**APPENDIX E: PUBLIC COMMENTS AND RESPONSES**

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**On behalf of the "KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors" Work Group***

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**Note regarding Chapter & Recommendation numbering:** Chapter 9 (Hyperuricemia, Gout and Mineral and Bone Disease) was added post-public comment, and thus all subsequent chapters were renumbered. References to recommendations in Public Comments correspond to the **Public Review** version of the guideline.

**Chapter 1: Goal of Evaluation, Framework for Decision-Making, and Roles & Responsibilities**

| COMMENT | RESPONSE |
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| Overall this is an excellent compendium of the state of knowledge regarding living donors. As any analysis of this type should, it uncovers areas that have been overlooked and calls for additional investigation to safeguard live renal donation. | Thank you for your support. |
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| I agree wholeheartedly with moving toward a quantitative framework toward quantifying lifetime risk of ESRD for donors in the absence and presence of living donation. This proposal is an excellent starting point. The difficulty will be how transplant centers choose a threshold. Two points about this matter are: 1) I have not found any research on how potential donors receive information on risk of ESRD and incorporate them into their decision to donate. If not done, this should be investigated in future research. It would be important to hear from patient and patient groups regarding their feeling toward the risk calculators and their utility. 2) A binary decision on an accept/reject threshold seems too strong: 1) estimates, especially for lifetime ESRD risk, are still imprecise, so misclassification will happen; and 2) it does not allow any room for patient preferences. A three-tiered classification may be preferable, e.g. tier 1: low risk; tier 2: intermediate risk, more intense counseling and shared decision making (if supported by patient-centered research on decision making); tier 3: high risk, reject. 3) This will not alleviate | • The Research Recommendations for Ch. 1 now include a recommendation to: "*Determine the best methods of communicating individualized risk to donor candidates and their intended recipients so that the information is understood and supports informed patient decision-making*."<br>• We have tempered the description of the framework, emphasizing that while the proposed strategy enables decision-making based on a more comprehensive assessment of risk factors than is currently practiced, application of the currently available online tool in the clinical setting at this time requires clinician insight and interpretation.<br>• We appreciate that some racial groups (e.g. African Americans, Indigenous peoples in Canada and Australia) may be more likely to have a lifetime post-donation projected incidence of kidney failure that exceeds a transplant center's threshold for acceptable risk. We encourage the transplant community to develop strategies to make |

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| and can potentially worsen the lack of access to live donor transplants for disadvantaged racial groups, e.g. African-Americans and Aboriginal Australians, as the lifetime risk for these groups in the absence of donation is higher. This should be acknowledged. | access to kidney transplant equitable to all without placing certain donors at unreasonable risk (where poor long-term outcomes in the donor will also psychologically harm the recipient). |
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| Excluded donor candidates should be referred to the adequate specialist. | The text was clarified to explain that the donor evaluation team has an obligation to ensure there is an appropriate plan for follow-up care for medical conditions discovered during the evaluation which preclude donation. |
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| Important cradiopapathy /sic/. | We do not understand this comment. |
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| 1.1.2: The impact in terms of kidney function, albuminuria and blood pressure seems minimal for the living donor (Ref: N Engl J Med 2009; 360: 459-69) | This comment refers to the Minnesota experience (Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med* 2009; 360: 459-469). The study is cited and was carefully considered in the development of these guidelines. |
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| 1.1.4: Follow-up of living donor is considered binding on aspects relating to the quality and safety of organs for transplantation (Ref: Proposal for a Directive of the European Parliament and of the Council on Standards of quality and safety of organs intended for Transplantation. European Union website) | This was added to the rationale and references in Ch. 19. (Post-Donation Follow-up Care): "*The "European Standards of Quality and Safety of Organs Intended for Transplantation" states that adequate follow-up is part of internationally recognized measures aimed at protecting living kidney donors and ensuring the quality and safety of organ donation.*" |
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| 1.1.5: The need for adequate donor selection, the evaluation of medical, psychological and social risks, and the need for specific care and monitoring, are highlighted in the consensus documents for living donor from the forum of Amsterdam (Ref: Transplantation 2004; 78: 491-2) | The Amsterdam guidelines (and multiple other living kidney donor guidelines) were reviewed in detail to inform the development of this guideline, and are cited throughout the document. |
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| Overall, this looks great! Here are a couple of suggestions: 1) "nonmalfeasance" should be written as nonmaleficence. 2) "capacity" should be written as competency. While every human has capacity, they may not | • Thank you. We corrected the spelling of "nonmaleficence."<br>• We now refer to Ch. 2 (Informed Consent) to address some of the issues, to avoid redundancy with Ch. 1. |

