# TABLE OF CONTENTS

Disclaimer ........................................................................................................................................ iii  
Work Group Membership ............................................................................................................. iv  
KDIGO Board Members .............................................................................................................. vi  
Reference Keys ........................................................................................................................... vii  
Abbreviations and Acronyms ....................................................................................................... viii  
Preface........................................................................................................................................... x  
Chapter 1: Goals of Donor Candidate Evaluation, Framework for Decision Making, and Roles & Responsibilities of Care Providers ......................................................................................... 1  
Chapter 2: Informed Consent ........................................................................................................ 14  
Chapter 3: Compatibility Testing, Incompatible Live Donor Transplantation, and Donor Exchanges ................................................................................................................................. 23  
Chapter 4: General Pre-Operative Evaluation and Management ................................................. 28  
Chapter 5: Evaluation of Kidney Function in Kidney Donor Candidates ...................................... 31  
Chapter 6: Evaluation of Proteinuria in Kidney Donor Candidates ............................................. 41  
Chapter 7: Evaluation of Hematuria and Indications for Kidney Biopsy in Kidney Donor Candidates ........................................................................................................................................ 50  
Chapter 8: Evaluation of Kidney Stones in Kidney Donor Candidates ........................................ 54  
Chapter 9: Evaluation of Blood Pressure in Kidney Donor Candidates ...................................... 57  
Chapter 10: Evaluation of Metabolic and Lifestyle Risk Factors for Accelerated GFR Decline and/or Long-Term Atherosclerotic Cardiovascular Disease (ASCVD) in Kidney Donor Candidates ....................................................................... 65  
Chapter 11: Testing to Minimize Risks of Infection Transmission from Living Donors to Recipients ......................................................................................................................... 78  
Chapter 12: Cancer Screening to Reduce Risks of Transmission from Donors to Recipients and to Reduce Risks of Post-Donation Malignancy-Related Complications .............................................................................. 96  
Chapter 13: Evaluation of Genetic Renal Disease in Kidney Donor Candidates .......................... 101  
Chapter 14: Pregnancy and Living Kidney Donation .................................................................. 106  
Chapter 15: Psychosocial Evaluation and Acceptance Criteria .................................................. 109  
Chapter 16: Acceptable Surgical Approaches for Donor Nephrectomy and Anticipated Outcomes .................................................................................................................................... 116  
Chapter 17: Ethical, Legal and Policy Considerations ................................................................. 124  
Chapter 18: Post-Donation Follow-Up Care ................................................................................ 128  
References ..................................................................................................................................... 133
DISCLAIMER

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon the best information available as of November 2015. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information will be published in its entirety in the final publication and is kept on file at KDIGO.

Note: This draft version of the KDIGO Clinical Practice Guideline on the Evaluation and Follow-up Care of Living Kidney Donors is not final. Please do not quote or reproduce any part of this document.
WORK GROUP MEMBERSHIP

Work Group Co-Chairs
Amit X. Garg, MD, PhD  
Western University  
London, Canada

Krista L. Lentine, MD, PhD  
Saint Louis University School of Medicine  
St. Louis, USA

Work Group
Patricia L. Adams, MD  
Wake Forest School of Medicine  
Winston-Salem, USA

Josefina Alberú, MD  
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán  
Mexico City, Mexico

Mohamed A. Bakr, MD  
Mansoura University  
Mansoura, Egypt

Josep M. Campistol, MD, PhD  
University of Barcelona  
Barcelona, Spain

Lorenzo Gallon, MD  
Northwestern University  
Chicago, USA

Catherine A. Garvey, RN, BA, CCTC  
University of Minnesota  
Minneapolis, USA

Sandeept Guleria, MS, DNB, FRCS (Eng), FRCSEd, FRCS (Glasgow), FRCP (Edin)  
Indraprastha Apollo Hospitals  
New Delhi, India

Andrew S. Levey, MD  
Tufts Medical Center  
Boston, USA

Philip Kam-Tao Li, MD, FRCP, FACP  
Chinese University of Hong Kong  
Hong Kong, China

José Osmar Medina Pestana, MD, PhD  
Universidade Federal de São Paulo  
São Paulo, Brazil

Dorry L. Segev, MD, PhD  
Johns Hopkins University School of Medicine  
Baltimore, USA

Faissal A. Shaheen, MD  
The Saudi Center for Organ Transplantation  
Riyadh, Saudi Arabia

Sandra J. Taler, MD  
Mayo Clinic  
Rochester, USA

Kazunari Tanabe, MD, PhD  
Tokyo Women's Medical University  
Tokyo, Japan

Linda Wright, MHSc, MSW, RSW  
University of Toronto  
Toronto, Canada

Martin Zeier, MD  
University Hospital Heidelberg  
Heidelberg, Germany

KDIGO gratefully acknowledges the valuable contributions from CKD Prognosis Consortium and its members for their meta-analyses which serve as the basis for the donor selection framework presented in this report: Josef Coresh MD, PhD, Morgan E. Grams MD, PhD, Yingying Sang MS, Kunihiro Matsushita MD, PhD, Shoshana Ballew PhD, Alex R. Chang MD, Eric K. H, Chow MSc, Csaba P. Kovesdy MD, Girish N. Nadkarni MD, MPH, Varda Shalev MD, MPA. KDIGO also gratefully acknowledges expert reviewers who provided valuable feedback on specific chapters, including: Daniel C. Brennan MD, Mary Amanda Dew PhD, Robert Gaston MD, Rebecca Hays MSW, Peter C. Harris, PhD, York Pei MD, Emilio Poggio MD, Robert Steiner MD, Christie P. Thomas MD, Roser Torra, MD, PhD, Vicente E. Torres, MD, PhD, and Matthew Weir MD.
Evidence Review Team
University of Minnesota Department of Medicine
Minneapolis VA Center for Chronic Disease Outcomes Research
Minneapolis, USA

Timothy J. Wilt, MD, MPH, Professor of Medicine and Project Director
Areef Ishani, MD, MS, Chief, Section of Nephrology, Assoc Professor of Medicine, Investigator
Yelena Slinin, MD, MS, Assistant Professor of Medicine, Investigator
Michelle Brasure, PhD, MSPH, MLIS, Project Manager & Investigator
Maureen Carlyle, MPH, Research Assistant
KDIGO EXECUTIVE COMMITTEE

Garabed Eknoyan, MD
Norbert Lameire, MD, PhD
Founding KDIGO Co-Chairs

Kai-Uwe Eckardt, MD
Immediate Past Co-Chair

Wolfgang C. Winkelmayer, MD, ScD
KDIGO Co-Chair Elect

Bertram L. Kasiske, MD
KDIGO Co-Chair

David C. Wheeler, MD, FRCP
KDIGO Co-Chair

Josef Coresh, MD, MHS, PhD

Olivier Devuyst, MD, PhD

Kai-Uwe Eckardt, MD

Andrew S. Levey, MD

Sarala Naicker, MB ChB, MRCP, FRCP, FCP (SA), PhD

Gregorio T. Obrador, MD, MPH

Roberto Pecoits-Filho, MD, PhD

Brian J.G. Pereira, MBBS, MD, MBA

Yusuke Tsukamoto, MD

Angela Yee-Moon Wang, MD, PhD, FRCP

Christoph Wanner, MD

Elena Zakharova, MD, PhD

KDIGO Staff

John Davis, CEO
Danielle Green, Managing Director
Michael Cheung, Chief Scientific Officer
Tanya Green, Communications Director
REFERENCE KEYS

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Implications</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 “We recommend”</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
<td>Most patients should receive the recommended course of action.</td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
<td></td>
</tr>
<tr>
<td>Level 2 “We suggest”</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
<td>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.</td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
<td></td>
</tr>
</tbody>
</table>

*The additional category “Not Graded” was 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. The 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>
<thead>
<tr>
<th>Grade</th>
<th>Quality of Evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of effect is very uncertain, and often will be far from the truth.</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>ABOc</td>
<td>ABO compatible</td>
<td></td>
</tr>
<tr>
<td>ABOi</td>
<td>ABO incompatible</td>
<td></td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin-to-creatinine ratio</td>
<td></td>
</tr>
<tr>
<td>ADPKD</td>
<td>Autosomal dominant polycystic kidney disease</td>
<td></td>
</tr>
<tr>
<td>AER</td>
<td>Albumin excretion rate</td>
<td></td>
</tr>
<tr>
<td>aHUS</td>
<td>Atypical hemolytic uremic syndrome</td>
<td></td>
</tr>
<tr>
<td>APOL1</td>
<td>Apolipoprotein L1</td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
<td></td>
</tr>
<tr>
<td>CKD-PC</td>
<td>Chronic Kidney Disease Prognosis Consortium</td>
<td></td>
</tr>
<tr>
<td>CDC</td>
<td>Complement-dependent cytotoxicity</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>CKD Epidemiology Collaboration</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylenetriamine pentaacetic acid;</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
<td></td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediamine tetraacetic acid</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>eGFRcreat</td>
<td>eGFR from serum creatinine</td>
<td></td>
</tr>
<tr>
<td>eGFRcys</td>
<td>eGFR from serum cystatin C</td>
<td></td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
<td></td>
</tr>
<tr>
<td>ELISPOT</td>
<td>Enzyme-linked immunosorbent spot</td>
<td></td>
</tr>
<tr>
<td>ERT</td>
<td>Evidence review team</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
<td></td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td>FXM</td>
<td>Flow cytometry crossmatch</td>
<td></td>
</tr>
<tr>
<td>GBM</td>
<td>Glomerular basement membrane</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development, and Evaluation</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
<td></td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
<td></td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
<td></td>
</tr>
<tr>
<td>HTLV</td>
<td>Human T-cell lymphotrophic virus</td>
<td></td>
</tr>
<tr>
<td>ILDA</td>
<td>Independent living donor advocate</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive-care unit</td>
<td></td>
</tr>
<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
<td></td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon gamma release assay</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
<td></td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent tuberculosis infection</td>
<td></td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
<td></td>
</tr>
<tr>
<td>KPD</td>
<td>Kidney paired donation</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
<td></td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
<td></td>
</tr>
<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
<td></td>
</tr>
<tr>
<td>mGFR</td>
<td>Measured glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
<td></td>
</tr>
<tr>
<td>MTB</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td></td>
</tr>
<tr>
<td>NAT</td>
<td>Nucleic acid testing</td>
<td></td>
</tr>
<tr>
<td>OPTN</td>
<td>Organ Procurement and Transplantation Network</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Protein/creatinine ratio; Polymerase chain reaction</td>
<td></td>
</tr>
<tr>
<td>PER</td>
<td>Protein excretion rate</td>
<td></td>
</tr>
<tr>
<td>PHS</td>
<td>Public Health Service</td>
<td></td>
</tr>
<tr>
<td>PRA</td>
<td>Panel reactive antibody</td>
<td></td>
</tr>
<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disorder</td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td>RPR</td>
<td>Rapid plasma reagin</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>TBMN</td>
<td>Thin basement membrane nephropathy</td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin skin testing</td>
<td></td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network of Organ Sharing</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
<td></td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted mean difference</td>
<td></td>
</tr>
<tr>
<td>WNV</td>
<td>West Nile virus</td>
<td></td>
</tr>
</tbody>
</table>
PREFACE

Since the inception of Kidney Disease: Improving Global Outcomes (KDIGO) there has been much discussion over whether to make guideline recommendations when there is little or no evidence. Combining guideline recommendations that have no supporting evidence with others that are evidence-based may appear to overrate the former and underrate the latter. It has also been argued that making recommendations that have little or no supporting evidence may discourage investigators from performing further studies to produce the evidence that is needed. On the other hand, caregivers often express the need for guidelines that describe a comprehensive approach to patient care and do not ignore important issues simply because there is no evidence. Caregivers still want to know what a group of experts would do in situations where there is no evidence available.

KDIGO’s approach is to provide comprehensive recommendations with transparency, whereby guideline Work Groups make all recommendations that they deem necessary to inform cohesive patient care while also making it clear which recommendations are supported by evidence and which are not. Guideline recommendations with supporting evidence identified by the Evidence Review Team’s (ERT) systematic review are graded on the strength of recommendation (1 for strong or 2 for weak) and on the strength of evidence (A, B, C or D for strong, moderate, weak and very weak, respectively) in accordance to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Recommendations on topics that were not included in the systematic review or for which no evidence was identified are clearly indicated as “Not Graded.” Ungraded recommendations may be made by the Work Group for a number of reasons, but most commonly because the clinical scenario covered by the recommendation is not one that is amenable to clinical research. These include common sense recommendations where there are no reasonable alternatives to a recommended action, and hence a clinical trial could never test the question being addressed. Ungraded recommendations may also be appropriate to offer guidance that is considered to be necessary for purely ethical reasons.

The current guideline on the evaluation and care of the living kidney donor is, by the nature of its subject, heavily populated with ungraded recommendations. A systematic review for relevant evidence was conducted by an independent ERT according to KDIGO protocol. The scope for this review was determined by the Work Group with input from the public and ERT members, some of whom also had expertise in kidney transplantation. However, the Work Group was directed to make all recommendations that they felt necessary to ensure a comprehensive evaluation of kidney donor candidates, a safe donation process, and appropriate follow-up care after donation. The ERT worked closely with the Work Group to assure that clear distinctions were made between the few recommendations that could and should be graded based on the systematic review in keeping with the GRADE criteria, and the many recommendations that needed to remain ungraded. In addition, the Work Group was charged with formulating a research agenda, particularly in topic areas for which recommendations were written without adequate evidence but yet such evidence would be possible if there were appropriately designed clinical studies. We recognize, however, that research is an open-ended endeavor and the Work Group’s recommendations for future research are not intended to be comprehensive or exclusive.
Finally, in the course of developing the current guideline, the Work Group concluded that the framework for assessing the suitability of candidates for living kidney donation needed to be changed. This overarching paradigm is grounded on the principle that the evaluation of living donor candidates should include a comprehensive determination of risk to the donor, based on simultaneous consideration of a composite profile of risk factors. Previous guidelines have recommended the assessment of a living donor candidate one risk factor at a time; if a donor candidate’s exposure to an individual risk factor exceeded a predetermined threshold acceptable for the transplant program with respect to any of the several risk predictors evaluated (e.g., hypertension, glucose intolerance, obesity, etc.) the donor candidate was turned down. In this scenario, how values of individual characteristics above or below the threshold alter the risk of post-donation outcomes has been poorly understood, leading to inconsistent practice in the choice of specific thresholds for a characteristic used to accept or decline a living donor candidate. The Work Group determined that this one-size-must-fit-all approach should be replaced by a more comprehensive approach that assessed a combination of demographic, clinical and donation-related factors and their interactions in determining the overall risk. No previous guidelines have advocated this approach to the evaluation of living donor candidates, and there is a paucity of data even to demonstrate its feasibility and applicability. The Work Group therefore collaborated with the Chronic Kidney Disease-Prognosis Consortium (CKD-PC) to conduct a meta-analysis to produce a comprehensive risk-prediction model. The endpoint for this model, end-stage renal disease (ESRD), is not the only outcome of importance to donors and healthcare providers, but it is arguably the most important.

It should be stressed that the model developed by the CKD-PC, and the online risk prediction tool based on the model, were intended to be a “proof of concept” exercise and not a final answer to the question of how to evaluate each donor candidate. The model needs to be properly validated. Although it can provide a useful estimate of ESRD risk for a particular donor candidate, the uncertainty of estimated projected risk and the need for additional data to improve the model must be emphasized. However, improved versions of the risk prediction tool will not negate this central framework for decision making or its inherent benefits in facilitating transparency and communication between caregivers and donor candidates and in improving the evidence base to support the donation decision.

We wish to thank the Work Group Co-Chairs, Drs. Amit Garg and Krista Lentine, along with all of the Work Group members who volunteered countless hours of their time to develop this guideline. We also thank the ERT at the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, KDIGO staff, Canadian Blood Services, Canadian Society of Nephrology, and The Transplantation Society for their support which made this project possible. We especially thank Michael Cheung, who helped to facilitate the production of the guideline and to edit the final guideline document. Finally, we are very grateful to members of the CKD-PC, particularly Drs. Josef Coresh and Morgan Grams, who carried out the analysis that produced the risk assessment tool which underpins the proposed paradigm shift in the evaluation of living kidney donor candidates.

Bertram L Kasiske, MD
David C Wheeler, MD, FRCP
KDIGO Co-Chairs
CHAPTER 1: GOALS OF DONOR CANDIDATE EVALUATION, FRAMEWORK FOR DECISION-MAKING, AND ROLES & RESPONSIBILITIES OF CARE PROVIDERS

1.1. Goals of the Donor Evaluation

1.1.1: Assure that the donor candidate is acting voluntarily and not under pressure or coercion. \( \text{(Not Graded)} \)

1.1.2: Assess donor candidate benefits and risks of kidney donation. \( \text{(Not Graded)} \)

1.1.3: Accept or exclude donor candidates according to transplant center policies. \( \text{(Not Graded)} \)

1.1.4: Facilitate donor candidate decision-making through education and counseling regarding their benefits, risks, methods to minimize risk and their need for post-donation follow-up. \( \text{(Not Graded)} \)

1.1.5: For accepted donor candidates, formulate a plan for donation and post-donation follow-up. \( \text{(Not Graded)} \)

1.1.6: For excluded donor candidates, formulate a plan for appropriate care of conditions identified during the evaluation. \( \text{(Not Graded)} \)

1.2. Framework for Decision-Making for Acceptance and Exclusion of Donor Candidates

1.2.1: For living kidney donation to proceed, there must be agreement by the donor candidate, the intended recipient and the transplant center team that concurs with transplant center policies and informed consent. \( \text{(Not Graded)} \)

1.2.2: Transplant center policies must be defensible based on current understanding of benefits and risks of kidney donation, and should apply to all donor candidates evaluated at the transplant center. \( \text{(Not Graded)} \)

1.2.3: Each transplant center should establish policies describing psychosocial criteria that are acceptable for donation, including the relationship between the donor candidate and the intended recipient. \( \text{(Not Graded)} \)

1.2.4: Each transplant center should establish policies describing medical criteria that are acceptable for donation, including, when possible, numeric thresholds for short-term and long-term post-donation risk above which the transplant center will not proceed with kidney donation. \( \text{(Not Graded)} \)

1.2.5: The transplant center team should provide the donor candidate with individualized quantitative estimates of short-term and long-term medical risks from kidney donation, if possible. Risks should be expressed as absolute rather than relative risks, with recognition of associated uncertainty, and in a manner that is easily understood by donor candidates. \( \text{(Not Graded)} \)
1.2.6: The transplant center team should evaluate donor candidate medical risks in comparison to the pre-determined threshold for acceptance. If a donor candidate’s post-donation risk is above the transplant center’s acceptable threshold, the medical risk is not acceptable for donation. If the donor candidate’s post-donation risk is below the transplant center’s acceptable threshold, the medical risk is acceptable for donation. *(Not Graded)*

1.2.7: If the donor candidate is acceptable according to a transplant center’s psychosocial and medical criteria, the donor candidate should decide whether to proceed with donation. *(Not Graded)*

1.2.8: If the donor candidate is not acceptable, the transplant center should exclude the candidate from donation and explain the reason for non-acceptance. The excluded candidate should be informed that he or she can seek evaluation at another center. *(Not Graded)*

1.2.9: The transplant center should protect the donor candidate’s privacy regarding the medical and psychosocial evaluation, including all considerations in the decision to donate or not to donate. The transplant center should communicate only the final outcome of the decision to the recipient and other parties. *(Not Graded)*

1.3. Roles and Responsibilities in Living Donor Transplantation

1.3.1: Healthcare providers for patients with kidney failure should offer education on treatment options including dialysis, living donor and deceased donor transplantation, and direct their patients interested in transplantation and donor candidates to centers with expertise in this field, preferably prior to the need for kidney replacement therapy. *(Not Graded)*

1.3.2: A multidisciplinary transplant center team of practitioners knowledgeable in kidney transplantation and donation should evaluate, care for, and formulate a plan of care including long-term follow up after donation. *(Not Graded)*

1.3.3: For each donor candidate-intended recipient pair, conflict of interest should be minimized by providing at least one key healthcare team member who evaluates the donor candidate, participates in determination of candidacy, and is not involved in the care or evaluation of the intended recipient. *(Not Graded)*

1.3.4: Donor candidates should be provided with adequate time to contemplate information relevant to making the decision to donate. *(Not Graded)*

1.3.5: The transplant center team should organize the donor evaluation efficiently to meet the needs of donor candidates, intended recipients and the transplant center. *(Not Graded)*
RATIONALE

Goals and Principles of Donor Evaluation

Evaluation of candidates for living kidney donation requires balancing ethical principles of autonomy, beneficence, non-malfeasance, voluntarism, confidentiality and justice. Determining acceptability or non-acceptability of donor candidates requires balance between the potential risks and anticipated benefits of donation for the donor, independent of 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. Protection of patient privacy must be ensured for medical, psychosocial and decision-making components. However information regarding donor lifestyle or exposures that increase the risk for transmission of infectious diseases 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.

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

Framework for Decision Making: A Quantitative Framework for a Transplant Center’s Criteria to Accept or Decline a Live Kidney Donor Candidate

A central objective of donor candidate evaluation and acceptance is to minimize risks of perioperative and long-term adverse outcomes after donation. 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 derive individualized, quantitative estimates of post-donation risk. Prior living kidney donor guidelines describe post-donation risk in relation to single pre-donation characteristics assessed in isolation, and generally agree on the single donor pre-donation characteristics that associate with a higher risk of poor post-donation outcomes. However, prior guidelines differ on the recommended specific threshold for a characteristic that should be used to accept or decline a living donor candidate, and are unclear about how values above or below the threshold alter the risk of post-donation 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.\textsuperscript{1, 3, 4}

An important advance would be to quantify the combined impact of all a donor candidate’s pre-donation demographic characteristics (i.e., age, sex and race) and health characteristics at the time of evaluation (e.g., kidney function, blood pressure, body mass index [BMI] etc.) and risks attributable to donation on their risk of serious adverse outcomes after donation. Serious post-donation adverse outcomes can be medical or psychological, and may occur during the perioperative period, in a fixed period of long-term follow-up (e.g., 15 years after donation), or for the remaining lifespan of the donor (Figure 1).

Figure 1. Framework to accept or decline donor candidates based on a transplant center’s threshold of the acceptable post-donation risk. The decision by the transplant center whether to accept or decline a donor candidate is grounded upon on whether an individual’s estimated projected post-donation lifetime risk is above or below threshold set (dotted line) by the transplant center. The same threshold applies to all donor candidates. The threshold may vary across regions, but should be generally consistent among centers within a region. For example, candidate A (green) would be accepted because the estimated projected post-donation risk is far below the threshold, candidate B (yellow) would be accepted with caution because the estimated projected post-donation risk is close to the threshold, and candidate C (red) would be declined because the estimated post-donation projected risk is far above the threshold.

As described within this overall framework, a transplant center can use various methods to establish its threshold for acceptable outcomes after kidney donation. For example, assume after due consideration a transplant center decides a lifetime post-donation risk of kidney failure of 5% is their threshold for acceptable risk; if a candidate’s projected risk is estimated to be above this threshold, the center 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 post-donation
outcomes is too high. A poor outcome can have a very negative impact on the donor, on their recipient, and on public opinions about living donation.

We recommend each transplant center should strive to develop and communicate a quantitative threshold of ‘acceptable risk’ for each serious post-donation adverse outcome they wish to avoid. This threshold should be both evidence-based and consensus-based, and there are various sources of evidence and processes by which consensus can be achieved. The threshold can vary across regions, but should be fairly consistent among centers within a region, and once established, ideally should be applied consistently and transparently for all donor candidates evaluated at a center (unless subsequently revised). When a donor candidate’s estimated risk is below this acceptable risk threshold, the transplant center should accept a donor candidate, and it should be the candidate’s decision whether to proceed with donation or not after being informed of the risks. When a candidate’s estimated risk is above this acceptable threshold, the transplant center is justified in declining the candidate and can ground their decision in a quantitative framework.

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 amenability to quantitative risk estimation when possible. We focus particularly on the post-donation development of kidney failure requiring dialysis or transplantation because it is a central outcome of a donor candidate’s long-term risk, and we describe our methods to advance estimates of this risk for US donor candidates. Finally, we describe the path for future work necessary to strengthen this framework, which includes the need for additional data.

**Perioperative medical outcomes**

The incidence of perioperative death after kidney donation is low. The 90-day all-cause mortality in a recent US study of 80,347 donors was reported to be ~ 1 in 3000 (0.03%) based on 25 deaths. Given the low incidence of perioperative mortality, estimates for pre-donation characteristics that alter the risk of perioperative death are imprecise. For example, in this same study, a pre-donation history of hypertension was associated with a 1 in 270 incidence 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% confidence interval for the provided estimate was also wide, ranging from 1 in 75 to 1 in 2220. Thus, even if a transplant center defines an acceptable risk threshold for perioperative mortality (for example, an incidence less than 1 in 1000), it will be difficult to reliably determine a given donor candidate’s estimated risk of this outcome according to their profile of pre-donation characteristics.

With respect to perioperative complications, the Evidence Review Team for this guideline identified two systematic reviews that examined perioperative outcomes in relation to the demographic characteristics of accepted donors. The quality of evidence was rated as very low (see Guideline Evidence Report, Key Question 2 and 3). In one review a group of carefully selected older donors (mean age 66 years old, range 60 to 85 years at donation) when compared to a group of younger donors did not differ statistically in their operative time,
intraoperative blood loss, and length of hospital stay.\textsuperscript{7} In both reviews, groups of carefully selected obese donors (mean BMI of 34.5 kg/m\textsuperscript{2}, range 32 to 39 kg/m\textsuperscript{2}) did not differ statistically from groups of non-obese donors in their rates of perioperative complications, operative time, blood loss and length of hospital stay.\textsuperscript{7,8} Since then a large US study considered pre-donation 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).\textsuperscript{9} 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% versus 7.2%); among African Americans (10.4%) and whites (8.7%) compared with other race 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%). As future data become available, it may become possible for transplant centers to precisely estimate the risk of well-defined, serious perioperative complications according to a donor candidate’s individual profile of baseline characteristics. To make a decision whether to accept or decline a donor candidate, a center can then estimate the risk of such an outcome in a given donor candidate, and compare estimated risk against their center’s threshold of acceptable risk.

\textbf{Long-term medical outcomes}

Donating a kidney is a decision with long-term (lifetime) implications for the donor. While there are many outcomes to consider after kidney donation, a central medical outcome directly related to having one kidney removed is the long-term risk of developing kidney failure requiring dialysis or transplantation. 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 according to the long-term (lifetime) risk of post-donation 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 clinical characteristics at the time of evaluation plus risk attributable to donation (Figure 2). Demographic characteristics include age, sex and, race. Clinical characteristics include glomerular filtration rate (GFR), albuminuria, BMI, blood pressure, diabetes status, smoking history, and family history of kidney disease, and other factors. The risk attributable to donation also varies according to demographic and clinical 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.
Figure 2: Framework to accept or decline donor candidates based on a transplant center’s threshold of the acceptable post-donation lifetime risk of kidney failure based on pre-donation demographic and clinical characteristics and risk attributable to donation. The decision by the transplant center whether to accept or decline a donor should be informed by an individual’s composite estimated projected post-donation lifetime ESRD risk, including estimated projected risk in the absence of donation (i.e., demographic and clinical characteristics denoted in blue and beige, respectively) and estimated projected risk attributable to donation (brown).

Challenges to determining the post-donation lifetime risk of kidney failure based on the current literature include limitations of study follow-up (the largest studies follow most donors for less than two decades after donation rather than for their lifetime), and an average age of 40 for a living kidney donor, where if an event of kidney failure were to occur it would be expected much later in life (i.e., ages 60 to 90). Another challenge is that there is some uncertainty about the magnitude by which donation increases kidney failure risk. Traditionally it was said that donating a kidney did not alter a person’s lifetime risk of developing kidney failure. However, 3 recent studies support that the risk of kidney failure is higher after donation compared to risk among non-donors with similar baseline demographics and health status. Available data suggest that the average donation attributable risk is approximately 27 per 10,000 (0.3%) at 15 years, but there is substantial uncertainty in the estimate, and there is not sufficient data to project lifetime donation attributable risk. Furthermore, the extent to which donation-attributable risk varies according to individual characteristics is not known, although available evidence suggests there is higher donation-attributable risks in some subgroups, such as African Americans compared to white and Hispanic donors.
At this time, 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 pre-donation characteristics. Furthermore, if in the future the risk of kidney failure attributable to donation becomes more precisely understood in relation to an individual’s profile of baseline characteristics, then demographic, clinical characteristic-related, and donation-related risks can be aggregated to project individualized estimates of long-terms risks of post-donation kidney failure.

To help advance this paradigm we enlisted the help of the CKD-Prognosis Consortium (CKD-PC) to project the 15-year and lifetime incidence of kidney failure in the absence of donation based on demographic and clinical characteristics at the time of evaluation for low-risk persons from large population cohorts. CKD-PC is a research group composed of investigators who analyze large cohort data for the purpose of collaborative meta-analyses. The methods and results of these analyses will be published by the time this draft guideline is released for public review and they are presented in expanded form herein.

