae of gestational hypertension and preeclampsia that develop in postdonation pregnancies, including effects on long-term kidney outcomes.
- Explore perceptions of pregnancy risk information by women with different characteristics to improve education, counseling, and informed consent processes.

CHAPTER 16: PSYCHOSOCIAL EVALUATION

Except in the case of Recommendation 16.7, the ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 16 and therefore the following recommendations are “Not Graded.”

Evaluation

- 16.1: Donor candidates should receive in-person psychosocial evaluation, education and planning from health professionals experienced in the psychosocial concerns of donor candidates and donors.
- 16.2: To ensure voluntariness, at least a portion of the psychosocial evaluation of the donor candidate should be performed in the absence of the intended recipient, family members and other persons who could influence the donation decision.

16.3: Whenever possible, the psychosocial evaluation of the donor candidate should be performed by health professionals not involved in the care of the intended recipient.

16.4: Transplant programs should follow protocols for assessing the donor candidate’s psychosocial suitability, available support, preparation and concerns for donation.

Selection

16.5: Transplant programs should follow protocols defining psychosocial factors that either exclude donation, or prevent further evaluation until resolution.

Disclosures and Support

16.6: We suggest that donor candidates be informed that donors usually have good quality of life after donation (2D).

16.7: Transplant programs should assist donor candidates and donors in receiving psychosocial or psychiatric support as needed.

RATIONALE

Evaluation

The psychosocial evaluation of the living kidney donor candidate serves many functions. This evaluation helps determine if a candidate is psychologically fit for donation, for example, by assessing if the donor candidate’s motivations are appropriate and identifying psychosocial risk factors for poor outcomes. The evaluation also helps address any donor candidate concerns, and ensures potential psychosocial risks and benefits of kidney donation are disclosed and understood. The psychosocial evaluation can also be used to

develop a tailored plan to support the donor candidate in having a positive psychosocial experience throughout the evaluation and donation processes. We recommend that all donor candidates, irrespective of their relationship with the intended recipient, should be evaluated using uniform criteria.

A recent systematic review of living kidney and liver donor candidates summarized 34 publications (guidelines, consensus statements and transplant program clinical protocols) on the content of the psychosocial evaluation (including the elements to be considered and acceptance criteria) and the process of the psychosocial evaluation (including who should be evaluated, how the evaluation should be performed, and the timing of the evaluation).⁴⁰⁸ The authors concluded that, at present, there is little good evidence, concrete guidance or consensus on what to screen for, how to handle psychosocial problems, or how to perform the psychosocial evaluation. These findings confirmed that there is substantial practice variation in regard to psychosocial evaluations. The authors concluded that, consistent with prior systematic reviews,²⁰ most recommendations in prior publications are based on expert opinions (via consensus conference) and individual transplant program experiences. The ERT assessed evidence related to psychosocial outcomes after donation.

Should all Donors have a Psychosocial Evaluation?

Our recommendations are consistent with several prior guidelines and policies in some countries, which indicate that psychosocial assessment is a necessary part of the evaluation of each donor candidate.^{38,48,50,51,54,55,409}

In What Setting Should the Evaluation Be Performed?

While the initial screening may be performed by telephone, particularly for donor candidates living far from the transplant center, the main psychosocial evaluation should be conducted as a face-to-face interview, as has also been recommended in several prior reports.⁴⁰⁸ Third parties should not be present during at least a portion of the interview, to maintain confidentiality and minimize the effect of external influences on the donor candidate's responses. This suggestion is consistent with some prior reports.⁴⁰⁸ In other reports the presence of a relative or significant other during a portion of the interview (as long as they are not the intended recipient) is cited as potentially beneficial to the donor candidate and the assessment process, in that such participation may promote reliability of the information reported and provide information about support the donor candidate will need during the donation and recovery periods.⁴⁰⁸

Who Should Perform the Psychosocial Evaluation?

Our recommendations are similar to many prior guidelines and national policies that recommend performance of the psychosocial evaluation by various healthcare professionals (eg, psychiatrist, psychologist, clinical social worker, or a psychiatric nurse) who meet qualifications of appropriate training, knowledge and skill in mental health and the psychosocial concerns of transplantation.^{51,54} As with prior recommendations we suggest that the psychosocial evaluation should be performed by an individual who is not involved in the care of the intended recipient to reduce conflicts of interest in evaluating the donor candidate.⁵⁰

TABLE 23.

Recommended processes and content of the psychosocial evaluation

| Process | Content element |
|---|---|
| Assessment of suitability and preparation | <p>The following should be assessed in each donor candidate:</p> <ul style="list-style-type: none"> • Motivation for donation • Expectations of the outcomes of donation, including impacts on their future relationship with the recipient. The donor candidate should be counseled if these expectations appear to be unrealistic. • History of current or past psychiatric disorders • History of current or past substance abuse or dependence (eg, use of alcohol, illicit drugs or prescription drugs) • Support system, including available family, friends and workplace supports, and coping strategies (including available programs) to minimize any negative impacts from donation • Preparation for the possible medical impact of donation, and any expected impact on their activities after donation • Preparation for the possible emotional impacts of donation (both positive and negative) • Preparation for the possible financial impacts of donation, including potential impact on employment status and wages, expenses for medical care, travel and dependent care, and any effects on insurability or rates • Understanding and acceptance of their responsibility for making good health choices after donation, including the need to organize and adhere to recommended routine medical follow-up • Behaviors that increase the risk of a donor transmitting an infectious disease to the recipient |
| Education | <ul style="list-style-type: none"> • The process and requirements of informed consent should be reviewed (see chapter 2 of this guideline for complete details) • Concerns about medical, emotional and financial impacts of donation should be elicited and addressed with appropriate education and/or referral to a knowledgeable member of the transplant team • Donor candidates can be told that most prior donors have experienced good psychosocial outcomes, although some people experience psychosocial difficulties after donation |
| Planning and support | <ul style="list-style-type: none"> • An individualized plan to support the donor candidate in having a positive psychosocial experience throughout the evaluation and donation processes should be developed for each candidate, guided by donor candidate concerns and psychosocial risk factors that can be managed without excluding donation |

Protocols for Assessing the Donor Candidate's Psychosocial Suitability

It is important for transplant programs to follow pre-determined protocols in evaluating each donor candidate's psychosocial suitability equitably. The protocol should include a comprehensive list of the processes and content of the psychosocial evaluation (Table 23). Recommended components of the psychosocial evaluation specified in prior guidelines include mental health history,^{47,48,51,54,196,409} substance use history,^{47,48,51,54,409} understanding of risks,^{47,51,55} ability to make an informed choice,⁵¹ coping capacity,^{47,51,409} social support,^{47,48,51,409} risk factors for poor psychosocial outcomes (details unspecified),^{51,409} motivation and voluntariness,^{47,51,409} and donor-recipient relationship.^{47,48}

Considerations for Nondirected Donor Candidates

Practice patterns related to the psychosocial evaluation of nondirected donors vary considerably worldwide.⁴¹⁰⁻⁴¹² Our opinion is that candidacy criteria should be similar whether an individual is being assessed for directed or nondirected donation, recognizing that some elements of the informed consent may vary, including those related to how the intended recipient is selected, time frames for donation, travel requirements, and opportunities or prohibitions about contact with the recipient after donation and transplant.

Selection

Which Predonation Characteristics are Associated with a Greater Chance of Poor Psychosocial Outcomes after Donation?

The ERT identified 2 studies examining whether the association between donation (donors vs healthy nondonors) and long-term psychological outcomes were modified by an individual's baseline characteristics (Evidence Report Tables 9 and 11, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Tables D6 and D8, SDC, <http://links.lww.com/TP/B432>). The quality of this evidence was graded as very low. In one study the association between donation (donors vs nondonors) and long-term mental quality of life score was not modified by age.⁴¹³ In the other study, the cumulative incidence of recorded depression diagnoses was lower in donors compared with matched beneficiaries in the same insurance system, among both men and in women.⁴¹⁴

The ERT summarized the results of several studies wherein donors with a characteristic were compared to donors without the characteristic, to see if the 2 groups differed on the chance of a poor psychosocial outcome. The quality of this evidence was graded as low to very low. These results are challenging to interpret because: many studies reported different psychosocial outcomes that were not directly comparable; the effects were not always seen across all psychosocial outcomes measured within a study; the results of characteristics associated with outcomes were inconsistent across the studies; and the likelihood a donor with the characteristic would experience the outcome was often reported in relative rather than absolute terms (see Evidence Report Tables 10, 12, 14, 15, 20, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Tables D7, D9, D11, D12, D17, SDC, <http://links.lww.com/TP/B432>).