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| have competency given health status or mental impairment. 3) Instead of saying living donor candidate, say potential living donor. The latter way is used more conventionally in the literature. The former way gets confused with transplant candidate (the recipient). 4) Confidentiality is not an ethical principle *per se*; rather, it is a virtue. 5) voluntarism or voluntariness (I would use the latter term instead), as the Belmont Report explains, is an element of the informed consent process and comprises an application of the principle of respect for persons, rather than a principle in and of itself. | • "Living kidney donor candidate" is the terminology we have adopted throughout this guideline - we think this is a more accurate (less nebulous) term than "potential kidney donor", and would like to see "donor candidate" adopted in the literature going forward.<br>• We have made these changes in the text; please also refer to Ch. 2, where we discuss many details about the handling of personal health information.<br>• Other experts on the panel preferred "voluntarism"; the principle underlying voluntary nature is explained in the text to avoid any misunderstanding. |
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| We should accept or not donor candidates based on medicine evidence or guidelines. If the transplant center policies are not admitted regarding to medicine evidences or guidelines, it should not be considered. | If we followed your comment correctly we agree – the revised text in Ch. 1 reflects this sentiment. |
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| 1.1.3: There should have a one guideline in accepting or excluding donor candidates. Criteria must be set and abide by all agencies. | When possible medical practice should be uniform, but that is not always possible in the presence of local contextual factors. |
| 1.1.6: there should have an evaluation for excluded donors. what is/are the reason/s why they are excluded. | We have updated Ch. 1 to clarify that the evaluation team has an obligation to share reasons for exclusion with the donor candidate. |
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| While I agree with the recommendation that the excluded donor candidates should be offered evaluation at a different center, many typically do not. Many of them also do not have primary care physician or medical insurance. Follow-up of the abnormal clinical investigations or findings in that setting has always been a difficult aspect of excluded donors. I am not sure that the simple advice that they need to seek medical follow-up on their own is sufficient from a moral obligation point-of-view. The other point is that the excluded donor care is mentioned in the guideline 1.2.8, no explanation was provided in the following rationale. | We removed the description of referral to another program (this can be done in practice, but some public comments expressed that this was too prescriptive to articulate in a guideline). As reflected in the revised text, we agree the transplant program has a moral and professional obligation to coordinate a plan for follow-up of medical issues identified during the evaluation that resulted in a donor candidate being excluded, even if the program does not directly provide the care. |

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| 1.1.6: ...formulate a plan for... - may be changed to: ...refer to appropriate care of conditions... | The wording “formulate a plan” provides flexibility, which may involve care at the center or care coordinated by the primary physician or other specialists, depending on the nature of a discovered condition. The transplant program does have a professional obligation to ensure that excluded donor candidates will receive the care they need, which is a principle we aimed to convey in this section. |
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| 1. Under Goals and Principles of Donor Evaluation: The last sentence states: The transplant center must have a mechanism for resolving disagreement among team members regarding acceptance and exclusion of donor candidates. One concept that we feel is important is that this mechanism for disputes have an external arbitration to avoid perceived conflicts of interest. i.e., member from another department (Ethics) within the institution. | We agree. The sentence now reads: "*The transplant program must have a mechanism for resolving disagreement among team members regarding suitability of donor candidates that avoids conflicts of interest*." |
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| 2. While I agree and embrace the concept that each transplant center should develop and communicate a quantitative threshold of ‘acceptable risk’ for each serious post-donation adverse outcome they wish to avoid, and the notion that this threshold should be both evidence-based and consensus-based, I think the suggestion that this should be consistent among centers within a region is a difficult concept to apply. This would, in effect, require programs align multiple facets of their programs to include the quality programs. It would necessitate common protocols, processes, and infrastructure to facilitate evaluation and measurement of the thresholds and outcomes. For example, not all centers perform stress tests on all donors, this would be one factor that might be taken into consideration in a predictive model, but if all centers do not evaluate patients in a similar fashion, the model would lack predictability. As more data emerge nationally, the threshold will become clear and will be both evidence-based and consensus-based. This will emerge without any effect introduced by practice variation from different centers as large numbers will provide the power. | Thank you for the feedback. We removed the suggestion that the acceptable risk threshold should be consistent within a region. |
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| 3. Using a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of kidney failure is an important recommendation. If possible, developing this concept more is key and this | We agree, and strengthened the prose and the example in Table 1 to reflect this point. |