For donor candidates in the United States we suggest an approach that uses a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of post-donation kidney failure (Table 1 top panel). An alternative approach centered on estimated lifetime risk of kidney failure in the absence of donation may also be considered, but is more complicated because the acceptable threshold risk may not be constant for all donors (Table 1 bottom panel). Both strategies enable decision-making based on a more comprehensive assessment of risk factors than is currently practiced. However, for both strategies, with existing data there is considerable uncertainty in estimating lifetime risk, so that these approaches represent a general framework for decision-making that requires additional supporting data for validation and refining the precision of estimates. Thus at this time, transplant centers and donor candidates may consider other factors in their acceptance criteria for living kidney donation in addition to quantitative risk estimates.
Table 1. Approaches to implementation of a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of kidney failure

<table>
<thead>
<tr>
<th>Threshold based on estimated post-donation lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use the online tool (<a href="http://www.transplantmodels.com/esrdrisk/">http://www.transplantmodels.com/esrdrisk/</a>) to estimate the projected lifetime risk of kidney failure in the absence of donation according to baseline demographic and clinical characteristics considered in the online tool.</td>
</tr>
<tr>
<td>2. Compare the quantitative projected estimate to the center’s post-donation threshold of acceptable risk (recognizing that the estimate provided by the current online tool does not include donation-attributable risk).</td>
</tr>
<tr>
<td>3. Exercise caution when there is concern that the individual has risk factors not captured in the online tool (e.g., familial or genetic risk) or when the absolute difference between pre-donation risk and post-donation risk could be large (such as for young people with pre-donation demographic and clinical characteristics associated with increased risk).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Threshold based on estimated lifetime risk in the absence of donation (pre-donation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use the online tool (<a href="http://www.transplantmodels.com/esrdrisk/">http://www.transplantmodels.com/esrdrisk/</a>) to estimate the projected lifetime risk of kidney failure for US donor candidates in the absence of donation according to baseline demographic and clinical characteristics considered in the online tool.</td>
</tr>
<tr>
<td>2. Compare the quantitative estimate to a “pre-donation threshold” of acceptable risk set by the transplant center.</td>
</tr>
<tr>
<td>3. A pre-donation risk threshold is not required to be the same for all donor candidates, since the risk attributable to donation is unlikely to be the same for persons with different demographic and clinical profiles. For example, available evidence suggests donation-attributable risks may be higher in African Americans compared to white and Hispanic donors. Donation-related risks may also vary by other demographic and clinical factors, but such risks are yet to be quantified.</td>
</tr>
<tr>
<td>4. The choice of pre-donation threshold should not be influenced by recipient characteristics or perceived urgency of transplantation.</td>
</tr>
</tbody>
</table>

In summary, we advocate for a quantitative paradigm wherein transplant centers accept or decline donor candidates using the strongest evidence-based criteria to simultaneously consider a profile of risk factors (demographic and clinical characteristics at evaluation and risk attributable to donation) currently available so as to reach 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 according to multiple pre-donation 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 pre-donation characteristics may also have important impacts on post-transplant recipient outcomes, and this topic also warrants future consideration.
Roles and responsibilities of participants in donor identification, evaluation, care and follow-up

Transplant centers bear the primary responsibility for evaluation, care and follow up of living kidney donor candidates and living kidney donors. The main responsibilities of the transplant center are to establish and maintain policies and a team of professionals to guide and perform these tasks. However, many other entities share in these responsibilities (Table 2). The decision to donate should be regarded as a shared responsibility between the donor candidate, the donor candidate’s primary physician, and the transplant center. Transplant centers 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 center’s/regulators’ upper bound of acceptable risk)
- Embrace a long-term relationship with the donor, because some risks are uncertain or evolving
<table>
<thead>
<tr>
<th>Entity</th>
<th>Responsibilities</th>
<th>Phases of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Nephrologist</td>
<td>• Educate recipient candidates regarding early referral, preemptive and living donation options and resources for identifying donor candidates</td>
<td>• Referral of recipient candidates&lt;br&gt;• Referral of donor candidates</td>
</tr>
<tr>
<td>Dialysis Unit/General Nephrology Clinic</td>
<td>• Educate recipient candidates regarding early referral, preemptive and living donation options and resources for identifying donor candidates</td>
<td>• Referral of recipient candidates&lt;br&gt;• Referral of donor candidates</td>
</tr>
<tr>
<td>Transplant Center</td>
<td>• Educate recipient candidates regarding early referral, preemptive and live donor transplantation options&lt;br&gt;• Educate donor candidate regarding all phases of the donation process, known outcomes and existing uncertainties.</td>
<td>• Recipient candidate education&lt;br&gt;• Donor candidate education, screening and evaluation&lt;br&gt;• Donor candidate and donor pre-, peri- and post-operative care&lt;br&gt;• Coordination of long-term donor follow-up</td>
</tr>
<tr>
<td>Recipient Candidate Health Insurance Carrier</td>
<td>• Provide coverage for costs related to recipient candidate evaluation and transplantation, including coverage of donor evaluation and treatment costs</td>
<td>• Donor candidate evaluation&lt;br&gt;• Donor candidate pre-, peri- and post-operative care&lt;br&gt;• Early post-donation follow-up</td>
</tr>
<tr>
<td>Donor/Donor Candidate Health Insurance Carrier</td>
<td>• Educate donor candidate regarding coverage primarily under recipient’s insurance carrier and any anticipated out-of-pocket expenses</td>
<td>• Long-term care after the early post-donation period</td>
</tr>
<tr>
<td>Donor/Donor Candidate Primary Care Physician</td>
<td>• Educate donor candidate regarding individual donor candidate health concerns&lt;br&gt;• Participate in pre- and early post-donation care as needed&lt;br&gt;• Long-term care after donation</td>
<td>• Preparation for donor candidate evaluation&lt;br&gt;• Referral to the transplant center&lt;br&gt;• Care before and in the long-term after donation</td>
</tr>
<tr>
<td>Donor/Donor Candidate Physician/Nephrologist</td>
<td>• Perform donor candidate evaluation without influence by recipient considerations&lt;br&gt;• Oversee evaluation testing&lt;br&gt;• Provide education&lt;br&gt;• Participate candidacy determination&lt;br&gt;• Participate in care during surgical stay, early post-donation, and long-term after donation as needed, including serving as resource for primary providers</td>
<td>• Education and evaluation&lt;br&gt;• Candidacy determination&lt;br&gt;• Care before, during and after donation</td>
</tr>
<tr>
<td>Donor Surgeon</td>
<td>• Evaluate donor candidate for surgical risks and planning including consideration of donor anatomy.&lt;br&gt;• Provide education on surgical procedure, risks and recovery&lt;br&gt;• Participate in candidacy determination&lt;br&gt;• Provide care during surgery and peri-operative period, and as needed post-donation</td>
<td>• Education and evaluation&lt;br&gt;• Candidacy determination&lt;br&gt;• Pre-, peri- and early post-operative care; late post-donation care as needed</td>
</tr>
</tbody>
</table>
| Nurse Coordinator | • Educate donor candidate on recipient options, donor risks and procedures  
• Facilitate and oversee completion of evaluation  
• Assist with arranging surgery and inpatient care  
• Arrange and oversee post-operative care, and early and late post-donation donor follow-up | • Initial communication, intake, education and evaluation, time of surgery, and post-donation follow-up |
| --- | --- | --- |
| Dietitian | • Review dietary choices and metabolic status including measures of obesity  
• Provide guidance for nutritional treatment if indicated, including recommendations to address obesity | • Education and evaluation |
| Social Worker/Psychologist/Psychiatrist | • Perform donor candidate psychosocial evaluation including assessment of motivation  
• Educate donor candidate on recipient candidate options  
• Provide donor candidate with information and support services related to donation, including possible funds available to assist with donation-related expense  
• Discuss potential worst case scenarios including loss of income because of surgery, donation-related complications, or failure of the transplant; and assess the candidate’s ability to cope with adverse outcomes  
• Support for an informed donation decision  
• Assist donor with planning for care around the time of surgery and creation of a long-term follow-up plan | • Education and evaluation  
• Candidacy determination  
• Post-donation care as needed |
| Independent Living Donor Advocate  
(The role of independent donor advocacy may be served by another team member as long as criteria for independence and advocacy functions are satisfied) | • Verify that donor candidate has information needed to make a voluntary and informed decision to donate  
• Verify consent to donation  
• Function independently from the recipient’s team  
• Advocate for the rights of the donor | • Education and evaluation  
• Candidacy determination  
• Care before, during, and after donation |
| Regulatory and Oversight Agencies | • Create policies for minimum standards of donor candidate informed consent, evaluation, care and donor follow-up | • Referral of donor candidates  
• Education and evaluation  
• Candidacy determination  
• Care before, during, and after donation |
Research Recommendations

- Strengthen and better estimate the long-term risks of kidney failure, including incorporation of data from cohorts observed for longer periods of time (ideally over the lifetime) and from diverse countries. Risks should be estimated according to a comprehensive profile of donor candidate characteristics, genetic, familial and other novel factors.

- Further study the long-term risks attributable to donation, especially the risk of long-term kidney failure, with an effort to quantify donation-related risks according to demographic and clinical characteristics.

- Each transplant center may establish (and communicate) their own thresholds of ‘acceptable risk,’ accounting for regional considerations such as the opportunity for deceased kidney donation. Engage in consensus-building activities among transplant professionals, donors and recipients to help establish uniform thresholds of unacceptable risk, including attention to appropriate regional variation. Strategies that may help inform consensus include:
  - Estimate the risk of long-term kidney failure among previously accepted donors, such as those captured in large national databases.
  - Estimate long-term kidney failure projections based on donor acceptance criteria specified in prior guidelines.

- Determine the best methods of communicating individualized risk 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 justify pre-donation support or counseling (e.g., target pre-donation BMI) which may help to minimize the risk of adverse post-donation events.

- Develop tools to predict a donor candidate’s risk for adverse short- and long-term psychosocial outcomes and a broader spectrum of medical outcomes according to their profile of pre-donation characteristics.
CHAPTER 2: INFORMED CONSENT

Informed consent to be evaluated as a living kidney donor candidate, and informed consent to undergo living donor nephrectomy, is a process rather than a discreet event. The transplant center 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 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. Details of specific donation-related surgical, medical, and psychosocial risks are provided in other sections of the guideline.

Process and Requirements of Informed Consent

2.1: The transplant center should seek consent from the living donor candidate for the evaluation. (Not Graded)

Capacity

2.2: The transplant center should ensure a donor candidate has the capacity to provide informed consent (i.e., has the ability to understand the risks, benefits and consequences of donation) before proceeding with donation. (Not Graded)

2.3: Only under extraordinary circumstances and with ethical and legal reviews, transplant centers can consider using a substitute decision maker to approve a donor candidate who lacks the capacity to provide informed consent (e.g., children or those who are mentally challenged). (Not Graded)

Disclosure

2.4: The donor candidate should be informed about what may be discovered from the testing done during the evaluation, and what the transplant center will do with such information. The transplant center should have a policy on how or whether information is disclosed, and to what degree follow-up care is arranged as appropriate, for each of the following scenarios: (Not Graded)

- A health condition that may require further care
- A health condition that could affect the donor candidate’s insurability, or the cost of their insurance
- An infectious disease where there is a requirement to share the information with public health authorities
- A discovered misattributed biological relationship between the donor candidate and intended recipient (such as misattributed paternity in a father-child relationship)
2.5: The donor candidate should be informed of: (Not Graded)

- The likely medical, psychological, social and economic outcomes of donation, potential risks and potential benefits for the donor, and anticipated outcomes for the recipient (for specific details see other chapters of this guideline). Uncertainty in the risk estimates should be discussed when risk cannot be accurately quantified based on available data.
- Treatment alternatives available to their intended recipient.
- The need for separate additional consents for some tests during the evaluation.(e.g., receipt of intravenous contrast for renal imaging).
- Programs and personnel available to help support a positive donation experience (e.g., financial reimbursement programs for out-of-pocket expenses).
- The center’s recommendations for follow-up care, including the likely time and financial impacts of care and the need for regular, ongoing healthcare and healthy lifestyle choices. Any requirements the center has to obtain concerning ongoing personal health information from the donor in follow-up should also be discussed.
- The center’s policy about providing care to the donor following evaluation and donation.
- If it is a crime to receive any valuable consideration (money, property) for their donation.
- A description of the withdrawal process from donor evaluation, with the right of the candidate to decline to donate at any time with the full support of the transplant center.
- The transplant center makes the final determination of whether the donor candidate is eligible for donation based on the results of their evaluation. The donor candidate should be informed by the transplant center if and why he/she does not meet the center’s criteria for donation. The donor candidate should also be informed on how the transplant center will support them if they are disappointed in the event of failure to meet criteria for donation.

2.6: The donor candidate should be informed of how the transplant center will handle their personal health information. This includes the following: (Not Graded)

- Personal health information collected during the donor evaluation is confidential and protected under privacy law similar to other information in their health record.
- The transplant center only discloses a candidate’s personal health information to the intended recipient or other parties with the donor’s permission.
- The donor candidate will be asked for permission to disclose certain personal health information to their intended recipient, so that their intended recipient can provide informed consent for the transplant to occur. Depending on the setting this information may include the donor candidate’s identity, immune compatibility between the donor candidate and intended recipient, and a donor candidate’s medical history that could affect the risk of disease transmission (e.g., infections, malignancy).
Understanding

2.7: The transplant center should assess the donor candidate’s understanding of the relevant information on the risks and benefits of donation to establish that the candidate has an adequate understanding of these facts. *(Not Graded)*

Voluntarism

2.8: The evaluation team should verify that the donor candidate is willing to donate a kidney and that this decision is made voluntarily without coercion or undue pressure. *(Not Graded)*

2.9: The center should support a donor’s decision to withdraw from the evaluation process or decline to donate in a way that is respectful and confidential. *(Not Graded)*

2.10: When a donor candidate decides not to donate and has difficulty communicating that decision to the intended recipient or others, the center should assist the donor candidate with this communication. *(Not Graded)*

RATIONALE

The ethical principles of autonomy, beneficence, non-maleficence, voluntarism, confidentiality and justice form the basis of informed consent to be evaluated as a living kidney donor candidate and to undergo living donor nephrectomy. Informed consent for a donor candidate requires that they are capable of making the decision to donate or not and includes adequate disclosure of the potential risk and benefits of donation, understanding of the possible outcomes, and voluntariness in the decision to donate or not.

Process of informed consent

Transplant programs need a defensible process to ensure that the requirements of informed consent are met.²,¹⁵-¹⁸ Unfortunately, informed consent processes have been shown to vary widely across transplant programs worldwide, with discrepancies noted in standards, consistency and implementation.¹⁶,¹⁷,¹⁹-²¹ It has been recommended that the informed consent structure and process be the same for donor candidates regardless of relationship (or lack thereof) between the donor candidate and their intended recipient.¹⁶,²²

It is optimal for the donor candidate and intended recipient evaluations to be performed by separate teams to minimize the risk of any perceived or actual conflict of interest. A recommendation that the donor candidate be evaluated by a medical team independent of the intended recipient evaluation also features in several past guidelines.²³-²⁷ 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 understanding of information. In the United States, to minimize any conflict of interest, living donor recovery hospitals must designate and provide each donor candidate with an Independent Living Donor Advocate (ILDA) who is independent of the intended recipient.
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. 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. While avoidance of conflict of interest is a central principle, it also remains important that healthcare professionals in the donor candidate and intended recipient evaluation teams work together to ensure effective communication and coordination of the transplant process. 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 the donor candidate has the capacity to provide informed consent, and is able to communicate their decisions based on a correct understanding of the information disclosed to them. Local laws and guidelines should be followed regarding minimum age criteria to become a living kidney donor. For example, prior guidelines have described an age < 18 years old as a contraindication to donation, with donation from younger persons only to be considered in highly exceptional circumstances after ethical and legal counsel. Donor candidates who are unable to provide informed consent, either by being minors or due to mental incapacity, should become a living kidney donor only in the rarest of circumstances, with the assistance of substitute decision-maker and following legal and ethical reviews.

Information disclosed to the donor candidate

Programs must have a process to communicate relevant information to donor candidates that enables informed decision making. Some prior guidelines have suggested use of a standardized checklist to ensure all items are disclosed.

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.

Participating in donor evaluation includes risks of discovery. This includes 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 where there is a reporting requirement to public health authorities. Transplant centers 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 purposes of assessing immune compatibility may identify misattributed biological relationships as an incidental finding. For example, misattributed paternity is estimated to occur in about 1 to 3% of father-child living kidney donor-recipient pairs, or approximately 0.25% to 0.5% of all living kidney donations. Transplant centers should also have a policy on how or whether this information is disclosed.
In general, education about the process and potential outcomes of living donation should be introduced in a manner conducive to donor candidate learning and understanding. Prior guidelines and policy statements have recommended that discussions be provided in a language where the donor candidate is able to engage in a meaningful dialogue with transplant center staff, with communication strategies and materials that are culturally sensitive. It is said the information should also be presented in a sympathetic environment, using simple language, allowing time for questions, with information that is appropriate to the family’s understanding and experience, at a pace determined by donor candidate’s needs. The information to be disclosed to the donor candidate is described in many prior guidelines and policy statements and presented in this guideline is the most comprehensive list of elements to date.

The donor candidate should be made aware of specific donation-related surgical, medical, and psychosocial outcomes and risks as provided in other chapters in this guideline. This includes a discussion about uncertainty in some long-term outcomes, when specific risks cannot be accurately quantified based on available data. There is no medical benefit to donating a kidney. The donor candidate should be made aware of anticipated recipient outcomes (such as 1-year, 5-year and median recipient and graft survival), and treatment alternatives available to their intended recipient, including deceased kidney donor transplantation and different types of dialysis. US policy requires that donor candidates are provided with current national and center-specific one-year transplant recipient patient and allograft survival statistics, while other guidelines suggest the donor candidate should be informed if any of their characteristics make a short-term adverse outcome more likely. Some regulations describe the minimum content elements that must be disclosed in the informed consent process, which should be respected as locally applicable. The donor candidate also provides consent for some tests performed during the evaluation, such as consent to receive intravenous contrast for renal imaging.

The donor candidate should be made aware of transplant center programs and personnel available to support a positive donation experience. This can include psychological support in the setting of an early 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 time and financial impacts of donation-specific recommended lifelong healthcare. The donor candidate should also understand how this care will be provided after donation, and the transplant center’s policy about providing donation-related healthcare after donation. In the United States transplant centers are required to collect and report follow-up data on donors for 2 years after the procedure.

In virtually all places worldwide it is a crime to knowingly acquire or obtain any human organ for valuable consideration (i.e., 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. The donor candidate should understand the withdrawal process from evaluation, and their right to withdraw at any time prior to transplantation with the full support of the transplant center (described further below in this guideline chapter). Finally, while transplant centers respect the autonomy of a donor candidate
to proceed with donation based on their preferences, needs and values, centers remain ethically justified to decline a donor candidate who does not meet their eligibility criteria for donation (when the donation is deemed too risky). A donor candidate should understand the transplant center makes the final determination of whether the donor candidate is eligible for donation or not based on the results of their evaluation. The donor candidate should be informed by the transplant center if and why they do not meet the center’s criteria for donation. Being told they do not meet a transplant center’s acceptance criteria has been distressing for some past donor candidates, as many are heavily invested in the donation process. The donor candidate should be informed on how the transplant center will support them if they are disappointed in the event of failure to meet criteria for donation. This may include ongoing follow-up communication with the evaluation team; counseling related to the outcome of the evaluation; alternative ways of helping the intended recipient, including assistance in communicating the result to the intended recipient; and the possibility of referral to another center for a second opinion if the donor candidate does not accept the decision.

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 with their intended recipient or other parties if they provide permission to do so. The donor candidate should also appreciate 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. For example, in directed donation, while a donor candidate may wish to keep their act of donor evaluation initially confidential, at some point they may need 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, at some point donor candidates and intended recipients provide permission to make the other aware whether they are immunologically compatible or not. During the donor evaluation process, it may be appreciated 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 pathogens based on their behavioral characteristics. Some jurisdictions require standardized behavioral screening during the evaluation and consent by the donor candidate for informing 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. Prior to donation the transplant center should also obtain permission from the donor candidate to share certain post-donation personal health information with the recipient, for the rare circumstance where soon after transplant it is discovered the donor has evidence of a serious infectious disease or malignancy.

It is possible that the intended recipient has health information that could impact the transplant outcome, which the transplant team believes the donor candidate has a right to know. For example, some donor candidates may want to know if the recipient lost a previously transplanted kidney due to medication nonadherence. Prior British guidelines and other policy statements recommend relevant information about the intended recipient be disclosed to the donor candidate if the intended recipient has given consent, and that the transplant not proceed unless the relevant information is shared. However, in the current
guideline we have not recommended informing the donor candidate under what circumstances personal health information about the intended recipient will be shared; the question as to what constitutes as relevant information beyond a finding that the intended recipient was approved by their evaluation team remains undefined.

Donor candidates who are immunologically incompatible with an intended recipient should be informed of the availability of kidney paired donation (KPD) and the considerations related to pursuit of this treatment option. Logistics, outcomes and risks specific to kidney paired donation are discussed in Chapter 3 of this guideline. As discussed in Chapter 3, participation in kidney paired donation requires specific informed consent, and minimum content elements may be specified by the paired donation program. The transplant center should inform the donor candidate of policies regarding confidentiality and anonymity in kidney paired donation and non-directed donation, and should ensure donor acceptance of these policies before donation. Some centers now permit biologically compatible pairs to participate in kidney paired donation; when this option is discussed, donor candidates who are biologically compatible with their intended recipient should voluntarily decide whether to pursue this option or not.

A donor candidate’s understanding of the provided 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 centers, require all donor candidates to exercise a minimal period for this adequate consideration, which is referred to as a ‘cooling-off’ period.

In current routine care, an assessment of a donor candidate’s knowledge and understanding of the possible outcomes of donation is typically done through discussions with healthcare professionals. Optimal methods to provide education and assess understanding in living kidney donor candidates is not currently well defined. 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 post-operative physical pain or the time needed to fully recover after surgery.

The voluntary nature of kidney donation

Voluntarism is established when a transplant center ensures the donor candidate is free from undue pressure or coercion in deciding whether or not to donate. Voluntarism should be respected by all members of the transplant team; as discussed above, additional safeguards may include use of ILDAs or external reviews of planned donations. Special groups such as prisoners have unique considerations in this regard. Interviewing the donor candidate without the intended recipient is important in the assessment of voluntarism. Trust is
maintained when the transplant center assures a donor candidate that their 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, which can be applied to the ambivalent donor candidate who has not decided to proceed, but who also has not elected to close out the donation process.16

Transplant teams should support the donor candidate who decides to withdraw from the evaluation process or decline to donate in a way that is respectful and confidential. So-called ‘medical alibis’, providing the donor candidate with a false medical reason for them to justify their unsuitability as a living donor, are discouraged as they are untruthful and can undermine trust in the transplant center and patient/physician relationship. Thiessen et al. recommend that all prospective donors be offered a general statement regarding an ‘unsuitability to donate’ at any time; there is controversy about whether the donor team can assist the donor candidate with wording that includes factual medical findings which may or may not preclude donation (such as mildly elevated blood pressure or risk factors for metabolic syndrome). 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 living kidney donor evaluation team should assist the donor with this communication, which may involve communication through the recipient evaluation team to the intended recipient.

Research Recommendations

- Determine the best method to achieve informed consent from living kidney donor candidates, including what methods are most useful to impart information and what methods are most useful to assess understanding.19

- Develop standardized criteria for if and when the intended recipient 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 non adherence), so that the donor candidate can make an informed decision about whether to proceed with donation or not.

- Perform post-donation surveys to measure donors’ assessments of the quality of standardized informed consent processes, including if the information provided prior to donation met the donor’s needs and prepared them for the donation.54

- Compare post-donation experiences of donors who donated prior to and following the implementation of country specific regulations for the practice of living donation.

- Evaluate appropriate circumstances for and approaches to substitute decision making and use of surrogate consent.
• Develop consensus criteria for participation of biologically compatible pairs in kidney paired donation, and logistics and procedures for informed consent while considering safeguards against coercion or undo pressure in this setting.

• Develop consensus for ethical and 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.55
CHAPTER 3: COMPATIBILITY TESTING, INCOMPATIBLE LIVE DONOR TRANSPLANTATION, AND DONOR EXCHANGES

Blood Type Compatibility and Histocompatibility Testing

3.1: Donor candidate compatibility evaluation should be performed and interpreted in the context of testing required to support good graft outcomes in the intended recipient. (Not Graded)

3.2: ABO blood typing should be performed in donor candidates before organ recovery, including routine duplicate testing to reduce the risk of unintended blood type-incompatible transplantation. (Not Graded)

3.3: ABO subtype testing should be included when donation is planned to recipients with anti-A antibodies. (Not Graded)

3.4: Human leukocyte antigen (HLA) typing for MHC Class I (A,B,C) and Class II (DP, DQ, DR) characterization should be performed in donor candidates being evaluated to donate to transplant candidates with anti-HLA antibodies (i.e., panel reactive antibody (PRA) level >0%) as part of the assessment of biological compatibility. (Not Graded)

Selection Criteria based on Blood Type Compatibility and Histocompatibility

3.5: If the living donor candidate and intended recipient candidate are blood type or crossmatch incompatible, transplantation should proceed only if there is a predetermined incompatibility management protocol. (Not Graded)

Counseling and Informed Consent Regarding Options and Outcomes for Biologically Incompatible Pairs

3.6: Donor candidates who are ABO or HLA incompatible with their intended recipient should be informed of average patient and graft survival expectations for planned incompatible compared with compatible live donor transplantation and deceased donor transplantation, as well as average patient survival on dialysis, based on currently available regional and local outcome statistics. (Not Graded)

3.7: Donor candidates who are immunologically incompatible with their intended recipient should be informed of the availability of paired kidney donation, and that participation in such donor exchange programs is voluntary. (Not Graded)

3.8: All non-directed donor candidates should be informed of opportunities for donating into a chain or paired exchange program, if regionally available, to maximize utility of their gift. (Not Graded)
3.9: Transplant centers should inform donor candidates participating in kidney paired donation about the risks and benefits of non-exchange donation options, the unique aspects of exchanges including recipient selection, time frames for donation and transplant procedures, any travel requirements for the donor, options for kidney transport and risks of possible organ redirection due to unforeseen circumstances. (Not Graded)

3.10: Transplant centers should inform donor candidates participating in exchanges of opportunities or prohibitions for obtaining information about or contact with the recipient after an exchange or non-directed donation. The transplant center should ensure donor candidate acceptance of these policies before donation. (Not Graded)

RATIONALE

Blood Type and Compatibility Testing

ABO blood typing should be performed in living donor candidates before organ recovery, including routine duplicate testing, to reduce the risk of unintended blood type-incompatible transplantation. Unintended ABO-incompatible transplantation should be avoidable with ABO typing of the donor and the recipient; however, human errors have led to cases of accidental ABO-incompatible organ transplantation in contemporary practice. ABO-subtype testing should be performed when donation is planned to recipients with anti-A antibodies. We recommend HLA typing for MHC class I (A, B, C) and class II (DP, DQ, DR) characterization in living donor candidates to recipient candidates with anti-HLA antibodies (i.e., PRA >0%), as part of the assessment of compatibility during preoperative planning because of the reported association between the presence of HLA-C and/or HLA-DP and DQ and a higher incidence rate of graft rejection. While recipient care is out of the scope of this guideline, it is important to emphasize that recipient candidates should undergo anti-donor antibody examinations, including complement-dependent cytotoxicity (CDC) or Flow Cytometry Crossmatching (FXM) and Luminex assays, to determine the history of sensitization, and this testing should be current before proceeding with donor nephrectomy and live donor transplantation.

Counseling Regarding Transplant Options and Expected Outcomes

Biological incompatibility remains a significant barrier to expansion of live donor kidney transplantation. Estimates based upon blood group prevalence in the US suggest that more than 35% of willing, healthy potential live donors are blood group incompatible with their intended recipients (1). Options for transplant candidates whose only willing, healthy donor is ABO or HLA incompatible include: planned incompatible transplantation (with preconditioning/desensitization treatment of the intended recipient as needed), kidney paired donation (KPD), transplant from a different live donor (if one is available), or waiting for a compatible deceased donor organ. 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 vs. incompatible transplantation, outcomes after incompatible transplantation vs. dialysis, and the likelihood of transplantation with options including paired exchange programs.

**Kidney Paired Donation (KPD)**

KPD has emerged as a successful approach to address antibody incompatibilities for those who have a willing, but incompatible live donor candidate. The fastest growing modality for live donor transplantation is KPD, rising from 2 cases in 2000 to approximately 700 cases reported to the Organ Procurement and Transplantation Network (OPTN) in 2013. 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.

Donor candidates who are immunologically incompatible with their intended recipient should be informed of the availability of KPD, and the considerations related to pursuit of this treatment option. Logistics, outcomes and risks specific to KPD are discussed in this chapter. Participation in KPD requires specific informed consent, and minimum content elements may be specified by the paired donation program. The transplant center should inform the donor candidate of policies regarding confidentiality and anonymity in KPD and non-directed donation, and should ensure donor acceptance of these policies before donation. Some centers 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 to pursue this option or not.

