Proposed Scope of Work for Kidney Disease: Improving Global Outcomes (KDIGO) Guideline on the Evaluation and Follow-up Care of Living Kidney Donors

Introduction
Kidney Disease: Improving Global Outcomes (KDIGO) is an independent organization dedicated to improving the care of patients with kidney disease worldwide through the development and coordination of clinical practice guidelines.\(^1\) In the past decade KDIGO has produced evidence-based guidelines on the treatment of hepatitis C; management of mineral and bone disease; care of kidney transplant recipients; acute kidney injury; glomerulonephritis; management of blood pressure and anemia in chronic kidney disease (CKD); and most recently, evaluation and management of CKD (http://www.kdigo.org/). Our newest guideline on the management of dyslipidemia in CKD will be released this November. The KDIGO guideline development process relies on independent, multidisciplinary, international work groups; close collaboration with professional methodology experts who perform systematic evidence reviews; cooperation and collaboration with stakeholder professional societies; and open public review of each guideline. In each guideline the evidence and strength of recommendations are graded using the internationally accepted Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.\(^2\)

This guideline proposal is designed to briefly describe the rationale for a guideline on this topic, the scope or topics that the guideline intends to cover, the target audience, areas where systematic searches of the medical literature will yield pertinent evidence, as well as a potential path forward. Together with our partners: The Transplantation Society, Canadian Society of Nephrology, Canadian Blood Services and the International Society of Nephrology, we welcome your comments concerning the proposed Scope of Work presented here. Our intent is to ensure that feedback from potential stakeholders of this global guideline is duly considered before a formal systematic review of the literature is undertaken.

Rationale for a Guideline on the Evaluation of Living Kidney Donors
Worldwide the use of living kidney donors varies widely. Among countries with active kidney transplant programs in 2009-10, defined by at least 50 transplants in those two years, the proportion of kidney transplants that were obtained from living donors varied from less than 10% in Chile, Croatia, Cuba, Czech Republic, Estonia, Finland, France, Italy, Poland, Portugal, Slovakia, and Uruguay; to greater than 75% in Algeria, India, Iran, Japan, Kenya, Kuwait, Lebanon, Mexico, Nepal, Nigeria, Pakistan, Philippines,
Sudan, Syria, Tunisia, and Turkey. In the US, where the most kidney transplants are performed, over 35% are from living donors.

Despite the widespread adoption of living kidney donation, there remain concerns regarding patient safety. In addition, there is great variability in practice. A number of guidelines have appeared and a recent systematic review of these guidelines concluded:

“Multiple major guidelines for living kidney donation have been published recently, resulting in unnecessary duplicative efforts. Most do not meet standard processes for development, and important recommendations about thresholds for exclusion based on comorbidities are contradictory. There is an urgent need for international collaboration and coordination to ensure, where possible, that guidelines for living donation are consistent, evidence based, and comprehensive to promote best outcomes for a precious resource.”3

Scope
This guideline will include both the evaluation of potential living kidney donors and the care of donors after donation. A number of previous expert opinion-based guidelines have been published on living kidney donation. A recent systematic review found 9 clinical practice guidelines and 1 consensus statement addressing the topic.3 The Amsterdam Forum was a conference on the care of the living kidney donor held in the Netherlands, April 1–4, 2004.4 Although not a clinical practice guideline per se, the consensus summary statement of this conference outlined many of the issues that guidelines must grapple with pertaining to complications and the care of living kidney donors. By implication, these same issues will be addressed in this guideline, and additional prospective topics and questions currently under consideration are enumerated in Appendix A on page 6.