In some studies, predonation characteristics that were associated with reduced chance of poor psychosocial outcomes (ie, with a better psychosocial prognosis) included a lack of

residual ambivalence about donation (ie, no lingering hesitation or uncertainty), more education, an absence of predonation psychiatric diagnoses, an absence of feeling morally obligated to donate, more social support, lower predonation expectations of health consequences after donation, less financial burden, and the feeling of having received adequate attention from the transplant team.⁴¹⁵⁻⁴¹⁹ A systematic review of prospective studies of postdonation health-related quality-of-life (HRQoL) published after completion of the ERT's systematic review for this guideline found that, among 9 studies examining risk factors for impaired HRQoL, low psychological functioning before donation was the most common predictor.⁴²⁰

What Psychosocial Criteria Should Exclude Donation?

Psychosocial elements that should be reviewed with the donor candidate and the psychosocial criteria that either exclude donation, or prevent further evaluation of the donor candidate until the issue is resolved, are summarized in Table 24. Donation should not occur when there is evidence of, or expectation of, unreasonable secondary gain. The Declaration of Istanbul endorses measures to protect individuals from the unregulated sale of organs.⁴²¹ At least 18 prior reports have described relative and absolute psychosocial contraindications to donation.⁴⁰⁸

Disclosures and Support

What Should Donor Candidates be Told about their Likely Psychosocial Outcomes after Donation?

The psychosocial evaluation provides an opportunity to share what emotions the donor candidate might experience after donation, and the anticipated short- and long-term psychosocial outcomes after donation.

Kidney donation has a profound and multifaceted impact on the lives of many donors and influences their identity, roles and relationships. Two recent systematic reviews summarize qualitative data about donor experiences after donation.^{422,423} On average, donors experienced increased self-esteem, empowerment, and community awareness, but

TABLE 24.

Recommendations for psychosocial factors that either exclude donation, or prevent further evaluation until resolution

Psychosocial contraindications to donation

- A wish not to donate or marked ambivalence about donating
- Evidence of, or high suspicion of, undue pressure
- Evidence of, or high suspicion of, unreasonable or illegal secondary gain (such as an unregulated financial transaction)
- A failure to meet the requirements of informed consent (see chapter 2).
This includes a donor candidate, who despite counseling, continues to have unrealistic expectations about the donation experience or potential outcomes
- Psychiatric conditions that can be treated to improve the donor candidate's predonation mental fitness and chance of a good postdonation outcome
- Past or present substance use disorder
- A psychosocial profile that predicts a level of postdonation risk that exceeds a transplant program's acceptable risk threshold. Such a profile may include an active substance use disorder, or the absence of needed psychosocial or financial support

some also described a lack of emotional support. A subsequent systematic review of 34 prospective studies of postdonation HRQoL (1990 to 2014) found that, after mild reductions early after nephrectomy, HRQoL returned to baseline or was slightly reduced by 3 to 12 months, particularly for fatigue, but was still comparable with general population norms.⁴²⁰

In general, donors demonstrate good quality of life and have low rates of donation regret. That said, living donation is not without psychosocial risk, and some donors have experienced psychosocial difficulties after donation (eg, depression, anxiety, stress, worries about health), and such problems have impacted their functioning and ability to return to work.

One study was identified by the ERT that reported psychosocial outcomes in a group of donors compared with healthy nondonors, and the evidence quality was graded as very low (Evidence Report Table 8, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table D5, SDC, <http://links.lww.com/TP/B432>).⁴¹³ In the reviewed multicenter study, average values of 3 HRQoL scores among donors (a median of 6 years after donation) were similar to a group of nondonors and population norms. There was also no significant difference between the 2 groups in marital status, mental health visits and psychotropic medication use.

A report of 2455 living donors from 3 large US centers known as the Renal and Lung Living Donors Evaluation Study (RELIVE) cohort (93% white race, 72% biologically related to recipient) found that HRQoL scores in living donors in the decades after donation were similar or better than the US population.⁴¹⁵ However, 9% of RELIVE study respondents reported one or more of the following poor psychosocial outcomes: “fair” or “poor” overall donor experience, financial burden, regret or discomfort with decision to donate, or psychological difficulties since donation.⁴²⁴ Recipient graft failure was the only identified predictor of reporting one or more of these poor psychosocial outcomes, and was associated with 77% higher risk (OR, 1.33_{1.77,2.34}). Another report of 4650 privately insured living kidney donors in the United States described lower rates of depression diagnoses after donation compared with rates among age- and sex-matched beneficiaries in the same insurance system.⁴¹⁴ A systematic review published in 2006 summarized 51 studies describing 5139 donors who were assessed on average 4 years after donation.⁴²⁵ Most donors who participated in follow-up reported no depression or anxiety, with questionnaire scores similar to the general population. The majority reported no change or an improved relationship with their recipient, spouse, family members and nonrecipient children. Some experienced an increase in self-esteem. A majority expressed no change in their attractiveness. Most donors (96%) did not regret their donation decision.

Based on these data, we suggest that donor candidates be informed that in general, donors demonstrate good quality of life after donation. However, donor candidates should also be informed that some people experience psychosocial difficulties after donation (eg, depression, anxiety, a negative change in their relationship with the recipient, more pain than expected, a recovery time that is slower than expected, a decline in their vitality, unexpected expenses related to donation recovery, anticipated benefits that were short-lived or not met at all) or anxiety related to worries about their health (including a fear of kidney failure).^{78,425}

What Should Donors Be Told About How Donation May Impact Them Financially?

Donor candidates and living kidney donors incur personal direct and indirect expenses as part of the evaluation and donation processes, even in countries where the donor’s medical expenses are paid by the recipient’s insurance or the health-care system. Major costs include transportation, accommodation, child care, lost income (or vacation time), and missed time from work.^{426,427} In a prospective Canadian follow-up study, the mean cost associated with donation was \$3268 (Canadian dollars); however for 15% of donors, costs exceeded \$8000.⁴²⁸ The expenses incurred during the predonation evaluation are also described in another recent study from the United States.⁴²⁹ These findings have led to recommendations that living donor candidates receive counseling about financial costs before donation, and have fostered governmental and other programs in multiple countries to reimburse donors for their legitimate expenses and attempt to maintain financial neutrality.⁴³⁰⁻⁴³²

However, there are limitations to many current cost mitigation programs. In the United States, the National Living Donor Assistance Center (NLDAC) (via a Health Resources and Services Administration grant) offers grants to offset travel and lodging costs for living donors and an accompanying person during the evaluation, donation and follow-up, but reimbursement eligibility is means tested and is based on the incomes of both the living donor candidate and recipient; further, nondirected donors have limited access because they cannot provide recipient income information. In the United States, many states have enacted legislation to offer tax deductions or credits, or other benefits, to living organ donors.⁴³³ These programs vary state by state, are underused, and have not been studied with regard to impact on financial burden of donation. Several studies have considered whether kidney donation affects one’s ability to obtain life, disability and health insurance.⁴³⁴⁻⁴³⁶ These issues are country-specific, and should be considered in donor candidate counseling and support.

A 2016 convenience sample of informed consent forms for living donor and transplant candidate evaluation from 9 geographically diverse US programs identified misconceptions about defraying donation-related costs, reinforced by ambiguous language or omissions in the donor informed consent documents.⁴³⁷ Donor candidates should receive clear, accurate education on how to access available financial support as well as the limitations of available resources. In 2016, the AST launched an online financial toolkit to help donor candidates learn about the finances of being a living organ donor; this dynamic resource will be expanded and updated over time.⁴³⁸ Although developed from the perspective of US-based policies and resources, the information may be helpful to donor candidates in other countries. See chapter 18 for a discussion of policy related to financial support and removal of economic disincentives to donation.

How Should Transplant Programs Help Donor Candidates and Donors in Need of Psychosocial Support?

Tailored plans to support each donor candidate in having a positive psychosocial experience throughout the evaluation and donation processes should be developed, guided by donor candidate concerns and psychosocial risk factors that can be managed without excluding donation.

Candidates ultimately excluded from living donation for any reason may experience feelings of emotional distress, disappointment and guilt, frustration from inability to control one's own body and health, and in the case of planned donation to a spouse or dependent, caregiver burden or ongoing impact of the intended recipient's illness on the donor's lifestyle.⁷⁵ The transplant program should assist excluded donor candidates who have difficulty accepting their candidacy decision in receiving needed psychosocial support or psychiatric help.