Donor candidates participating in kidney exchanges should be informed of the risks and benefits of non-exchange donation options, kidney transport, possible organ redirection due to unforeseen circumstances, and the inability to provide information on the actual recipient. 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 live donor kidneys can be accomplished safely without adversely impacting transplant outcomes, obviating the need for donor travel. In an initial survey of 30 US centers transporting 56 live donor kidneys (2007–2010), the creatinine nadir was <2.0 mg/dL 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. Continued feasible and safe transport of live donor kidneys in the US has been reported.

Non-directed donors (donor without an identified recipient) have the unique potential to expand the donor pool through chain transplantation. Non-directed donor candidates should be informed of opportunities for donating into a chain or paired exchange program, if regionally available, to maximize the utility of their gift.

Entry into an exchange should be considered preferable to incompatible transplantation if the exchange 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. Thus, for some transplant candidates, incompatible transplantation may offer their best option for transplantation without prolonged waiting times.

**Blood Type-Incompatible Transplantation**

While incompatible transplantation without pre-conditioning/desensitization treatment of the recipient may lead to hyperacute rejection and allograft loss, thereby compromising the utility or even leading to loss of the donated organ, predetermined incompatibility management protocols have been developed in recent decades. In 1987, successful live donor ABO incompatible (ABOi) transplantation was introduced in Japan using pre-transplant antibody depletion, to expand access to transplantation in the absence of legal recognition of brain death. 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 live donor ABOi 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. In contrast, some European and Asian studies have found no increases in early or longer-term complications after ABOi transplantation, possibly reflecting differences in preconditioning management protocols. Even in US experience, following an early reduction in graft survival relative to blood ABOc live donor kidney transplant recipients, the average long-term graft survival in ABOi live donor transplant recipients is not inferior to, and often exceeds, that of ABOc deceased donor transplant recipients. In the US, recipients of ABOi live 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.

**HLA-incompatible Transplantation**

HLA-incompatible transplantation remains the most difficult hurdle in achieving successful transplant outcomes. FXM+/CDC- incompatibility may be acceptable with management including B-cell-depleting treatments (e.g., anti-CD 20 antibody, rituximab) and/or splenectomy and/or intravenous immune globulin (IVIg), but increased risk of early rejection remains, requiring additional immunosuppression and attendant risks to the recipient. Nonetheless, while allograft survival after HLA-incompatible live donor kidney transplantation is inferior to compatible transplantation, incompatible transplantation after desensitization can offer a substantial survival benefit compared with dialysis or waiting for a deceased donor kidney. Among 211 patients who underwent desensitization and live donor kidney transplantation at one center, recipient survival was 80.6% at 5-years and 80.6% at 8-years, substantially higher than survival rates of 65.6% and 49.1%, respectively, in matched controls who continued to undergo dialysis or underwent HLA-compatible transplantation at any time.
after the date of transplantation in the matched desensitized patient, and markedly higher than among those who remained on dialysis (51.5% and 30.5%, respectively).\textsuperscript{59}

**Research Recommendations**

- Continue efforts to define mediators of clinical outcomes and optimal management of incompatible live donor transplantation to support donor and recipient selection, informed consent and transplant utility, including:
  - Elucidation of the mechanisms of antibody production and long-term impact on the allograft
  - Standardized, controlled comparisons of preconditioning and post-transplant immunosuppressive protocols for ABOi transplantation

- A long-term, appropriately powered RCT is needed to compare the outcomes of options for highly sensitized candidates including participation in KPD with varying waiting times versus live donor transplantation after various desensitization protocols.
4.1: Donor candidates should receive guideline-based evaluation and management used for other non-cardiac surgeries to minimize their risk of perioperative complications. These dimensions of care include a detailed history and exam to assess risk factors for cardiac, pulmonary, bleeding, anesthesia-related and other perioperative complications. (Not Graded)

4.2: Donor candidates who smoke should be advised to stop and commit to lifelong abstinence to reduce their risk of perioperative and long-term complications. (Not Graded)

RATIONALE

Purpose of the evaluation

The purpose of the general preoperative evaluation is 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 acceptably low to proceed with donation; and to counsel the donor candidate on how to minimize their risk of perioperative complications (i.e., 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 pre-surgical function as quickly as possible. Recommendations on how to achieve this 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 prior to donation (such as prior surgeries, anesthesia-related reactions and bleeding disorders).23, 31, 76 The effect of donation-specific surgical techniques on perioperative outcomes is described elsewhere (Chapter 16).

Transplant teams appreciate that a small proportion of donors will unfortunately experience serious perioperative complications after donation despite careful pre-donation evaluation and perioperative management. When a donor experiences a serious perioperative complication it can be devastating for the donor, their intended recipient and the public perception of living kidney donation.

Rate of perioperative complications

Living kidney donor nephrectomy is an elective surgical procedure which carries a low risk for complications as compared to other types of surgical procedures. The 90-day all-cause mortality in a recent US study of 80,347 donors was reported to be ~ 1 in 3000 (0.03%) based on 25 deaths.6
A US study recently described the incidence of perioperative complications in a large sample living kidney donors from 1998 to 2010. Outcomes were assessed through administrative data rather than adjudication, 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%). Another US 28-center study of 3074 living kidney donors from 2004 and 2005 described an overall complication rate of 10.6% and a major complication rate of 4.2%. A Norwegian study of 1022 living kidney donations performed between 1997 and 2008 recorded 30 (2.9%) major complications and 184 (18%) minor complications.

**Preoperative and perioperative management to minimize the risk of perioperative complications**

There is no evidence to suggest additional preoperative testing beyond guideline-based evaluation and management strategies used for other non-cardiac surgeries results in a reduced incidence of perioperative complications in kidney donors.

Some transplant centers routinely perform preoperative non-invasive cardiac testing in older living kidney donor candidates (i.e., stress electrocardiogram, nuclear stress test), but this practice is not supported by existing evidence. Recent US guidelines do not recommend cardiac testing for those undergoing non-cardiac 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 two blocks on ground level or carry two bags of groceries up one flight of stairs without symptoms). Outside the context of perioperative evaluation, other guideline groups recommended against non-invasive cardiac testing for asymptomatic coronary artery disease, or conclude that there is insufficient evidence to warrant such testing.

Recent guidelines on the assessment of bleeding risk prior to surgery or invasive procedures describe the following: (i) Indiscriminate coagulation screening prior to surgery to predict postoperative bleeding in unselected patients is not recommended; (ii) A careful bleeding history includes details of a family history of bleeding, previous excessive post-traumatic or postsurgical bleeding, and current use of anti-thrombotic drugs; (iii) If the bleeding history is negative, no further coagulation testing is indicated; (iv) A comprehensive assessment is warranted if the bleeding history is positive. In a recent multi-center randomized trial of 10,010 patients undergoing non-cardiac 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. The trial authors recommend aspirin not be started prior to 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 (i.e., 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. 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 history 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). 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.

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

Research Recommendations

- Develop contemporary estimates of the risk of perioperative complications according to an individualized profile of pre-donation characteristics, according for changes in baseline comorbitity burdens.
- Perform RCTs to formally assess the efficacy of evaluation and perioperative management techniques to minimize the risk of perioperative complications after live donor nephrectomy.
CHAPTER 5: EVALUATION OF KIDNEY FUNCTION IN KIDNEY DONOR CANDIDATES

Graded recommendations below were extrapolated from the 2012 KDIGO CKD Guideline.

**Measurement**

5.1: We recommend expressing kidney function as glomerular filtration rate (GFR) and **NOT** as serum creatinine concentration. *(IA)*

5.2: We recommend expressing GFR in mL/min/1.73 m² rather than mL/min. *(IB)*

5.3: We recommend initial evaluation of GFR (screening) using estimated GFR from serum creatinine concentration (eGFR<sub>cr</sub>). *(IB)*

5.3.1: We recommend that serum creatinine be measured using an assay standardized to the international reference standard. *(IB)*

5.3.2: We recommend that eGFR<sub>cr</sub> should be computed using the 2009 CKD-EPI creatinine equation or other equations that are more accurate than the 2009 CKD-EPI equation. *(IB)*

5.4: We suggest confirmation of GFR using one or more of the following, if eGFR<sub>cr</sub> is out of range of reliability, depending on the accuracy and reproducibility at the transplant center: *(2B)*

5.4.1: Measured GFR (mGFR) using an exogenous filtration marker: Urinary or plasma clearance of inulin, urinary or plasma clearance of iothalamate, urinary or plasma clearance of <sup>51</sup>Cr-EDTA, urinary or plasma clearance of iohexol, and urinary clearance of <sup>99</sup>m-Tc-DTPA are preferred. Other methods, including imaging, are less accurate. *(Not Graded)*

5.4.2: Measured creatinine clearance (mCl<sub>cr</sub>) should be used if mGFR is not available. *(Not Graded)*

5.4.3: Estimated GFR from the combination of serum creatinine and cystatin C (eGFR<sub>cr-cys</sub>) should be used if mGFR and mCl<sub>cr</sub> are not available. *(Not Graded)*

5.4.3.1: We recommend that serum cystatin C be measured using an assay traceable to the international reference standard. *(IB)*

5.4.3.2: We recommend that eGFR<sub>cr-cys</sub> should be computed from the 2012 CKD-EPI equations. *(IB)*
5.4.4: Repeat estimated GFR from serum creatinine (eGFR\textsubscript{cr}) if mGFR, mCl\textsubscript{cr} and eGFR\textsubscript{cr-cys} are not available. (Not Graded)

5.5: If there is evidence of greater than expected asymmetry of kidney size on medical imaging, assess individual kidney GFR by using radionuclides or contrast agents that are excreted by glomerular filtration (e.g., \textsuperscript{99m}Tc-DTPA). (Not Graded)

Criteria for Acceptable Pre-Donation GFR

5.6: mGFR \geq 90 \text{ mL/min/1.73 m}^2 should be considered as an acceptable level of kidney function for kidney donation. (Not Graded)

5.7: The decision to approve donor candidates with mGFR 60-89 ml/min/1.73 m\textsuperscript{2} should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)

5.8: Donor candidates with mGFR <60 ml/min/1.73 m\textsuperscript{2} should be excluded from donation. (Not Graded)

5.9: If the donor candidate’s mGFR is acceptable but there is a difference in size or function between the two kidneys that is greater than expected, the transplant center should consider procuring the kidney with smaller size or lower function and leaving the donor with the kidney with larger size or higher function. (Not Graded)

RATIONALE

Goal of evaluation

- Provide accurate assessment of level of GFR and prediction of lifetime risk of ESRD (pre- and post-donation) based on level of pre-donation GFR and other factors.
- Allow identification and exclusion of donor candidates whose post-donation risks are expected to exceed the acceptable lifetime risk for ESRD established by the transplant center.
- Provide counseling regarding level of risk for donor candidates whose lifetime risks for ESRD are expected to be below the acceptable risk established by the transplant center.
- Provide counseling regarding the need for follow-up of decreased GFR after donation.

Measurement

For this section, grading is based on physiological principles and recommendations for general clinical practice from KDIGO 2012 CKD guideline.\textsuperscript{87} These recommendations were based on a systematic review of the literature, which included people before and after kidney donation.\textsuperscript{88} There is no evidence to suggest that kidney donors differ from other populations regarding these recommendations.
GFR as an index of kidney function. The level of glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. The basis 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 m² 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 thresholds for decision-making that can applied to most donors across the usual distribution of body size.

Measurement methods. The KDIGO 2012 CKD guidelines recommend 2-stage testing (initial testing followed by confirmatory testing as necessary). Estimated GFR (eGFR) based on serum creatinine (eGFRcr) is the recommended initial test. Serum creatinine assays should be traceable to the international reference standard. In the North America, Europe, and Australia, the 2009 CKD-EPI creatinine equation should be used unless other equations have been shown to be more accurate. eGFRcr using the 2009 CKD-EPI creatinine equation has minimal bias at normal GFR; however, it is imprecise (Figure 3), thus it is useful for an initial evaluation. 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.

Performance of the CKD-EPI 2009 Creatinine Equation


Figure 3
A variety of confirmatory tests are available. KDIGO recommends measured GFR (mGFR) using exogenous filtration markers and clearance calculations. Many methods are available, with variable accuracy.\textsuperscript{90} mGFR is not available in all centers, so other alternatives are acceptable. Measured creatinine clearance (mCl\textsubscript{cr}) is acceptable if mGFR not available. mCl\textsubscript{cr} is available worldwide, however it is less accurate than mGFR.\textsuperscript{90} mCl\textsubscript{cr} overestimates mGFR due to creatinine secretion. The magnitude of overestimation is 15% or more at normal GFR, based on older data using non-standardized serum creatinine assays. The magnitude of overestimation may be higher using standardized assays.

A recent study suggests that eGFR may be sufficiently accurate for decision-making without the need for mGFR in many cases.\textsuperscript{91} A web-based calculator is available to compute post-test 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 pre-test probabilities for mGFR and test performance for eGFR using serum creatinine (eGFR\textsubscript{cr}) or the combination of creatinine and cystatin C (eGFR\textsubscript{cr-cys}). Very high and very low post-test probabilities provide reassurance that mGFR is above or below the threshold levels for decision-making. Transplant centers can determine what post-test probabilities are sufficient for clinical decision-making in the absence of mGFR and mCl\textsubscript{cr}. Studies validating these computations in donor candidates are not yet available. Future studies should address prediction accuracy among racial and ethnic groups for whom the accuracy of eGFR is less certain (e.g., non-black, non-white persons).

KDIGO recommends that eGFR based on serum cystatin C (eGFR\textsubscript{cys}) or the combination of serum creatinine and cystatin C (eGFR\textsubscript{cr-cys}) is acceptable if mGFR is not available. In general eGFR\textsubscript{cys} is not more accurate than eGFR\textsubscript{cr}; however using two filtration markers improves precision of GFR estimates compared to using either marker alone; thus eGFR\textsubscript{cr-cys} is generally recommended over eGFR\textsubscript{cr} or eGFR\textsubscript{cys}.\textsuperscript{92,93} Advantages of cystatin C over creatinine are that cystatin C is not affected by muscle mass and current equations do not require specification of race. Therefore, eGFR\textsubscript{cys} maybe more accurate than eGFR\textsubscript{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 cystatin C equation or creatinine-cystatin C equation should be used unless other equations have been shown to be more accurate. If cystatin C is not available, eGFR\textsubscript{cr} can be used for decision-making.

Assessment of individual (“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, and asymmetry in kidney size suggests asymmetry in kidney function.

Criteria for Acceptable Pre-Donation GFR

GFR in the general population. The normal level of GFR in young men and women is >90 ml/min/1.73 m\textsuperscript{2}. The normal mean (SD) GFR in healthy young (age <40 years) adults is approximately 120-130 ml/min/1.73 m\textsuperscript{2}.\textsuperscript{87} GFR between 60 and 89 ml/min/1.73 m\textsuperscript{2} is
considered to be decreased compared to the usual level for young adults, but does not meet the KDIGO criterion for the definition of 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. Mean GFR is lower in older populations than in young populations. Other kidney functions are also lower in older populations (e.g., renal plasma flow, maximal urinary concentration) and kidney structure is altered in older populations (e.g., 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 ESRD, CVD and death. In general populations, compared to a reference eGFR of 95 ml/min/1.73 m², the relative risk (RR) for complications related to decreased eGFR is apparent between 60 and 75 ml/min/1.73 m² and is exponentially higher at lower eGFR (Figure 4).\textsuperscript{94-96} KDIGO 2012 guideline defines GFR <60 ml/min/1.73 m² for 3 months or more as satisfying the criteria for CKD. GFR <30 is defined as severely reduced, and GFR < 15 ml/min/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 ESRD, CVD and death. The RR for these outcomes in older people with lower eGFR compared to 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.\textsuperscript{97}
Figure 4. The data above are based on creatinine-based eGFR (eGFRcr) using the MDRD Study equation. Comparable data are not available for mGFR. However, studies using more accurate GFR estimates confirm these results. For the outcomes of ESRD, 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 eGFRcr. The increase in risk is even greater if cystatin C is used to estimate GFR, either with or without creatinine (eGFRcr-cys or eGFRcys), compared to eGFRcr.

A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 US general population cohorts who are similar to kidney donor candidates found that lower GFR is associated with an increased risk for ESRD over median cohort follow-up of 4 to 16 years. For example, a decrement of 15 ml/min/1.73 m² in eGFR was associated with an adjusted hazard ratio (HR) of 6.61 (95% confidence interval [CI] 4.87-8.96) in participants with an eGFR <60 ml/min/1.73 m² and an adjusted HR of 1.63 (1.53–1.74) in participants with an eGFR 60-89 ml/min/1.73 m², but no significant higher risk in participants with eGFR >90 ml/min/1.73 m². Variations in the projected 15-year and lifetime risks of ESRD according to level of eGFR from this analysis are displayed graphically in Figures 5 and 6 according to age, sex and race for healthy persons (assuming systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus). This analysis demonstrates that lower eGFR is associated with increased lifetime risk for ESRD in all demographic subgroups. For eGFR ≥90 ml/min/1.73 m², lifetime risk for white men and white women was less than 1% at all ages, but exceeded 2% for black men and women less than 30 and 20 years, respectively (Figure 2). Lifetime risk for eGFR 60-89 was less than 1% at ages greater than 60 years. While these displays are useful for visualizing the impact of baseline eGFR on increased ESRD risk, we endorse consideration of eGFR within the assessment of predicted long-term ESRD risk based on a donor candidate’s complete demographic and clinical profile (as opposed to consideration of single risk factors in isolation).
Figure 5. Estimated 15-yr incidence (%) of ESRD in the United States according to baseline eGFR and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.¹¹
**GFR after kidney donation.** GFR declines after kidney donation. A person with a pre-donation GFR of >90 ml/min/1.73 m² would be expected to have a 1-year post-donation GFR >60 ml/min/1.73 m². In general, a donor immediately loses approximately 50% of renal mass, but in the setting of health, there is rapid compensatory hyperfiltration leading to a net reduction in GFR of only 30% (25% to 40%) after donation (decrement in GFR of 25 to 40 mL/min per 1.73 m²).9,8,10

In prior guidelines a GFR level of 80 mL/min is frequently cited as the minimal threshold for an adequate level of kidney function prior to donation.15,101 Limited data show a higher risk for lower GFR among kidney donors with lower pre-donation GFR. (Evidence Report Table 16)
There is theoretical justification for concern about development of kidney disease after nephrectomy. In experimental animals, hemodynamic alterations associated with 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 following kidney donation.\textsuperscript{102, 103}

Many studies show that the risk for ESRD and other complications in donors appears to be lower than the risk in the general population, even though GFR is lower (Evidence Report Appendices, Table D5). One likely explanation is that donors are carefully evaluated to rule out CKD as well as causes of CKD (hypertension, diabetes, CVD), which are associated with higher risk of adverse outcomes in association with lower eGFR in the general population. Another possible explanation is that a low GFR in the setting of reduced renal mass may be more stable than a low GFR due to other causes of kidney disease.

Recent studies show a higher risk for ESRD in donors than in comparable healthy general population: an average estimated risk difference of approximately 0.3% at 15 years after donation (30.8 per 10,000 (95% CI, 24.3-38.5) in kidney donors and 3.9 per 10,000 (95% CI, 0.8-8.9) in matched healthy non-donor counterparts.\textsuperscript{10} In this study, the incidence of ESRD was higher in individuals who are older vs. younger at the time of donation, in men vs. women, in blacks vs. whites, and in biologically related vs. unrelated donors, but risk based on pre-donation eGFR were not been reported. Data on lifetime estimates of ESRD in donors were not available.

\textbf{Individual kidney GFR.} Many factors determine the preferred kidney to remove for transplantation. If GFR is acceptable, but there is asymmetry in kidney function, it is preferable to transplant the kidney with lesser function and leave the donor with the kidney with greater function.

On average, kidney function and size are correlated. The average kidney length and volume in healthy adults are approximately 12 cm and 300 ml, respectively, but vary based on age, sex and body size.\textsuperscript{104-106} 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 >10% (for example, a difference in kidney length >1.2 cm or kidney volume >30 ml). An equivalent difference in kidney function would be >10% (>55% vs. <45% of two-kidney function). Based on low quality evidence, one prior guideline suggested considering a radionuclide imaging study if the difference between kidney lengths is >2 cm, and that a difference in function >10% between the kidneys may be considered significant.\textsuperscript{23} No studies were found meeting our ERT’s criteria for review.

\textbf{Comparison to Prior Guidelines}

Some guidelines recommend that living donors have a GFR of 80 mL/min or greater, based on the level of GFR in the donor (not adjusted for BSA) that was associated with the best outcomes in the recipient, not the donor.\textsuperscript{107} Alternatively, some guidelines recommend a GFR
level within two 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. A 2007 survey of practices by transplant centers in the US revealed that approximately 90% of centers used mClcr, while the other 10% of centers used the clearance of an exogenous filtration marker, and that approximately 67% of transplant centers used a threshold of 80 mL/min or more to accept donors, while 25% used a threshold based on age- and sex.

By comparison, our recommendations are more consistent with accepted measurement methods and thresholds in general clinical practice, but acknowledge that there is variation in GFR measurement methods and uncertainty in the appropriate threshold for decision-making to accept or decline donor candidates. For this reason, we recommend GFR measurement by urinary or plasma clearance of a specific exogenous filtration markers, which are known to be more accurate than mClcr, but allow other methods. We recommend a higher threshold value of mGFR (≥90 ml/min/1.73 m²) to routinely accept a donor candidate, and lower threshold value of mGFR (<60 ml/min/1.73 m²) to routinely decline a donor candidate, and a wide intermediate range of mGFR (60-89 ml/min/1.73 m²) in which transplant centers can individualize decisions based on other risk factors. Of note, this intermediate range would generally include a mClcr of 80 ml/min as well as previously recommended age and sex thresholds for mGFR.

Research Recommendations

- Evaluate the accuracy of eGFRcr, eGFRcys and eGFRcr-cys for the prediction of mGFR in the evaluation and selection of living donor candidates.
- Evaluate lifetime risk of ESRD in living donor candidates and living donors according to pre-donation GFR.
CHAPTER 6: EVALUATION OF PROTEINURIA
IN KIDNEY DONOR CANDIDATES

Graded recommendations below were extrapolated from the 2012 KDIGO CKD Guideline.

Measurement

6.1: We suggest expressing proteinuria as albuminuria and NOT as total urine protein. (2B)

6.2: We recommend reporting albuminuria in a random urine single time point collection as albumin-to-creatinine ratio (ACR) in mg/g [mg/mmol], rather than albumin concentration as mg/dL. (1B)

6.3. We suggest initial evaluation of albuminuria (screening) using urine albumin creatinine ratio (ACR) in a random (untimed) urine specimen. (2B)

6.4: Confirmation of albuminuria should be obtained using: (Not Graded)
   6.4.1: Albumin excretion rate (AER, mg/d) in a timed urine specimen
   6.4.2: Repeat ACR if AER cannot be obtained

Criteria for Acceptable Pre-Donation Albuminuria

6.5: Urine AER <30 mg/d should be considered as an acceptable level for kidney donation. (Not Graded)

6.6: The decision to approve donor candidates with AER 30-100 mg/d should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)

6.7: Donor candidates with urine AER >100 mg/d should be excluded from donation (Not Graded)

RATIONALE

Goal of evaluation

- Provide accurate assessment of level of albuminuria and prediction of lifetime risk of ESRD based on level of albuminuria and other factors.
- Identification and exclusion of donor candidates whose post-donation risk is expected to exceed the acceptable risk for ESRD established by the transplant center.
- Provide counseling regarding level of risk for donor candidates whose lifetime risk for ESRD is expected to be below the acceptable risk established by the transplant center.
- Provide counseling regarding follow-up of albuminuria GFR after donation.

**Measurement**

For this section, grading is based on physiological principles and recommendations for general clinical practice from the KDIGO 2012 CKD guideline. There is no evidence to suggest that kidney donors differ from the general population regarding these recommendations.

**Proteinuria as a marker of kidney damage.** Urine albumin is the preferred measure of urine protein for assessment 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 serum proteinuria reflects decreased tubular reabsorption (tubular proteinuria). Conditions other than kidney disease can also cause proteinuria: low molecular serum proteinuria may also reflect overproduction (for example, 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).

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 proteinuria 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 guidelines recommend 2-stage testing (initial testing followed by confirmatory testing). 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 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 guidelines therefore recommend 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 (CER) and multiplying this quantity by ACR to estimate AER. 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.”

**Urine PCR.** Tests for total urine protein cannot substitute for tests for urine albumin. PCR is insensitive than ACR, so even negative tests must be confirmed by tests for albumin. Increased PCR suggests increased ACR, but non-albumin 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 α1-microglobulin, β2 microglobulin, monocolonal 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 (“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.**

The preferred confirmatory test is urine AER, expressed as mg/day. 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 α1-microglobulin, β2 microglobulin, monoclonal heavy or light chains (also known as ‘Bence Jones’ proteins) can be undertaken if significant non-albumin proteinuria is suspected. These assays can be performed at the same time as tests for albuminuria.

**Criteria for Acceptable Pre-Donation Albuminuria**

**AER in the general population.** The normal level of AER in healthy young men and women is less than 10 mg/d. The normal mean (SD) AER is approximately 7 mg/d, with a coefficient of variation for repeated measurements of approximately 30%. 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. Mean AER is lower 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 ESRD, CVD and death. In general populations, compared to a reference albumin-to-creatinine ratio (ACR) of 5 mg/g (0.5 mg/mmol), the RR for complications related to increased ACR is higher at higher ACR, without an apparent threshold when expressed on the log scale.\textsuperscript{112} For this reason 10-29 mg/g is considered “high normal.” The risk of higher ACR is independent of the eGFR (Figure 4). KDIGO 2012 guidelines define AER >30 mg/d for 3 months or more as satisfying the criteria for CKD. AER <30 mg/d in young men and women is considered normal to mildly increased; AER 30-300 mg/d is defined as moderately increased compared to the young adult level; and AER >300 mg/d is defined as severely increased compared to the young adult level. Approximate ranges for other measures of urine protein are as shown in Table 3. 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.

Higher albuminuria in older people is associated with increased risk for CKD outcomes, including ESRD, CVD and death. The RR for these outcomes in older people with higher urine ACR compared to 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.\textsuperscript{97}

A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 U.S. general population cohorts found that each 10-fold increase in urinary ACR was associated with three-times the risk of ESRD over median cohort follow-up of 4 to 16 years, although the finding was not statistical significant (adjusted HR: 2.94, 95% CI 0.99 - 8.75).\textsuperscript{11} Variations in the projected 15-year and lifetime risks of ESRD according to urine ACR from this analysis are displayed graphically in Figures 7 and 8 according to age, sex and race for healthy persons (assuming age-specific eGFR, systolic blood pressure 120 mmHg, BMI 26 kg/m², and absence of diabetes mellitus). This analysis demonstrates that higher albuminuria is associated with higher lifetime risk for ESRD in all subgroups, with higher risk in men than women and blacks than whites. For urine ACR <10 mg/g, lifetime risk for white men and

Table 3. Adapted from KDIGO 2012 CKD guideline\textsuperscript{87}

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal to mildly increased (A1)</th>
<th>Moderately increased (A2)</th>
<th>Severely increased (A3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER (mg/24 hours)</td>
<td>&lt; 30</td>
<td>30-300</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>PER (mg/24 hours)</td>
<td>&lt; 150</td>
<td>150-500</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td>&lt; 3</td>
<td>3-30</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>(mg/g)</td>
<td></td>
<td>30-300</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>PCR (mg/mmol)</td>
<td>&lt; 15</td>
<td>15-50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>(mg/g)</td>
<td></td>
<td>150-500</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>Protein reagent strip</td>
<td>Negative to trace</td>
<td>Trace to +</td>
<td>+ or greater</td>
</tr>
</tbody>
</table>

Abbreviations: AER: albumin-to-creatinine ratio; ACR: albumin excretion rate; PER: protein-to-creatinine ratio; PCR: protein excretion rate. Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using 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 <10 mg/g (<1 mg/mmol) is considered normal; ACR 10-30 mg/g (1-3 mg/mmol) is considered "high normal." ACR >22000 mg/g (> 2200 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.
white women was less than 1% at all ages, but exceeded 2% for black men and women less than 30 and 20 years, respectively (Figure 8). In whites, lifetime risk at ACR 100 mg/g was less than 1% at age greater than 50 in men and 40 in women. In blacks, lifetime risk at ACR 30 mg/g was less than 1% at age greater than 60 in men and women. While these displays are useful for visualizing the associations of baseline ACR with ESRD risk, we endorse consideration of ACR within the assessment of predicted long-term ESRD risk based on a donor candidate’s complete demographic and clinical profile (as opposed to consideration of single risk factors in isolation).

Figure 7. Estimated 15-yr incidence (%) of ESRD in the United States according to baseline albumin-creatinine ratio (ACR, mg/g) and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.11
Figure 8. Estimated lifetime incidence (%) of ESRD in the United States according to baseline albumin-creatinine ratio (ACR, mg/g) and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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 ESRD in the low-risk population, and thus are likely imprecise. Reproduced from Grams et al.11

Proteinuria after kidney donation. Proteinuria increases after kidney donation. Some but not all studies demonstrate donors have an increase in proteinuria compared to non-donor control groups (Figures 9-10).98-100 In prior guidelines a PER <150 mg/d was frequently cited as the minimal threshold for an adequate level of kidney function prior to donation.23, 27, 113, 114 This level corresponds roughly to AER <30 mg/d, which includes normal and mildly increased (Figure 1 from KDIGO 2012 CKD guideline87). 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, which followed 4793 living donors an average of 7 years (range 2–25 years). 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 which only considered those nine studies which consistently defined proteinuria as >300 mg/day based on 24 h urine. The pooled incidence of proteinuria among these nine studies which followed a total of 1799 donors for 7 years was 10% (95% CI 7–12%).