Evidence Review
The Evidence Review Team (ERT) will review existing Living Kidney Donor guidelines and their recommendations, compile existing systematic reviews in living kidney donation, and perform targeted systematic reviews on key topics in the evaluation and acceptance criteria of living kidney donations, complications, and long-term outcomes.5-6

Target Audience
This guideline is intended for medical professionals and other caregivers (e.g. doctors, nurses, transplant coordinators, pharmacists) who are involved in the evaluation and care of living kidney donors. It is not developed for insurance providers, administrative/regulatory personnel or patients per se, although carefully crafted explanations of guideline recommendations could potentially provide useful information for prospective donors or recipients.
Pertinent Evidence Review Topics
KDIGO typically formulates evidence review questions using the PICOD framework: target Population, Intervention of interest, the Comparator intervention, key Outcomes, and the Duration over which the outcomes are assessed. For most evidence questions pertinent to this guideline, the populations are made up of candidates for living kidney donation or donors after donation. However, for some questions (e.g. expected rate of decline in kidney function with age) evidence may be extrapolated from the general population. The intervention is kidney donation and the comparator is usually equally healthy individuals who did not donate. Outcomes are benefits and harms potentially attributable to donation, and study time frame can be either as short as perioperative or a lifetime after donation.

We anticipate that there will few pertinent randomized controlled trials and most evidence will be from observational studies that will vary in quality. These studies and outcomes will include:

**Risks and benefits to the donor**
- Longitudinal and cross-sectional studies in donors (with and without controls) measuring:
  - Death or the need for renal replacement therapy
  - Kidney function and the rate of function decline
  - Proteinuria and/or albuminuria
  - Cardiovascular disease and cardiovascular disease risk factors
  - Financial risk, including inability to obtain insurance coverage
  - Other complications
  - Psychosocial outcomes (positive and negative) impacting quality of life
  - Issues of coercion or organ commerce
- Small case series and case reports examining:
  - Major (life-threatening) donor complications
  - Perioperative complication rates by surgery type
- Observational studies in the general population that indirectly assess donor risk with respect to:
  - Rate of decline of kidney function with age
  - Influence of kidney function on CVD, CVD risk factors and other complications

**Risks and benefits to the recipient**
- Longitudinal and cross-sectional studies describing donor characteristics that influence graft and recipient survival, including donor age, obesity, blood pressure, kidney function, quality of life, etc.
- Small case series and case reports describing transmissible diseases and other complications
The KDIGO Guideline Process

1. The need for a guideline originates from stakeholders, including individuals and professional societies, and KDIGO itself.
2. A guideline proposal is drafted by KDIGO and funding is solicited by KDIGO and other collaborating stakeholders. There is no direct, single-industry sponsorship of a guideline. However, industry may sponsor KDIGO and professional societies that sponsor guidelines.
3. Guideline Work Group (WG) Co-Chairs are nominated by stakeholders and KDIGO, and an ERT is sought.
4. KDIGO selects WG Co-Chairs, based on knowledge of evidence-based medicine, expertise with the guideline topic, and no or manageable conflicts of interest.
5. WG Co-Chairs and KDIGO select WG members to include adequate domain expertise, as well as stakeholder and international representation.
6. WG Co-Chairs meet with the ERT to outline draft Scope of Work; initial evidence review strategy is devised.
7. The tentative Scope of Work is made available for public comment.
8. Scope of Work is finalized based on feedback received.
9. The ERT performs literature searches and formal systematic reviews; 80-90% of data extractions are complete prior to the first face-to-face WG meeting.
10. At the first WG meeting, guideline methodologies and conflicts of interest are reviewed. The WG reviews the evidence presented by the ERT, and suggests additional articles and search topics. The WG begins drafting recommendations.
11. KDIGO Chief Scientific Officer works with the WG Co-Chairs and members of the WG to draft the guideline recommendations and accompanying text. The ERT completes the evidence review.
12. At the second WG meeting, guideline recommendations are edited and the strength of recommendations and evidence supporting the recommendations are assigned according to the GRADE system.
13. The guideline draft is completed, reviewed by the KDIGO Board of Directors, and edited as necessary by the WG and KDIGO staff.
14. The guideline is released for public commenting and sent to targeted reviewers for structured review. Reviewer comments are collated and returned to the WG. Based on the feedback, modifications to the guideline document are made at the discretion of the WG and they have final say in the guideline content and wording of the recommendations.
15. The guideline is submitted for publication.
16. The guideline WG Co-Chairs or WG members are asked to review any KDIGO educational products used in dissemination and implementation of the guideline to ensure that such materials accurately reflect the meaning and intent of the original guideline.
17. A revision of the guideline is generally planned based on the WG’s assessment of durability and likelihood of new evidence affecting guideline recommendations. However, the guideline WG Co-Chairs, along with the KDIGO Co-Chairs, are responsible for monitoring any new evidence that may prompt the need to review and modify the guideline.
References