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| threshold should be the main driver of acceptance as it is difficult to predict how donation will affect the subsequent risk of kidney failure. | |
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| 4. In table 2: Roles and responsibilities of participants in donor candidate identification, evaluation, care and follow-up: Would consider the addition of educating the donor candidate on the importance of post-donation follow-up. Under the responsibilities for Donor/Donor Candidate Physician/Nephrologist, Donor Surgeon, nurse coordinator, and ILDA. | Table 2 was revised to address this point. |
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| AAKP supports simplification and standardization of the living donor workup, existing algorithms and checklists. AAKP supports the removal of disincentives to transplant donation, and advocates study of potential transplant incentives where appropriate. Uninephrectomies in the elderly are somewhat controversial. Thus, AAKP recommends an abundance of caution and counseling when these donors are considered for organ donation. A birth weight of less than 2.5 kg when known should be taken into consideration when evaluating a prospective living kidney donor candidate. Persons who donate a kidney should receive adequate education and guidance about the potential risks of developing kidney disease, with emphasis on measures that optimize CKD prevention (e.g., nephrotoxins, control of blood pressure, etc.) | We agree with all statements and highlight these points are throughout Ch 1. We did not include a practice recommendation related to birth weight, as reliable sources of birthweight information are often not available during the evaluation and precise risk relationships have not yet been defined, but we included birthweight as a potential novel risk factor warranting further study in the Research Recommendations. |
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| I submit these comments on behalf of members of the Living Donor Committee of the United States Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) (Dr. Lentine recused herself from Committee discussions given her central involvement with the KDIGO project.) We have carefully reviewed the KDIGO Guidance document. It is truly a remarkable document, in terms of its breadth and scope, the extensive data gathering and systematic review of evidence, and the well-reasoned recommendations that are offered. The document has much to offer to the transplant community and it will certainly be a valuable resource for both policy and clinical practice. Thank you for the opportunity to read and comment on it. | Thank you. |

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| At the most general level, we recommend that greater explanation be provided concerning the logic for grading vs. not grading recommendations. As we note in our comments, many recommendations are associated with empirical evidence, yet they are left ungraded. The reasoning for no grading is not clear. A second general comment is that many additional recommendations are offered in the Rationale sections of the Chapters; it is not clear what led a recommendation to be listed in the Recommendations section vs. those that seem to be strongly suggested in the Rationale sections. | Thank you for the comment. We added a Methods Chapter with details of these processes to the guideline document. The complete Evidence Review is also available as an Appendix and is summarized in a separate publication. |
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| Chapter-specific comments for your consideration are offered below:<br>Chapter 1: The discussion in the Rationale section on establishment of thresholds of donor risk is thought-provoking and very timely. With regard to the specific recommendations offered for Chapter 1, it seems surprising that there are no recommendations regarding information about transplant candidate/recipient outcomes that should be provided to individuals considering serving as living donors. In addition, it is stated in the Rationale section that donor candidates should be given the opportunity to withdraw if they do not consent to sharing relevant personal health information but (a) this is not explicitly included in the list of recommendations and (b) there is no recommendation regarding information about the transplant candidate that should be disclosed to the living donor candidate (or whether the recommendation would be simply to indicate to the living donor candidate that such information cannot/will not be shared with the donor candidate). The Rationale section also states that transplant centers are responsible for confirming that the donor candidate understands the likely risks and benefits of donation, but this responsibility is also not recognized in any of the recommendations. It is recognized that some of the potential recommendations stated above are recognized in other chapters (e.g., regarding the provision of information about transplant candidate/recipient outcomes; addressed in Chapter 2). However, the Chapter 1 section on Framework for Decision-Making seems incomplete without the inclusion of such recommendations. In short, is there a possibility of at least cross-referencing across Chapters in order to make the document more accessible to readers/users? In addition, with regard to the statement about center responsibility for confirming donor understanding, it is recommended that the language be further clarified in the Rationale and in potential | • Thank you. The prose now reads: "*The transplant program has the responsibility to disclose anticipated risks and benefits to the donor candidate and intended recipient, tailored when possible for the characteristics of each donor candidate*".<br>• We improved the description of sharing of personal health information, including cross-referencing to Ch. 2 which provides much more detail on this topic. Ch. 2 also includes a clear recommendation to confirm a donor candidate's understanding of presented information.<br>• We also increased the emphasis on the importance of acknowledging the uncertainty in some long-term risk estimates. |

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| recommendations to confirm that the donor candidate also understands the lack of long-term data about risks. This would be consistent with the excellent considerations on pages 6-9 and 13 about long-term risks and study limitations. We recognize that Chapter 2 includes a recommendation that the donor be informed about uncertainty in risk estimates (which is slightly different than the issue of lack of data), but since the broad topic of risk is discussed in Chapter 1, it would seem that it needs to be addressed more clearly in Chapter 1—in either its Rationale section (which could refer to Chapter 2 recommendations), or in the Chapter 1 recommendations themselves. The Rationale includes the statement that the donor candidate…must accept the need for long-term follow-up. This language was viewed by Living Donor Committee members as unduly passive and as failing to recognize the need for active involvement of the donor. For example, the language could be modified to clarify that the donor must accept responsibility for seeking out long-term care from their primary care physician and/or their transplant center on a regular basis. Of particular concern, none of the recommendations for Chapter 1 are graded. Various research recommendations are offered in the Rationale section.<br>The implication of the ungraded recommendations combined with the research recommendations is that there is no relevant research on any of the recommendations offered. Yet there is a body of evidence that would seem to be relevant. For example, there are studies that have examined modes of communication of risk information to ensure understanding. Some of that literature is in transplantation; some comes from other fields. It is not completely clearly why that evidence was not considered, which might have led to some ungraded recommendations becoming graded? Another general point is that, throughout the document, we recommend that there be a clearer explanation of why some items are listed specifically as recommendations, while other elements are recommendations made only in the Rationale sections of the Chapters. | |
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| Beyond the realistic responsibilities and resources of centers. | We did not follow this comment. Is this comment saying the guideline recommendations are beyond realistic responsibilities and resources of programs? Which recommendations? While we considered practical constraints in our recommendations, we also believe that ethically and |