Figure 9. Proteinuria after kidney donation. Figure adapted from Ibrahim HN et al.99
Figure 10. Proteinuria after kidney donation. Reproduced from Garg AX et al.100
Comparison to Prior Guidelines

Some guidelines recommend that accepted living donor candidates have a PER less than 150-300 mg per day, based on the usually accepted normal range, generally without reference to measurement methods. A survey of practices by transplant centers in the USA reported in 2007 revealed that approximately 76% of centers used a PER in a 24-hour urine collection, and that 50% of transplant centers used a threshold of 300-1000 mg, corresponding to moderately increased (approximately one-third of these required qualification by other evaluations), while 36% used a threshold of <150 mg/d.\textsuperscript{109}

By comparison, our recommendations are more consistent with the more 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 for decision-making 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 <30 mg/d to routinely accept a donor candidate, which corresponds to normal and mildly increased. We recommend an intermediate range of AER 30-100 mg/d in which to individual decisions based on other risk factors, which corresponds to the lower range for moderately increased.

Research Recommendations

- Assess the accuracy of urine ACR compared to AER for evaluation and selection of living donor candidates
- Evaluate lifetime risk of ESRD in living donors according to pre-donation urine albuminuria.
CHAPTER 7: EVALUATION OF HEMATURIA AND INDICATIONS FOR KIDNEY BIOPSY IN KIDNEY DONOR CANDIDATES

Evaluation

7.1: All donor candidates should be screened for the presence of microscopic hematuria. (Not Graded)

7.2: Donor candidates with persistent microscopic hematuria should undergo testing to identify possible underlying causes which may include (potential tests in parentheses): (Not Graded)

- Infection (urinalysis and urine culture)
- Nephrolithiasis/microlithiasis (urography and a 24-hr urine stone panel)
- Malignancy (multiphasic computerized tomography, or urography with and without IV contrast, or magnetic resonance urography AND cystoscopy, along with a focused history evaluating demographic and clinical cancer risk factors)
- Glomerular disease (measurement of GFR, urinary protein, focused review of family history of kidney disease, and consideration of renal biopsy)

Donor Selection

7.3: Hematuria from a reversible cause, such as infection, that resolves with treatment is not a contraindication to kidney donation. (Not Graded)

7.4: Some donor candidates with microscopic hematuria also have other characteristics which associate with a higher lifetime risk of ESRD (such as a low GFR, high levels of albuminuria, hypertension, or evidence of a glomerular disease on kidney biopsy such as IgA nephropathy). Such donor candidates should generally be excluded from kidney donation. (Not Graded)

RATIONALE

Evaluation of hematuria

The presence of hematuria is not normal and should always be evaluated when found in a donor candidate. This evaluation can help determine if hematuria is due to a correctable cause (e.g., urinary tract infection), a malignancy (which could be transmitted to the intended recipient), or a glomerular disease such as IgA nephropathy which may be associated with increased lifetime chance of ESRD after donation.

Persistent microscopic hematuria has been variably defined in the literature, but a common definition comprises microscopic evidence of >2-5 red blood cells per high-power
field of urinary sediment on 2-3 separate occasions, unrelated to exercise, trauma, sexual activity or menstruation. Consensus-based guidelines of the American Urological Association state that while a positive dipstick reading warrants microscopic examination to confirm or refute 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. The estimated prevalence of microscopic hematuria varies widely from 0.18% to 16%. A recent population-based study of 1.2 million persons aged 16 to 25 in Israel identified prevalent asymptomatic persistent microscopic hematuria in 0.3% of individuals.

Persistent microscopic hematuria may be associated with underlying urologic abnormalities (e.g., stones, tumors), but also with underlying glomerular pathology. The most common glomerular causes of persistent isolated microscopic hematuria include IgA nephropathy, Thin Basement Membrane Nephropathy (TBMN), and Alport syndrome.

Consensus-based guidelines address the evaluation of asymptomatic microhematuria in the general population. The 2012 recommendations from the American Urological Association include assessment of risk factors for urinary tract malignancies (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures), radiological evaluation (e.g., multi-phasic computed tomography (CT) urography, without and with intravenous (IV) contrast, or magnetic resonance urography), and cystoscopy in patients age 35 or older regardless of history of use of anticoagulation therapy. Urine cytology and urine markers (NMP22, BTA-stat, and UroVysion FISH) are not recommended as a part of the routine evaluation of the asymptomatic microhematuria patient, but may be considered in patients with persistent microhematuria following a negative work-up or those with other risk factors for urinary tract malignancies / carcinoma in situ.

While 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 with up to 35 yrs of follow-up identified small but significant increase in long-term renal risk associated with persistent asymptomatic isolated microscopic hematuria, quantifying ESRD rates of 34.0 vs 2.05 per 100,000 person-years among those with versus without persistent microscopic hematuria (adjusted HR: 18.5, 95% CI (12.4–27.6)). While participants were required to have serum creatinine values “within the normal range” and 24-hr urine protein <200 mg, this study does not provide information on ESRD risk after comprehensive evaluation and selection including measured renal function.

Prior living donor guidelines have recommended evaluation for underlying causes of hematuria including urine culture and imaging, cystoscopy is age older than 40, urine cytology and “complete” (Amsterdam)”extensive” urological evaluation. A recent Canadian protocol describes 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. In the absence of an identified cause, evaluation by renal biopsy has been advised if hematuria is >1+ or possibly caused by glomerular disease/glomerulopathies.
**Donor candidate acceptance**

The Evidence Review performed in concert with the development of this guideline did not identify any qualifying studies related to associations of hematuria from any cause with outcomes after kidney donation.

Epidemiological studies of TBMN suggest increased risks of hypertension and proteinuria compared to the general population over time, but progression to ESRD is rare and thought to require an additional insult.\textsuperscript{124}

Data on outcomes after live kidney donation in persons with TBMN are limited to small series with short-term followup. One series of 512 consecutive prospective donors at a US center identified asymptomatic, microscopic hematuria over 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); >20\% glomerulosclerosis in patient with a family history of Schimke's syndrome (immune-osseous dysplasia). Two of the 4 with TBMN proceeded with donation, aged 44 and 53 yrs; after 15 mo followup, donors were free of hypertension, proteinuria, and recipients had “excellent” graft function.\textsuperscript{125} A Korean series including 5 living donors with TBMN defined by pre-donation biopsy reported favorable short-term outcomes, including mean serum creatinine 0.94 ± 0.32 mg/dL and no cases of new onset hypertension or proteinuria over mean follow-up period of 34.7 ± 42.5 months.\textsuperscript{126}

Notably, TMBN is often defined based on pathological description rather than as a distinct clinical entity. Carrier states for Alport mutations may present clinically as TBMN. High frequencies of eventual proteinuria (75\%) and ESRD (8-30\%) have been reported in female carriers of X-linked Alport syndrome mutations.\textsuperscript{127} A recent study identified adverse renal outcomes in 234 Alport carriers (including 29 autosomal recessive and 205 X-linked mutation carriers): ESRD developed in 17.5\% at a median age of 49 yrs, and outcomes including ESRD, proteinuria and impaired renal function were similar in X-linked and autosomal recessive carriers,\textsuperscript{128} 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 yrs, 3/6 developed new onset hypertension, 2/6 developed new onset of proteinuria. Creatinine clearance remained >40 ml/min in all donors at up to 14 yrs.\textsuperscript{129} Thus, while data are limited, female carriers of X-linked Alport syndrome (i.e., \textit{COL4A5} mutation) should be discouraged from kidney donation because of their own increased risk of hypertension and adverse renal outcomes even in the absence of donation.

IgA nephropathy that presents with hematuria and minimal proteinuria is often a progressive disease. In one series of 72 consecutive patients with histologically confirmed IgA nephropathy who presented with hematuria and minimal proteinuria (0.4 g/day or less) in Hong Kong followed for a median of 84 mo, 33\% developed proteinuria, 26\% became hypertensive, and 7\% developed impaired renal function.\textsuperscript{130}
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 pre-donation hematuria was identified in 8.3% (18.6% vs 6% in those with vs without family history of IgA nephropathy or Alport syndrome). 95% of those with persistent pre-donation hematuria continued to have persistent hematuria after donation over median 27 mo follow-up (compared with 28% of those with pre-donation occasional hematuria and 5% without pre-donation hematuria). Pre-donation hematuria was associated with increased likelihood of persistent proteinuria (dipstick $\geq 1+$) after donation (without dysmorphic RBC: adjusted OR 3.8; with dysmorphic RBC: adjusted OR 12.3). Pre-donation hematuria was not associated with post-donation renal function during observation, but persistent post-donation hematuria with dysmorphic RBC was associated with significant GFR decline over the study period.

While a number of prior living donor guidelines recommend renal biopsy as part of the evaluation of persistent microhematuria before donation, 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”. A Canadian protocol defines IgA nephropathy and Alport syndrome (including carrier status) as exclusions to donation.

The 2013 “Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy” include several consensus-based recommendations related to live donation selection: A) “Individuals with TBMN may be kidney donors if they have normal blood pressure (BP), proteinuria, and renal function” and if a biopsy is done and Alport syndrome is excluded.” Close monitoring and use of nephroprotective strategies are advised. B) “Individuals from families with autosomal recessive Alport syndrome who have only one of the causative mutations (parents, offspring, some siblings) may be renal donors if they have normal BP, proteinuria levels, and renal function; if coincidental renal disease has been excluded by renal biopsy; and if X-linked Alport syndrome has been excluded by genetic testing.” The document recommends “discouraging affected mothers of males with X-linked Alport syndrome from renal donation because of their own risk of kidney failure.”
CHAPTER 8: EVALUATION OF KIDNEY STONES IN KIDNEY DONOR CANDIDATES

Evaluation

8.1: All donor candidates should have a detailed personal history about any prior kidney stones, and family history review for any first degree relatives with kidney stones. (Not Graded)

8.2: All donor candidates should have renal imaging (such as a CT angiogram) to assess renal anatomy prior to nephrectomy. Any imaging done as part of the donor evaluation should be examined for the presence of kidney stones. (Not Graded)

8.3: For all donor candidates with a history of kidney stones or evidence of kidney stones on imaging, the cause should be determined whenever possible. (Not Graded)

Donor Selection

8.4: A decision to proceed with donation in a candidate with prior or current kidney stones should be based on a risk assessment of recurrence. (Not Graded)

8.5: When proceeding with donor nephrectomy in someone with a current unilateral stone, we suggest the kidney with the stone be removed, and that the donor be left with no significant stone in their remaining kidney. (Not Graded)

Counselling

8.6: Individuals with current or prior evidence of kidney stones who donate a kidney should be encouraged to follow evidence-based dietary recommendations for the general population to minimize the risk of stone recurrence after donation. (Not Graded)

8.7: All donors who develop kidney stones after donation should receive consensus-based recommended investigations used in the general population to understand reasons for stone formation. (Not Graded)

8.8: All donor candidates and donors who develop kidney stones should receive evidence-based treatments to reduce their risk of stone recurrence. (Not Graded)

RATIONALE

The risk of developing kidney stones after donation or receiving a urologic procedure for kidney stones after donation does not differ between living kidney donors without a pre-donation history of kidney stones and selected non-donors matched for similar baseline health as the donors.133

Kidney stones are common, and an estimated 10-15% of the general population will develop a kidney stone in their lifetime. The most common type of kidney stone is calcium oxalate, and a 50% lifetime probability of recurrence of stone formation has been reported in symptomatic stone formers. However, the risk of recurrence after any single stone is difficult
to predict in any individual. Compared to older adults, younger adults have more remaining years to live prior to death, and so have a higher lifetime chance of kidney stone recurrence.

Characteristics associated with a higher lifetime risk of stone recurrence include:
- Younger age (< 40 years)
- Frequent, recurrent kidney stones (despite any measures to minimize stone formation)
- Prior or current stones in both kidneys (vs. only in one kidney)
- An ongoing metabolic reason for stone development such as cystinuria, hyperoxaluria, uricosuria, hypercalciuria, and renal tubular acidosis.
- Atypical urinary anatomy that predisposes to infection (struvite) stones.
- Evidence of nephrocalcinosis on renal imaging.

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.

Approximately 5-10% of individuals have evidence of an asymptomatic kidney stone on imaging performed as part of the donor evaluation. The widespread use of computed tomography (CT) scans for donor evaluation may detect very small calcifications in the kidneys in patients who are asymptomatic and have no history of passing a kidney stone; very small 1-2mm calcifications in the renal papillae found on CT scans are referred to as Randall’s plaques. These plaques have an uncertain prognostic significance.

Kidney stones may be associated with a higher risk of CKD. One or more episodes of kidney stones was associated with a 2-fold higher risk of ESRD in one population-based study from Alberta, Canada. The association was stronger in patients with 2 or more episodes of kidney stones versus a single episode of kidney stones. The CKD-PC analyzed multiple different cohorts, and found the association between a prior history of kidney stones and ESRD was not consistent across different cohorts. This is the reason why a prior history of kidney stones does not appear as a variable in the online tool to predict the lifetime chance of kidney failure in the absence of donation. There are no data comparing rates of recurrent kidney stones, or long-term kidney function, in donors with and without pre-donation kidney stones.

A recent review summarizes evidence for preventing future stones in patients with a past calcium stone. There is low-strength evidence that increased fluid intake (versus normal fluid intake) halves recurrent stone risk (RR: 0.45, 95% CI 0.24 – 0.84). There is low-strength evidence that reducing soft-drink consumption decreases recurrent symptomatic stone risk (RR: 0.83, CI 0.71 – 0.98). In patients with multiple past calcium stones, most of whom increased their fluid intake, there is moderate-strength evidence that thiazides (RR: 0.52 CI 0.39 – 0.69), citrates (RR: 0.25, CI 0.14 – 0.44), and allopurinol (RR: 0.59, CI 0.42 – 0.84) 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.
Published series have reported on the safety and success of $ex \ viva$ ureteroscopy to remove stones from explanted donor kidneys before transplantation.
CHAPTER 9: EVALUATION OF BLOOD PRESSURE
IN KIDNEY DONOR CANDIDATES

Blood Pressure (BP) Measurement and Interpretation

9.1: Blood pressure should be measured prior to donation on at least two occasions by clinic staff trained in accurate measurement technique, using equipment calibrated for accuracy. *(Not Graded)*

9.2: When the presence or absence of hypertension in a donor candidate is indeterminate (high-normal or variable) based on history and clinic measurements, blood pressure should be further evaluated using ambulatory blood pressure monitoring (ABPM) or repeated standardized blood pressure measurements. *(Not Graded)*

Criteria for Acceptance based on Pre-Donation BP / Hypertension Status

9.3: Normal blood pressure, as defined by guidelines for the general population in the country or region where donation is planned, is acceptable for donation. *(Not Graded)*

9.4: Donor candidates with hypertension that can be controlled to <140/90 mmHg using one or two antihypertensive agents, and who do not have evidence of end-organ damage, may be acceptable for donation. The decision to approve donation in persons with hypertension should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. *(Not Graded)*

9.5: Donor candidates with hypertension should be excluded from donation if:

- blood pressure cannot be controlled to <140/90 mmHg using one or two antihypertensive agents,
- evidence of end-organ damage is present, or
- predicted lifetime incidence of ESRD exceeds the transplant center’s threshold of acceptable risk

Pre-Donation Counseling related to Hypertension for All Donor Candidates

9.6: All donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for hypertension and cardiovascular disease, including healthy diet, smoking cessation, achievement of healthy body weight, and regular exercise according to guidelines for the general population. These measures should be initiated prior to donation and maintained lifelong. *(Not Graded)*

9.7: Donor candidates should be counseled that blood pressure rises with aging, and that donation may accelerate the rise in blood pressure and the need for antihypertensive treatment over that expected with normal aging. *(Not Graded)*
Pre-Donation Management and Counseling of Potentially Acceptable Donor Candidates with Hypertension

9.8: If the donor candidate has known hypertension or is newly diagnosed with hypertension during the evaluation, treatment should be adjusted or initiated according to guidelines for the general population in the country or region where donation will occur. Blood pressure control should be confirmed by standardized blood pressure measurements taken over at least several weeks, prior to approval for donation. (Not Graded)

9.9: Persons with hypertension who are approved to donate should receive pre-donation counseling on the potential risk for donation-related increase in blood pressure, association of uncontrolled hypertension with end-organ damage in particular to their remaining kidney, the importance of maintaining a healthy lifestyle, and the importance of blood pressure follow-up after donation. (Not Graded)

RATIONALE

Hypertension Risk Assessment and Counseling

**Blood pressure (BP) measurement.** It is important to use an accurate, calibrated device and the appropriate sized blood pressure cuff based on arm length and circumference, as 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 two separate occasions by trained staff, or on one occasion plus ABPM to minimize anxiety effects in donor candidates. Automated serial BP measurements can also eliminate a “white coat” effect. Multiple prior guidelines and policies for the evaluation and care of living kidney donor candidates recommend assessment of pre-donation BP on several occasions, and/or consideration of ABPM in donor candidates with elevated office readings, receiving antihypertensive therapy, or older at evaluation.

**Hypertension** is defined by office BP readings of systolic blood pressure (SBP) $\geq 140$ mmHg or diastolic blood pressure (DBP) $\geq 90$ mmHg, out-of-office daytime mean ABPM or home measurements of SBP $\geq 135$ mm Hg or DBP $\geq 85$ mm Hg, or the need for medication to control BP. As some antihypertensive agents may have other primary indications aside from BP control (e.g., such of diuretics for edema control or beta-blockers for migraines), indication for 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. Population-based studies suggest that 20-25% of adults may have white coat hypertension. 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. Population-based studies suggest that 10-30% of adults may have masked hypertension.\(^{142, 143}\)

**Risk factors for hypertension.** Potentially modifiable risk factors for hypertension include use of certain medications (e.g., non-steroidal anti-inflammatory agents, decongestants, stimulants, anorexics) and presence of certain lifestyle factors (e.g., excess alcohol intake, use of dietary supplements, or smoking).\(^{144-146}\) Non-modifiable 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 pre-donation 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,\(^{147}\) British Transplantation Society guidelines\(^{23}\) 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 albumin excretion rate (AER) $>30$ mg/d (ACR $>30$ mg/g or 3 mg/mmol), reduced renal function (e.g., GFR $<60$ ml/min/1.73 m\(^2\)), hypertensive retinopathy, and/or evidence of left ventricular hypertrophy by electrocardiogram or by echocardiogram if performed.\(^{138}\)

**Lifestyle modification** can effectively treat hypertension without medication or with fewer medications and lower dosages required to achieve BP control.\(^{147}\) 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 patents 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 two prior guidelines,\(^{15, 139}\) while the SEN-ONT 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.\(^{31}\)

**Impact of GFR Reduction on Blood Pressure in the General Population and After Donation**

Reduced kidney function may cause or worsen hypertension in the general population.\(^{148}\) While it is well documented that BP rises with aging\(^{149}\), 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 (hyperfiltration in the remaining kidney, changes in vascular tone and renin-angiotensi-
aldosterone regulation) and/or heightened detection at donor follow-up. 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, and comparisons to unselected general rather than healthy populations, which may fail to capture donation-related effects. Use of antihypertensive medications was lower in a cohort of privately-insured prior donors compared with age- and sex-matched unscreened beneficiaries in the same insurance plan. In contrast, a systematic review including data for 5,145 predominantly Caucasian donors estimated 6 mmHg higher weighted mean SBP and 4 mmHg higher weighted mean DBP in donors compared with controls after an average of 7 years (Evidence Report Appendices, Table D1). An administrative claims linkage study of 1,278 (primarily Caucasian race) living donors in Ontario, Canada followed for a mean of 6 years (range 1 to 16 years) found a higher incidence of claims-based hypertension diagnoses (16.3% versus 11.9%, HR: 1.4, 95% CI 1.2–1.7) among living donors compared with matched controls who were also screened for the absence of baseline comorbidities through administrative claims. Among more recent donor cohorts, higher rates of post-donation hypertension diagnoses and antihypertensive medication use in African American compared with Caucasian donors have been reported. While these patterns parallel hypertension prevalence differences in the general population, one small study found higher rates of post-donation hypertension among 103 African American donors compared with race-matched “healthy” non-donor controls (41% vs 18% at an average of 6.8 years post-donation) (Evidence Report Appendices, Table D10). Furthermore, many donors in this study were unaware of their hypertension. Associations of age at donation and sex with post-donation hypertension have been inconsistent (Evidence Report Appendices, Tables D7 and D9).

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

Hypertension as a Cause of CKD in the General Population

Hypertension is a contributing cause of CKD in the general population. A recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 U.S. general population cohorts found that every 20 mmHg increase in SBP was associated with a 42% increase (adjusted HR: 1.42, 95% CI 1.27-1.58) in the risk of ESRD over median cohort follow-up of 4 to 16 years. Use of anti-hypertensive medications was also associated with increased ESRD risk (adjusted HR: 1.35, 95% CI 1.01-1.82 over cohort follow-up). Variations in the projected 15-year and lifetime risks of ESRD according to level of SBP from this analysis are displayed graphically in Figures 1 and 2 according to age, sex and race for healthy persons (assuming age-specific GFR, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus). While these displays are useful for visualizing the impact of higher SBP on increased ESRD risk, we endorse consideration of BP within the assessment of predicted long-term ESRD risk based on a donor candidate’s complete demographic and clinical profile (as opposed to consideration of single risk factors in isolation).
Figure 11. Estimated 15-yr incidence (%) of ESRD in the United States according to baseline blood pressure and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.11
Clinical consequences of hypertension vary by race in the general population. Treating mild-to-moderate primary hypertension may not halt nephropathy progression in non-diabetic African Americans, whereas hypertension control slows nephropathy progression in European Americans [ref]. Recent literature supports that at least a portion of renal failure previously attributed to hypertensive nephrosclerosis in persons of African descent may be genetically mediated by coding variants in the gene for a secreted lipoprotein, apolipoprotein L1 ($APOL1$) and not modifiable by antihypertensive therapy (Chapter 13).156-159

**Evidence Regarding Pre-Donation Hypertension as a Risk Factor for Adverse Outcomes after Kidney Donation**

Living donor candidates undergo a rigorous evaluation process which includes measurement of renal function and urinary protein, but subtle scarring of the kidney from
hypertensive nephrosclerosis may be undetected by these tests. Compensatory hyperfiltration in the remaining kidney is normal after nephrectomy; however, subclinical pathology or aging processes may impair compensation and reduce post-donation GFR.

Our evidence review identified 3 studies, rated as low quality evidence in reporting post-donation outcomes according to pre-donation BP or hypertension status (Evidence Report Appendices, Tables D16 and D17). In a combined cohort of donors and matched healthy non-donors in Norway, each 1 mmHg increase in SBP was associated with small but significant increase in risk of cardiovascular death and ESRD over up to 25 years follow-up. A small study including only 6 hypertensive donors reported CKD in 67% (4/6) of hypertensive compared with 22% of non-hypertensive donors at an average of 5.4 years. A third study including 16 hypertensive donors was deemed at high risk of bias. A 2008 systematic review by Young et al also included this study, but concluded that results from this and two additional studies that compared decrement in GFR among hypertensive donors to normotensive donors were substantially heterogeneous and conflicted, and thus results were not pooled.

Additional studies that did not meet criteria for our evidence review include a large study based on linkage of the U.S. transplant registry with national death records that found higher perioperative mortality among donors with versus without pre-donation hypertension (36.7 vs 1.3 per 10,000). While reported baseline hypertension was not associated with long-term mortality, SBP ≥ 140 mmHg at donor registration was associated with 3-times the adjusted RR of death over 12-years as SBP <120 mmHg (adjusted HR 3.3, 95% CI 1.1–9.7). A single-center study of 24 Caucasian, older (mean age 53 yrs) donors with pre-donation hypertension (awake ABPM >135/85 mmHg and clinic/RN BP >140/90 mmHg) that was not included in the evidence review based on sample size found similar post-donation GFR reduction and urine protein excretion as in normotensive donors, and no increase in urinary protein excretion compared with pre-donation values over a mean 282 days of follow-up.

Multiple prior guidelines and policies for the evaluation and care of living kidney donor candidates identify hypertensive “end organ damage,” including proteinuria, microalbuminuria, left ventricular hypertrophy, and hypertensive retinopathy, as relative contraindications or exclusions to kidney donation. Other relative contraindications or exclusions to donation defined in prior guidelines include uncontrolled hypertension; need for >1 drug or >2 drugs for adequate control; age younger than 50 at evaluation; non-Caucasian or African American race; or the presence of several comorbidities or cardiovascular risk factors. 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 this time there is limited evidence from the donor population to ground recommendations for donor acceptance based on hypertension status alone. Rather than enumerating demographic characteristics such as age or race to define exclusions among donor candidates with hypertension, we recommend adherence to the general framework that compares predicted lifetime ESRD incidence according to baseline profile of demographic and clinical traits including BP (in the absence of donation) to the center’s acceptance threshold.
Research Recommendations

- There is a need for well-designed studies to quantify the impact of live kidney donation on hypertension risk, as well as the impact of hypertension before and after donation on clinical outcomes including lifetime ESRD incidence.
- Focused studies of possible variation in the risk and consequences of hypertension according to other characteristics, including baseline demographic and other clinical factors are also needed.
CHAPTER 10: EVALUATION OF METABOLIC AND LIFESTYLE RISK FACTORS FOR ACCELERATED GFR DECLINE AND/OR LONG-TERM ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) IN KIDNEY DONOR CANDIDATES

Identification of Metabolic and Lifestyle Risk Factors

10.1: Potentially modifiable metabolic and lifestyle health risk factors should be identified and addressed by counseling to promote long-term health of the donor candidate. Relevant factors include: obesity, glucose intolerance, dyslipidemia, cigarette smoking and other forms of tobacco use, inactivity, and personal and family history of cardiovascular disease. (Not Graded)

Evaluation and Acceptance Related to Measures of Obesity

10.2: Body mass index (BMI) should be computed during the donor candidate evaluation based on weight and height measured in the clinic, and classified based on World Health Organization (WHO) criteria for the general population or race-specific categories. (Not Graded)

10.3: Donor candidates with morbid obesity (BMI ≥ 40 kg/m²) should be excluded from donation. (Not Graded)

10.4: The decision to approve donation in candidates with obesity defined by BMI ≥ 30 to 40 kg/m² should be individualized based in part on the predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)

10.5: Donor candidates with a prior history of bariatric surgery should be assessed for risk of nephrolithiasis and nephrocalcinosis by renal imaging and 24-hour urine supersaturation/stone profile. Those with multiple kidney stones or hyperoxaluria should be excluded from donation. (Not Graded)

10.6: While the minimum time limit for sustained weight loss in obese donor candidate to ensure safety after donation is not known, it is reasonable to assess the stability of recent weight loss over one to several months prior to donation. (Not Graded)

Evaluation, Acceptance and Counseling Related to Measures of Glucose Tolerance

10.7: Prior diagnosis of diabetes mellitus, history of gestational diabetes, and family history of diabetes should be assessed during the donor candidate evaluation. (Not Graded)

10.8: Glycemia should be assessed by fasting blood glucose and/or glycated hemoglobin (% HbA1c) prior to donation. (Not Graded)

10.9: 2-hour glucose tolerance testing or % HbA1c 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 be used to classify
diabetes or prediabetes status using established criteria for the general population. (Not Graded)

10.10: Persons with diabetes mellitus should be excluded from donation. (Not Graded)

10.11: The decision to approve donation in persons with prediabetes should be individualized based on their predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)

10.12: Donor candidates with prediabetes should be counseled 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. (Not Graded)

Evaluation and Acceptance Related to Lipid Profiling

10.13: Fasting lipid profile (including total cholesterol, LDL, HDL and triglycerides) should be measured prior to donation as part of an overall cardiovascular risk assessment. (Not Graded)

10.14: Donor candidates with severe or uncontrolled hyperlipidemias should be excluded from donation due to increased risk of premature ASCVD in the general population. (Not Graded)

10.15: The decision to approve donation in persons with mild or moderate dyslipidemia should be individualized based on their predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)

Evaluation and Acceptance Related to Cigarette Smoking

10.16: Present and past use of other tobacco products should be assessed during the donor candidate evaluation. (Not Graded)

10.17: Donor candidates who use tobacco products should be advised of the risks of perioperative complications, cancer, cardio-pulmonary disease and ESRD, and should be referred to locally available tobacco cessation support programs. (Not Graded)

10.18: Active smokers should be encouraged to quit smoking for at least 4 weeks prior to donation surgery to decrease the risk of perioperative complications. (Not Graded)

10.19: All donor candidates should be encouraged to abstain from tobacco products to decrease their risks of cancer, cardio-pulmonary disease and ESRD. (Not Graded)

10.20: The decision to approve donation in active smokers should be individualized based on their predicted lifetime incidence of ESRD in relation to the transplant center’s acceptance threshold. (Not Graded)
Counseling

10.21: All donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for obesity, prediabetes, dyslipidemia and cardiovascular disease, including healthy diet, regular exercise, moderation of alcohol use, and avoidance of tobacco products. These lifestyle interventions should be initiated prior to donation and maintained lifelong. (Not Graded)

RATIONALE

This section addresses the evaluation and management of metabolic and lifestyle factors associated with ESRD, atherosclerotic cardiovascular disease (ASCVD) 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 ESRD risk, but are relevant to a comprehensive pre-donation health assessment. While donation itself may not increase the risk related to a given factor, traditional ASCVD 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 ACSVD. All factors considered in this section are potentially modifiable by lifestyle and/or medical care.