Appendix A: Proposed Guideline Scope

Roles and Responsibilities
1. Donor identification, evaluation and follow up roles of
   a. dialysis physicians
   b. dialysis units
   c. transplant center
   d. recipient physician
   e. recipient health insurance
   f. donor physician
   g. donor health insurance carrier
   h. regulatory agencies
2. Variation among countries

Framework for Decision-Making
1. How should one describe risk to potential donors?
   a. It is probably most appropriate to express risk for short-term complications as percent within a defined time, and risk for long-term complications as life-time risk.
   b. For both short-term and long-term risks, knowledge of excess risk is required.
   c. It is appropriate to acknowledge that there can be risk thresholds above which the transplant team can decline, irrespective of the donor request.
   d. For risks below this threshold, and if risks cannot be quantified, it would be appropriate to acknowledge that the donor is responsible for making the decision, with advice from the transplant team.
2. Who is responsible for decision-making?

Informed Consent and Expected Perioperative and Long Term Outcomes
1. Capacity to give consent to donate
   a. Legal requirements
   b. Minimum age
   c. Voluntarism
   d. Understanding of likely risks and benefits of donation
   e. Donor awareness of alternative treatment options for the recipient
2. Consent for donor evaluation
   a. Discovery of a health condition that may impact insurability
   b. Discovery of a reportable infectious disease
   c. Discovery of misattributed paternity and whether this information will be disclosed
   d. Anticipated timeline, out-of-pocket costs to the donor for the evaluation
   e. Information not shared without permission between donors and recipients
   f. Risk of lost anonymity (health information) for related and paired donors
   g. Providing information on transplant center-specific outcomes
   h. Risk of transport of organs for paired donation
3. Aspects of the process of donor evaluation
   a. How the medical evaluation is performed, who does it? (e.g. independent donor advocate)
b. Unique aspects of paired exchange, altruistic donation.
   i. Paired exchange: N-way exchanges, domino paired exchange – shipping of kidneys vs. patients; fairness in exchanges. Minimum criteria for various exchange programs.
   ii. How should one ensure equity of donor quality in chains?
   iii. Should standardized evaluation/acceptance protocols be used?

c. What tests should be performed in the follow-up of living kidney donors?
   i. What tests, how long, how often?
   ii. Should testing differ for donors with abnormalities: hypertension, older age, obesity, stones, etc.?
   iii. How should this testing be paid for and monitored?
   iv. What are the indications for intervention?

d. How should findings from the donor evaluation influence follow-up, e.g. hypertension, kidney stones, low eGFR?

e. What medical information about the donor should be shared with the intended recipient?

4. Transplant center donor follow-up
   a. What obligation do transplant centers have for the long-term follow-up care (medical, psychosocial) of past living kidney donors?
   b. What obligation do transplant centers have to follow-up on donor psychological health when recipient has a poor outcome?

5. Post-operative complications (generally expressed as percentages)
   a. Death
   b. Infection
   c. Venous thromboembolism
   d. Cardiovascular event
   e. Failure of renal artery clips
   f. Pain
   g. Others
   h. How outcomes and complications vary by type of surgery:
      i. Open vs. laparoscopic
      ii. Single port nephrectomy
      iii. Vaginal extraction