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| | morally justified practices must be endorsed even if implementation requires resources. |
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| I think you are not being forthright about relative risks of donation on page 7. You need to say 8 to 11-fold were the published increments. It is stated in a way that makes this difficult to derive. Those estimates were vigorously defended. Let's state them. You can still say you have limited confidence in them after that if in fact that is now your position. Those risks are based on loss of GFR at donation and ultimately grounded in well accepted epidemiology of CKD in non-donor settings. On page 9, top box #3. I don't know what this is saying. "Don't trust the online calculator."? | We improved our description in Table 1 for greater transparency. We also emphasized that the modeling we undertook represents an important first step in supporting empiric decision making, but that more work is needed to improve precision in the estimates of long-term risk. |
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| Number 3 page 9 in the bottom box seems to undo the excellent position you took on a single uniform risk exclusion threshold for all donor candidates. If we can have different thresholds for different demographics, we might as well have a separate risk threshold for hypertensive and diabetic candidates because they are demographically challenged too. On page 13 you say centers may take into account availability of deceased donor kidneys (essentially "urgency") but you say in #4 second box p 9 not to do this (which may be right but the counterargument is that the greater the recipient need, the more likely the donor's decision is to be rational.) In the end, it will be wrong if centers get to set their own risk thresholds and those thresholds are allowed to markedly differ. That means that someone is doing something wrong. | We revised Table 1 to address such concerns. We also wish to respect that different programs may have different risk thresholds, based on important contextual factors. For example, in India, hemodialysis is often a bridge to a living donor kidney transplant, as the costs of long-term hemodialysis are prohibitive to many Indian citizens. |
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| The data provided in this chapter is by nature empiric and hence is not graded. | Thank you for the comment. |
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| Agreement with recommendations and other suggestions: | |
| Overall there was agreement with the recommendations except we felt that recommendation 1.1.6 needed to be qualified. Our recommended changes to the wording of the recommendations were as follows (changes underlined): | Thank you. |

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| 1.1.1: Assure that the donor candidate is acting voluntarily and not yielding to pressure or coercion. *(Not Graded) (pressure and coercion are inherently present)* | The final recommendation reads: "*The donor candidate's willingness to donate a kidney voluntarily without undue pressure should be verified*." Please also refer to Ch. 2 which provides more detail about the elements of informed consent. |
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| 1.1.4: Facilitate donor candidate decision-making through education and counseling regarding their individualized benefits, risks, methods to minimize risk and their need for post-donation follow-up. *(Not Graded)* | We incorporated the individualized risk concept in the final recommendation, which reads: "*Donor candidate decision-making should be facilitated through education and counseling on individualized risks and benefits, methods to minimize risks, and the need for post-donation follow-up*." |
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| 1.1.6: For excluded donor candidates, formulate a plan for appropriate care of conditions identified during the evaluation. *(Not Graded) This is not appropriate for transplant center* | We revised the recommendation to read: "*For an excluded donor candidate, a plan for any needed care and support should be formulated*." We believe that the transplant program has an obligation to formulate a plan for care, which can certainly include referral for management to other healthcare professionals. |
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| **1.2 Framework for Decision-Making for Acceptance and Exclusion of Donor Candidates** | |
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| Absolutely agree with these very delicate issues. | Thank you. |
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| I really wanted to make a comment about the online tool to predict ESRD in potential donors before and after donation. I really think how "imprecise" this is needs much more explanation. I cannot find at least easily a z-statistic / ROC/AUC of the model from the main text. The devil is in the detail here: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1510491/suppl_file/nejmoa1510491_appendix.pdf. See Table S3, page 30: they meta-analysed a number of studies and derived C-statistics from them (AUCs for ROC curves), allowing up to 20% missing data value (imputed) if needed. These are 0.675 to 0.889, mean of their numbers is 0.7815. Bear in mind flipping a coin is 0.5, so we need to have explained how reliable this tool is. | We expanded the discussion of the limitations of the modelling. We also clarified the new online tool represents a first (albeit important) step in generating the information necessary to make donor selection and decision making more transparent and defensible. We emphasize the need for continued research to strengthen precision and minimize uncertainty in these estimates. |