Definitions and Assessment of Metabolic Status

According to WHO, the prevalence of diabetes mellitus has increased from 30 million people worldwide in 1985 to 135 million in 1995, and to 217 million in 2005. The rising prevalence of diabetes is linked with the obesity epidemic, which is estimated to affect 300 million adults worldwide. Underlying causes of the obesity epidemic may be modifiable, and include sedentary lifestyles, high-fat and energy-dense diets, and increased urbanization.

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 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), obese (BMI 30-34.9 kg/m²), and morbidly obese (BMI >35 kg/m²). 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 vary from WHO standards in non-Caucasians, 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.

Multiple prior guidelines for the evaluation and care of living donors recommend measurement of fasting plasma glucose and consideration of oral glucose tolerance testing and/or % HbA₁c as part of the donor evaluation.²³, 25, 139, 167

The World Health Organization (WHO) defines diabetes mellitus as: fasting plasma glucose ≥ 7.0mmol/l (126 mg/dl), random plasma glucose ≥ 11.1mmol/l (200 mg/dl) or plasma glucose concentration > 11.1 mmol/l (200 mg/dl) two hours after a 75g anhydrous glucose load in an oral glucose tolerance test (OGTT). A 2011 addendum included recognition of HbA₁c of
48 mmol/mol (6.5%) as an additional criterion for diagnosing diabetes if assays are standardized to criteria aligned with international reference values, but also indicated that HbA1c less than 48 mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests.

The WHO defines **Impaired Glucose Tolerance (IGT)** as fasting plasma glucose < 7.0 mmol/l (126 mg/dl) or two-hour post-load plasma glucose ≥7.8 and <11.1 mmol/l (140 mg/dl and 200 mg/dl), while **Impaired Fasting Glucose (IFG)** is defined as fasting plasma glucose 6.1 to 6.9 mmol/l (110mg/dl to 124 mg/dl). Definitions of IFG by other organizations (e.g., ADA) vary.

Dyslipidemias are classified based on elevations in total cholesterol and LDL-cholesterol, and low levels of HDL-cholesterol. Hypertriglyceridemia is an independent ASCVD risk factor.

**Obesity as a Risk Factor for Adverse Outcomes in the General Population and after Living Kidney Donation**

Increased risk of perioperative complications including wound and surgical site infections in obese patients is well established in the general surgical literature. The evidence review performed to support this guideline included 2 systematic reviews that examined perioperative outcomes according to BMI, with quality of source studies rated as low. Among six studies reporting operative time, all but one found a modest but statistically significant increase in operative time among donors with BMI ≥ 30 compared to <30 kg/m² (mean difference 16.9 minutes) (Evidence Report Appendices, Table C6). 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.

For longer-term outcomes in the general population, obesity has been identified as a risk factor for diabetes mellitus and may be a direct risk factor for kidney disease, separate from mediation by diabetes mellitus in the form of obesity-related glomerulopathy. The evidence review performed to support this guideline identified 5 studies comparing long-term outcomes among donors by pre-donation BMI, rated as low quality, with follow-up ranging from 6.7 to 15.1 years (Evidence Report Appendices, Table D12). The one included study that addressed mortality and ESRD was based on a cohort of 1901 living donors from Norway. The study found that baseline BMI increase was associated with increased risk of cardiovascular death (adjusted HR per BMI unit: 1.05, 95% CI 1.01–1.08, P = 0.006), but not with all-cause mortality or with ESRD, over a median of 15 years of followup, after adjustment for age, gender, year of inclusion, SBP, and smoking. In contrast, a linkage of the U.S. transplant registry with national death records that was not included in the evidence report found no associations of BMI at donation with perioperative mortality or death over 12 years. Three studies examined associations of pre-donation BMI with post-donation renal function, and found that BMI increase was correlated with modest reductions in estimated glomerular filtration rate (eGFR) at follow-up or increased odds of measured glomerular filtration rate (mGFR) <60 (OR per BMI unit: 1.12, 95% CI 1.02–1.23). Two studies examined associations
of pre-donation BMI with post-donation hypertension and found, respectively, modest increases in mean arterial pressure (91.2 vs 88.2 mmHg) or increased odds of hypertension requiring medication (OR per BMI unit: 1.12, 95% CI 1.02–1.23). One study examining psychosocial outcomes found a graded increase in the odds of impairment in the physical component of health-related quality of life (HRQoL) across pre-donation BMI strata, compared with BMI <25: BMI 25-29.9, OR: 1.84 (95% CI 1.31-2.65), BMI 30-34.9, OR: 2.85 (95% CI 1.84-4.42), BMI ≥35, OR: 4.32 (95% CI 2.37-7.87).

Multiple prior guidelines for the evaluation and care of living kidney donor candidates recommend BMI >35 kg/m² as an absolute or relative contraindication to donation. The CARI guidelines consider BMI >30 kg/m² a contraindication to donation, whereas other guidelines recommend careful evaluation for other comorbidities in donor candidates with BMI >30 kg/m². With regard to other metrics of obesity aside from BMI, the SEN-ONT guideline defines waistline >82 cm in women or >102 cm in men as additional relative contraindications to donation. CARI guidelines advise measurement of waist circumference within the assessment of overweight and obese donor candidates, and the US Joint Societies Workgroup defines abdominal circumference as part of the definition of metabolic syndrome. In contrast, based on our evidence review, we conclude that this time there is limited evidence from the donor population to ground recommendations for donor acceptance based on BMI alone among obese donor candidates. Instead we recommend adherence to the general framework that compares predicted lifetime ESRD incidence according to baseline profile of demographic and clinical traits including BMI (in the absence of donation) to the center’s acceptance threshold.

To inform prediction of lifetime ESRD in the donor evaluation, recent meta-analysis based on data from nearly 5 million healthy persons identified from 7 U.S. general population cohorts found a modest association of BMI >30 kg/m² with increased risk of ESRD over median cohort followup of 4 to 16 years (adjusted HR: 1.16, 95% CI 1.04-1.29). Variations in the projected 15-year and lifetime risks of ESRD according to BMI level from this analysis are displayed graphically in Figures 13 and 14 according to age, sex and race for healthy persons (assuming age-specific GFR, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus). While these displays are useful for visualizing the impact of higher BMI on increased ESRD risk, among those with BMI 30 to 40 kg/m², we endorse consideration of BMI within the assessment of predicted long-term ESRD risk based on a donor candidate’s complete demographic and clinical profile (as opposed to consideration of single risk factors in isolation).

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.
**Figure 13.** Estimated 15-yr incidence (%) of ESRD in the United States according to baseline BMI and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.11*
Figure 14. Estimated lifetime incidence (%) of ESRD in the United States according to baseline BMI and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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 ESRD in the low-risk population, and thus are likely imprecise. Reproduced from Grams et al.11

Diabetes as a Cause of CKD/ESRD in the General Population and Kidney Donors

Type 2 diabetes is a leading cause of CKD worldwide and accounts for approximately 50% of acquired, adult-onset ESRD.\textsuperscript{170, 171} Patients with diabetes mellitus are commonly excluded from live kidney donation. One report of 71 donors with baseline glucose intolerance including 27 older patients (mean age 58 yrs) with diabetes defined by 2-hr glucose tolerance testing found no ESRD events and similar survival compared to donors without glucose intolerance over a mean follow-up of 88 months (Evidence Report Appendices, Table D14).\textsuperscript{172}

A recent meta-analysis based on data from nearly 5 million persons identified from 7 U.S. general population cohorts found that, compared with non-diabetic persons, those with type 2 diabetes but otherwise good health had 3-times the risk of ESRD over median cohort followup of 4 to 16 years (adjusted HR: 3.01, 95% CI 1.91-4.74). Variations in the projected
15-year and lifetime risks of ESRD and type 2 diabetes from this analysis are displayed graphically in Figures 15 and 16 according to age, sex and race for healthy persons (assuming age-specific GFR, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus). Based on the strong association of type 2 diabetes with ESRD risk, we recommend that diabetic persons should generally be excluded from kidney donation. This recommendation resonated with multiple prior guidelines for the evaluation and care of kidney donors, although the European Best Practices qualifies an exception of “exceptional circumstances” and the British Transplantation Society offers the opinion-based recommendation 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”.

Non-insulin Dependent Diabetes Mellitus

Figure 15. Estimated 15-yr incidence (%) of ESRD in the United States according to non-insulin dependent diabetes mellitus status and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.11
Non-insulin Dependent Diabetes Mellitus

Figure 16. Estimated lifetime incidence (%) of in the United States according to non-insulin dependent diabetes mellitus status and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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 ESRD in the low-risk population, and thus are likely imprecise. Reproduced from Grams et al.11

Prediabetes represents an intermediate category of hyperglycemia, which poses increased risks for future type 2 diabetes mellitus and cardiovascular disease (CVD).170 Important risk factors for diabetes and prediabetes include increasing age, high-risk ethnicity or race, obesity, and history of diabetes in a first degree relative. Without active intervention, 6 to 23% of persons with prediabetes progress to diabetes within 1 year. Risk of progression of prediabetes to diabetes can be reduced with lifestyle changes and weight loss. 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.

Data from one small cohort suggested that carefully screened prediabetic living kidney donors may revert to normal fasting glucose and do not seem to have significantly increased risk of impaired kidney function in the short term (Evidence Report Appendices, Table D14). Based on retrospective review of information from 45 donors with IFG defined by at least one predonation fasting glucose >100 mg/dl [5.55 mmol/L] (and enrolled from a larger sample of 143 donors who met this definition), 58% reverted to normal glucose tolerance at a mean
follow-up of 10.4 years. Compared with donors with normal fasting glucose matched for age, sex, race and year of donation, a higher proportion of donors with IFG developed diabetes during follow-up (1.6% vs 2.2%, \( P = 0.06 \)). However, eGFR and urinary albumin excretion were similar in donors with versus without IFG at evaluation. Limitations of this analysis include the small sample, inability to study 69% of the donors meeting the study definition of IFG, and use of a more liberal definition of IFG, which was less stringent than the WHO definition.

Prior recommendations regarding candidacy of persons with prediabetes for kidney donation are conflicting. The European Best Practices state that IGT is not a contraindication to donation,\(^{141}\) whereas other guidelines consider prediabetes a relative contraindication\(^{31,139}\) or a condition warranting careful consideration,\(^{23}\) while CARI considers prediabetes as well as past history of gestational diabetes to be absolute contraindications.\(^{167}\) Given the lack of current data specific to the donor population, we conclude that decision to approve donation in persons with prediabetes should be individualized based on their predicted lifetime ESRD incidence in relation to the center’s acceptance threshold.

**Assessment and Application of other Cardiovascular Risk Factors in the Donor Evaluation**

Dyslipidemia is a modifiable risk factor for ASCVD, and hypertriglyceridemia and low HDL are components of the metabolic syndrome. With regard to associations of lipid levels with outcomes after donation, one study identified in the evidence report compared renal function and albuminuria at 5 yrs among donors with versus without predonation metabolic syndrome, where metabolic syndrome was defined as meeting three or more of the criteria: 1) waist circumference of >88 cm in women or >102 cm in men; 2) hypertriglyceridemia; 3) hyperlipidemia; 4) hyperglycemia; and 5) hypertension (>130/85) (Evidence Report Appendices, Table D15). Although small differences in the outcomes were suggested, statistical comparisons were not performed. No studies were identified comparing post-donation outcomes based on lipid status alone. A recent meta-analysis based on data from nearly 5 million persons identified from 7 U.S. general population cohorts found no associations of total cholesterol or LDL-cholesterol with ESRD risk over median cohort followup of 4 to 16 years.

Several prior guidelines recommend fasting lipid profiling as part of the donor evaluation,\(^{25,139,173}\) but do not define donor selection criteria based on lipid levels alone. The US Joint Societies Workgroup defines hypertriglyceridemia and low HDL as components of the metabolic syndrome, and consider IFG and other components of metabolic syndrome a relative contraindication in persons younger than 50 years old.\(^{139}\) While data are limited, we conclude that donor candidates with severe or uncontrolled hyperlipidemias should be excluded from donation due to increased risk of premature ASCVD inferred from the general population. The decision to approve donation in persons with mild or moderate dyslipidemia should be individualized based on their predicted lifetime ESRD incidence in relation to the center’s acceptance threshold.
Cigarette smoking is a strong, modifiable risk factor for ASCVD (as well as other adverse health outcomes such as lung disease and cancer), and may cause direct renal damage through microvascular injury and promotion of atherosclerosis. A recent meta-analysis based on data from nearly 5 million persons identified from 7 U.S. general population cohorts found that, compared with non-smokers over median cohort followup of 4 to 16 years, current smokers has 76% increase in the risk of ESRD (adjusted HR: 1.76, 95% CI 1.29-2.41) and past smokers had 45% increase risk (adjusted HR: 1.45, 95% CI 1.23-1.71). Variations in the projected 15-year and lifetime risks of ESRD for smoking status from this analysis are displayed graphically in Figures 17 and 18 according to age, sex and race for healthy persons (assuming age-specific GFR, urine ACR 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and absence of diabetes mellitus).

Figure 17. Estimated 15-yr incidence (%) of ESRD in the United States according to baseline smoking status and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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. Reproduced from Grams et al.11
Figure 18. Estimated lifetime incidence (%) of ESRD in the United States according to baseline smoking status and demographic profile from the CKD-PC

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m² for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine ratio (ACR) 4 mg/g [0.4 mg/mmol], BMI 26 kg/m², and no diabetes mellitus or anti-hypertensive 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 ESRD in the low-risk population, and thus are likely imprecise. Reproduced from Grams et al.11

Although data on the outcomes associated with smoking among living donors are limited, an analysis of linked U.S. transplant registry and national death records found that while smoking was not significantly associated with perioperative mortality, donor who smoked had ~5-times the adjusted mortality over 12 years compared to non-smoking donors.6 Some prior guidelines for the evaluation and care of living donors advise assessment of smoking within the donor evaluation, without recommending an application to selection.25, 139 Others advise encouraging smoking cessation without defining an exclusion criterion.23, 141 Two guidelines recommend smoking cessation 4 weeks prior to donor nephrectomy,15, 31 with emphasis on long-term abstinence by SEN-ONT.31 The 2000 NKF/AST guidelines recommended consideration of smokers as donors only if they are tobacco free for 6 months and have normal pulmonary studies.2 We conclude that decision to approve donation in active smokers should be individualized based on their predicted lifetime ESRD incidence in relation to the center’s acceptance threshold, considering smoking status and other clinical and demographic characteristics.
Research Recommendations

- Future studies should compare outcomes for donors with standard cardiovascular risk (related primarily to age) to outcomes for donors with metabolic and lifestyle risk factors for CVD with regard to long-term mortality, cardiovascular events, ESRD events and late kidney function.
- Assess effectiveness of pre-donation interventions including counseling and weight or lifestyle changes on long-term donor outcomes.
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 (e.g., risk of local endemic infections or travel to endemic areas), awareness of current patterns of geographically endemic infections, and focused microbiological screening.

11.1: All donor candidates should be screened for factors associated with increased likelihood of recent HIV, HBV and HCV infections. The 2013 US Public Health Service (PHS) Guideline provides an evidence-based instrument for this assessment (Box 1). (Not Graded)

11.2: Donor candidates should be screened for factors associated with increased likelihood of endemic or unexpected infections, including: geographic, seasonal, occupational, animal and environmental exposures (Box 2). (Not Graded)

11.3: Microbiological screening should be performed in all donor candidates for the following pathogens: Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and Treponema pallidum (Syphilis); urine culture should also be performed. Options for testing modalities, timing of testing in relation to donation, and implications of results to guide preventative strategies to reduce recipient infection or for donor exclusion are presented in Table 4. (Not Graded)

11.4: Microbiological screening should be performed if regional epidemiology or individual clinical or social history suggests increased risks for the following infections: Mycobacterium tuberculosis (MTB), Strongyloides, Trypanosoma cruzi, West Nile virus, Histoplasmosis, Cocciidiomycosis (Table 4). Other unexpected pathogens that have been reported in organ-derived infection transmissions are provided in Box 3. (Not Graded)

11.5: In general, donor risk factor and microbiological screening should be performed or updated as close to donation as possible. For HIV, HBV and HCV, microbiological screening should be current within 28 days of donation. (Not Graded)
Box 1. US Public Health Service (PHS) 2013 Screening for factors associated with increased likelihood of recent HIV, HBV or HCV infection. Adapted from Seem DL et al.175

- 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 six factors address sexual contact; the definition of “had sex” refers to any method of sexual contact, including vaginal, anal and oral contact:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Have you had sex with a person known or suspected to have Human immunodeficiency Virus (HIV), Hepatitis B virus (HBV), or Hepatitis C virus (HCV) infections in the preceding 12 months?</td>
</tr>
<tr>
<td>2.</td>
<td>If male: Have you had sex with another man in the preceding 12 months?</td>
</tr>
<tr>
<td>3.</td>
<td>If female: Have you had sex with a man with a history of male-sex-with-male (MSM) behavior in the preceding 12 months?</td>
</tr>
<tr>
<td>4.</td>
<td>Have you had sex in exchange for money or drugs in the preceding 12 months?</td>
</tr>
<tr>
<td>5.</td>
<td>Have you had sex with a person that has injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months?</td>
</tr>
<tr>
<td>6.</td>
<td>Have you injected drugs (by intravenous, intramuscular, or subcutaneous route) for nonmedical reasons in the preceding 12 months?</td>
</tr>
<tr>
<td>7.</td>
<td>Have you been in lockup, jail, prison, or a juvenile correctional facility for more than 72 hours in the preceding 12 months?</td>
</tr>
<tr>
<td>8.</td>
<td>Have you been newly diagnosed with or have been treated for syphilis, gonorrhea, Chlamydia, or genital ulcers in the preceding 12 months?</td>
</tr>
</tbody>
</table>

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
<td>Have you been on hemodialysis in the preceding 12 months?</td>
</tr>
</tbody>
</table>

**US PHS Risk factors also include:** A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for HIV, HBV, or HCV infection. A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection.
Box 2. Social and clinical factors associated with increased likelihood of geographically endemic infections and infections related to specific exposures. Adapted from OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee (DTAC)\textsuperscript{176}

<table>
<thead>
<tr>
<th>Geographic risks (including duration of time spent in a location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Home country/region</td>
</tr>
<tr>
<td>• Place of birth (outside versus inside home region)</td>
</tr>
<tr>
<td>• Prolonged residence outside home region (recent or distant)</td>
</tr>
<tr>
<td>• Occupational or recreational travel to other countries and/or regions?</td>
</tr>
<tr>
<td>• Countries of origin for close family members</td>
</tr>
<tr>
<td>• Ingestion of well water</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupational risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Healthcare workers</td>
</tr>
<tr>
<td>• Veterinarians, animal care workers</td>
</tr>
<tr>
<td>• Landscapers, park rangers, and other outdoor workers</td>
</tr>
<tr>
<td>• Occupations with international travel, such as Peace Corps, international journalists</td>
</tr>
<tr>
<td>• Medical mission trips (consider a three-month washout period prior to donation to allow identification of subclinical disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seasonal risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Warm weather and insect exposure – e.g., local West Nile Virus, Dengue, Chikungunya virus, local rickettsial infections, Lyme disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hobbies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hunting/dressing game, taxidermy</td>
</tr>
<tr>
<td>• Time living outdoors including camping, swimming in lakes, drinking stream water, insect exposures</td>
</tr>
<tr>
<td>• Adventure sports</td>
</tr>
<tr>
<td>• Gardening</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Significant animal exposure (wild and/or domestic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large numbers of cats or dogs or any unusual pets, including whether pets reside mainly indoors or outdoors</td>
</tr>
<tr>
<td>• Laboratory/research animals</td>
</tr>
<tr>
<td>• Veterinarian/Veterinarian assistant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family members and close contacts with potential risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Geographic or seasonal infections previously diagnosed in close family members or other contacts may predict risk for subclinical infection in donor candidate</td>
</tr>
</tbody>
</table>

| Personal history of seasonal or geographic infection in donor candidate, even if remote |
Box 3. Recognized organ donor-derived infection transmissions. Adapted from Fishman *et al.* \(^{177}\)

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adenovirus</td>
<td>- <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>- BK Polyoma virus</td>
<td>- <em>Nocardia</em> spp.</td>
</tr>
<tr>
<td>- Cytomegalovirus</td>
<td>- <em>Rickettsia rickettsii</em> (Rocky Mountain Spotted Fever)</td>
</tr>
<tr>
<td>- Epstein-Barr virus</td>
<td>- <em>Treponema pallidum</em> (Syphilis)</td>
</tr>
<tr>
<td>- Herpes simplex virus</td>
<td>- <em>Borrelia</em> (Lyme disease)</td>
</tr>
<tr>
<td>- HIV</td>
<td></td>
</tr>
<tr>
<td>- HBV</td>
<td></td>
</tr>
<tr>
<td>- HCV</td>
<td></td>
</tr>
<tr>
<td>- Hepatitis E virus</td>
<td></td>
</tr>
<tr>
<td>- Human T-cell lymphotropic virus 1 and 2</td>
<td></td>
</tr>
<tr>
<td>- Influenza A/B</td>
<td></td>
</tr>
<tr>
<td>- Lymphocytic choriomeningitis virus</td>
<td></td>
</tr>
<tr>
<td>- Parvovirus B19</td>
<td></td>
</tr>
<tr>
<td>- Rabies</td>
<td></td>
</tr>
<tr>
<td>- West Nile virus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <em>Aspergillus</em> spp.</td>
<td>- <em>Babesia microti</em></td>
</tr>
<tr>
<td>- <em>Candida</em> spp.</td>
<td>- <em>Balamuthia mandrillaris</em></td>
</tr>
<tr>
<td>- <em>Coccidioides immitis</em></td>
<td>- <em>Malaria</em> spp.</td>
</tr>
<tr>
<td>- <em>Cryptococcus neoformans</em></td>
<td>- <em>Naegleria fowleri</em></td>
</tr>
<tr>
<td>- <em>Histoplasma capsulatum</em></td>
<td>- <em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td>- <em>Scopulariopsis brevicaulis</em></td>
<td>- <em>Trypanosoma cruzi</em></td>
</tr>
<tr>
<td>- <em>Zygomycetes</em> (Mucor)</td>
<td>- <em>Schistosoma</em> spp.</td>
</tr>
<tr>
<td></td>
<td>- <em>Strongyloides stercoralis</em></td>
</tr>
</tbody>
</table>
Table 4. Microbiological screening to reduce the risk of living donor-derived infection transmission. Sources: Refs 175, 176, 178-184

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Target Population for Testing</th>
<th>Screening Tests</th>
<th>Confirmatory / Additional tests</th>
<th>Timing of Testing</th>
<th>Implications of Positive Test for Donation &amp; Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV (1/2)</td>
<td>All donor candidates</td>
<td>Anti-HIV-1/2 Ab or Ag/Ab combination assay</td>
<td>HIV NAT or HIV Ag/Ab combination assay</td>
<td>At initial screening and at least 28d prior to donation</td>
<td>• Donation from HIV+ persons contraindicated unless as part of an approved research protocol for HIV+ recipients</td>
</tr>
<tr>
<td>HBV</td>
<td>All donor candidates</td>
<td>Anti-HBc Ab and HBsAg</td>
<td>HBV NAT</td>
<td>At initial screening and at least 28d prior to donation</td>
<td>• Donation from HBsAg+ persons contraindicated for HBV- recipients, but may be considered for HBsAg+ recipients or recipients with HBV protective immunity, with informed consent of the recipient, possible anti-viral HBV treatment of the recipient and post-transplant monitoring • Donation from isolated HBcAb+ persons may be considered with informed consent of the recipient and post-transplant monitoring; consider HBV immunoglobulin and anti-HBV antiviral treatment in non-immune recipients</td>
</tr>
<tr>
<td>HCV</td>
<td>All donor candidates</td>
<td>Anti-HCV Ab</td>
<td>HCV NAT also recommended in all donors</td>
<td>At initial screening and at least 28d prior to donation</td>
<td>• Donation from HCV+ persons contraindicated unless as part of an approved research protocol for HCV+ recipients</td>
</tr>
<tr>
<td>CMV</td>
<td>All donor candidates</td>
<td>Anti-CMV IgG Ab</td>
<td></td>
<td></td>
<td>• Used to guide post-transplant anti-viral prophylaxis and monitoring in the recipient, based on recipient serology and center protocol</td>
</tr>
<tr>
<td>EBV</td>
<td>All donor candidates</td>
<td>Anti-EBV IgG Ab</td>
<td>(anti-viral capsid antigen and/or anti-nuclear antigen)</td>
<td></td>
<td>• Used to guide assessment for and monitoring of risk of post-transplant lymphoproliferative disorder, especially in EBV negative children</td>
</tr>
<tr>
<td><strong>Treponema pallidum</strong> (Syphilis)</td>
<td>All donor candidates</td>
<td>Rapid plasma regain (RPR)</td>
<td>Anti- <em>T. pallidum</em> Ab</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| **Mycobacterium tuberculosis** (MTB) | Persons with any of the following risk factors:  
• Lived in endemic regions  
• Social or environmental risk factors such as: working in healthcare, jail/prison exposure, known MTB 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 (AFB) staining, culture and/or NAT testing for active infection | • Donation is contraindicated from persons with active MTB infection. Consideration of donation after treatment of active MTB should be individualized  
• Donation may be considered from persons with latent MTB infection after initiation of chemoprophylaxis in the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant |
| **Strongyloides** | Persons with any of the following risk/clinical factors:  
• Born in or lived in tropical / subtropical countries with substandard sanitation  
• Significant exposure to soil in the Appalachia or the southeastern USA including walking barefoot  
• Unexplained eosinophilia and travel to an endemic area  
• Prior history of Strongyloides infection | • Anti-Strongyloides Ab (IgG)  
• Serology preferred to stool examination, as stool screening tests may be negative in asymptomatic chronic infection<sup>183</sup> | | • Donation may proceed after treatment of the donor with an appropriate anti-parasitic agent such as ivermectin |
| Trypanosoma cruzi (Chagas) | Persons with any of the following risk factors:  
- Born or lived in endemic areas of Mexico, Central and South America  
- Children of woman who lived in endemic area  
- Recipients of blood transfusion in endemic areas  
- Prior history of Chagas | Anti-T. cruzi Ab (EIA or IFA test) | NAT insensitive for chronic phase disease due to low levels of parasitemia | Donation may be considered from persons with chronic Chagas disease after treatment of the donor candidate before donation, informed consent of the recipient, and recipient monitoring after transplant |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>West Nile virus (WNV)</td>
<td>Persons with history of mosquito exposure or blood transfusions; risk varies by geography and season</td>
<td>Anti-WNV Ab IgM is available, but NAT advised in initial screening</td>
<td>WNV NAT</td>
<td>Within 7-14d of donation when testing indicated</td>
</tr>
</tbody>
</table>
| Histoplasmosis | Born or lived in Midwestern USA, Mississippi or Ohio River valleys | Chest radiograph (may be suggestive but not diagnostic)  
- Anti-Histoplasmosis Ab (complement fixation, immunodiffusion or EIA) | Urine or serum antigen testing | Donation may be considered from persons with pulmonary-limited histoplasmosis after treatment of the donor candidate before donation, resolution of clinical signs/symptoms and of antigenuria/antigenemia (if present at diagnosis), informed consent of the recipient, and recipient monitoring after transplant |
| Coccidiomycosis | Born or lived in desert areas of the southwestern USA | Chest radiograph (may be suggestive but not diagnostic)  
- Anti-Coccidioides Ab (complement fixation, immunodiffusion or EIA) | Urine or serum antigen testing | Donation may be considered from persons with 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 |

Abbreviations: Ab, antibody; Ag, antigen; AFB, acid-fast bacilli; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EIA, enzyme immunoassay; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFA, immunofluorescent antibody; NAT, nucleic acid testing
RATIONALE

The goals of infectious disease screening within the donor candidate evaluation are to identify illnesses that may require management to protect the health of the donor candidate, and to assess risks of donor-derived disease transmission to the intended recipient.\textsuperscript{178, 185}

One way of categorization of donor-derived infections considers the dimension of ‘expected’ versus ‘unexpected’.\textsuperscript{177, 186} The risks of ‘expected’ donor-derived infection transmission are defined by donor and recipient screening, such as the high risks transmission of CMV, 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.\textsuperscript{187-192} ‘Unexpected’ donor derived infection arises despite routine donor screening, such as HIV or HCV transmission from a seronegative donor due to false negative serologic testing or infection in a “window period.” Unexpected infectious disease transmissions through organ transplantation are rare but may result in serious morbidity and mortality.\textsuperscript{177, 193} Although most ‘unexpected’ disease transmissions have involved deceased donors, recent transmissions of HIV and HCV demonstrate that recipients of living donors may also be at risk.\textsuperscript{193, 194} Notably, while reporting of suspected or documented donor-derived infection transmissions is required in the USA, 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 \textit{de novo} infection in the recipient.\textsuperscript{195} 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.\textsuperscript{195} ‘Proven’ denotes clear evidence of the same infection 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.\textsuperscript{195}

The risk of donor-derived disease transmission can be mitigated by the donor evaluation, including history taking (clinical, social, 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 or social or clinical risk factors should reduce the likelihood of procuring an organ that would transmit infection, while preserving availability (avoiding false-positive test results) (Table 4). Approaches to screening should consider the virulence of a particular pathogen, available testing assays, and residual window periods for transmission despite screening\textsuperscript{183, 193} as discussed according to specific pathogen below. Risks versus benefit must be balanced in the decision to use organs from infected donors, incorporating pre-donation 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. All donor candidates should undergo testing for IgG Hepatitis B core Ab (Anti-HBcAb) and Hepatitis B surface antigen (HBsAg). HBV DNA nucleic acid testing (NAT) can further stratify transmission risk in donor candidates from Hepatitis B virus endemic areas who are Anti-HBcAb+, those with possible mutant HBV infections, and those with abnormal liver 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 at least within 28-day prior to donation.