In approximately 5% of living kidney donor transplants the recipient or their graft does not survive the first year. Understandably, poor recipient outcomes can be a source of stress and disappointment to the donor, and the transplant program should provide postdonation psychosocial support at such times. In some studies, but not others, poor recipient outcomes have been associated with poor psychosocial outcomes in donors.^{413,414,439-443} In one study, most of the adverse recipient events were beyond the first year posttransplant.⁴¹⁴ Most donors will not experience poor short- or long-term medical or psychosocial outcomes after donation, but for those who do, the transplant program should participate to ensure that the donor receives psychosocial support or psychiatric help. The responsibility to ensure that donors receive psychological support when outcomes are poor is also described in a prior guideline.⁴⁰⁹ The Declaration of Istanbul states that all donors should be offered psychosocial services as a standard component of follow-up,⁴²¹ and the CARI guideline recommends follow-up of the psychosocial impact of living kidney donation for every living donor during the first year after donation.⁴⁰⁹ Incomplete or inconsistent follow-up after the early postdonation period may lead to under-recognition of donation-related psychosocial problems in the longer-term. Models for the collection of long-term psychosocial outcomes after donation exist internationally, including the European Living Donation and Public Health (EULID) project, an 11-nation registry that uses an online tool for reporting follow-up information included psychosocial and socioeconomic outcomes.⁴⁴⁴ The national Swiss Living Donor Health Registry (SOL-DHR) follows donors lifelong and includes an 8-Item Short-Form (SF-8) and social-status questionnaire.⁴⁴⁵

RESEARCH RECOMMENDATIONS

- Better define the optimal processes and content of the psychosocial evaluation. For example, there are emerging efforts to help standardize the psychosocial evaluation through the development of semi-structured evaluation tools.⁴⁴⁶
 - Duerinckz et al,⁴⁰⁸ on behalf of the Ethical Legal Psychological Aspects of Transplantation Organization, summarized surveys or tools used for psychometric testing in the donor candidate evaluation from prior guidelines, consensus statements and transplant program protocols such as mood questionnaires, personality interviews and drug abuse screening. The type, number and content of tools described in prior guidelines were variable.
 - The same group also recently provided a conceptual framework for the key elements in the psychosocial evaluation of living kidney donor candidates, including assessment of: i) motivation (eg, coercion, ambivalence); ii) the presence of psychopathology (eg, cognitive disturbance, mood or

anxiety disorder); iii) available social resources (eg, social support, workplace support); and iv) information disclosure, understanding and risk processing (eg, elements of informed consent).⁴⁴⁷

- Determine which components of the psychosocial interview should be structured to cover relevant material while addressing the unique needs and questions of a given donor candidate.
- Perform clinical trials to compare evaluation approaches, acceptance criteria, and interventions to minimize the risk of poor postdonation psychological outcomes.
 - For example, in a recent randomized trial of 113 potential kidney donors with some evidence of residual ambivalence to donation, it was suggested that motivational interviews (vs additional health education or standard care) reduced ambivalence to donation, anxiety symptoms, unexpected family-related problems, and the risk of negative physical symptoms after donation.⁴¹⁷

CHAPTER 17: ACCEPTABLE SURGICAL APPROACHES FOR DONOR NEPHRECTOMY

Except in the case of Recommendations 17.3 and 17.7, the ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 17 and therefore the following recommendations are “Not Graded.”

- 17.1: Renal imaging (eg, computed tomographic angiography) should be performed in all donor candidates to assess renal anatomy before nephrectomy.
- 17.2: The surgeon should have adequate training and experience for the surgical approach used for the donor nephrectomy.
- 17.3: We suggest that “mini-open” laparoscopy or hand-assisted laparoscopy by trained surgeons should be offered as optimal approaches to donor nephrectomy. However, in some circumstances, such as for donors with extensive previous surgery and/or adhesions, and at centers where laparoscopy is not routinely performed, open nephrectomy (flank or laparotomy) may be acceptable. (2D)
- 17.4: Robotic, single-port, and natural orifice transluminal nephrectomy should generally not be used for donor nephrectomy.
- 17.5: Nontransfixing clips (eg, Weck Hem-o-lok) should not be used to ligate the renal artery in donor nephrectomy; instead, renal artery transfixation by suture ligature or anchor staple within the vessel wall should be used.
- 17.6: In the absence of reasons to procure the right kidney (vascular, urological or other abnormalities), the left kidney should be procured in laparoscopic donor nephrectomy because of the relative technical ease associated with a longer venous pedicle.
- 17.7: We suggest laparoscopic procurement of the right rather than the left living donor kidney may be performed if the surgeon has adequate training and experience. (2D)
- 17.8: Procurement of a living donor kidney with 3 or more arteries should only be undertaken by surgeons with adequate experience.
- 17.9: A donor candidate with atherosclerotic renal artery disease or fibromuscular dysplasia involving the orifices of both renal arteries should not donate.

RATIONALE

The choice of surgical approach and the organ for procurement (left vs right kidney) should take into consideration the experience of the surgeon as well as any renal functional, parenchymal, vascular or urological abnormalities. Relevant outcomes to consider in comparing surgical approaches

include: mortality; perioperative complications (eg, bleeding, reoperation, incisional hernias); quality of life, including pain and wound cosmesis; recovery time; and graft outcomes in the recipient. Studies often report operative time as a surrogate measure for risks of anesthesia-related complications. The ERT identified 4 recently published systematic reviews describing perioperative outcomes after living donor nephrectomy.⁴⁴⁸⁻⁴⁵⁰

Laparoscopic versus Open Nephrectomy

The ERT identified 3 systematic reviews comparing outcomes after laparoscopic versus open nephrectomy^{448,450,451} (Evidence Report Table 3, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table C3, SDC, <http://links.lww.com/TP/B432>). Collectively, these reviews provide very low to high quality evidence for several outcomes, including operative time, blood loss, warm ischemia time, reoperation, length of hospital stay, and return to work. Overall, laparoscopic and open donor nephrectomies have comparable outcomes with regard to donor safety and graft function. Simple open (flank subcostal retroperitoneal) donor nephrectomy is generally performed with shorter operative times than laparoscopic nephrectomy but may incur slightly higher blood loss. Open nephrectomy is no longer considered the standard of care due to a longer incision and generally longer associated hospital stay, higher analgesia requirements, and longer convalescence period. By 2013, almost all living donor nephrectomies in the United States were performed laparoscopically, and, with increasing experience, few are converted to open procedures.⁹⁴ However, in unusual circumstances, such as for donors with extensive previous surgery and/or adhesions, and at centers where laparoscopy is not routine, open nephrectomy (flank or laparotomy) may be justified. Of note, as for most surgical procedures, experience is likely to be an important determinant of outcomes, and trials and observational series were generally performed at experienced centers by limited numbers of surgeons.

Operative Time

Fonouni et al⁴⁴⁸ reported a trend towards longer average operative time for laparoscopic compared with open donor nephrectomy, and Yuan et al and Wilson et al confirmed longer operative times for laparoscopic procedures.^{450,451} Meta-analysis by Yuan et al⁴⁵¹ estimated that laparoscopic nephrectomy requires an average of 51 minutes longer surgical time (95% CI, 33-68 minutes). Surgery times averaged 2 to 3 hours for open nephrectomy and 3 to 4 hours for laparoscopic nephrectomy.

Blood Loss

Five of the 8 publications included in the review by Fonouni et al⁴⁴⁸ reported less perioperative blood loss with laparoscopic nephrectomy, while the other 3 found no significant differences in blood loss between the approaches. Meta-analysis by Yuan et al,⁴⁵¹ including 12 studies with 917 donors, found a small but statistically significant increase in perioperative blood loss with open vs laparoscopic nephrectomy (mean difference, -99.6 mL; 95% CI, -165.9 to -33.4) or open versus hand-assisted laparoscopy (-112.8 mL; 95% CI, -169.1 to -56.0).⁴⁵¹

Warm Ischemia Time

Data regarding warm ischemia times with laparoscopic versus open nephrectomy are conflicting. In 9 of the 11 publications evaluated by Fonouni et al,⁴⁴⁸ longer warm ischemia times were reported in the laparoscopic nephrectomies compared with open nephrectomies. Similarly, all included studies in the review by Wilson et al⁴⁵⁰ found longer warm ischemia times in the laparoscopic groups, with differences ranging from 2 to 17 minutes. In contrast, based on data from 15 trials including data for 1598 donors, Yuan et al identified a small, significant decrease in warm ischemia time with laparoscopic compared with open nephrectomy (mean difference, -1.8 minutes; 95% CI, 1.3-2.2); warm ischemia time also trended lower for hand-assisted laparoscopy compared with open nephrectomy (mean difference, 0.4 minutes; 95% CI, -0.2 to 1.0), but this difference was not statistically significant. Overall, there were no clinically important differences in warm ischemia times with laparoscopic versus open donor nephrectomies. Wilson et al⁴⁵⁰ found no significant differences between laparoscopic and open nephrectomy for early graft loss (RR, 0.06_{0.31}^{1.48}), delayed graft function (RR, 0.52_{1.09}^{2.30}), acute rejection (RR, 0.87_{1.41}^{2.27}), ureteric complications (RR, 0.69_{1.51}^{3.31}), donor kidney function at 1 year (standardized mean difference, 0.15; 95% CI, -0.11 to 0.41) or graft loss at 1 year (RR, 0.15_{0.76}^{3.85}).

Reoperation

Fonouni et al⁴⁴⁸ included 7 publications (both trials and meta-analyses with unreported donor sample sizes) reporting reoperation rates, and found mixed results. Although 4 of the publications found no difference between the groups, 3 found higher reoperation rates in the laparoscopic compared with the open group. Based on data from 6 studies, Wilson et al⁴⁵⁰ found fewer reoperations with open nephrectomy compared with laparoscopic nephrectomy, but this difference was not statistically different (RR, 0.09_{0.57}^{3.64}).