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| 1.2.1: For living kidney donation to proceed, the informed consent must include that "the donor and recipient are acting voluntarily and not under pressure or coercion. The consent term must clearly state that the donation is in accordance with the World Health Organization Resolution WHA63.22, from May 2010. The Resolution provides an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes. | These details are provided in Ch. 2 (Informed Consent). We added cross-referencing to Ch.2 in Ch. 1. |
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| 1.2.2: Transplant center policies must follow the same WHO resolution. | We added mention and referencing of the WHO resolution to the revised text. |
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| 1.2.3: The way that this is worded, it might be interpreted to exclude anonymous donation where there is no relationship between the donor and recipient. | Thank you. We revised the recommendation to read: "*Each transplant program should establish policies describing psychosocial criteria that are acceptable for donation, including any required relationship between the donor candidate and the intended recipient."* |
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| 1.2.3: Each transplant center should establish policies describing psychosocial criteria: Social criteria does not make sense for the professional team, in my opinion what is mandatory is documentation of donor's mental health 1.2.7: psychosocial criteria | Please see prior comments. Please see also Ch. 16 (Psychosocial Evaluation), which provides many more details about these criteria. |
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| 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. To protect the privacy of people, I suggest, explain the reason for non-acceptance just to donor. I fully agree with the statement (page 4) which can be emphasized more: 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. | We agree and clarified the wording to refer to the donor candidate. We also refer the reader to Ch. 2, wherein we discuss handling of medical information in the donor candidate evaluation process. |

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| 1.2.4: Long-term mortality associated with the donation is not higher than that of the general population adjusted for age and comorbidities (Ref: Transplantation 2005; 79 (6 Suppl): S53-66) | At least 7 studies to date report no higher risk of mortality in donors compared to the general population, including healthy non-donor controls. One Norwegian study reported a higher risk of late mortality in donors compared to healthy non-donors. These data were reviewed by the Evidence Based Review Team for this Guideline, and are summarized in the evidence reports. |
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| 1.2.5: Live donor should be offered specialized follow-ups lifelong and anticipate the emergence of unfavorable conditions such as overweight, hypertension, diabetes or proteinuria that may threaten the survival of the only functioning kidney (Ref: Transplant Proc 2009; 41: 2512- 4, Transplantation 2009; 87: 317-8) Other complications also should be consider for classification like anemia, bone diseases. | We were not prescriptive regarding how long-term follow-up should be organized by a transplant program, given variations in resource, healthcare systems and contextual factors. Rather we emphasize the importance of follow-up care. Please see Ch. 19 for a detailed discussion of Post-Donation Follow-up Care. |
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| 1.2.8: I am not really supportive of donors transplant center shopping if they are rejected at one center. | Please see prior comments. We removed this suggestion. |
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| I believe that a center should have a threshold above which they feel that donation is too risky however the current tools are imprecise especially with respect to lifetime risk. Therefore I believe that a center should be able to use a lower risk threshold for some donors where they believe that there is a great deal of uncertainty around lifetime risk. This illustrates the limitation of the proposal to use the risk calculator for lifetime risk as at present there is not enough data to provide reasonable estimates especially for younger donors. Furthermore the risk calculator does not apply to ethnic populations other than black or white and does not account for family history so that centers will still have to use other criteria thus the numeric thresholds, although ideal, are not yet ready for use. However it is the right approach in the longer term but not yet developed enough for broad use. It is valuable for older donors where the error margins are not likely as large. | Thank you. We expanded the discussion of the limitations of the modelling. We also clarified that the new online tool represents a first (albeit important) step in generating the information necessary to make donor selection and decision making more transparent and defensible, but emphasize the need for continued research to strengthen precision and minimize uncertainty in these estimates. We revised Table 1 to clarify how the tool should be used. |