Donation from HBsAg+ persons is contraindicated for HBV- recipients, but may be considered for HBsAg+ recipients or recipients with HBV protective immunity, with informed consent of the recipient, possible anti-viral HBV treatment of the recipient and post-transplant monitoring.

Kidney transplant recipients from Anti-HBcAb+/HBsAg-/HBV DNA- donors appear to have little risk of acquiring active HBV infection. In a review of 9 studies including 1385 renal allograft recipients from Anti-HBcAb+/HBsAg- donors, 45 patients (3.24%) showed seroconversion of HBV markers as follows: HBsAg+ (N=4), Anti-HBcAb+ (N=32), Anti-HBsAb+ (N=5), and either Anti-HBcAb+ or HBsAb+ (N=4). Among the 0.28% with HBsAg acquisition, none developed symptomatic hepatitis. This study did not examine the influence of recipient anti-HBsAg status or the use of prophylactic antiviral treatment. Patient or renal allograft survival were not worse among patients with HBsAg acquisition or HBsAb or HBcAb seroconversion. HBV NAT testing should be performed in donor candidates with isolated HBcAb+ to further stratify transmission risk. If the donor is anti-HBc+ and HBV DNA-, the risk of transmission is negligible, especially if the recipient is Anti-HBsAb+ or has been effectively immunized against HBV. Still the recipient should be informed of the small potential risk of disease transmission, and post-transplant monitoring should be performed. The additional use of HBV immunoglobulin and anti-HBV drugs may be considered, especially in non-immune recipients.

Hepatitis C Virus

Evaluation of donor candidates should include US PHS risk factor screening for increased risk of HCV infection. All donor candidates should undergo microbiological testing for HCV infection as close as possible to the date of the organ recovery, but at least within 28-day prior to donation. 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 potential living donors should be tested for both anti-HCV Ab and for HCV RNA by NAT.

Prior to the advent of new anti-viral therapies, active HCV in the donor was generally 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 kidneys of the donor. HCV has been transmitted to naïve organ recipients from infected living and deceased donors. Organ transplantation from an HCV+ donor is associated with significant
risk of HCV transmission, especially to HCV- recipients. In two reports, among recipients of organs from anti-HCV+ donors, 14 to 100% tested positive for anti-HCV antibodies after transplantation, and 57 to 96% tested positive for HCV RNA by PCR. Recipients of organs from HCV+ donors have a high risk of acquiring HCV infection and liver disease. In one report, 75% of the 29 recipients of organs (19 kidneys, 6 hearts, 4 livers) from 13 anti-HCV positive donors became anti-HCV or HCV RNA positive. In another study, only 13 of 46 (29%) kidney recipients of HCV recombinant immunoblot assay (RIBA)-positive donors developed post-transplant liver disease, but HCV RNA was not checked and significant clinical concern persists for disease transmission from HCV+ organ donors.

From the recipient perspective, the survival implications of transplantation of kidneys from HCV+ donors into HCV RNA+ recipients is controversial. An earlier study suggested good long-term patient and graft survival, and low risk of liver disease. Among HCV+ patients who received organs from HCV+ donors, five-year and 10- year patient survival was 84.8% and 72.7%, compared with 86.6% and 76.5%, respectively, among recipients from HCV- donors (p =0.25). Rates of decompensated chronic liver disease were similar with use of HCV+ and HCV- donors, 10.3% versus 6.2%. However, increased mortality and adverse liver outcomes have been demonstrated in more recent single-center as well as large registry studies. The reason for the observed differences in mortality rates has not been defined, but may reflect differences in immunosuppression or superinfection with another HCV genotype. Distinct from comparison of outcomes among transplant recipients from HCV+ versus HCV- donors, one large registry study demonstrated a survival advantage associated with receiving a kidney from an anti-HCV+ donor, compared with remaining on the deceased-donor waitlist (adjusted HR: 0.76). Avoiding superinfection might require matching donors and recipients based on the involved HCV genotype, an approach limited by obvious time constraints in cadaveric donation, but possible in living donor transplantation. The safety of this approach requires more research.

The availability of new HCV antiviral drugs as interferon-free regimens may change the acceptability of transplantation from HCV+ donors, although studies of safety and cost-effectiveness are needed. In the case of living donation, relevant outcomes include long-term donor health in addition to the risk of disease transmission to the recipient.

**Human Immunodeficiency Virus**

Evaluation of donor candidates should include US PHS risk factor screening for increased risk of HIV infection. All donor candidates should undergo microbiological testing for HIV infection as close as possible to the date of the organ recovery, but at least within 28-day prior to donation. HIV infection is a contraindication to organ donation to HIV- recipients as the transmission of HIV by organ 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. NAT testing can reduce the window period for HIV to between 5.6 and 10.2 days.
In contrast with undetected donor disease and transmission, medical advancements in HIV anti-viral therapy have led to consideration of planned kidney transplantation from HIV+ donors into HIV+ recipients, such as recent experience describe in South Africa. In the U.S., the National Organ Transplant Act (1984) prohibited the knowing procurement or transplantation of organs from an HIV infected donor. In 2013, the HIV Organ Policy Equity Act (the HOPE Act) in the U.S. repealed this prohibition and authorized the Organ Procurement and Transplantation Network (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 U.S. are being developed by the National Institutes of Health.

High 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. The period from HIV exposure to the development of HIV antibodies is 22 days on average, but can be up to 6 months. HBV surface antigen (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. The window period for detection of HCV infection by ELISAs 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. For example, in 2007 in the USA, a previously uninfected 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 (two kidneys, liver and heart) were transplanted to four recipients. NAT of donor sera and post-transplant sera from all recipients were positive for HIV and HCV. 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. Based on this case, it was suggested that to reduce the risk for transmission of HIV through living-donor organ transplantation, transplant centers should screen living donors for HIV as close to the time of organ recovery and transplantation as possible, using sensitive tests for both chronic and acute infections, namely, antibody and NAT testing.

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 (Box 1). Living donor candidates with behaviors associated with an increased risk of acquiring HBV or HCV that were identified during evaluation should receive individualized counseling on specific strategies to prevent exposure to these viruses during the
time period prior to surgery. Recommendations regarding microbiological testing include:

- All potential organ donors (living or deceased) should be tested for antibodies to HIV (i.e., 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 (e.g., 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-HBc Ab 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 potential living donors should be tested for HIV, HBV and HCV as close as possible to the date of the organ recovery operation, but at least within the 28-day time period prior to surgery.

Whether retesting closer to the transplant (e.g., 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. A survey of live donor transplant programs in New York State in 2012 found that most responding centers had policies to re-test living donors within 14 days of the transplant procedures, and while rarely centers encountered repeat testing-associated delays, no cancellations occurred.

**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 post-transplant recipient care. Infection with EBV manifests as a spectrum of diseases/malignancies ranging from asymptomatic viremia through infectious mononucleosis to post-transplant lymphoproliferative disorder (PTLD). EBV disease and its associated PTLD is 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 US, 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 <0.2% and 0.6% respectively, for adult recipients. When the donor is EBV+ and the recipient is EBV-, particularly in children, clinical vigilance is required following transplantation to detect PTLD. Intensity of EBV viral load and immunosuppressive therapies influence the risk for PTLD.

**Cytomegalovirus**

Cytomegalovirus (CMV) 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 (PCR).\textsuperscript{222} The main clinical utility of CMV serology is stratification of a transplant recipient’s risk of CMV disease based on donor and recipient status.\textsuperscript{189, 190, 223}

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 the 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 practicable 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 Ab for risk stratification and guidance of appropriate surveillance and/or antiviral prophylaxis after transplantation.\textsuperscript{224}

**Syphilis**

Transmission of syphilis by organ transplantation has been documented.\textsuperscript{225} In the US, all assays currently FDA-cleared for detecting evidence of *T. pallidum* infection in organ and tissue donors are serologic assays.\textsuperscript{226} There are two types of serologic assays: non-treponemal 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 two after successful treatment of syphilis.\textsuperscript{226} 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 non-treponemal assay such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) test, which should be confirmed later with a treponemal immunoassay. A recent study showed 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 results in deceased and live organ donors.\textsuperscript{227}

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 testing, specimen collection and the time available to perform testing must be considered for choosing an appropriate donor screening assay.\textsuperscript{226} For living donors, the time constraint is reduced and thus the screening with non-treponemal assays with confirmation by treponemal assays is preferred if feasible.

Transmission of syphilis has been reported in the UK to two 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.\textsuperscript{225}
Donation from live persons with latent syphilis may be considered after treatment of the donor
candidate before donation (e.g., with penicillin), informed consent of the recipient, and
recipient monitoring after transplant.

**Tuberculosis (TB)**

The incidence of post-transplant TB varies substantially depending on the local
prevalence of MTB infection, which ranges from 1\% in Germany to nearly 14\% in India.\textsuperscript{184}
Studies in the US and Europe have estimated that 0.35–6.6\% of transplant recipients develop
TB (across organ and donor types), and that 4\% post-transplant TB cases are donor-derived.\textsuperscript{184,}
\textsuperscript{228}TB is one of the more common bacterial causes of donor-derived infection in the US.\textsuperscript{229}

Consensus-based recommendations for the diagnosis and management of TB in
transplant donors include:\textsuperscript{179, 184, 230}

- 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 >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 included history of untreated TB and 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 (AFB) smear and culture in potential kidney donors 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 tuberculosis
  infection are limited in sensitivity and have a relatively low predictive value for
  development of active MTB.\textsuperscript{231} The specificity of TST is related to the burden of MTB
  in that region or country, and IGRA has superior specificity in populations where use of
  Bacillus Calmette-Guérin (BCG) vaccination is common based on use of specific
  antigens absent in BCG strains
  - Immune testing of all donor candidates or selective testing based on risk profile
    are considered acceptable options
  - Asymptomatic persons without signs of active TB are considered to have latent
    TB infection (LTBI).
- Donation from persons with active TB is contraindicated. Risk of transmission from donors with previous appropriately treated active TB appears to decline with longer time from treatment. Donation may be considered with consideration of informed consent of the recipient and consideration of chemoprophylaxis under the guidance of an infectious disease specialist.

- Potential living donors with LTBI should be offered chemoprophylaxis according to local or national guidelines. Donation may be considered from persons with LTBI 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 treatment has been recommended. Chemoprophylaxis of recipients from donors with LTBI should be considering, especially if the donor did not complete chemoprophylaxis.230

A recent study in Korea, a country with an intermediate prevalence of tuberculosis, prospectively evaluated living donors using the TST and *Mycobacterium tuberculosis*-specific enzyme-linked immunosorbent spot (ELISPOT) IGRA.232 Of 205 living donors, 31% had a positive TST and 47% had a positive ELISPOT. Based on the high rate of suspected latent MTB infection detected by screening solid organ transplant donors using TST and ELISPOT in a country of intermediate burden of MTB, the authors recommended further study of the cost effectiveness of recipient chemoprophylaxis.232

**Urine Culture**

Urine should be sent for culture from all donor candidates at evaluation, and ideally repeated close to the time of donation (e.g., within the preceding 2 weeks). Acute symptomatic disease is a reason to postpone the donation event. 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 (e.g., assessment for cortical scarring). Any active bacterial or fungal infection in the donor should be treated and, ideally, resolved prior to transplantation.193 Antibiotic prophylaxis should be given to the recipient if resolution of infection is not confirmed before donation.

**Seasonal and geographically endemic infections**

A number of geographically endemic and seasonal diseases have been transmitted through organ donors including: *Strongyloides*, *Trypanosoma cruzi* (Chagas disease), West Nile virus (WNV), Histoplasmosis, Coccidiomycosis, Aspergillus, Toxoplasmosis, Malaria, Creutzfeldt–Jacob disease, human T-cell lymphotrophic virus (HTLV), and Schistosomiasis.178, 182, 183 Other viral, fungal, bacterial and parasitic pathogens recognized as sources of organ donor-derived infection transmissions are listed in Box 3. The donor 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 (Box 2). Live donation affords sufficient time for microbiological testing, donor treatment and deferral of transplantation until
resolution of infection. In many cases, organ donation if possible after treatment of the donor candidate before donation, informed consent of the recipient, recipient monitoring and possible prophylaxis after transplant (Table 4).

**Strongyloidiasis** typically occurs only in the setting of specific environmental exposures. Donor-derived hyperinfection with high associated mortality has been reported, including from kidney transplantation.\textsuperscript{233-235} Consensus-based recommendation of the 2013 American Society of Transplantation Infectious Diseases Community of Practice workgroup and the OPTN/UNOS Disease Transmission Advisory Committee (DTAC) and support screening in the following potential organ donors:\textsuperscript{176, 183}

- 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. Strongyloidiasis has occurred in most countries with the exception of Canada, Japan and Northern Europe.
- Persons with significant exposure to soil in Appalachia or the southeastern US, including walking barefoot.
- Persons with unexplained eosinophilia and travel to endemic area.
- Persons reporting a prior history of strongyloides infection.

Serology 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.\textsuperscript{183} Strongyloides IgG antibody testing (ELISA-based) is available in many reference labs.

Infected donors should be treated with a minimum of two doses of ivermectin prior to donation (200 mg/kg orally daily on 2 consecutive days)\textsuperscript{176, 183} 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. Following treatment, follow-up laboratory testing of the donor prior to donation for confirmation of cure has been deemed unnecessary, unless re-exposure has occurred.\textsuperscript{176, 183}

**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 American Society of Transplantation Infectious Diseases Community of Practice Workgroup, and OPTN/UNOS Disease Transmission Advisory Committee (DTAC) and support screening in the following potential organ donors: \textsuperscript{176, 181, 183}.

- 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 \textit{T. cruzi} infection status is positive or unknown
• Persons who have received a blood transfusion in endemic regions
• Persons reporting a prior history of Chagas disease

Reported outcomes of 32 transplant recipients who received organs from 14 T. cruzi seropositive donors in the US from 2001 to 2011 included 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 transplant recipients.\textsuperscript{236} Recommended monitoring post-transplant comprised regular testing by PCR, hemoculture, and serology. Thirteen recipients had no or incomplete monitoring; transmission was confirmed in five 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 PCR, hemoculture and serology; transmission was confirmed in 4 of 19 recipients with no cases of symptomatic disease. Based on such evidence, recent guidelines support consideration of kidney donation from infected donors on an individual basis with consent of the recipient.\textsuperscript{176, 181, 183} Recipients must be informed of the need for participation in close monitoring of therapeutic interventions in the event of infection, as the medications available for treatment are not FDA-approved and are generally only provided through specific protocols. Consideration of the recipient’s access to testing and monitoring is also imperative, as geographic concerns may impact the ability to follow the patient closely.

\textit{West Nile Virus (WNV)} is a flavivirus that is transmitted by mosquitoes in an enzootic cycle with birds. When testing is indicated, screening potential live donors by WNV NAT within 7–14 days of donation has been recommended.\textsuperscript{178, 180} The 2013 American Society of Transplantation Infectious Diseases Community of Practice workgroup recommended delaying donation for 28d when NAT screening is positive, followed by repeat NAT and IgM testing with the following management pathways based on the results:\textsuperscript{178}

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

\textbf{Comparisons to Prior Guidelines}

UNOS 2014 Policy for Live Donor Medical Evaluation requires similar screening tests as recommended in the current guideline: anti-CMV Ab, anti-EBV Ab, anti-HIV 1,2 Ag/Ab, HBsAg, anti-HBcAb, , anti-HCV Ab, and syphilis testing.\textsuperscript{25} Transplant centers are required to determine whether the donor has MTB exposure risk factors and to test accordingly. Centers are also required to develop protocols to determine who to screen for geographically endemic and seasonal infections such as strongyloides, \textit{Trypanosoma cruzi} and WNV.

The British Transplantation Society has also recommended testing for HBV, HCV, EBV, CMV and HIV as their level B1 recommendation (Quality of Evidence has been graded
as Moderate, “We recommend” is the strength of the recommendation) for donor screening.23

The Spanish Society of Nephrology (SEN) and Spanish Transplant Organization (ONT) recommendations for living-donor kidney transplantation 2010 included the following as routine tests in the donor evaluation: HIV [a], Hepatitis B: HBsAg [a], anti-HBcAb IgM/IgG [b], HBsAb, HBV DNA in plasma if anti-HbcAb+, Hepatitis C (ELISA and PCR) [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 recipient have to undergo treatment with positive results’.31

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 SEN and ONT guidelines were published in 2010, new research published above supports revision of some categories of [a] ‘Donation is contraindicated with positive results.’

**Research Recommendations**

- Define the incidence of disease transmission through improved monitoring and reporting. Determining the relative importance of specific pathogens and risk mitigation strategies requires collection of global data.

- Optimize and standardize methods of microbiological assays for donor screening and diagnosis.

- Results of planned US National Institutes of Health (NIH) studies on transplantation from HIV positive donors to HIV positive recipients should provide guidance on outcomes and appropriate consideration of such transplants in clinical practice.

- Similar research studies should be designed to determine whether transplantation from HCV positive donors into HCV positive recipients can be performed with acceptable safety and outcomes for the donor and recipient in the era of new antiviral medications.
CHAPTER 12: CANCER SCREENING TO REDUCE RISKS OF TRANSMISSION FROM DONORS TO RECIPIENTS AND TO REDUCE RISKS OF POST-DONATION MALIGNANCY-RELATED COMPLICATIONS

12.1: Donor candidates should undergo cancer screening consistent with clinical practice guidelines for the country or region where donation will occur, as appropriate for age, sex and risk profile. Transplant centers should ensure that screening is current according to guideline criteria at the time of donation. (Not Graded)

12.2: In general, candidates with active malignancy should be excluded from live kidney donation. In some cases of active malignancy with low transmission risk, a clear management plan, and minimal donor health implications, live kidney donation may be considered on a case-by-case basis. Persons with small (T1a) renal cell carcinoma curable by nephrectomy may be considered as living kidney donors on a case-by-case basis, with informed consent of the donor candidate and their intended recipient. (Not Graded)

12.3: Donor candidates with a past history of cancer with “intermediate” (1-10%) or “higher” risk of transmission or recurrence should be excluded from live kidney donation. Live kidney donation from donor candidates with a history of malignancies with a “low” risk (<1%) of transmission or recurrence may be considered on a case-by-case basis with informed consent of the donor candidate and their intended recipient. (Not Graded)

RATIONALE

The goals of malignancy screening within the donor candidate evaluation are two-fold. First, it is necessary to identify cancers that require management to protect the health of the donor candidate. Reduced renal function may compromise long-term health outcomes in individuals requiring cancer treatments with nephrotoxic or cardiovascular side effects (e.g., some chemotherapies or radiation treatments). Potential psychosocial stresses of live 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 Information

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. Some of these recommendations account for a family
history of cancer (e.g., breast, colon) and other risk factors. 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.

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

**Recurrence Risk after Treated Cancer in the General Population**

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.

**Donor-Derived Malignancy Transmission Data**

Cases of malignancy transmission from deceased / 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 to December 2012. 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 potential living donor. 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 site for decades and then reactivate upon exposure to immunosuppression, and transmission can be lethal. 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. 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, 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 potential living donors
with a prior history of skin cancer resection should be reviewed to ensure that the cancer was
not a melanoma before approving donation.

In 2011, United Network of Organ Sharing (UNOS) Disease Transmission Advisory
Committee (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 histories;\textsuperscript{24} this is recently reviewed in Kirchner et al.\textsuperscript{178}
Classification was based on review of cancer registry reports, published literature, and data
submitted to the Organ Procurement and Transplantation Network (OPTN). This article did
not differentiate between cancers 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 0–0.1% transmission events per organ
  transplanted from donors with the specific tumor, and includes non-melanoma skin
  cancers, non-invasive carcinoma of the bladder (for non-renal 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 >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
  ventriculopertitoneal or ventriculoarterial shunt, metastasis or high grade (III/IV)
  histology, metastatic carcinoma, sarcoma, lung cancer Stage I-IV, and renal cell
carcinoma >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 organ from donors with “intermediate risk” malignancies could be considered for transplantation with careful informed consent for recipients who face substantial mortality without transplantation.

Considerations Related to Renal Cell Carcinoma

The development of kidney cancer in a patient with a single kidney is very concerning. The age-stratified lifetime cumulative incidence of kidney cancer is low (assuming a life expectancy of 80 years):

Cases of back table excision of small renal cell carcinomas after donor nephrectomy, followed by use of the kidney for transplantation have been reported.\textsuperscript{245-248} 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 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, chances of possible discard without transplantation after nephrectomy, and donor and recipient understanding and acceptance of these risks.

Prior Living Donor Guidelines

Prior guidelines and policies for the evaluation and care of living donors recommend careful history taking, clinical examination, and investigation to exclude occult malignancy prior to donation, especially in those older than age 50 years or with certain risk factors including family history.\textsuperscript{15, 23, 25} The Amsterdam Forum recognized that risks of specific cancers may vary across countries.\textsuperscript{15} “Active malignancy” is commonly cited as a contraindication to live kidney donation,\textsuperscript{15, 23, 25} although exceptions were noted for low-grade non-melanoma skin cancer.\textsuperscript{15}

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.\textsuperscript{15, 23, 25} Breast cancer is included, although the European Association of Urology (EAU) qualifies the restriction to “advanced” disease.\textsuperscript{32} Renal cell carcinoma was included as a contraindication to live donation in prior guidelines.\textsuperscript{15, 23, 25} 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 (e.g., colon cancer (Dukes A, >5 years ago), non-melanoma skin cancer, or carcinoma \textit{in situ} of the cervix).\textsuperscript{15, 23} The Amsterdam Forum further qualified that prior treatment of the malignancy does not
decrease renal reserve, place the donor at increased risk for ESRD, or increase the operative risk of nephrectomy as criteria for approving donation in a person with prior cancer.\textsuperscript{15}
CHAPTER 13: EVALUATION OF GENETIC RENAL DISEASE IN KIDNEY DONOR CANDIDATES

Genetic kidney diseases are an important consideration when screening potential living kidney donors. Examples of kidney diseases with some genetic basis include autosomal dominant polycystic kidney disease (ADPKD), APOL1-related kidney disease, atypical hemolytic uremic syndrome (aHUS), Alport syndrome, Fabry’s disease, familial focal segmental glomerulosclerosis, and hereditary interstitial kidney diseases. A family history of a genetic kidney disease with an autosomal recessive mode of inheritance (such as cystinosis or some forms of familial focal segmental glomerulosclerosis) often does not contraindicate a person from becoming a living kidney donor.

Evaluation

13.1: All donor candidates should be asked detailed questions about a genetic (family) history of kidney disease (e.g., type of disease, time of onset). (Not Graded)

13.2: If the intended recipient is genetically related to donor candidate, information about the recipient’s cause of kidney failure (with permission of the recipient) should be shared and reviewed carefully by the donor evaluation team. (Not Graded)

Acceptance

13.3: The presence of most genetic kidney diseases in the donor candidate should preclude donation. (Not Graded)

13.4: After a normal evaluation, it may be uncertain whether a donor candidate has a genetic predisposition to kidney disease that could manifest later in life. In such a setting, any decision to proceed with donation should be individualized after a full discussion with the donor candidate, and the potential outcomes of donation if the disease is present. (Not Graded)

Counselling

13.5: All donor candidates must provide informed consent to have genetic testing if it is indicated as part of their evaluation process. This includes understanding the impact of receiving a diagnosis of a genetic renal disease on their insurability, should this arise in the evaluation process. (Not Graded)

13.6: All candidates who wish to donate a kidney to a relative with a genetic kidney disease should be counseled that this will preclude them from donating a kidney in the future to other relatives (e.g., children) who may have the same genetic kidney disease. (Not Graded)
Kidney Diseases with a Genetic Basis

13.7: The safety of proceeding with donation when a candidate has a first degree relative with genetic kidney disease should be carefully assessed on a case-by-case basis. *(Not Graded)*

For Specific Genetic Kidney Diseases

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

13.8: A diagnosis of ADPKD precludes donation. *(Not Graded)*

13.9: An individual with a first degree relative with ADPKD can proceed with kidney donation when they meet age-specific imaging criteria which reliably rule out the presence of ADPKD. Current criteria include the following: *(Not Graded)*

- ≥40 years of age, with fewer than two kidney cysts seen on a conventional ultrasound when one counts the number of cysts in both kidneys combined.
- age 30 to 39, with no cysts seen in either kidney on a conventional ultrasound.
- age 16 to 40, with fewer than five cysts seen on non-contrast magnetic resonance imaging, when one counts the number of cysts in both kidneys combined (and provided all cysts are less than 1.0 cm in diameter).

APOL1

13.10: If a donor candidate is of African ancestry and has a first degree relative with non-diabetic kidney disease, consideration should be given to genotype for apolipoprotein L1 (*ApoL1*) risk variants. Evidence of 2 APOL1 allele risk variants increases an individual’s lifetime chance of kidney failure even in the absence of donation. The implications of testing results should be included in the donor candidate’s counseling and informed consent. *(Not Graded)*

RATIONALE

Living donors who are biologically related versus unrelated to a recipient have a higher incidence of ESRD. In a large study from the United States, the 15-year cumulative incidence of ESRD was 0.34% versus 0.15%.10 Evaluation teams are understandably concerned about donor candidates with a family history of a hereditary type of kidney disease. Unfortunately, far too often the donor evaluation team does not have a clear cause of kidney failure in the intended recipient, and assume the recipient does not have a genetic cause of kidney disease.

Some donor candidates have a known family history of genetic kidney disease. Some of these diseases may first manifest later in life and are not identified when donor evaluation testing occurs at a younger age. An individual with a later onset genetic predisposition to kidney disease might particularly have a high lifetime chance of kidney failure were they to donate a kidney in earlier life; the presence of genetic predisposition and nephrectomy together
may amplify the incidence of long-term adverse kidney outcomes in a donor. It would be unfortunate to remove a kidney for donation from such an individual. For this reason, it is important for transplant centers to have a defensible approach for ruling out inherited kidney disease when there is a positive family history of kidney failure.

Many of the standard tests done as part of the donor evaluation process should be interpreted with special consideration in the setting of a known 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.

The genetic inheritance patterns and implications of some kidney diseases have been traditionally well appreciated. With advances in genetic medicine the implications of new risk alleles such as \textit{APOL1} are being better understood. However, testing for other genetic conditions is currently imperfect or evolving. A challenge in the evaluation is the degree of certainty with which a transplant team can be confident that a donor candidate with a family history of kidney disease does not have a genetic kidney disease themselves. The presence of uncertainty often results in a discussion of the issues with relevant stakeholders, with a consensus decision as to whether to proceed with donation or not.

\textbf{ADPKD}. Recent studies and a controversy conference summarize diagnostic criteria for ADPKD.\textsuperscript{249,250} Simple cysts occur more frequently with increasing age in the general population. Age-dependent imaging criteria for diagnosis and disease exclusion have been established for at-risk adults with unknown ADPKD gene type (\textit{PKD1} or \textit{PKD2}). Conventional ultrasound is suboptimal to detect disease in a younger donor candidate with a first degree relative with ADPKD. In this setting, in patients younger than the age of 40 years, the finding of fewer than five renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion (where all the cysts are also less than 1.0 cm in length). A computed tomography (CT) angiogram of the kidneys is frequently done as part of the donor evaluation to assess the renal vasculature, and may be expected to have a comparable performance to MRI, although this has not been proven.