Length of Hospital Stay

Among 9 publications (with unreported donor sample sizes) reviewed by Fonouni et al,⁴⁴⁸ 4 of the 9 found no difference in length of hospital stay between the groups, while the remaining 5 found longer length of stay with open versus laparoscopic nephrectomy. Meta-analysis of 16 studies (including 1681 donors) by Yuan et al⁴⁵¹ identified significantly shorter length of hospital stay after laparoscopic compared with open nephrectomy (mean difference, -1.3 days; 95% CI, -1.7 to -0.8).⁴⁵¹ Significant trends toward shorter length of stay were found with standard laparoscopic (mean difference, -1.3 days; 95% CI, -1.9 to -0.7) and hand-assisted laparoscopic (mean difference, -1.3 days; 95% CI, -2.1 to -0.5) compared with open nephrectomy.⁴⁵⁰

Return to Work

The time to return to work was reported in one systematic review based on pooled data from 9 studies capturing 1016 donors. Laparoscopic nephrectomy was associated with a statistically significant and clinically meaningful reduction in time to return to work (mean difference, -16.4 days; 95% CI, -23.0 to -9.7).⁴⁵¹

Pain and Physical Functioning

Among 6 studies describing analgesia requirements in the review by Wilson et al,⁴⁵⁰ 4 reported significant reductions in morphine requirements with laparoscopic versus open nephrectomy. One study showed that donors who underwent laparoscopic nephrectomy required fewer days of analgesia postdischarge (3.3 vs 7.8 days, $P < 0.001$), while another reported a nonsignificant reduction in visual analogue pain scale scores after laparoscopic nephrectomy. The meta-analysis by Yuan et al⁴⁵¹ of 3 studies including 306 donors showed superior 36-item Medical Outcomes Study Short Form (SF-36) physical functioning (mean difference, 6.6; 95% CI, 2.3-10.8; $P = 0.002$) and bodily pain scores (mean difference, 5.9; 95% CI, 1.6-10.3; $P = 0.007$) with laparoscopic compared with open nephrectomy.

What Prior Guidelines Recommend

Other guidelines have also recommended laparoscopic or minimally surgical invasive approaches for living donor nephrectomy^{48,50,54,452} based on evidence supporting lower morbidity, less pain and analgesia requirements, and earlier return to normal activity compared with open nephrectomy. CARI notes equivalent rates of major complications with laparoscopic versus open nephrectomy (with complications after laparoscopy largely due to catastrophic bleeding due to failure of intraoperative securing of the vascular pedicle), larger resource requirements for laparoscopy, but advantages with laparoscopy in terms of reduced analgesia requirements and faster return to normal activity.⁴⁵³ The European Association of Urology concludes that laparoscopy offers equivalent complication rates and graft outcomes as open nephrectomy but shorter convalescence and better cosmetic results.⁵⁵ The Japanese Society of Endourology emphasizes the importance of experience, recommending that institutions commencing laparoscopic living donor nephrectomy should do so under the direction of an accredited laparoscopist.⁴⁵²

Minimally Invasive Nephrectomy Approaches: Standard Laparoscopic Versus Hand-Assisted Laparoscopic Nephrectomy

Three systematic reviews presented evidence comparing standard living donor laparoscopic nephrectomy and hand-assisted laparoscopic living donor nephrectomy, and summarize very low to low quality evidence supporting similar outcomes across these approaches^{448,450,451} (Evidence Report Table 4, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table C4, SDC, <http://links.lww.com/TP/B432>).

Operative Time

Yuan et al⁴⁵¹ reviewed 7 trials including 387 donors that compared hand-assisted laparoscopic nephrectomy to standard laparoscopic nephrectomy, and found no statistical difference in operating time by meta-analysis (mean difference, -24.6 minutes; 95% CI, -50.8 to 1.7).

Blood Loss

Wilson et al⁴⁵⁰ reported varying results for blood loss across the studies of standard laparoscopic and hand-assisted nephrectomy included in their review, but overall found no significant differences between the groups. Similarly, Yuan

et al⁴⁵¹ found no significant differences in blood loss with standard compared with hand-assisted laparoscopic nephrectomy (mean difference, -20.7 mL; 95% CI, -43.9 to 2.6).

Warm Ischemia Time

Yuan et al⁴⁵¹ found a small, statistically significant reduction in warm ischemia time with hand-assisted compared with standard laparoscopy (mean difference, -1.0 minutes; 95% CI, -1.4 to -0.6), but this small difference does not appear to be clinically meaningful.

Length of Hospital Stay

Based on 6 studies comprising 320 donors, donors undergoing standard laparoscopic nephrectomy had a slight reduction in average length hospital stay compared to those undergoing hand-assisted laparoscopic nephrectomy (mean difference, 0.3 days; 95% CI, 0.1-0.6),⁴⁵¹ although the difference (less than 1 day) appears to be modest.

A clinical trial at 2 centers published after these systematic reviews described 190 donors randomized to hand-assisted or standard laparoscopy for left donor nephrectomy.⁴⁵⁴ Hand-assisted laparoscopy resulted in shorter operative time (mean, 159 vs 188 minutes; $P = 0.001$) and a small reduction in warm ischemia time (2 vs 5 minutes; $P < 0.001$). Intraoperative complication rate (5% vs 11%, $P = 0.12$), length of stay (both 3 days; $P = 0.14$), postoperative complication rate (8% vs 8%; $P = 1.00$), potential graft-related complications (6% vs 13%; $P = 0.14$), and physical function at 1 month follow-up ($P = 0.55$) did not significantly differ between the groups.

Novel Minimally-Invasive Nephrectomy Approaches

In recent years, innovations in laparoscopic surgery have provided transplant surgeons with a range of techniques and minimally invasive instruments. Robotic-assisted, total robotic, and single port nephrectomies have been described in case reports, small series, and small trials at experienced centers.⁴⁵⁵⁻⁴⁵⁹

A systematic review and meta-analysis published after the ERT's systematic review for this guideline examined 190 articles published through March 2016 reporting short-term complications after minimally invasive donor nephrectomy⁴⁶⁰; of these, outcomes from 41 articles that compared 2 or more minimally invasive nephrectomy approaches were included in a meta-analysis. Publication dates of identified articles ranged from 2000 to 2015; most studies were retrospective case series. Although the sample included some prospective series, there were only 16 RCTs. The distribution of 32 038 donors according to operative technique was: laparoscopic, 57.4%; hand-assisted laparoscopic, 25.3%; mini-open, 4.5%; hand-assisted retroperitoneoscopic, 3.8%; retroperitoneoscopic, 3.7%; single-port laparoscopic (ie, laparoscopic single-site surgery [LESS]), 3.8%; and robotic-assisted laparoscopic, 1.3%. Overall, conversion rate to traditional open nephrectomy was 1.1%. Intraoperative complication rate was 2.3%, most commonly bleeding (1.5%). Postoperative complications occurred in 7.3% of donors, including infectious complications in 2.6% (mainly wound infections, 1.6%) and bleeding in 1.0%. Reported mortality rate was 0.01%.

Among 7 studies (2 RCTs, 2 prospective, and 3 retrospective) comparing laparoscopic ($n = 1159$) with retroperitoneoscopic

($n = 311$) techniques, there were no significant differences in rates of conversion, overall intraoperative or perioperative complications.⁴⁶⁰ Based on 8 studies (3 RCTs, 5 prospective) comparing mini-open ($n = 322$) to endoscopic ($n = 288$) techniques (ie, laparoperitoneoscopic, retroperitoneoscopic, with or without hand assistance), intraoperative complications were more frequently seen in endoscopic procedures (8.2% vs 3.4%; RR 1.132.45_{5.35}; $P = 0.02$). This difference was mostly due to intraoperative organ damage, which demonstrated a trend in favor of open procedures (0% vs 2.8%; RR 0.915.18_{29.35}; $P = 0.06$). The postoperative complication rate was comparable after mini-open versus laparoscopic donor nephrectomy. Ten studies (3 RCTs, 1 prospective study, 6 retrospective series) compared single-port ($n = 764$) with multiport laparoscopic ($n = 1214$) procedures, among which pulmonary complications were more frequently reported after LESS donor nephrectomy (1.5% vs 0%; RR 1.257.51_{44.94}; $P = 0.03$). The slightly higher incidence of postoperative pain after LESS compared with multiport nephrectomy was not statistically significant (2.7% vs 0.8%; RR 0.903.56_{14.11}; $P = 0.07$).

Limitations of this systematic review⁴⁶⁰ include the varying study designs, outcome definitions and ascertainment methodologies. A Cochrane review of RCTs published through January 2016 comparing LESS donor nephrectomy with laparoscopic donor nephrectomy identified 3 studies including 179 patients, and concluded that data were insufficient for drawing inferences on outcomes.⁴⁶¹ At the present time, given the current limited experience and lack of robust safety and outcomes data, robotic, single-port, and natural orifice transluminal nephrectomies are not currently standard of care approaches to living donor nephrectomy and should only be performed by surgeons with adequate training and experience, and after informed consent.