6. Long-term (lifetime) medical outcomes
   i. how various donor characteristics influence donor outcomes
   ii. sharing both what is known, and lack of knowledge that exists (uncertainty)
   a. Life expectancy / mortality
   b. End-stage renal disease
   c. Cardiovascular events
   d. Hypertension (and blood pressure)
   e. Measures of kidney function: Realized GFR, rate of change of GFR, proteinuria
   f. Kidney stones
   g. Future pregnancies
   h. Chronic pain
   i. Outcomes associated with non-donor CKD in the general population
      i. Acute kidney injury, fracture, bleeding
7. Emotional / psychological / financial outcomes (benefits) to the donor
   a. Relationship with recipient, family members, anxiety, depression
   b. Donor quality of life
   c. Expenses
   d. Impact of donation on insurability (life, medical)
8. Anticipated outcomes for the recipient (survival, graft survival)
   a. Survival benefit compared to other ESRD treatment modalities included deceased donor
      1) how various donor characteristics influence recipient outcomes
      2) how various recipient characteristics (i.e. recurrence of renal disease) influence
         recipient outcomes (for informed consent of the donor)

Evaluation and Acceptance Criteria
Medical
9. How should geography alter the threshold of risk tolerance, e.g. when living donation is the only
   ESRD treatment option?
10. Pre-donation glomerular filtration rate (GFR)
    a. What level of GFR is safe and acceptable for an individual to be a living kidney donor?
    b. Should this level differ by age?
    c. How should GFR be assessed? [See KDIGO CKD GL]
    d. Should GFR be expressed standardized to body surface area? [See KDIGO CKD GL]
    e. How many times should the GFR be measured prior to donation, and how recent prior
to donation?
    f. How should local cost, and availability / quality of testing influence the measurement of
       GFR?
11. Pre-donation kidney split function
    a. When should it be assessed (i.e. asymmetry of kidney disease)?
    b. How should it be measured?
    c. How should results influence which kidney should be removed?
12. Pre-donation hypertension
    a. Acceptable methods (and frequency) of assessing BP prior to donation [See KDIGO GL].
    b. Are patients with pre-donation hypertension acceptable to be a donor? Which BP
       thresholds / amount of medications used to control BP? Is acceptability influenced by
       donor age (i.e. acceptable in older donors).
    c. How does donor concurrent conditions (age, BMI, metabolic risk, family history)
       influence the approach to hypertension?
    d. How does race/ethnicity influence the approach to donor hypertension?
13. Kidney stones (history or imaging)
    a. How is a kidney stone defined in the current imaging era? Is a calyceal tip stone an
       actual stone?
    b. In addition to history, what imaging should be done to assess for kidney stones?
    c. When is a person with history of kidney stones (symptomatic or imaging) eligible to be a
       kidney donor?
    d. What tests are necessary when there is a history of stones (i.e. 24 hour urine, PTH)?
    e. Which kidney should be selected for donation? What if there are bilateral stones?
14. Impaired fasting glucose, impaired glucose tolerance, diabetes, metabolic syndrome or family
    history of diabetes.
    a. What testing should be done?
    b. What conditions preclude donation?
c. What interventions mitigate the risk, e.g. weight loss.

15. Donor family history
   a. Coronary artery disease
   b. Cancer (particularly renal cell cancer)
   c. Kidney disease
   d. Diabetes
   e. Hypertension

16. Pre-donation genetic renal diseases (including disease in the recipient)
   a. Evaluation of an individual with 1st degree relative with polycystic kidney disease
   b. Alport’s disease
   c. Other genetic risks, e.g. Apo L1 in African Americans

17. Pre-donation persistent hematuria
   a. What testing should be done to screen for hematuria? (e.g. urinalysis as screening; number of tests)
   b. What testing should be done to evaluate it when it is present? When is kidney biopsy indicated?
   c. What conditions preclude donation: IgA nephropathy, thin basement membrane disease?

18. Pre-donation proteinuria / albuminuria
   a. What testing should be done to evaluate its presence? (e.g. what measurements, proteinuria vs. albuminuria, how many tests?)
   b. What level of proteinuria / albuminuria precludes donation?

19. Pre-donation history of gestational diabetes / hypertensive disorder in pregnancy
   a. Does a remote history of such a condition preclude donation?

20. Pre-donation body mass index
   a. What body mass index is safe prior to donation?
   b. What is evidence that those who lose weight maintain it after donation?
   c. Is there a role during donor evaluation to promote long-term good health behaviors.