When imaging fails to rule out the presence of ADPKD in a donor candidate with a first-degree relative with ADPKD, DNA testing can sometimes help diagnose or exclude the condition. Linkage-based genetic diagnoses of ADPKD using polymorphic markers flanking the two disease genes is now rarely performed. Rather, direct mutation screening (by Sanger or next generation sequencing) is the current method of choice for molecular diagnosis of ADPKD.\textsuperscript{251,252} Up to 15\% of patients with suspected ADPKD have a negative comprehensive mutation screen. The first-degree relative with ADPKD undergoes \textit{PKD1} and \textit{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 an absent family history 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.\textsuperscript{249}

**APOL1 genotype.** The use of *APOL1* genotyping in the donor evaluation is currently grounded primarily in evidence extrapolated from non-donor populations. Recent literature supports that at least a portion of renal failure previously attributed to hypertensive nephrosclerosis in persons of African descent may be genetically mediated by coding variants in the *APOL1* gene. Having at least one *APOL1* allele risk variant confers resistance to lethal *Trypanosoma brucei* infections, and these variants are observed in populations of African descent but essentially absent among Caucasians. 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 variant alleles.\textsuperscript{253} Carrying 2 *APOL1* risk variant alleles has been associated with focal segmental glomerulosclerosis and HIV-associated nephropathy histopathologies, proteinuria, reduced GFR, younger age at dialysis and more rapid progression of kidney disease among African Americans in the general population.\textsuperscript{156-159} The presence of 2 *APOL1* risk alleles in deceased donors also correlates with nearly 4-times the RR of allograft loss compared with 0 or 1 risk alleles.\textsuperscript{254} A case report of possible *APOL1*-mediated adverse donor and recipient outcomes after twin-to-twin live kidney donation among young men of Afro-Caribbean descent was recently described.\textsuperscript{255} Broad use of *APOL1* genotyping within evaluation protocols has been advocated by individual experts but not others.\textsuperscript{253} As a new test, the utility of *APOL1* testing not been described in prior living donor guidelines. The impact of *APOL1* screening on donor exclusion rates and outcomes are yet to be defined.

**Alport syndrome.** Alport syndrome is a genetic disease which alters collagen biosynthesis. Collagen is an important structural component of the basement membranes in the kidney, inner ear and eye. Alport syndrome is primarily an X-linked disorder (~80\% of families), but can also be inherited in an autosomal recessive (~15\% of families) and autosomal dominant fashion (very rare).\textsuperscript{256, 257} Most women who are heterozygotes for X-linked Alport syndrome exhibit hematuria (95\% of women in one European cohort). Overall, the severity of their nephropathy is variable and most will not develop kidney failure in their lifetime.\textsuperscript{257} There is little information on the outcomes of such heterozygotes who proceed with kidney donation (after confirming an absence of proteinuria, hypertension, low GFR and other manifestations of the disease such as sensorineural hearing loss). Gross et al. described 6 mothers with Alport syndrome (across several European centres) who donated kidneys to their children with the disease.\textsuperscript{258} 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; renal function declined 25–60\% in four of the six donors over the observed 2–14 years after nephrectomy, although no donor’s creatinine clearance was <40 ml/min at the time of follow-up evaluation; four of the six developed microalbuminuria or proteinuria, and hypertension was diagnosed in four of six donors. Not dismissing a mother’s desire to care for her child or the possible guilt associated with passing on a genetic kidney disease,\textsuperscript{259} if donation is entertained it should only be done so in older women who have time to manifest any kidney disease, and after a careful deliberation and consideration of all other alternatives (including other living donors). In the evaluation of male potential living kidney donors, those > 20 years of age without hematuria are very unlikely to have X-linked Alport syndrome.
**Fabry disease.** 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. Most affected males require renal replacement therapy by the time they are 35–45 years of age. Heterozygote 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 heterozygote females develop kidney failure in their lifetime. There is very little information on the outcomes of heterozygotes who proceeded with kidney donation (see case report 260). As with heterozygotes with Alport syndrome, if donation is entertained it should only be done so in older women who have time to manifest any kidney disease, and after a careful deliberation and consideration of all other alternatives.

**Familial focal segmental glomerulosclerosis.** In recent years, many inheritable genetic forms of focal segmental glomerulosclerosis (FSGS) have been described, caused by mutations in proteins that are important for podocyte function.261 There are case reports of individuals who have developed FSGS, proteinuria and kidney failure after donating a kidney to a sibling with kidney failure with FSGS.262 The role of genetic testing in relatives with a family history of kidney failure from FSGS or steroid resistant nephrotic syndrome is yet to be determined.

**Atypical hemolytic uremic syndrome.** There are case reports of individuals who donated a kidney to a relative with atypical hemolytic uremic syndrome (aHUS) with kidney failure, where the donor developed HUS in the year following donation.263 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 ruling out the presence of HUS 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 recipient with aHUS. Others suggest determining whether a donor candidate shares a genetic susceptibility factor to HUS to determine whether or not they may be suitable donor.264

**Hereditary interstitial kidney disease.** Autosomal dominant interstitial kidney disease is a rare and heterogeneous genetic disorder. Individual families may have a large number of affected individuals. Mutations in at least four 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-1β.265,266 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. Potential living donors can be offered target mutation screening to assess whether the disease is absent, if they are biologically related to a patient with kidney failure who has evidence of the pathogenic mutation.
CHAPTER 14: PREGNANCY AND LIVING KIDNEY DONATION

Evaluation

14.1: All women should be asked about their prior obstetrical history, including a prior history and details of any hypertensive disorder of pregnancy or gestational diabetes. *(Not Graded)*

14.2: All women should be asked about their future childbearing interest and potential, as this information has implications for counselling and the need to rule out pregnancy at the time of donor nephrectomy. *(Not Graded)*

14.3: Abdominal computed tomography (with iodinated contrast) and nuclear medicine glomerular filtration rate (GFR) testing in women who are pregnant, or may be pregnant, should be guided by current local radiology guidelines. *(Not Graded)*

Selection

14.4: A transplant center should not preclude a motivated, well-informed donor candidate from donation simply on the basis of her desire to have children after donation. *(Not Graded)*

14.5: A donor candidate with a prior history of hypertension during pregnancy (which includes preeclampsia) may be acceptable for donation, provided a transplant center after reviewing the nature of this hypertension and her other characteristics, believe the candidate’s post-donation long-term risk of ESRD is low (and below their acceptable threshold of risk). *(Not Graded)*

14.6: Any decision to proceed with donor nephrectomy in the year after delivery requires consideration of the psychological needs of the new mother and baby, and supports available during the time of transplantation. A decision to proceed with donation in this time period also requires anesthesia and analgesia planning for nursing mothers. *(Not Graded)*

Counseling

14.7: A woman should never donate during gestation. A woman with childbearing potential should be told about the need for contraception or abstinence from the time she is approved for donation, to the time she has recovered after her nephrectomy. The absence of pregnancy should be confirmed by a β-hCG quantitative pregnancy test immediately before donation. *(Not Graded)*

14.8: Women who are capable of having children after donation should be counselled about the possible impact donation may have on future pregnancies. This includes the possibility of a greater likelihood of being diagnosed with gestational hypertension or preeclampsia. *(Not Graded)*
RATIONALE

Childbearing potential is determined by a woman’s age, history of menopause, and history of prior sterilization.

When evaluating donor candidates, knowledge about a prior history of a hypertensive disorder during pregnancy and its severity is important, as when such a history is present (vs. when it is absent) it is associated with a higher risk of ESRD.\textsuperscript{267} One meta-analysis\textsuperscript{268} concluded that women were at greater risk of microalbuminuria after a preeclamptic pregnancy compared with a normal pregnancy (5 to 10 year incidence of 31\% vs. 7\%). This meta-analysis was, however, restricted by inclusion of small studies of variable quality and most of the women either had severe preeclampsia or underlying disease such as diabetes mellitus. A population-based study from Norway suggested women were at greater risk of ESRD 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\%).\textsuperscript{269} The risk remained evident after exclusion of women with known kidney disease, diabetes or hypertension, before pregnancy. A Taiwanese study also described a greater risk of ESRD in pregnant women who developed a hypertensive disorder during pregnancy compared to a normal pregnancy (approximate 12-year cumulative incidence after pregnancy of 0.6\% vs. < 0.1\%).\textsuperscript{270} In general, characteristics associated with a lower long-term risk of ESRD after a history of hypertension in pregnancy include: i) a mild (vs. severe) hypertensive event during pregnancy, ii) last hypertension event in pregnancy that was more than 10 years ago, iii) no evidence of hypertension, microalbuminuria or low normal GFR in the current donor evaluation, iv) no wish for future pregnancies.

Performing a computed tomography (with iodinated contrast) or nuclear medicine GFR test in women with childbearing potential should be guided by local radiology guidelines. For example, some guidelines suggest such tests should be avoided in a woman is pregnant, but if pregnancy cannot be excluded and a patient’s menstrual period is not overdue one may proceed with testing.\textsuperscript{271}

Approximately 1\% of all patients develop postoperative venous thromboembolic disease after donor nephrectomy. Local guidelines should guide management decisions about the use of estrogen-based oral contraceptive medications prior to surgery.

We agree that well-informed young women should be supported by transplant centers in their donation decisions. A 2015 American Consensus Conference concluded that information on pregnancy risk needs to be shared in the informed-consent process for donor candidates with reproductive potential.\textsuperscript{272} Two retrospective cohort studies, one from the US 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 (Table 5).\textsuperscript{273, 274} Another recent retrospective cohort study from Canada demonstrated gestational hypertension or preeclampsia was more likely to be diagnosed in kidney donors than matched non-donors with similar indicators of baseline health (11\% vs. 5\%).\textsuperscript{275} The two groups did not differ significantly with respect to other maternal or fetal outcomes (Caesarean section, postpartum hemorrhage, preterm birth with gestation < 37
weeks, low birth weight < 2500 g), and there were no maternal deaths, stillbirths, or neonatal deaths in either group (however the wide confidence intervals mean that a clinically important risk among donors was not ruled out). The donor characteristics and maternal and fetal outcomes in post-donation pregnancies from the three studies (US, Norway and Canada) are presented in the Table 5. Most women in these cohorts were of white race.

Table 5. Donor characteristics and maternal and fetal outcomes in post-donation pregnancies from three studies [Norway, Minnesota (United States) and Ontario (Canada)] modified from Garg AX et al.275

<table>
<thead>
<tr>
<th>Characteristic or Outcome</th>
<th>Norway Study</th>
<th>Minnesota Study</th>
<th>Ontario Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>69</td>
<td>239</td>
<td>85</td>
</tr>
<tr>
<td>Family history of kidney failure — %</td>
<td>NR</td>
<td>96</td>
<td>65</td>
</tr>
<tr>
<td>Mean glomerular filtration rate before donation — ml/min/1.73 m²</td>
<td>NR</td>
<td>91</td>
<td>114</td>
</tr>
<tr>
<td>White race — %</td>
<td>98</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>No. of pregnancies after donation</td>
<td>206</td>
<td>490</td>
<td>131</td>
</tr>
<tr>
<td>Mean age at time of donation — yr</td>
<td>27</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Mean age at time of pregnancy — yr</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>One or more pregnancies before donation — no. (%)</td>
<td>NR</td>
<td>98 (41)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Mean or median interval between donation and subsequent pregnancy — yr</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes after donation</th>
<th>Norway Study</th>
<th>Minnesota Study</th>
<th>Ontario Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational hypertension or preeclampsia</td>
<td>9/106 (8)</td>
<td>55/490 (11)</td>
<td>15/131 (11)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>3/106 (3)</td>
<td>28/490 (6)</td>
<td>7/131 (5)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>6/106 (6)</td>
<td>27/490 (6)</td>
<td>8/131 (6)</td>
</tr>
<tr>
<td>Death</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Fetal — no./total no. (% of pregnancies)</td>
<td>19/106 (9)</td>
<td>35/490 (7)</td>
<td>10/131 (8)</td>
</tr>
<tr>
<td>Birth weight &lt;2500 g</td>
<td>9/106 (8)</td>
<td>NR</td>
<td>8/131 (6)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3/106 (3)</td>
<td>2/490 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal death &lt;28 days after birth</td>
<td>0</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>
CHAPTER 15: PSYCHOSOCIAL EVALUATION
AND ACCEPTANCE CRITERIA

The psychosocial evaluation of a living kidney donor candidate serves many functions. It helps determine if a candidate is psychologically suitable for donation (for example, assessing if the donor candidate’s motivations are appropriate and confirming the absence of any psychopathology); 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 a given donor candidate in having a positive psychosocial experience throughout the evaluation and donation processes.

Evaluation and Pre-donation Counseling

15.1: All donor candidates should have a face-to-face psychosocial evaluation and counseling session with a trained health professional (e.g., social worker, psychologist, psychiatrist or other physician, or nurse) experienced in the psychosocial dimensions of living kidney donation and transplantation. The psychosocial evaluation should ideally be performed with the donor candidate in the absence of the potential recipient or other family members to minimize risks of conflict of interest or external pressures. (Not Graded)

15.2: When feasible, the psychosocial evaluation of a donor candidate should be performed by a health professional not involved in the care of the intended recipient. (Not Graded)

15.3: The following elements should be reviewed with the donor candidate during the psychosocial evaluation: (Not Graded)

- The process and requirements of informed consent (see Chapter 2 of this guideline for complete details)
- Their motivation for donation
- Their expectations of the outcomes of donation, including impacts on their future relationship with the recipient. The donor can be counseled if these expectations are unrealistic.
- A history of current or past psychiatric disorders
- A history of current or past substance abuse or dependence (e.g., use of alcohol, illicit drugs or prescription drugs)
- Their support system, including available family, friend and workplace supports, and coping strategies (including available programs) to minimize any negative impacts from donation
- Their preparation for the possible medical impacts of donation, and any expected impact on their activities following donation.
• Their preparation for the possible emotional impacts of donation (both positive and negative). Donor candidates can be told that most prior donors have experienced good psychosocial outcomes.
• Their preparation for the possible financial impacts of donation, including potential impacts on employment status and wages, expenses for medical care, travel and dependent care, and any effects on insurability or rates.
• Their 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.

15.4: Non-directed living kidney donors (i.e., persons donating to a list or pool, rather than to an identified recipient) should be evaluated using the same criteria as living kidney donors with an identified recipient. (Not Graded)

Psychosocial Acceptance Criteria for Donation

15.5: The presence of any of the following conditions in a donor candidate either precludes donation, or prevents further evaluation until the issue is resolved. (Not Graded)

• A wish not to donate or marked ambivalence about donating
• Evidence of, or high suspicion of, undue coercive pressure
• Evidence of, or high suspicion of, unreasonable secondary gain (such as an unregulated financial transaction)
• A failure to meet the requirements of informed consent (for details see Chapter 2 of this guideline). This includes the donor candidate, who despite counseling, continues to have unrealistic expectations about the donation experience or potential outcomes.
• Diagnosable psychiatric conditions which can be treated to improve the donor candidate’s pre-donation mental fitness and chance of a good post-donation outcome
• Active substance abuse or dependence that affects decision-making or puts the donor candidate at a level of post-donation risk that is higher than acceptable to the transplant program
• A psychosocial profile which puts the donor candidate at a level of post-donation risk that exceeds a transplant center’s acceptable threshold. Such a profile may include active substance abuse or dependence, or the absence of needed psychosocial or financial support.

Follow-up Support

15.6: The transplant program should assist a donor candidate or prior donor in receiving needed psychosocial support or psychiatric help. (Not Graded)
RATIONALE

**Overview of prior guidelines:** A recent systematic review of living kidney and liver donor candidates summarized 34 publications (guidelines, consensus statements and transplant center 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). The authors concluded that, at present, there is no consensus nor strong evidence or concrete guidance on what to screen for, how to handle identified psychosocial problems, and how to perform the psychosocial screening. These findings largely confirmed that there is a large practice variability in regard to psychosocial evaluations. The authors concluded there is limited high quality evidence, and concurred with prior systematic reviews, that most recommendations in prior publications are based on groups of expert opinions (via consensus conference) and individual transplant center experiences. The evidence review performed to support this guideline included assessment of evidence related to psychosocial outcomes after donation. However, given that current evidence is limited and generally low quality, the recommendations regarding psychosocial evaluation and acceptance criteria in this KDIGO guideline are also primarily based on expert opinion.

**Should all donors have a psychosocial evaluation?** Our recommendations are consistent with several prior guidelines and regulations in some countries, which indicate a psychosocial assessment is a necessary part of the evaluation of each donor candidate (see Summary of LKD Guidelines # 30).

**In which setting should the evaluation be performed?** We believe the main psychosocial be conducted as a face-to-face interview, as has also been recommended in several prior reports. We suggest third parties not be present during at least a portion of the interview, to maintain confidentiality and minimize the effect of any external influences on the donor candidate’s responses. This suggestion is consistent with some prior reports. 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, so as to promote reliability of the information reported and to provide information about what supports the donor candidate will need during the donation and recovery periods.

**Who should perform the psychosocial evaluation?** Our recommendations are similar to many prior guidelines and national policies which recommend performance of the psychosocial evaluation by various healthcare professionals (e.g. psychiatrist, psychologist, clinical social worker, or a psychiatric nurse) who meet qualifications of appropriate knowledge and skill in mental health and the psychology of transplantation. As for the medical evaluation, we agree with prior recommendations that the psychosocial evaluation be performed by an individual who is not involved in the care of the intended recipient (so as to reduce any actual or perceived conflict of interest in evaluating the donor candidate). (See Summary of LKD Guidelines # 30).
**What psychosocial criteria preclude donation?** In our recommendations, we describe psychosocial elements that should be reviewed with the donor candidate and the psychosocial criteria that either preclude donation, or prevent further evaluation of the donor candidate until the issue is resolved. We recommend against donation when there is evidence of, or expectation of, unreasonable secondary gain, and the Declaration of Istanbul takes measures to protect individuals from the (unregulated) sale of organs.277 At least 18 prior reports have described relative and absolute psychosocial contraindications to donation (summarized elsewhere 276. Prior reported contraindications include high suspicion of secondary gain, undue coercive pressure to donate, current un- or undertreated diagnosable psychiatric disorders which affect the decision-making process (until treated improve the donor candidate’s pre-donation mental fitness and chance of a good post-donation outcome), active substance abuse or dependence that affects decision-making process or medical risk profile, inability to provide informed consent, unresolved ambivalence, or the presence of unrealistic expectations from the donation process despite counseling.276 Some prior guidelines state that the presence of risk factors for poor psychosocial outcomes after donation does not necessarily exclude donation, but that the goal of the evaluation is to identify areas for additional support or therapeutic interventions to optimize outcomes.276

**What should donor candidates be told about their likely psychosocial outcomes after donation?** The psychosocial evaluation provides an opportunity to share with a donor candidate what emotions they might experience after donation, and the anticipated short- and long-term psychosocial outcomes after donation.

Two recent systematic reviews summarize qualitative data about donor experiences after donation.278, 279 Kidney donation has a profound and multifaceted impact on the lives of many donors and influences their identity, roles and relationships. Donors experienced increased self-esteem, empowerment, and community awareness, but some also described a lack of emotional support.

In general, donors demonstrate a good quality of life and have a low rate of donation regret. That said, live donation is not without psychosocial risk, and some donors have experienced psychosocial difficulties after donation (e.g., depression, anxiety, stress, worries about health), and such problems have impacted their function and capability to return to work.

A single study was identified by the evidence review team that reported psychosocial outcomes in a group of donors compared to healthy non-donors, and the methodological quality was graded as very low (Evidence Report Table 8).280 In the reviewed multicenter study, average values of three health-related quality of life scores among donors (a median of 6 years after donation) were similar to a group of non-donors and population norms. There was also no significant difference between the two groups in marital status, mental health visits and psychotropic medication use.

A recent report of 2455 living donors from three large US centers (93% white race, 72% biologically related to recipient) found that health-related quality of life scores in living donors in the decades following donation were similar or better than the US population.281 Another report of 4650 privately insured living kidney donors in the US described lower rates
of recorded depression diagnoses after donation compared to rates among age- and sex-matched insurance beneficiaries. A systematic review published in 2006 summarized 51 studies totaling 5139 donors who were assessed on average 4 years after donation. 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 non-recipient 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.

Donor candidates can be informed that some people do experience psychosocial difficulties after donation (e.g., 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, and 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).

Which pre-donation characteristics are associated with a greater chance of poor psychosocial outcomes after donation? The evidence review performed to support this guideline identified two studies examining whether the association between donation (donor vs. healthy non-donor) and long-term psychological outcomes were modified by a person’s baseline characteristics. The quality of this evidence was graded as very low. In one study the association between donation (donor vs. non-donor) and long-term mental quality of life score was not modified by a person’s age. In the other study the cumulative incidence of recorded depression diagnoses was lower in donors compared to matched insurance beneficiaries, among both men and in women.

The evidence review team summarized the results of several studies where donors with a characteristic were compared to donors without the characteristic, to see if the two groups differed on the chance of a poor psychological 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 D5-D9, D11, D12, D18 and Tables 9, 10, 12, 14, 15, and 20).

In some studies, pre-donation characteristics that were associated with a lower chance of poor psychosocial outcomes included a lack of residual ambivalence about donation (i.e., no lingering hesitation or uncertainty), more education, an absence of pre-donation psychiatric diagnoses, an absence of feeling morally obligated to donate, more social support, lower pre-donation expectations of health consequences after donation, less financial burden, and the feeling of having received adequate attention from the transplant team.

What should donors be told about how donation may impact them financially? Potential and actual living kidney donors incur personal direct and indirect expenses as part of the evaluation
and donation procedure, even in countries where the donor’s medical expenses are paid by the recipient’s insurance or the healthcare system. Major costs include transportation, accommodation, child care, lost income (or vacation time) from missed work. 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. The expenses incurred during the pre-donation evaluation are also described in another recent study from the United States. These findings have led to recommendations that potential living donors receive counseling about financial costs prior to donation, and have fostered governmental and other programs in multiple countries to reimburse donors for their legitimate expenses and attempt to maintain financial neutrality. However, there are limitations to many current cost mitigation program. In the US, the National Living Donor Assistance Center (NLDAC) (via a Health Resources and Services Administration grant) offers grants to offset travel costs for living donors and their supports, but reimbursement eligibility is means tested and is based on the incomes of both living donor and recipient; further, non-directed donors have limited access because they cannot provide recipient income information. In the US, some states have enacted legislation to offer tax deductions or credits, or other benefits, to living organ donors. These programs vary state by state, are underused, and have not been studied with regard to impacts on financial burdens of donation. Donor candidates should receive education on how to access available financial supports as well as the limitations of available resources.

Several studies have considered whether kidney donation affects one’s ability to obtain life, disability and health insurance. These issues are country-specific, and should be considered in donor candidate counseling and support.

How do we support donors when the recipient or donor outcome is poor? In about 5% of living kidney donor transplants the recipient or their graft does not survive the first year. Understandably, poor recipient outcomes can be source of high stress to the donor, and the transplant program should provide post-donation psychosocial support at such times. In some studies, but not others, poor recipient outcomes has been associated with poor psychological outcomes in donors. In one study, most of the adverse recipient events were beyond the first year post-transplant. Most donors will not experience poor short- or long-term medical outcomes after donation, but for those who do the transplant program should help and provide psychosocial support. The responsibility to provide psychological support to donors when outcomes are poor is also described in prior guidelines. The Declaration of Istanbul says that all donors should be offered psychosocial services as a standard component of follow-up, and another guideline recommends follow-up of the psychosocial impact of living kidney donation for every living donor during the first year after donation. (See Summary of LKD Guidelines #33) Incomplete or inconsistent followup after the early post-donation 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 followup information included psychosocial and socioeconomic outcomes. The national Swiss Living Donor Health Registry (SOL-DHR) follows donors lifelong and includes an Eight-Item Short-Form (SF-8) and social-status questionnaire.
Should the methods of evaluation and criteria for donor candidate acceptance criteria differ between directed and non-directed donor candidates? Practice patterns related to the psychological evaluation of non-directed donors vary considerably worldwide.\textsuperscript{307-309} Our opinion is that candidacy criteria should be similar whether an individual is being assessed for directed or non-directed donation, recognizing that some elements of the informed consent may vary (see Chapter 2 for a description of some unique features in non-directed donation, including how the intended recipient is selected, time frames for donation, travel requirements and opportunities or prohibitions about contact with the recipient after the transplant).

Research Recommendations

- RCTs are needed to test evaluation approaches and interventions to minimize the risk of post-donation poor psychological outcomes. For example, in a recent randomized trial of 113 potential kidney donors with some evidence of residual ambivalence to donation, it is suggested that motivational interviews (versus additional health education or standard care) reduced ambivalence to donation, anxiety symptoms and unexpected family-related problems after donation, and reduced the risk of negative physical symptoms.\textsuperscript{285}

- The optimal components of the psychosocial interview should be better defined. For example, there are ongoing efforts to help standardize the psychosocial evaluation through the development of semi-structured evaluation tools.\textsuperscript{310} Duerinckz N et al., on behalf of the Ethical Legal Psychological Aspects of Transplantation (ELPAT) Organization, summarized surveys or tools used for psychometric testing in the donor candidate evaluation from prior guidelines, consensus statements and transplant center protocols such as mood questionnaires, personality interviews and drug abuse screening.\textsuperscript{276} The type, number and content of tools described in prior guidelines were variable. The same group has also recently provided a conceptual framework for the key elements in the psychosocial evaluation of living kidney donor candidates.\textsuperscript{311} This includes an assessment of: i) motivation (e.g., coercion, ambivalence), ii) the presence of psychopathology (e.g., cognitive disturbance, mood or anxiety disorder), iii) available social resources (e.g., social support, workplace support), and iv) information disclosure, understanding and risk processing (e.g., elements of informed consent). Further study should better define which components of the psychosocial interview should be structured to cover relevant material, compared to open ended to help meet the unique needs and questions of a given donor candidate.
CHAPTER 16: ACCEPTABLE SURGICAL APPROACHES FOR DONOR NEPHRECTOMY AND ANTICIPATED OUTCOMES

16.1: All donor candidates should have renal imaging (such as a CT angiogram) to assess renal anatomy prior to nephrectomy. (Not Graded)

16.2: In general, the chosen approach to donor nephrectomy should be limited to approaches for which the lead surgeon during the case has adequate training and experience. (Not Graded)

16.3: We suggest that “mini-open”, laparoscopy, or hand-assisted laparoscopy by trained surgeons should be offered as optimal approaches to donor nephrectomy. However, in unusual circumstances, such as for donors with extensive previous surgery and/or adhesions, open nephrectomy (flank or laparotomy) may be justified. (2D)

16.4: Robotic and single-port nephrectomies are not currently standard of care approaches to live donor nephrectomy and should only be performed by surgeons with adequate training and experience, and after informed consent. (Not Graded)

16.5: Use of nontransfixing clips (i.e., the Hem-o-lok clip) is contraindicated for control of the renal artery in laparoscopic donor nephrectomy due to associations with fatal and nonfatal hemorrhagic complications. Tissue transfixation (by suture ligature or anchor staple within the vessel wall) is absolutely necessary for arterial control during live donor nephrectomy. (Not Graded)

16.6: We suggest that laparoscopic procurement of the right kidney can be an appropriate alternative to laparoscopic left donor nephrectomy when undertaken by surgeons with adequate training and experience. (2D)

16.7: In general, the presence of asymptomatic renal parenchymal, vascular or urological abnormalities which are not contraindications to donation should favor use of the abnormal kidney for transplantation for the goal of leaving the donor with the “more normal” kidney. (Not Graded)

16.8: Because simple (Bosniak I) renal cysts are not associated with increased risk of complications or organ dysfunction, the presence of simple renal cysts are not a contraindication to live kidney donation. A kidney with a small simple cyst can be left in the donor, particularly if there are compelling reasons for donating the contralateral kidney. (Not Graded)

16.9: Use of live donor kidneys with Bosniak II or higher renal cysts should proceed only after careful assessment for the presence of solid components, septations, and calcifications on the preoperative CT scan (or MRI) to avoid accidental
transplantation of a kidney with cystic renal cell carcinoma. Bosniak II or higher cysts should not be left in the donor. *(Not Graded)*

16.10: Total nephrectomy and donation may be offered when a high grade Bosniak cyst or renal cell carcinoma is discovered during the course of clinical care, but only in the context of very careful informed consent about the alternative option of partial nephrectomy, the standard of care in the absence of donation of the affected kidney. *(Not Graded)*

16.11: Procurement of a live donor kidney with 3 or more arteries should be considered on a case-by-case basis and only undertaken by teams with adequate experience. *(Not Graded)*

16.12: Bilateral atherosclerotic renal artery disease or fibromuscular dysplasia involving the orifices of both renal arteries should be considered as contraindications to live kidney donation. *(Not Graded)*

**RATIONALE**

The choice of surgical approach for donor nephrectomy and the organ for procurement (left versus right kidney) should weigh local experience of the operating surgeon as well as any renal parenchymal, vascular or urological abnormalities in the donor candidate. Relevant outcomes to consider in comparing surgical approaches to nephrectomy include: mortality; perioperative complications (e.g., bleeding, reoperation, incisional hernias); quality of life impacts, including pain and wound cosmesis; recovery time; and graft outcomes in the recipient (for which warm ischemia is often reported as a surrogate). Published studies often report operative time as a surrogate for risks of anesthesia-related complications. The evidence review performed to support this guideline identified 4 recently published systematic reviews describing perioperative outcomes after live donor nephrectomy:

- Wilson *et al.* searched the literature through May 2010 and identified 6 RCTs analyzing 596 live kidney donors randomized to laparoscopic versus open nephrectomy.
- Yuan *et al.* searched the literature through October of 2011 and identified 14 RCTs and 16 prospective controlled trials enrolling a total of 2,243 donors. All RCTs included in the review by Wilson *et al.* were also included in the review by Yuan *et al.*
- Fonouni *et al.* searched PubMed through 2013 and included 11 reviews, including those by Wilson *et al.* and Yuan *et al.* and 4 RCTs (3 of which were included in the reviews by Wilson *et al.* and Yuan *et al.*)
- Liu *et al.* identified a single RCT and 28 comparative studies including a total of 32,426 cases to examine outcomes after left versus right laparoscopic live donor nephrectomy.