What Prior Guidelines Recommend

The ERBP also recommends that the choice between minimal invasive and standard laparoscopic procedure should be based on the local expertise.⁵⁰ No other guidelines recommend a preference for standard laparoscopy versus hand-assisted or other minimally invasive approaches.

Left Versus Right Laparoscopic Nephrectomy

In the absence of reasons to procure the right kidney (eg, vascular or urological abnormalities), the left kidney should be procured in laparoscopic living donor nephrectomy because of the relative technical ease associated with a longer venous pedicle. However, the choice of which kidney to procure should be made to minimize short-term and long-term complications in the donor. Thus, the presence of renal parenchymal, vascular or urological abnormalities which are not contraindications to donation may favor the use of an abnormal right kidney for donation and transplantation, for the goal of leaving the donor with the “more normal” kidney and/or to minimize complications related to multiple vascular pedicles. Recent evidence supports safe laparoscopic procurement of the right kidney without increased risk of adverse outcomes compared with procurement of the left kidney, although the evidence is weak. The ERT examined one systematic review by Liu et al⁴⁴⁹ comparing right with left laparoscopic living donor nephrectomy, and identified very low

quality evidence for similar operative times, blood loss, warm ischemia times, and length of stay at experienced centers (Evidence Report Table 5, SDC, <http://links.lww.com/TP/B434>; Supplemental Appendix Table C5, SDC, <http://links.lww.com/TP/B432>). Although complication rates of minimally invasive surgery are generally low with experienced surgeons, complications can be life threatening, and therefore proper training and experience is critical.

Operative Time

Among 14 studies including 2656 donors with available data, operative times were similar with left and right laparoscopic nephrectomy (weighted mean difference, 1.4 minutes; 95% CI, -11.7 to 14.4).⁴⁴⁹

Blood Loss

Based on data from 15 studies including 3033 donors, blood loss was similar between donors who underwent left versus right nephrectomy (weighted mean difference, 4.4 mL; 95% CI, -19.8 to 28.6).⁴⁴⁹

Warm Ischemia Time

Among 18 studies including 3516 donors, warm ischemia time was also similar among donors undergoing left versus right nephrectomy (weighted mean difference, -0.02 minutes; 95% CI, -0.4 to 0.05).⁴⁴⁹

Length of Hospital Stay

The mean length of hospital stay in 11 studies including 1370 donors was similar between those undergoing left versus right nephrectomy (weighted mean difference, 0.05 days; 95% CI, -0.08 to 0.02).⁴⁴⁹

A subsequent study of 58 599 living donor nephrectomies from a US registry, including 13.9% right nephrectomies, found statistically significant but numerically small differences in outcomes after right versus left donor nephrectomy, including higher rates of conversion from laparoscopic to open nephrectomy (1.9% vs 0.95%, $P \leq 0.00001$; OR 1.162.02_{2.52}), delayed allograft function (5.7% vs 4.2%, $P < 0.0001$; HR 1.241.38_{1.53}) and early graft thrombosis (1.1% vs 0.79%, $P = 0.006$; HR_{1.18}1.48_{1.86}).⁴⁶² The authors concluded that the laterality of donor nephrectomy should be based on surgeon preference and experience.

Laparoscopic Procedure Type for Right Nephrectomy

Use of hand-assisted laparoscopy over standard laparoscopy for right donor nephrectomy is controversial, as some authors report caudal position of the liver that limits the working space for the hand assisted approach.⁴⁶³ A trial at a referral center with longstanding expertise in the standard laparoscopic right nephrectomy explored the safety and feasibility of right hand-assisted approach by randomly assigning 40 donors to either approach.⁴⁶⁴ As compared with laparoscopic right nephrectomy, hand-assisted right nephrectomy resulted in slightly shorter warm ischemia time (2.8 vs 3.9 minutes; $P < 0.001$) and increased blood loss (187 vs 50 mL, $P < 0.001$), while operative time, complication rate, pain, hospital stay and 1 year quality of life scores were not significantly different between the groups.

Multiple Renal Arteries

Kidneys with multiple renal arteries are common. A study of CT scan results performed during living donor evaluation reported a prevalence of 18% to 30% for multiple renal arteries, with up to 15% bilateral involvement.⁴⁶⁵⁻⁴⁶⁷ Multiple renal arteries may adversely affect donor safety and recipient outcome. Multiple renal arteries may lead to intraoperative technical difficulties and complications, such as increased operative time, complicated dissection, or bleeding. Furthermore, either arterial reconstructions need to be created after procurement or multiple arterial anastomoses are needed in the recipient, both of which may be associated with complications. A small accessory artery that supplies a minor part of the upper pole (subjectively assessed using predonation CT scans) can often be safely sacrificed. However, an accessory artery that vascularizes the lower pole and the proximal ureter must be saved and reconstructed after nephrectomy. In the case of a complex venous anatomy, there is usually only one domain vein, and the remaining veins can be tied off. A systemic review by Ahmadi et al⁴⁶⁸ capturing reports of outcomes associated with vascular multiplicity in living donors in the past decade concluded that renal arterial multiplicity (up to 3 renal arteries) and venous anomalies should not be a contraindication to living kidney donation. Vascular anomalies require longer operative times to manage, but were not associated with significant negative impact on donor or graft outcomes with modern surgical techniques and high surgical skills. As most living donors with multiple renal arteries in the reported studies had a maximum of 3 renal arteries, conclusions cannot be drawn for donors with 4 or more arteries. Prior guidelines have also concluded that multiple arteries is generally not a contraindication to living kidney donation.^{48,54,55}

Nontransfixing Vascular Clips

Hemorrhagic deaths of living kidney donors from failure of nontransfixing vascular clips (eg, Weck Hem-o-lok; Teleflex Medical, Bannockburn, IL) used to ligate the donor renal artery were first documented in 2006.^{469,470} Despite a Class II recall of the Hem-o-lok clip for laparoscopic donor nephrectomy by the US FDA in 2006, and a FDA Black Box Warning that use of the Weck Hem-o-lok hemostatic clip to ligate the renal artery in living donor nephrectomy is contraindicated, use of these clips is still reported. A 2011 ASTS survey reported that Hem-o-lok or other clips are still used by some surgeons as sole means of arterial control in laparoscopic donor nephrectomy.⁴⁶⁹ Subsequently, in a 2013 survey of 645 members of the European Society for Organ Transplantation, 20% of respondents reported use of clips (locking and nonlocking) to close the arterial stump.⁴⁷¹ Of the 121 reported hemorrhagic events, slippage and dislodgement of clips occurred in at least 58 (47.9%).⁴⁷¹ All surgeons operating on a living organ donor should select vascular control techniques that entail tissue transfixion and assure a safe operative recovery. The Hem-o-lok and other surgical clips should not be used to ligate the donor renal artery.

What Prior Guidelines Recommend

The CARI guideline states that the use of a nontransfixing technique for securing the renal artery is not recommended, particularly with laparoscopic donor nephrectomy.⁴⁵³ In

the current guideline, we recommend that nontransfixing clips should *never* be used to ligate the renal artery in donor nephrectomy.

RESEARCH RECOMMENDATIONS

- Define the incidence of perioperative outcomes in representative donor samples (ie, not limited to experienced centers with a limited number of surgeons) according to nephrectomy surgical approach and side.
- Define outcomes of nephrectomy surgical approaches according to baseline donor characteristics (eg, BMI, renal vascular anatomy).
- Define the outcomes of novel minimally invasive approaches to donor nephrectomy to guide future recommendations and appropriate use of these techniques.
- Determine the optimal training and experience levels necessary to define proficiency with donor nephrectomy approaches.⁴⁷²

CHAPTER 18: ETHICAL, LEGAL AND POLICY CONSIDERATIONS

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 18 and therefore the following recommendations are “Not Graded.”

Ethical and Legal Framework

- 18.1: Local laws and regulations on living donation should be followed and explained as needed to donor candidates.
- 18.2: Where local laws or policies impede the ethical practice of living donation, avenues to advocate for change should be explored.
- 18.3: Autonomy (self-determination) in the willingness or not to be considered as a living donor should be respected during all phases of the evaluation and donation processes. Transplant programs should support autonomy through a fully informed consent process.

Policies for Donor Candidate Identification

- 18.4: Public awareness of opportunities for living donation should be increased through education, donor advocacy, evaluation efficiencies, and removal of disincentives.
- 18.5: Transplant candidates should be assisted in identifying living donor candidates, as long as these efforts respect donor autonomy and do not exert undue pressure to donate.
- 18.6: Donor candidates should be informed of the dangers of transplant tourism.
- 18.7: Transplant programs should define and disclose their policies for the acceptance of donor candidates identified through public solicitation.

Financial Support

- 18.8: Donor candidates should be informed of the availability of legitimate financial assistance for expenses from evaluation and donation.