21. Pre-donation lipid profile
   a. What testing?
   b. What is a safe lipid profile prior to donation?

22. Pre-donation history of active tobacco use (smoking)
   a. Are active smokers eligible to be donors?
   b. Does donor smoking affect donor or recipient outcomes?
   c. What techniques / strategies can be offered donors for smoking cessation?
   d. Is there a role during donor evaluation to promote long-term good health behaviors?

23. Pre-donation calculated 10-year incidence of cardiovascular disease
   a. Should this be estimated?
   b. What is an acceptable level of risk (compared to general population, should it differ by age)?

24. Should race / ethnicity be considerations in outcomes of living kidney donation?

25. When is a kidney with a neoplasm acceptable for transplantation?

26. Assessing immune compatibility between donors and recipients
   a. Which tests: blood group, HLA (which HLA, how), cross-match
   b. What compatibility is eligible for donation?
27. Pre-operative assessment
   a. Pre-op cardiac testing
   b. Bleeding risk
   c. Anesthesia risk
   d. Pulmonary assessment

28. Kidney imaging
   a. What imaging tests are most appropriate?
   b. What anatomical findings are acceptable, e.g. cysts, scars?

29. Acceptable surgical approaches and anticipated outcomes: laparoscopic v. open etc.

30. Paradigm for changes in surgical techniques

31. Minimizing risk of infection transmission from donors to recipients:
   a. How can one best detect behaviors that indicate high risk for contracting a transmissible disease? (type of testing, frequency or recency of testing prior to donation)
   b. What transmissible infections should be screened and how, e.g. HIV, HBV, HCV, EBV, Tuberculosis, CMV, HSV, human T-lymphotropic virus (HTLV), Strongyloides, Trypanosoma cruzi, West Nile, toxoplasmosis, malaria? How should geography determine which tests should be obtained?
   c. What should be told to a donor and a recipient about the risk of Creutzfeldt-Jakob disease transmission?
   d. When is a history of infectious disease in potential donor acceptable for donation?
   e. What should donors and recipients be told about the expected outcomes for an EBV-negative or CMV-negative recipient receiving a kidney from an EBV-positive or CMV-positive donor, respectively?

32. General health measures in the donor:
   a. Cancer screening (e.g. as recommended for age / sex in country where donation occurring)
   b. What types of cancer history preclude donation (malignancy transmission)?
   c. Pregnancy screening close to time of donation (in women of childbearing age)
   d. Other preventative healthcare

33. Other medical conditions
   a. Recurrent UTIs in a potential donor
   b. Sickle cell trait
   c. Non-renal genetic tests
   d. Incidentally discovered pulmonary, adrenal, and other neoplasia
   e. Previous genitourinary and abdominal surgery
   f. Recreational drug use

Psychosocial

34. Necessary psychosocial evaluation
   a. How the evaluation is performed – who does it?
   b. What are the elements of the evaluation (e.g. understand relationship between donor – recipient, confirm voluntary nature, no pressure; no unethical financial or other incentives; ensure full comprehension understanding of implications).
   c. Share with donor what they are likely to experience emotionally (beyond the medical facts).
   d. Detecting and dealing with pressure/coercion
      i. How to deal with families who decide who should donate
   e. Providing pseudo-medical contraindications “medical outs”
Ethical, Legal and Increasing the Number of Living Kidney Donors

35. How to handle public solicitation of donors by recipients
36. What level of financial support (removal of disincentives) is acceptable to living kidney donors?
37. Stance on transplant tourism (and associated risks)
38. Acceptability of certain types of donors: Lower age criteria to be a donor? Upper age criteria? Mentally challenged individuals? Prisoners?
39. What local laws and practices might influence donation decisions?
40. Role of the transplant center in setting donor acceptance criteria based on the center’s need for living donors
41. Should some local laws be changed?
42. What laws are needed to regulate donation?
43. Effective and acceptable strategies to increase rates of living kidney donation? (donor advocate, home visits, efficiencies in evaluation of kidney donors (information technology), removal of disincentives; how much should transplant centers support and encourage the identification of potential living kidney donors for kidney transplant recipients)