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| 1.2.5: This item has 2 sentences. The first sentence I entirely agree with. But for the second sentence, I recommend that risks should be provided in multiple ways - in *both* absolute and as relative risk formats so that potential donors can understand the data in its various meanings. Also, regarding 1.2.9: if the donor is eligible, the transplant team should not automatically communicate the donor's eligibility to the recipient UNLESS the donor gives permission to disclose this information. The way this is item is worded is not subtle enough. | Thank you. We emphasized conveying absolute risks to support donor candidate informed decision making. In our modelling description, we clarify how absolute and relative risks are used to develop estimates of absolute incidence. We agree with the comment about communication of eligibility and revised the recommendation to read: "*If a donor candidate is not acceptable, the transplant program should explain the reason for non-acceptance to the donor candidate*." |
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| I don't believe that the use of the online decision tool in the recent NEJM article that underlies the quantitative approach in these guidelines has been adequately validated for the uses envisioned by these guidelines. The online tool has a limited number of data elements. I also think it has a real potential to backfire and oversimplify what is a complex decision making process. The background discussion states that the use of the tool is designed to get away from the use of single risk factors and promote a more holistic assessment of potential donor risks.<br><br>I don't believe it will do that. I think the proposed tool has the potential to be the major driver of decision making that could force centers to make decisions that they might otherwise not make. It is not clear how one would use the numerical output of the tool to set a center-risk level. Also there is the statement that these risk levels should be "generally consistent among centers within a region." I don't see why this needs to be the case. Also there is no data that the risk of ESRD derived from the calculator is valid in the post-donation setting. The NEJM article leaves the mistaken impression that it quantifies post-donation risks, it does not do this. The data used to generate the ESRD risk is relatively short term and is much shorter than the time interval between donation and the development of ESRD in donors. Although the article points this out more than once I am not sure that the wider community will recognize the limitations of the ESRD predictions. In my view this approach is not ready for "prime time" and I worry that it will have effects opposite of its intention of promoting a more nuanced patient-specific living donation decision. I think it could also be used by potential | Thank you. Please see our responses to similar comments above. We believe the revised prose conveys sufficient caution to avoid some of the concerns you have outlined. We have also removed the suggestion that acceptable risk thresholds should be consistent within a region. |

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| donors to play off centers against each other by comparing online tool generated risk thresholds. I also wonder if there is the potential to misuse these center specific risk thresholds in a program oversight/regulatory framework i.e., UNOS or CMS (and I work for UNOS). Could this become part of a new metric to compare programs and outcomes? Some might see this as good but I'm not convinced it would be beneficial. Although this is well intentioned I don't think there is adequate data or experience to support this approach at this time. I think this online tool approach is something that centers may want to get experience using but I don't think there is any experience at this point that justifies including it as part of these influential KDIGO guidelines. | |
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| If the donor candidate is not acceptable, the transplant center should exclude the candidate from donation and explain the reason TO THE CANDIDATE DONOR for non-acceptance. | We agree and revised the recommendation to read: "*If a donor candidate is not acceptable, the transplant program should explain the reason for non-acceptance to the donor candidate*." |
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| It could be critical to give a precise measure of local donor risk on a single-center basis. | We agree and recommend provision of local risk data when available. |
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| While I agree with the recommendation that the excluded donor candidates should be offered evaluation at a different center, many typically do not. Many of them also do not have primary care physician or medical insurance. Follow-up of the abnormal clinical investigations or findings in that setting has always been a difficult aspect of excluded donors. I am not sure that the simple advice that they need to seek medical follow-up on their own is sufficient from a moral obligation point-of-view. The other point is that the excluded donor care is mentioned in the guideline 1.2.8, no explanation was provided in the following rationale. | Please see prior comments and responses – We removed the recommendation to offer evaluation at another program. We strengthened emphasis on the obligation to ensure donors and donor candidates have access to medical follow-up, including within the recommendation statements in Ch. 1, the supporting rationale, Table 2 and Ch. 19. |

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| I miss some sentences about legal aspects and also if there are national guidelines from health authorities. | We added reference to the European statements. |
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| Individualized quantitative risk estimates may not be truly "individualized" to a specific donor candidate. For instance, estimates derived from statistical models with 10 variables (e.g., age, race, sex, IDDM [yes/no], use of hypertensive medication [yes/no], eGFR, ACR, systolic blood pressure, history of smoking, and BMI: Grams, NEJM, 2015; DOI: 10.1056/NEJMoa1510491) may not distinguish between one individual with the high-risk APOL1 variants and a counterpart with the low-risk APOL1 variants (Parsa, NEJM, 2013; vol 369; no 23). Moreover, such individualized estimates do not have confidence intervals to express statistical, model, and parametric uncertainty. A strict threshold is prone to neglect these sources of underlying uncertainty in the so-called individualized estimate. For these reasons, decisions shared by BOTH care provider and candidate may be more appropriate -- and truly informed -- if they highlight the outlined limitations of absolute risk estimates. | Thank you. We revised the text to emphasize that application of the currently available online tool in the clinical setting at the present time requires clinician insight and interpretation, including consideration of additional factors such as genetic predisposition which were not available in data sources used to develop the first phase of risk model. We also emphasize these themes in the Research Recommendations and throughout other chapters, such as Ch. 14 (Genetics). |
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| 1. Under Goals and Principles of Donor Evaluation: The last sentence states: The transplant center must have a mechanism for resolving disagreement among team members regarding acceptance and exclusion of donor candidates. One concept that we feel is important is that this mechanism for disputes have an external arbitration to avoid perceived conflicts of interest. i.e., member from another department (Ethics) within the institution. | Please see prior similar comments and our responses above. |
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| 2. While I agree and embrace the concept that each transplant center should develop and communicate a quantitative threshold of 'acceptable risk' for each serious post-donation adverse outcome they wish to avoid, and the notion that this threshold should be both evidence-based and consensus-based, I think the suggestion that this should be consistent among centers | Please see prior similar comments and our responses above. |