**Open versus Laparoscopic Nephrectomy**

The evidence review identified 3 systematic reviews comparing outcomes after open versus laparoscopic nephrectomy (Evidence Report Appendices, Table C3).
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 approached 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 increased incision length and generally longer associated hospital stay, higher analgesia requirements, and longer convalescence period. As reflection of this change in standard of care, by 2013, almost all live donor nephrectomies in the US were performed laparoscopically, and, with increasing experience, few are converted to open procedures. Of note, as for most surgical procedures, experience is likely an important determinant of outcomes, as trials and observational series were performed at experienced centers by a limited number of surgeons.

**Operative Time:** Fonouni et al. reported a trend towards longer average operative time for laparoscopic compared to open donor nephrectomy, and Yuan et al. and Wilson et al. confirmed longer operative times for laparoscopic procedures. Meta-analysis by Yuan et al. 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 al. reporting perioperative blood loss favored laparoscopic nephrectomy, while the other 3 found no significant differences in blood loss between the approaches. Meta-analysis by Yuan et al., including 11 studies capturing data for 917 donors, found a small but statistically significantly increase in perioperative blood loss with open nephrectomy compared to standard laparoscopy (mean difference: 99.6 mL; 95% CI: 165.9 – 33.4) or the hand-assisted laparoscopy groups (112.8 mL, 95% CI: 169.1 – 56.0).

**Warm Ischemia Time:** Data regarding warm ischemic times on laparoscopic versus open nephrectomy are conflicting. In 10 of the 11 publications evaluated by Fonouni et al., longer warm ischemia times were reported in the laparoscopic nephrectomies compared to open nephrectomies (Evidence Report Appendices, Table C3). Similarly, all included studies in the review by Wilson et al. 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 1,598 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 – 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 al. found no significant differences between laparoscopic and open nephrectomy for early graft loss (RR: 0.31, 95% CI 0.06 – 1.48), delayed graft function (RR: 1.09, 95% CI 0.52 – 2.30), acute rejection (RR: 1.41, 95% CI 0.87 – 2.27), ureteric complications (RR: 1.51, 95% CI 0.69 – 3.31), donor kidney function at one year (standardized mean difference 0.15, 95% CI -0.11 – 0.41) or graft loss at one year (RR: 0.76, 95% CI 0.15 – 3.85).
**Reoperation:** Fonouni et al. included 7 publications (both trials and meta-analyses with unreported donor sample sizes) reporting reoperation rates, and found mixed results. While 4 of the publications found no difference between the groups, 3 found higher reoperation rates in the laparoscopic compared to the open group. Based on data from 6 studies, Wilson et al. found fewer reoperations with open nephrectomy compared to laparoscopic nephrectomy, but this difference was not statistically different (RR: 0.57; 95% CI: 0.09 – 3.64).

**Length of Hospital Stay:** Among 9 publications (with unreported donor sample sizes) reviewed by Fonouni et al., 4 of the 9 found no difference in length of stays between the groups, while the remaining 5 found longer length of stays with the open nephrectomy versus the laparoscopic group. Meta-analysis of 18 studies (including 1,851 donors) by Yuan et al. identified significantly fewer shorter lengths of hospital stay after laparoscopic compared with open nephrectomy (mean difference: −1.3 days; 95% CI: −1.9 – −0.7) and hand-assisted laparoscopic (mean difference: −1.3 days; 95% CI: −2.1 – −0.5) compared to open nephrectomy.

**Return to Work:** The time to return to work was reported in one systematic review based on pool data from nine studies capturing 1,016 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 – −9.7).

**Pain and Physical Functioning:** Among 6 studies describing analgesia requirements in the review by Wilson et al., four reported significant reductions in morphine requirements (standardized mean difference between 2.8 and 33.2 total mg), based on normalized data for two studies. One study within the review showed that laparoscopic donors required fewer days of analgesia post discharge (3.3 versus 7.8 days, *P* < 0.001), while another reported a non-significant reduction in visual analogue pain scale scores. The meta-analysis by Yuan et al. of three 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.

**Comparison to Prior Guidelines**

Consistent with our recommendation, prior guidelines and policies for the evaluation and care of living kidney donors recommend laparoscopic or minimally invasive approaches as preferred techniques for live donor nephrectomy 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 and open nephrectomy (with complications after laparoscopy largely due to catastrophic intra-operative securing of the vascular pedicle), larger resource requirements for laparoscopy, but advantages for laparoscopy in terms of reduce analgesia requirements and faster return to normal activity. EAU concludes that laparoscopy offers equivalent
complication rates and graft outcomes as open nephrectomy but shorter convalescence and better cosmetic results.\textsuperscript{32} 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.\textsuperscript{316}

**Standard ‘Pure’ 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\textsuperscript{312, 314, 315} (Evidence Report Appendices, Table C4).

**Operative Time:** Yuan et al. reviewed 7 trials (including 387 donors) comparing 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: $-50.8$ – $1.7$).\textsuperscript{315}

**Blood Loss:** Wilson et al. 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.\textsuperscript{314} Similarly, Yuan et al. found no significant differences in blood loss with standard compared with hand-assisted laparoscopic groups (mean difference: $-20.7$ mL; 95% CI: $-43.9$ – $2.6$).\textsuperscript{315}

**Warm Ischemia Time:** Yuan et al. found a small, statistically significant reduction in warm ischemic time with hand-assisted compared with standard laparoscopy (mean difference: $-1.0$ minutes; 95% CI: $-1.3$ – $-0.7$),\textsuperscript{315} 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 stays than those undergoing hand-assisted laparoscopic nephrectomy (mean difference: 0.3 days; 95% CI: 0.1 – 0.6),\textsuperscript{315} although the clinical and likely economic significance of this less than 1 day difference 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.\textsuperscript{318} Hand-assisted laparoscopy results in shorter operative time (mean, 159 vs. 188 min; $P =$0.001) and a small reduction in warm ischemia time (2 vs. 5 min; $P =$0.001). Intraoperative event 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 =$0.14), and physical function at 1 month ($P =$0.55) follow-up did not significantly differ between groups.
Comparison to Prior Guidelines

Consistent with our recommendation, ERBP states that the choice between minimal invasive and laparoscopic procedure should be based on the local expertise. No other guidelines recommend a preference for standard laparoscopy versus hand-assisted or other minimally invasive approaches.

Left versus Right Laparoscopic Live Donor Nephrectomy

In the absence of medical conditions motivating otherwise (such as renal parenchymal, vascular or urological abnormalities), the left kidney should be procured in laparoscopic live donor nephrectomy because of the relative technical ease and typically longer venous pedicle. However, minimizing potential for short-term and long-term complications in the donor is also an overarching principle. Thus, the presence of renal parenchymal, vascular or urological abnormalities which are not contraindications to donation may favor use of an abnormal right kidney for 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; importantly, there is inherent selection by experience at centers reporting outcomes after laparoscopic right nephrectomy, as most available evidence is observational. The evidence review examined one systematic review by Liu et al. comparing right with left laparoscopic live donor nephrectomy, and identified very low quality evidence for similar operative times, blood loss, warm ischemic times, and length of stay at experienced centers (Evidence Report Table 5). Again, although complication rate of minimally invasive surgery is generally low with experienced surgeons, complications can be life threatening; thus, proper training and experience is critical.

Operative Time: Among 14 studies (including 2,656 donors) with available data, operative times were similar with left and right laparoscopic nephrectomy (weighted mean difference (WMD): 1.4 minutes; 95% CI: −11.7 – 14.4).

Blood Loss: Based on data from 15 studies (including 3,033 donors), blood loss was similar between donors who underwent left or right nephrectomy (WMD: 4.4 mL; 95% CI: −19.8 – 286).

Warm Ischemia Time: Among 18 studies (including 3,516 donors), warm ischemia time was also similar among donors undergoing left or right nephrectomy (WMD: −0.02 minutes; 95% CI: −0.4 – 0.05).

Length of Hospital Stay: The mean length of hospital stay in 11 studies (including 1,730 donors) was similar between those undergoing left or right nephrectomy (WMD: 0.05 days; 95% CI: −0.08 – 0.02).
Laparoscopic procedure type and 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 hand assist. A trial at a referral center with longstanding expertise on the standard laparoscopic right nephrectomy explored the safety and feasibility of right hand-assisted approach by randomly assigning 40 donors to either approach. As compared to laparoscopic right nephrectomy, hand-assisted right nephrectomy resulted in slightly shorter warm ischemia time (2.8 vs. 3.9 min, \(P < 0.001\)) 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.

Novel Modalities such as Robotics

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 small series and case reports at experienced centers. Given the limited experience and lack of robust safety and outcomes data, robotic and single-port nephrectomies are not currently standard of care approaches to live donor nephrectomy and should only be performed by surgeons with adequate training and experience, and after informed consent.

Multiple Renal Arteries

Kidneys with multiple arteries are common in the general population and thus in potential live donors. CT series performed during live donor evaluation suggest a prevalence of 18% to 30% for multiple renal arteries, with up to 15% bilateral involvement. The presence of multiple renal arteries raises potential concern for 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 a potential for complications. A small accessory artery that supplies a minor part of the upper pole (subjectively assessed using pre-donation CT scans) can often be safely sacrificed. However, an accessory artery that vascularizes the lower pole and inherently the proximal part of the ureter must be saved and reconstructed after nephrectomy. In 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 al. capturing reports of outcomes associated with vascular multiplicity in live donors in the past decade concluded that renal arterial multiplicity (up to 3 renal arteries) and venous anomalies should not be a contraindication for live 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 three renal arteries, conclusions cannot be drawn for donors with 4 or more arteries. Use of kidneys with multiple arteries has not been addressed in prior guidelines.
Non-Transfixing Clips

Cases of hemorrhagic deaths of living kidney donors from failure of non-transfixing vascular clips (Hem-o-lok clips) used on the renal artery, resulting in sudden, massive bleeding, were first documented in 2006\textsuperscript{327,328}. Despite a Class II recall of the Hem-o-lok clip for laparoscopic donor nephrectomies by the FDA in 2006, and an FDA Black Box Warning that use of the Weck1 Hem-o-lock hemostatic clip to control the renal artery in live donor nephrectomy is contraindicated, the use of these clips is still reported. A 2011 American Society of Transplant Surgeons (ASTS) survey reported that Hem-o-lok or other clips are still used by some surgeons as a sole means of arterial control in laparoscopic donor nephrectomy.\textsuperscript{327} Subsequently, in a 2013 survey of 645 members of the European Society for Organ Transplantation, 20\% of respondents reported use of clips (locking and non-locking) to close the arterial stump.\textsuperscript{329} Of the 121 reported hemorrhagic events, slippage and dislodgement of clips occurred at least 58 (47.9\%).\textsuperscript{329} Importantly, live donor nephrectomies may be performed by urologists and minimally invasive surgeons as well as transplant surgeons, so broad and ongoing dissemination of the dangers of clip use is warranted. All surgeons operating on a living organ donor must select vascular control techniques that entail tissue transfixion and assure a safe operative recovery. The Hem-o-lok and other surgical clips must not be used to control the donor renal artery.

Comparison to Prior Guidelines

The CARI guideline states that use of a non-transfixing mechanism for securing the renal artery is not recommended, particularly with laparoscopic donor nephrectomy.\textsuperscript{317} We believe this recommendation must be expressed as an absolute contraindication.
CHAPTER 17: ETHICAL, LEGAL AND POLICY CONSIDERATIONS

Ethical and Legal Framework for Living Donation

17.1: Local laws and regulations on living donation should be respected and shared with living kidney donor candidates. (Not Graded)

17.2: Where local laws impede the ethical practice of living donation, transplant teams should explore avenues for advocacy to change the law. (Not Graded)

17.3: Donor autonomy (self-determination) 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, which addresses potential risks and benefits to the donor, as well as to the recipient. (Not Graded)

Policies for Identification of a Donor Candidate

17.4: Transplant centers should exercise their responsibility to increase public awareness of opportunities for living donation and assist donor candidates with testing arrangements. Appropriate strategies may include public education, donor advocacy, efficiencies in the evaluation of kidney donors (e.g., use of new information technology) and the removal of disincentives. (Not Graded)

17.5: Transplant centers should support and assist transplant candidates in identifying living kidney donor candidates, providing these efforts respect donor autonomy and do not exert undue pressure to donate. (Not Graded)

17.6: Transplant centers should inform and educate donors of the dangers of transplant tourism, and their jurisdiction’s legal position on this practice. (Not Graded)

17.7: Transplant centers should define and disclose their policy for accepting donor candidates identified through public solicitation. (Not Graded)

Financial Support for Living Donors

17.8: Transplant centers should inform donor candidates of the availability of legitimate cost replacement programs for expenses incurred related to being evaluated for and serving as a living donor. (Not Graded)

Policies for Communication and Post-Donation Follow-Up Care

17.9: Living non-directed kidney donors and donors participating in paired donation should be informed prior to the donation of the transplant center’s policy on contact with the recipient at all stages in the donation process. (Not Graded)
17.10: The extent of the physician-patient relationship following donation should be clarified, including whether the donor can seek medical care at the transplant center after the donation. (Not Graded)

17.11: In the unlikely instance where a living kidney donor develops kidney failure, there should be a process within each country to accelerate access to kidney transplantation for that donor using allocation priority systems, if available and feasible. (Not Graded)

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. All practitioners in transplant programs should be aware of relevant laws and regulations that pertain to the live donor transplant program. Ethical tenets and specific transplant program processes are applied to minimize donor risk.

When there is opportunity to identify needs for policy and legal changes to improve living donation, transplant programs should actively participate in the review and process to update or change laws and regulations as needed. Laws to regulate donation include those to: a) protect the vulnerable (e.g., the cognitively impaired, young people, dependent persons); b) respect autonomy (e.g., require informed consent); c) prohibit incentives to donate that may create coercion (e.g., payment for organs in money or in kind).

Transplant professionals have an ethical duty to act in the best interests of potential and actual donors and recipients seen at their center. Self-determination around the decision to donate reflects a view of people as autonomous agents. 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, which addresses potential risks and benefits to the donor, as well as to the recipient. Balancing the likely risks and benefits to the donor as well as respecting the donor’s wishes for donation/non-donation respects the principle of non-maleficence. Geography may alter the threshold of risk tolerance e.g., when living donation is the only treatment option for the recipient’s kidney failure. The decision to accept a living kidney donor candidate should consider all treatment options for the recipient.

Policies for Donor Candidate Identification

People may not be aware of or have accurate knowledge of living donation. Recipient candidates may not feel comfortable informing others of living donation for reasons including not knowing how to ask, misunderstanding of risks, and fear for harm to the donor candidate. Consequently, transplant programs have some responsibility to make the public aware of living donation through advocacy initiatives. Appropriate strategies may
include public education, donor advocacy, efficiencies in the evaluation of kidney donors (e.g., use of new information technology) and the removal of disincentives. Transplant centers should also support transplant candidates in identifying strategies that may aid identification of living kidney donor candidates. These efforts must respect donor autonomy and cannot exert undue pressure to donate. Critically, a wish not to donate must also be respected.341, 342

Transplant tourism often involves the illegal sale of organs. This practice has been associated with harms to living donors and poor outcomes for some recipients.343 The Declaration of Istanbul, created at the 2008 Istanbul Summit on Organ Trafficking and Transplant Tourism, emphasizes that organ trafficking and transplant tourism should be prohibited because they violate the principles of equity, justice and respect for human dignity.343 The Istanbul Declaration distinguishes transplant tourism from travel for transplantation. As articulated in the Declaration, travel for transplantation is the movement of organs, donors, recipients or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes transplant tourism if: 1) it involves organ trafficking and/or transplant commercialism or; 2) the resources (organs, professionals and transplant centers) devoted to providing transplants to patients from outside a country undermine the country’s ability to provide transplant services for its own population. Distinct from tourism, the Declaration of Istanbul specified that travel to a foreign country for live donor transplantation may be ethical if: 1) if the recipient has a dual citizenship and wishes to undergo transplantation from a live donor who is a family member in a country of citizenship that is not their residence; 2) the donor and recipient are genetically related and wish to undergo transplantation in a country not of their residence. Since the creation of the declaration, more than 100 countries have endorsed the principles.

Some people respond to public solicitations by offering to be a kidney donor.55 By evaluating these donor candidates, transplant centers are enabling donation.344 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.345

Financial Support for Living Donors

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 living donors.346 Initiatives to remove financial disincentives for kidney donation (i.e., replacement of costs incurred by the donation such as loss of income, travel, accommodations for the evaluation and donation) are acceptable as an issue of justice.291 Multiple prior living donation guidelines endorse reimbursement for out-of-pocket expenses incurred during the evaluation and donation process, independent of the final decision to proceed with donation.23, 24, 26, 343 Recommendations to offer life and disability insurance for living donors, or to pass legislation to ensure employment and insurability protections to donors, have also been advanced.32, 293, 347

In contrast, 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 public views of donation and transplantation will be damaged.348
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.\textsuperscript{343} However, the debate on the acceptability of incentives continues and a proposal has been made to research this issue further.\textsuperscript{348}

**Policies for Communication and Post-Donation Follow-Up Care**

Living anonymous donors are also referred to as non-directed living donors.\textsuperscript{308} These are living donors who offer a kidney to a transplant center to allocate, as they do not have an identified recipient. Non-directed donors may also donate by participating in a paired donor exchange program or as part of a series of matched donor and recipient pairs allowing for a chain of multiple transplants. A minority of non-directed living donors and their recipients request contact with each other post-donation. Clarification of the center’s policy on this prior to donation enables participants to adjust their expectations after donation.\textsuperscript{349}

ESRD is a rare event after live kidney donation, but in some countries with deceased donor allocation systems, allocation priority for deceased donor kidney transplantation has been promoted as an ethical strategy to protect the safety of living donors whose remaining kidney fails after donation. For example in the US, prior living donors receive additional priority points for deceased donor kidney transplants, which has been associated with higher transplant rates, shorter time to transplant, and receipt of higher quality allografts compared with candidates with otherwise similar clinical profiles.\textsuperscript{350,351} Priority for prior living donors can also be incorporated in kidney paired donation matching algorithms.\textsuperscript{43}

**Research Recommendations**

- Determine ethical standards for surrogate consent, including imminent death donation
- Explore approaches to and impacts of strengthening partnerships between general nephrologists, dialysis providers, and transplant centers regarding live donor kidney transplant education, access and disparities\textsuperscript{272}
- Examine impacts of patient and public education on increasing donation from living donors\textsuperscript{293,341}
- Examine strategies for reducing financial barriers to living donation, with particular attention to impact on current disparities in live donor kidney transplantation\textsuperscript{348}
- Determine optimal approach to allowing or restricting contact between non-directed kidney donors and their recipients\textsuperscript{349}
- Evaluate the outcomes of incentivizing organ donation via ethically and legally acceptable methods\textsuperscript{352,353}
CHAPTER 18: POST-DONATION FOLLOW-UP CARE

18.1: Living kidney donors should be monitored long-term for hypertension, CKD, and overall health status and well-being. Blood pressure, eGFR based on serum creatinine, and urine albumin testing are particularly important parameters to follow in kidney donors due to concerns for the impact of donation on long-term risk for development of hypertension and CKD. Assessment should include not only the absolute level of eGFR but also its trajectory over time. (Not Graded)

18.2: The following specific practices should be performed annually for each donor as part of post-donation follow-up care: (Not Graded)

- Blood pressure measurement
- Body mass index measurement
- Serum creatinine testing with estimation of GFR (eGFR)
- Evaluation for albuminuria
- Evidence of diabetes
- Review and promotion of healthy lifestyle practices including exercise, diet, avoidance of smoking
- Review of psychosocial health and well-being as it relates to their donation experience.

18.3: Follow-up information should be reported to national and/or regional registries to facilitate aggregation, assessment and dissemination of current donor outcomes data. (Not Graded)

18.4: Donors who develop hypertension or CKD should receive appropriate medical treatment for these conditions according to clinical practice guidelines for the conditions. (Not Graded)

18.5: Donors should receive age-appropriate healthcare maintenance according to clinical practice guidelines for the regional population. (Not Graded)

18.6: Metabolic conditions (e.g., diabetes), cardiovascular diseases (e.g., coronary artery disease, congestive heart failure), and cardiovascular risk factors (e.g., hyperlipidemia, obesity) or risk behaviors (e.g., smoking, sedentary lifestyle) should be evaluated during post-donation healthcare maintenance assessments and managed according to general population guidelines. (Not Graded)

18.7: Donor education provided prior to and at the time of donation should be reinforced by post-donation educational contacts from the transplant center such as newsletters, links to transplant center health recommendations or national guideline website documents to promote sustained healthy lifestyle choices and behaviors. (Not Graded)
18.8: When important new information becomes available on the long-term outcomes of living kidney donors that differs from what a donor was told prior to donation, the transplant program should use reasonable efforts to contact past donors and provide this information. (Not Graded)

RATIONALE

An individual’s presentation to a transplant center with an interest in living donation should be regarded as the initial stages of a long-term, collaborative relationship between two parties. The donor enters the relationship with an interest in offering an altruistic, selfless, and potentially life-saving gift of an organ for transplantation if he or she is healthy enough to donate and meets the transplant center’s requirements. Grounded in primary concern for the well-being of the donor, the transplant center should promote the donor’s autonomy and safety and long-term donor health throughout all phases of care including donor selection, donation surgery, and long-term follow-up and donation-related care. Responsibility for the coordination and performance of long-term donor follow-up has raised controversies regarding financial and time burdens on both centers and donors, especially in countries without universal health insurance. 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 2011 consensus conference report, 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 donor ethnicity, donor baseline comorbidity, changes in surgical technique and donor management.
- The need to acquire more robust outcomes data to improve the evaluation process and to provide reliable counseling for non-traditional donor candidates.
- The possibility of identification of individual donor problems through surveillance at a time when intervention is possible.
- Provision of program-specific feedback to guide quality assurance and performance improvement.
- Donation is a public trust and the transplant community has a professional obligation to continue to collect and monitor information on living kidney donor outcomes.

In the US, the country that performs the largest volume of live donor kidney transplants per year, follow-up reporting by centers to the national transplant registry is limited to two years of post-donation, and has historically suffered from missing data and frequent loss-to-follow-up. 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. Lack of health insurance appears more common among living kidney donors in the US than in the general US population. Lack of insurance and lower educational attainment may pose lesser obstacles in other countries where national healthcare is available. As part of the informed consent process, centers should educate donor candidates
on the importance of follow-up, disclose donor responsibilities for and potentials costs of follow-up participation, and develop a personal follow-up plan.\textsuperscript{360} Documentation of donor acknowledgement through a signed care plan has been proposed as part of education,\textsuperscript{361} 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. While donor education prior to and at the time of donation is vital to the decision to proceed with donation, there is a need to continue education 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 topics provided in that context.

Regarding the impact of center factors and practices on the quality of donor follow-up, among US centers in 2008–2012, large annual living donation volumes were associated with increased rates of follow-up deficiencies.\textsuperscript{357} However, implementation of mandatory thresholds for collection of post-donation clinical and laboratory data in the US in 2013 with regulatory implications has led to improved rates of early follow-up data collection, and high levels of follow-up were achieved by programs across the volume spectrum. Best practices of programs achieving high rates of post-donation follow-up appear to be grounded in: 1) program conviction that follow-up was 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.\textsuperscript{361} Open-ended, qualitative interviews of US programs found that programs with high rates of successful follow-up addressed all four of these concepts.\textsuperscript{361} Recent single-center experience supports the concept that institution of follow-up performance improvement initiatives with dedicated program resources is financially feasible and leads to more accurate and complete patient follow-up after nephrectomy.\textsuperscript{362}

The establishment of standardized follow-up at serial time points provides a pattern for follow-up care that the donor may then be more likely to appreciate and continue in the form of regular, yearly preventive healthcare visits. Regular contact between the donor and the transplant center also increases familiarity of staff with issues that develop after donation, providing an opportunity to modify education materials or processes in order to better manage these situations for future donors. Data collection at regular time points must be pertinent, attainable, and related to the donation process, and not overly burdensome on the donor or the transplant center.

While early follow-up is mandated in some countries including the US, Canada and Australia,\textsuperscript{24, 26, 76} short-term follow-up will detect major or severe adverse outcomes early after donation but will not detect gradually progressive mild or severe 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 (e.g., diabetes mellitus, hyperlipidemia), and cardiovascular conditions that may increase their risk of kidney disease and mortality. 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 primary data in dedicated,
funded research studies, and integration of donor registry data with other information sources such as health administrative data, ESRD and mortality registries are also important additional priorities for advancing understanding of long-term health outcomes after donation.\textsuperscript{363}

Some countries have instituted systematic approaches to longer-term live donor follow-up. The European Living Donation and Public Health (EULID) project began with an 11-nation assessment of living donation practices in Europe that recommended mandatory live donor registration and follow-up data collections through a centralized donor database system, and mandatory regulatory audits at the national and center level.\textsuperscript{305} 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 six centers of different European countries (Spain, Germany, France, Portugal, Sweden and Turkey) in 2009-2012 focused on monitoring donor psychosocial well-being and quality of life.\textsuperscript{364}

The Swiss Living Donor Health Registry (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.\textsuperscript{366} In 1993, a national protocol was initiated for all transplant centers to organize lifelong follow-up after nephrectomy at 1 year, 3 years, 5 years, 7 years, 10 years and biennially thereafter by sending a package to the kidney donor asking the donor to make an appointment with the present family physician of their choice. This contains the 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 filled in by the family physician. In 2002, requests were added for completion an additional Eight-Item Short-Form (SF-8) and social-status questionnaire. Non-responses are followed by contacting the recipient, the donor’s health insurance and the 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 state by centers is required by the Swiss Transplant Law. While 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-ups begin at week 3 to 4, then by month 3, follow by yearly monitoring for 5 years and every fifth year thereafter. Clinical assessment of donors including BP, blood tests and urinalysis examinations is performed by local county hospitals and 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\textsuperscript{th} yr follow-up, respectively (Hallvard Holdaas, personal communication). As many donors in other countries such as the US report regular follow-up with a primary provider,\textsuperscript{359} donor follow-up monitoring and care may be performed by primary care providers to preserve convenience for the donor if the center establishes communication with the primary physician for data collection and reporting as part of an individual follow-up plan. The center should be willing to assist in coordinating appropriate follow-up or provide this care if the donor requests it.

Follow-up care after kidney donation should focus on the monitoring and maintenance of general and kidney health by following healthy lifestyle practices (e.g., diet, maintenance of healthy weight, regular aerobic exercise), avoiding potentially nephrotoxic exposures (e.g., tobacco use, non-steroidal anti-inflammatory drugs, nephrotoxic medications), preventing the
development of diseases that may cause CKD (diabetes mellitus, CVD), and timely management such diseases if they occur. 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 their health. Since many donors develop low GFR that meets the criterion for diagnosis of CKD and the risk for CKD progressing to kidney failure is higher for donors than for non-donors of comparable health who did not donate, post-donation monitoring for kidney disease and CKD risk factors is appropriate. Hypertension is diagnosed more commonly in kidney donors than in persons with comparable baseline health, although this may reflect greater monitoring and earlier recognition rather than higher incidence. Living kidney donors who develop conditions that may cause kidney disease risk additional decline in GFR leading to kidney failure, based on a lower starting level of GFR after donation. Detection of these conditions should prompt appropriate medical treatment according to clinical practice guidelines either by the donor’s primary care provider or at the transplant center if the donor requests this. The transplant center should always be available as a resource for the donor’s primary care provider. New discoveries in the field of living donation may offer important information to help donors and providers optimize long-term post-donation outcomes. When important new information becomes available on the long-term outcomes of living kidney donors that differs from what a donor was told prior to donation, the transplant program should use reasonable efforts to contact past donors and their physicians to provide this information.

Research Recommendations

- Electronic communication: Examine online messaging systems to maintain contact with donors that can provide them with new educational information and simplify processes for result reporting. Potential approaches include websites or portals that provide tools that can be used to monitor donor health. Develop strategies for using inter-institution-compatible electronic medical records in the US and other countries to facilitate long-term reporting for donor outcomes by primary providers directly to national registries.

- Donor education: Improve and assess efficacy of educational resources to promote participation in regular post-donation follow-up and care, including adoption of healthy lifestyle practices.

- Donor outcomes: Establish, improve and integrate national/international donor registries to facilitate analysis of long-term outcomes for larger numbers of living donors for the goals of addressing knowledge regarding the long-term consequences of donation, provide data by which to modify donor eligibility criteria based on the outcomes of previous donors, support quality assurance assessments, and sustain and strengthen public confidence in the practice of living donation.
REFERENCES


52. Ross LF. What the medical excuse teaches us about the potential living donor as patient. *Am J Transplant* 2010; **10**: 731-736.


74. OPTN (Organ Procurement and Transplantation Network)/UNOS (United Network for Organ Sharing). National Data Reports, Graft Survival by Donor Type, Latest Data


164. Lee JH, Kim SC, Han DJ, et al. Risk factors for MDRD-GFR of less than 60 mL/min per 1.73 m2 in former kidney donors. *Nephrology (Carlton)* 2007; **12**: 600-606.


294. Lacetera N, Macis M, Stith SS. Removing financial barriers to organ and bone marrow donation: the effect of leave and tax legislation in the U.S. *J Health Econ* 2014; **33**: 43-56.


153