Communication of Policies

- 18.9: Nondirected donors and donors participating in paired donation should be informed of the transplant program's policy on contact with the recipient and other paired donation participants at all stages in the donation process.

- 18.10: Transplant programs should disclose the extent of the expected postdonation program-patient relationship before donation, including whether the donor can seek medical care at the transplant center after donation.
- 18.11: Regional policies should ensure access to kidney replacement therapy (dialysis and/or transplantation) for donors who develop kidney failure.

RATIONALE

Ethical and Legal Framework for Living Donation

Living kidney donation must be practiced within a framework of the laws and regulations of each country and its governing or regulatory bodies. The legal framework gives legitimacy to living donation and provides some protection to the donor.⁴⁷³ All practitioners in transplant programs should be aware of relevant laws and regulations that pertain to the living donor transplant program.⁴⁷⁴ Ethical tenets and specific transplant program processes are applied to minimize donor risk. See chapter 1 for discussion of the conceptual framework for decision-making related to donor acceptance, and roles and responsibilities in donation-related care, and chapter 2 for details on the processes and content of informed consent.

When there is opportunity to identify needs for policy and legal changes to improve the practice of living donation, transplant programs should actively participate in the review and process to update or change laws, regulations and policies as needed.⁴⁷⁵ Laws to regulate donation include, but are not limited to, those that: a) protect the vulnerable (eg, the cognitively impaired, young people, dependent persons)^{53,476,477}; b) respect autonomy (eg, require informed consent); c) prohibit incentives to donate that may create undue influence (eg, payment for organs in money or in kind).⁴³⁰ Other relevant laws and policies related to donor protections include insurability criteria related to donation status, state tax credits for donation-related expenses, and access to medical leave after donation.

Transplant professionals have an ethical duty to act in the best interests of donor candidates and donors. Self-determination related to the donation decision reflects a view of people as autonomous agents.⁴⁷⁸ Donor autonomy in the willingness to be considered as a donor candidate or to withdraw should be respected during all phases of the evaluation and donation process. Programs should support autonomy through a fully informed consent process (chapter 2). Balancing risks and benefits to the donor as well as respecting the donor's wishes for donation addresses the principle of beneficence.

In the United States, concern that kidney paired donation could be construed as violating the prohibition of NOTA to transfers of organs for valuable consideration was addressed with a specific amendment ("Norwood Act" of 2007) that explicitly defined paired donation as exempt from NOTA violation.⁴⁷⁹ Although nonsimultaneous chains initiated by nondirected donors do not technically fall within the exemption for kidney paired donation, there is arguably no need for an exemption with respect to chains initiated by nondirected donors because they are designed as a series of gifts, rather than as an exchange of valuable consideration. See chapter 3 for discussion of clinical and educational issues related to paired donation.

Policies for Donor Candidate Identification

People may not be aware of or have accurate knowledge of living donation.⁴⁸⁰ Recipient candidates may not feel comfortable sharing their need for an organ donor with their social network for reasons including not knowing how to ask, misunderstanding of risks, and fear for harm to the donor candidate.^{481,482} A 2015 *AST Live Donor Community of Practice* consensus statement on "Best Practices in Live Kidney Donation" deemed implementation of approaches to empower transplant candidates and their loved one in their search for a living donor to be a high priority.^{148,483} Developing effective methods to address the growing organ shortage, including through living donor transplantation, is the highest stated priority in the 2015 US OPTN Strategic Plan⁴⁸⁴ and was endorsed in a June 2016 White House Summit on Organ Donation.⁴⁸⁵ Appropriate strategies for promoting living donation might include education (public, clinic-based, home-based), use of advocated (eg, "live donor champions"), efficiencies in the evaluation of donor candidates (eg, use of new information technology) and the removal of disincentives.⁴⁸⁶⁻⁴⁹⁰ Effective interventions may include participation of family and friends of the transplant candidate to increase knowledge and awareness of living donation within the patient's social network. The evidence supporting use of social media tools to enable transplant candidates to share their need for a living donor with their social network is at an early stage,⁴⁹¹ but given the growing use of the internet and devices such as smartphones globally, application of technology to donor identification is anticipated to grow and was referenced by the White House Office of Science and Technology Policy.⁴⁹²

The ethical appropriateness of strategies for promoting living donation may vary with the entity employing the strategy.⁴⁹³ For example, direct promotion of donation by transplant programs may raise ethical concerns for conflict of interest and risk eroding public trust and the quality of donor decision-making, but training and support of advocated (eg, "live donor champions") can be an appropriate alternative if employed conscientiously, including the careful use of anticoercion training. Nonprofit groups separate from transplant programs may have more freedom in promoting donation without challenging ethical norms underlying the physician-patient relationship, but still bear ethical responsibilities to present evidence-based information and maintain public trust. Development of "best practices" related to use of well-designed, evidence-based approaches including technology to efficiently and ethically expand opportunities for willing, well-informed patients and potential donors to pursue living donor transplantation and living donation is an important priority. All strategies for living donor identification must respect donor autonomy and cannot exert undue pressure to donate. Critically, a wish not to donate must always be respected.⁴⁹⁴

Some people respond to public solicitations by offering to be a kidney donor.⁴⁹⁵ By evaluating these donor candidates, transplant programs are enabling donation.⁴⁹⁶ In this setting, the standard evaluation needs to address additional issues related to the parties' limited knowledge of each other, and the potential for exploitation.⁴⁹⁷ Recently, the Canadian Society of Transplantation issued a position paper that addressed issues such as privacy, informed consent, and donor follow-up associated with public donor solicitation.⁸⁴

Financial Support for Living Donors and Removal of Economic Disincentives

Financial support for living kidney donors can be divided into cost replacement and financial gain. Living donor candidates have the right to be informed of available legitimate cost-replacements programs for evaluation and donation-related expenses.^{430,432} Initiatives to remove financial disincentives to kidney donation (ie, replacement of costs incurred during the evaluation and donation such as lost income, travel costs, accommodation costs; avoidance of insurance discrimination) are acceptable as an issue of justice.⁴³⁰ Multiple prior living donation guidelines and viewpoints endorse reimbursement for out-of-pocket expenses incurred during the evaluation and donation processes, independent of the final decision to proceed with donation.^{47-49,498-500}

In the United States, the prohibition of organ exchange for “valuable consideration” in NOTA has been clarified as not prohibiting “reasonable payments associated with... the expenses of travel, housing, and lost wages incurred by the donor of a human organ in connection with the donation of the organ.”⁵⁰¹ To date, developing programs for wage reimbursement has posed the most challenges internationally, including the need for accepted definition of lost wages and the potentially large cost of reimbursing very high-income donors.⁵⁰² In December 2016, New Zealand passed legislation to provide 100% of a donor's earnings for up to 12 weeks after donation plus childcare assistance for donors who need it while they recover.⁵⁰³ Also in December 2016, the US NLDAC, which to date has provided funds to reimburse donation-related travel and lodging costs, announced that it will conduct an RCT to assess the impact of interventions intended to remove financial barriers to living organ donation through wage reimbursement.⁵⁰⁴ Recommendations to offer life and disability and/or health insurance for living donors, or to pass legislation to offer tax credits and ensure employment and insurability protections to donors, have also been advanced.^{55,432,500,505-508}

In 2016, the AST launched an online financial toolkit to help donor candidates learn about the finances of being a living organ donor; this dynamic resource will be expanded and updated over time.⁴³⁸ Although developed from the perspective of United States-based policies and resources, the information may be helpful to donor candidates in other countries. See chapter 16 for a discussion of the potential financial impact of living donation.

Financial Incentives for Donation

Payment for a kidney is illegal in almost all parts of the world. Suggestions to provide financial incentives for donation elicit some fears that vulnerable people such as the poor will be exploited, and that public views of donation and transplantation will be damaged.⁵⁰⁹ The Declaration of Istanbul asserts that because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited.⁴²¹ However, the debate on the acceptability of incentives continues and a formal examination of donor incentives within clinical trials has been proposed.^{509,510}

Communication of Policies and Postdonation Follow-Up Care

Living anonymous donors are also referred to as nondirected living donors.⁴¹¹ These are living donors who offer a

kidney to a transplant center to allocate, as they do not have an identified recipient. Nondirected donors may also donate by participating in a KPD program or as part of a series of matched donor and recipient pairs allowing for a chain of multiple transplants. Some nondirected living donors and their recipients may request contact with each other postdonation. Clarification before donation of the center's policy on such contacts enables participants to adjust their expectations after donation.⁵¹¹

The extent of the physician-patient relationship after donation should be communicated before donation, including whether the donor can seek medical care at the transplant center after the donation. See chapter 19 for discussion of postdonation follow-up recommendations.