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| within a region is a difficult concept to apply. This would, in effect, require programs align multiple facets of their programs to include the quality programs. It would necessitate common protocols, processes, and infrastructure to facilitate evaluation and measurement of the thresholds and outcomes. For example, not all centers perform stress tests on all donors, this would be one factor that might be taken into consideration in a predictive model, but if all centers do not evaluate patients in a similar fashion, the model would lack predictability. As more data emerge nationally, the threshold will become clear and will be both evidence-based and consensus-based. This will emerge without any effect introduced by practice variation from different centers as large numbers will provide the power. | |
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| 3. Using a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of kidney failure is an important recommendation. If possible, developing this concept more is key and this threshold should be the main driver of acceptance as it is difficult to predict how donation will affect the subsequent risk of kidney failure. | We expanded the discussion of the limitations of the modelling and the importance of ongoing work to improve the precision of long-term risk estimates. |
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| 4. In table 2: Roles and responsibilities of participants in donor candidate identification, evaluation, care and follow-up. Would consider the addition of educating the donor candidate on the importance of post donation followup. Under the responsibilities for Donor/Donor Candidate Physician/Nephrologist, Donor Surgeon, nurse coordinator, and ILDA. | Thank you. We revised this description in Table 2. |
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| Three issues with regards to the quantitative approach to predicting post-donation risk | |
| 1) Inadequate evidence to predict post-donation risk of outcomes in people who do NOT donate, and much less for those that do. Published literature on this topic is primarily a US cohort. | We agree and made this limitation more transparent in the revised text. |
| 2) This is not a concept that is intuitive to nephrologists and people involved in transplantation at the moment. I think if I asked someone involved in transplantation what 20-year risk of ESRD would they accept in a donor, most would not be able to answer that question. | We agree that concept is new and requires a shift from conventional intuition. However, we believe that defining a new framework for risk assessment is vital to advance the field to more defensible, transparent donor risk assessment, counseling and decisions-marking. |

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| 3) Online calculator http://www.transplantmodels.com/esrdrisk is difficult to use and not insightful for consumers. Needs to be adapted for all levels of health literacy. | We are continuing to improve the online tool based on the feedback received. The tool is dynamic and will continue to be updated with new data as it becomes available, and other enhancements over time. |
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| We strongly endorse the recommendation that risks are described in absolute terms and that donor candidates learn about the uncertainty of risks. We strongly encourage that risks of surgery be compared to "other surgical risks" as recommended by AST's Living Donor Community of Practice Consensus Conference (Tan et al, 2015). This is in response to 1.2.5. | We agree. Please see Ch. 19: Surgical Approaches, for a comprehensive description of the outcomes and risks of different approaches to donor nephrectomy. |
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| We must have a country policy and not a center policy. | Based on prior comments, we removed the suggestion that the acceptable risk threshold should be consistent within a region. To be respectful to variations in populations across regions and jurisdictions, we framed the points in Ch. 1 from the perspective of consistency at a given transplant program. |
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| Concerning 1.2.5 recommendation and rationale: | |
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| Donor autonomy does not overrule medical judgment *after a shared decision* has been made. This signifies that donor's opinion is not without any influence on the "center", especially in the presence of a "substantial uncertainty" on the different estimates. In other words, the transplant threshold for acceptable post-donation risk should not be a line, but a colored zone/band with a one-sided progressively more saturated color periphery. | We are saying there are clear risk thresholds where the transplant program will not proceed with donation. It is important to make those thresholds transparent, and allow informed donor autonomy and the ability to decide to proceed with to donation when estimated risk is within a transplant program's acceptable range. |
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| A detail on page 18: there is no medical benefit to donating a kidney. The concept about "medical" is now quite inclusive. I would suggest "there is no physical benefit, etc." | Thank you. This wording no longer exists in the final text. |
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| Congratulations for this tremendous work! | Thank you for your review and feedback. |