Kidney failure is a rare event after living kidney donation, but fatal in the absence of kidney replacement therapy. Federally funded programs to assure access to dialysis and transplantation can be promoted as a strategy to protect the safety of living donors if the remaining kidney fails after donation. Payment for dialysis services, payment for living or deceased donor transplantation, and allocation priority for deceased donor kidney transplantation are examples of such programs. Many countries provide substantial assistance for dialysis and transplantation as part of public health services. For example in the United States, prior living donors receive additional priority points for deceased donor kidney transplants,⁵¹² which has been associated with higher transplant rates, shorter time to transplant, and receipt of higher quality allografts compared to candidates with otherwise similar clinical profiles.⁵¹³⁻⁵¹⁵ However, the transplant center must report prior donor status for the patient to receive priority.⁵¹⁶ Priority for prior living donors can also be incorporated in KPD matching algorithms.⁶¹ In Israel, when a living donor develops ESKD subsequent to the donation, the living donor can designate a family member to receive priority on the deceased donor transplant waitlist.⁵¹⁷ The purpose is to reduce the disincentive to current donation based on concern that a family member may need a kidney transplant in the future. The impact of this priority on the national allocation system and on attitudes and concerns about living donation warrants further study.⁵¹⁸

RESEARCH RECOMMENDATIONS

- Explore approaches to and impact of strengthening partnerships between general nephrologists, dialysis providers, and transplant centers regarding living donor kidney transplant education, access and disparities.⁴⁸³
- Examine the impact of patient and public education on increasing donation from living donors.^{483,490,519}
- Develop “best practices” related to use of well-designed, evidence-based approaches to efficiently and ethically expand opportunities for willing, well-informed patients and potential donors to pursue living donor transplantation and living donation.^{492,496,497} Research on strategies to promote living donation should evaluate not only efficacy in increasing donation but also effects on attitudes, quality of donor decision-making, and informed consent.⁴⁹³
- Examine the experiences of individuals exposed to different forms of “nonargumentative” influences promoting living donation (ie, approaches to shaping behavior that do not attempt to persuade through reason, such as appeals to emotion, messenger effects, and social norms) and whether exposed individuals feel the influence was appropriate.⁴⁹³

- Examine strategies for reducing financial barriers to living donation, with particular attention to impact on current disparities in living donor kidney transplantation.^{432,502}
- Determine optimal approaches to allowing or restricting contact between nondirected kidney donors and their recipients.⁵¹¹
- Evaluate the outcomes of incentivizing organ donation via ethically and legally acceptable methods.^{520,521}

CHAPTER 19: POSTDONATION FOLLOW-UP CARE

The ERT search parameters did not identify evidence from eligible studies pertinent to the recommendations in chapter 19 and therefore the following recommendations are “Not Graded.”

- 19.1: A personalized postdonation care plan should be provided before donation to clearly describe follow-up care recommendations, who will provide the care, and how often.
- 19.2: The following should be performed at least annually postdonation:
- Blood pressure measurement
 - BMI measurement
 - Serum creatinine measurement with GFR estimation
 - Albuminuria measurement
 - Review and promotion of a healthy lifestyle including regular exercise, healthy diet and abstinence from tobacco
 - Review and support of psychosocial health and well-being
- 19.3: Donors should be monitored for CKD, and those meeting criteria for CKD should be managed according to the 2012 KDIGO CKD Guideline.
- 19.4: Donors should receive age-appropriate healthcare maintenance, and management of clinical conditions and health risk factors according to clinical practice guidelines for the regional population.

RATIONALE

Rationale for Postdonation Follow-Up

The living donor evaluation should be regarded as the initial stages of a long-term, collaborative relationship between 2 parties, the donor candidate and the transplant program.¹⁹⁶ The donor enters the relationship with an interest in offering an altruistic and life-extending gift of an organ for transplantation if he or she is healthy enough to donate and meets the transplant center’s acceptance criteria. Grounded in primary concern for the well-being of the donor, the transplant center should promote the donor’s autonomy, safety and long-term health throughout all phases of care including evaluation, donation surgery, long-term follow-up and donation-related care. Early postdonation follow-up care is routinely practiced as part of postoperative care. In contrast, responsibility for the coordination and performance of long-term donor follow-up has raised controversies regarding financial and time burden on both transplant centers and donors, especially in countries without universal health insurance.⁵²² Monitoring incurs costs and may provide only limited information for the majority of donors who may demonstrate stable clinical status and well-being. However, as articulated in a 2011 consensus conference report,⁵²³ these concerns are outweighed by fundamental ethical

principles and clinical needs to support the practice of living donation, including:

- The need to provide accurate outcomes information to donor candidates and their recipients as a basis for informed consent, especially regarding trends in outcomes and incremental hazards that may be associated with race/ethnicity, baseline comorbidity, changes in surgical approaches and management strategies.
- The need to acquire more robust outcomes data to improve the evaluation process and to provide reliable counseling for donor candidates tailored for demographic and health profile.
- The possibility of identification of individual donor clinical problems through surveillance at a time when intervention is possible.
- Provision of program-specific feedback to guide quality assurance and performance improvement.
- Recognition of the professional obligation of the transplant community to continue to collect and monitor information on living donor outcomes.

Similarly, the “European Standards of Quality and Safety of Organs Intended for Transplantation” states that adequate follow-up is part of internationally recognized measures aimed at protecting living kidney donors and ensuring the quality and safety of organ donation.⁵²⁴

Content of Follow-Up

Follow-up care after kidney donation should focus on the monitoring and maintenance of general and kidney health including reinforcement of healthy lifestyle practices (eg, healthy dietary habits, maintenance of healthy weight, regular aerobic exercise), avoidance of potentially nephrotoxic exposures (eg, tobacco use, nonsteroidal anti-inflammatory drugs, nephrotoxic medications), prevention of diseases that may cause CKD (eg, hypertension, diabetes mellitus, CVD), and timely management of such diseases if they develop after donation. As discussed in chapter 10, hypertension is diagnosed more commonly in kidney donors than in persons with comparable baseline health, although this may in part reflect greater monitoring and earlier recognition.^{224,229} Early detection and treatment of medical conditions that may subsequently affect GFR may protect the donor from further loss of GFR or other deterioration in health. Such conditions should be managed according to clinical practice guidelines either by the donor’s primary care provider, or at the transplant center if appropriate care is available.

Because many donors develop low GFR that meets criteria for diagnosis of CKD and the risk of someday developing kidney failure needing treatment with dialysis or transplantation is slightly higher as a result of donation (see chapter 5),^{30,32} postdonation monitoring for kidney disease and CKD risk factors is warranted. Living kidney donors should be monitored for CKD and managed according to the 2012 KDIGO CKD Guideline.¹²⁴ Donors should also receive age-appropriate healthcare maintenance, and management of clinical conditions and health risk factors according to clinical practice guidelines for the local or regional population.

Assessment of psychosocial metrics such as HRQoL have been recommended as part of postdonation follow-up to

monitor general well-being,⁵²⁵ and to help transplant centers identify donors at risk for poor psychosocial outcomes.^{414,526} Quality of life measures are collected as part of standard postdonation follow-up in some donor registries.^{445,527} Guidelines for metric thresholds indicating presence of an impairment that would prompt more attention by the clinician are not specifically defined in donors, but could be based on existing test standards (eg, scores below 0.50 standard deviation of the normative mean on the “Short Form” (SF) class of measure, SF-36, 12, or 8).

Follow-Up Timing and Processes

As part of the informed consent process for donation, transplant centers should educate donor candidates on the importance of follow-up, disclose donor responsibilities and potential costs of follow-up participation, and develop a personalized follow-up plan. Because donors in many countries report regular follow-up with a primary provider,⁵²⁸ donor follow-up and care may be appropriately performed by a primary care provider to preserve convenience for the donor. However, communication of follow-up information back to the transplant center is necessary for centers to be aware of the health status of their donors, to comply with reporting mandates (when applicable), and to direct additional care if needed. The role of a primary care provider in a donor’s follow-up plan should be established before donation. The transplant center should always be available as a resource for the donor’s primary care provider. Documentation of a donor’s acknowledgement of their responsibility to participate in follow-up through a signed care plan has been proposed as part of education,⁵²⁵ although efficacy in achieving follow-up participation has not been formally evaluated. Particular attention should be given to donors with risk factors for follow-up deficiencies and to those with baseline factors associated with increased risk of CKD over time.

Donor education before and at the time of donation is critical to support an informed donation decision, but there is a need to continue education on health promoting practices as the donor recovers and ages. A donor in the midst of making a decision to donate or dealing with the early outcomes of donation such as postoperative pain and financial pressures may not absorb all the information on long-term issues.

The establishment of standardized follow-up at serial time points provides a pattern for follow-up care that the donor may be more likely to continue on regular, yearly preventive healthcare visits.⁵²⁹ Regular contact between the transplant center and the donor and/or the donor’s primary care physician also increases familiarity of staff with issues that develop after donation, providing an opportunity to modify education materials or processes to better manage these situations for future donors. While regular healthcare maintenance is important over the lifetime after donation, data collection at regular time points by transplant centers should be pertinent to donation, attainable, and not overly burdensome on the donor or the transplant center.

Early follow-up of donors by transplant centers is mandated in some countries including the United States, Canada and Australia.^{47,49,73} In the United States, the country that performs the largest volume of living donor kidney transplants per year, follow-up reporting by centers to the national transplant registry is limited to 2 years postdonation, and has historically suffered from missing data

and frequent loss-to-follow-up.^{73,530-532} Follow-up deficiencies have correlated with patient factors including younger donor age, black race, lack of insurance, lower educational attainment, and greater distance to the transplant center.^{528,530,531} Lack of health insurance had been more common among living kidney donors in the United States than in the general US population, although that disparity has not been present in recent years, perhaps due to changes in the economy and policy changes including the Patient Protection and Affordable Care Act (ACA).^{533,534} Lack of insurance and lower educational attainment may pose lesser obstacles to follow-up in other countries where national healthcare is available. Among US centers in 2008 to 2012, large annual living donation volumes were also associated with increased rates of follow-up deficiencies.⁵³⁰ However, implementation of mandatory thresholds for collection of postdonation clinical and laboratory data in the United States in 2013 with regulatory implications has led to improved rates of early follow-up data collection, and high levels of follow-up have been achieved by programs across the volume spectrum.^{530,535}

There is a real need for comprehensive, long-term (lifetime) follow-up of living donors. Short-term follow-up may detect severe adverse outcomes early after donation but cannot detect gradual, progressive complications that occur late after donation. Clinically important events that may develop in the intermediate to long-term after donation include hypertension, CKD, metabolic conditions (eg, diabetes mellitus, hyperlipidemia) and CVD, which in turn may increase the risk of kidney failure and mortality.

Transplant programs achieve high rates of postdonation follow-up have practices that appear to be grounded in: 1) program conviction that follow-up is essential for donor safety and well-being; 2) emphasis on building and maintaining a relationship with each donor; 3) use of a systematic approach to follow-up; and 4) efforts to minimize the burden on donors.⁵²⁵ Open-ended, qualitative interviews of US programs found that programs with high rates of successful follow-up endorsed all 4 of these concepts.⁵²⁵ Recent single-center experience supports that institution of follow-up performance improvement initiatives with dedicated program resources is financially feasible and can result in more accurate and complete follow-up after donation.⁵³⁶

Donor Registries

When national or regional donor registries exist, capture of donor follow-up information, either through center reporting or direct donor contacts, facilitates data aggregation, assessment and dissemination of current donor outcomes data. Informed consent for collection of follow-up information for registry reporting should be requested during the consent for donor evaluation. In countries where registries do not exist, efforts should be made to establish and maintain a donor registry to support ongoing monitoring of postdonation outcomes, as the characteristics of accepted donors and care practices may evolve over time.

Some countries have instituted systematic approaches to longer-term living donor follow-up and registry reporting. The EULID project began with an 11-nation assessment of living donation practices in Europe that recommended mandatory living donor registration and follow-up data collections through a centralized donor database system, and

mandatory regulatory audits at the national and center level.⁴⁴⁴ An online registry is used for reporting of information on donor health status, quality of informed consent, and psychosocial and socioeconomic outcomes. The European Living Donor Psychosocial Follow-Up (ELIPSY), a study conducted in 6 centers of different European countries (Spain, Germany, France, Portugal, Sweden and Turkey) in 2009 to 2012, focused on monitoring donor psychosocial well-being and quality of life.⁵²⁷

The SOL-DHR provides a model for involvement of primary care physicians to achieve short- and long-term follow-up of donor health and well-being.⁴⁴⁵ In 1993, a national protocol was initiated for all Swiss transplant centers to organize lifelong follow-up after donation at 1, 3, 5, 7, 10 years, and biennially thereafter, by sending a package to the donor asking the donor to make an appointment with the family physician of their choice. The package contains brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples, and a prepaid envelope for sending the samples at room temperature to the central laboratory. The basic biennial follow-up questionnaire is completed by the family physician. In 2002, requests were added for completion an additional 8-Item Short-Form (SF-8) and social-status questionnaire by the donor. Nonresponses are followed by contacting the recipient, the donor's health insurance and public registries to identify whether the donor has died and, if so, the cause of death. Lifelong follow-up of the living donor's health status by centers is required by the Swiss Transplant Law. Although donors may choose to stop participating, compliance is promoted by informing donors about the aims of the protocol and the registry before their donation. Similarly, in Norway, donor follow-up includes initial contacts at weeks 3 to 4, month 3, then yearly monitoring for 5 years, and then lifelong contacts every fifth year thereafter. Clinical assessment of donors including BP, blood tests and urinalysis examinations is performed by local county hospitals. Durability of follow-up has been demonstrated as 99, 95, 84, and 77% of donors are still seen by local nephrologists at 1, 5, 10, and 15 years follow-up, respectively (*Dr. Hallvard Holdaas, personal communication*).

In 2017, the US Scientific Registry of Transplant Recipients began planning and transplant program enrollment for a Health Services Research Administration "Living Donor Collective" pilot project that seeks to achieve life-long living donor follow-up through direct contacts by staff and novel data linkages. A notable feature of the Collective is a plan to collect long-term outcomes data on all persons who present for donor candidate evaluation to provide information on donor exclusion practices and identify a set of healthy controls (eg, approved donors who do not donate due to recipient exclusions.) If successful, the goal is to expand to national participation.⁵³⁷

Given the current limited scope and duration of donor registries in many countries, and the possibility that some donors as independent decision makers may choose not to stay in contact with their transplant center, collection of outcome data in dedicated, funded research studies, and integration of donor registry data with other information sources such as health administrative data, ESKD and mortality registries are also important additional priorities for advancing understanding of long-term health outcomes after donation.⁵³⁸

What Prior Guidelines Recommend

The British Transplantation Society and The Renal Association UK Guidelines for Living Donor Kidney Transplantation state that:^{48,499}

- Life-long follow-up is recommended after donor nephrectomy. For donors who are resident in the United Kingdom, this should be offered locally or at the transplant center according to the wishes of the donor, but such arrangements must facilitate the collection of data for submission to the UK Living Donor Registry on long-term morbidity and mortality. Donors from overseas who travel to the United Kingdom to donate are not entitled to follow-up in the United Kingdom but should be given advice about appropriate follow-up before returning to their country of origin (C1).
- Arrangements must be made to ensure that the unsuitable donor, who is unable to proceed to donation, is appropriately followed up and referred for further investigation and management (B1).
- National Health Service Blood and Transplant has given a formal undertaking that any living kidney donor who develops kidney failure in the perioperative period as a consequence of donation will receive priority for a deceased donor kidney transplant (not graded).

Although it was not a specific guideline recommendation and no evidence was cited, the Amsterdam Forum suggested that "As in the general population, based on age and other medical risk factors (eg, hypertension, proteinuria, hyperlipidemia, impaired glucose tolerance test), kidney donors should undergo regular long-term follow-up of body weight, BP, blood glucose, serum creatinine, and urinalysis."³⁸ In the United States, OPTN policy enacted in 2013 requires transplant centers to collect and report the following information on their donors to the national registry at 6 months, 1 year, and 2 years postdonation: serum creatinine, urine protein and a set of clinical outcomes (eg, kidney complications, need for maintenance dialysis, development of hypertension or diabetes, loss of insurance due to donation).⁷³ Other guidelines also suggest postdonation follow-up for at least 1 year⁴⁹ or lifelong^{47,55} and provision of donation-related psychosocial services as needed during follow-up have also been proposed.^{47,409,498} As discussed in chapter 18 (Policy), living donors who develop ESKD in the United States receive priority for deceased donor kidney allocation.⁵¹²

RESEARCH RECOMMENDATIONS

- Develop communication and integrated care models to:
 - Examine electronic tools such as websites or portals to maintain contact with donors, facilitate data collection, and provide messaging to disseminate educational information to donors.⁵²²
 - Formulate strategies for using inter-institution-compatible electronic medical records to facilitate transmission of donor follow-up information, such as clinical data from care encounters, directly to national registries.⁵³¹
 - Formulate and assess the outcomes of center-based initiatives to provide long-term donor follow-up and support through integrated laboratory and clinical monitoring, expansion of preventive health strategies, and fostering of peer education through social support networks between past, current and future donors.⁵³⁹
- Establish, improve and integrate national/international donor registries to facilitate capture and analysis of long-term

outcomes information for large representative samples of living donors to: (1) address knowledge gaps related to the long-term consequences of donation, (2) provide data to inform donor selection criteria, (3) support quality assurance and program improvement at transplant centers, and 4) sustain and strengthen public confidence in the practice of living donation.^{523,531}

- Develop HRQoL metric thresholds to identify the presence of an impairment in postdonation psychosocial well-being warranting closer attention by the clinician
- Improve and assess the efficacy of educational resources to promote sustained healthy lifestyle choices and behaviors, and participation in regular postdonation follow-up and care, such as via newsletters, links to transplant center health recommendations or national guideline website documents.
- Develop and assess strategies for communicating new information that differs from what a donor was told before donation, to past donors and their physicians.

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