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| Pages 4, 5: "The same threshold applies to all donor candidates. The threshold may vary across regions, but should be generally consistent among centers within a region". "The threshold can vary across regions, but should be fairly consistent among centers within a region,". I am not sure what the justification is for this statement. Why would the threshold rationally or ethically vary? What comprises a region? It may be that one center in a region has a more rational and ethically defensible threshold than all the other centers. Should they change their threshold to be "consistent"? | Please see prior similar comments and our responses above. prior comments. We removed this suggestion from the Guideline. |
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| Page 9: "The choice of pre-donation threshold should not be influenced by recipient characteristics or perceived urgency of transplantation." This statement also does take into account the principles of shared decision making. If the donors views are given any weight in the decision, often the condition of the recipient is a major consideration for what risk they are willing to take. An inflexible principle like this guideline suggests is far too paternalistic. It is one thing to give full information to the potential donor and give our professional opinion, it is another to make a unilateral decision without taking into account the competing variables that the potential donor brings. We really do not know all the competing risks and benefits that donation might bring to a donor. This guideline only, in a one sided way is looking at the risks. | To clarify, all that is being specified is the absolute contraindication (threshold of risk) where a transplant program determines that a candidate is ineligible to become a kidney donor. This approach is patient-centric and more transparent than contemporary practice considering risk factors in isolation, as any candidate who has estimated risk below this threshold has the right to make an informed decision as to whether they wish to proceed with kidney donation or not. |
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| Pages 18-19: "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)." Again this statement claims to respect the autonomy of the potential donor but really does not since it is very "black and white", either the potential donor met eligibility or they do not. This in not consistent with 17.3. | Please see prior similar comments and our responses above. |

| **1.3 Roles and Responsibilities in Living Donor Transplantation** | |
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| 1.3.5: The transplant center team should organize, in accordance and involving the referring center/physician, the donor evaluation efficiently to meet the needs of donor candidates, intended recipients and the transplant center. (Not Graded) I work in the only hospital in Sardinia that provides a transplant program for about 1.5 million resident people and we are referent for several patients from the south of Italy that requires kidney/pancreas transplantation from living or deceased donor. Nothing would be done without a strong and synergistic cooperation with the colleagues in the periphery. This is especially true in those regions, like mine, where all the facilities are very distant between each other. These colleagues should be mentioned, because they do an excellent work and the more are involved, the better results. This is my experience. | This was revised to read: "*The transplant program should conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and the transplant program."* |
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| The challenge that was mentioned in this chapter is that the difficulty in creating cohort data for long term donor risk is lack of lengthy follow-up. I think we should discuss on how we can "embrace" a long-term relationship with the donor. Are there programs currently existing with that purpose on mind? | The concept is to emphasize that the living donor evaluation should be regarded as the initial stages of a long-term, collaborative relationship between two parties (the donor candidate and the transplant program), and that follow-up is a critical element of donor care. Please see Ch. 19: Post-Donation Follow-Up Care for a detailed discussion of the rationale for and practices of follow-up. |
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| 1.3.1: It has become clear that a condition to improve the results is to perform the transplant as early as possible, since the time on dialysis negatively affects patient and graft survival, with greater impact after six months (Ref: Nephrology 2008; 28 (2): 159-67, Kidney Int 2000; 58: 1311-7) | We agree and emphasized consideration of preemptive living donor transplantation when possible in Table 2. |
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| 1.3.2: The guides on the donor follow-up methods are scarce and make difficult graduating the recommendations; all are based on evidence III-IV (Ref. ww.nhmrc.gov.au/publications/subjects/organ htm) | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |

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| These recommendations take into consideration the concept of the independent living donor advocate as well as the cooling off period. I think this is incredibly important. | Thank you for the comment. |
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| 1.3.5: I think it is hard to define efficiency in this setting. | We clarified the recommendation to read: "*The transplant program should conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and the transplant program*." In the supporting prose we also discuss that the donor candidate must have adequate time to make an informed decision and must accept the need for long-term follow-up. |
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| The role of the primary care physician is quite different from country to country. | We agree and have prepared Ch.1 and Ch. 19 (Post-Donation Follow-up Care) with this perspective in mind. |
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| 1.3.4: Adequate time to contemplate information relevant to making a decision should not be confused with timely communications. See below: Our group has become increasingly aware of chronic and inconsistent donor communications, from transplant center to potential donor. These includes significant delays in everything from the timing of initial return calls to important scheduling or finding following up. These communication voids are causing donor confusion as to the timing and value of their potentially "life-saving" act. Be it justified as a transplant center's "cooling off" period or the reality of department under-staffing, we respectfully ask transplant centers to improve timely communications with potential donors, (particularly after their first call in) so they remain informed about the process, next steps and expected delays. The objective is to keep potential donors respectfully informed and confident that the center values their intent to help someone in need. | We agree and emphasize these issues in the revised text. |

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| 1.3.3 is not feasible for smaller teams. It is questionable whether this measure actually reduces conflict of interest since decisions need to be made at interdisciplinary conferences. | We appreciate this perspective. The final recommendation now reads: " *The transplant program should minimize conflict of interest by providing at least one key team member not involved in the care or evaluation of the intended recipient who evaluates a donor candidate and participates in the determination of donor acceptance."* |
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| 1. Under Goals and Principles of Donor Evaluation: The last sentence states: The transplant center must have a mechanism for resolving disagreement among team members regarding acceptance and exclusion of donor candidates. One concept that we feel is important is that this mechanism for disputes have an external arbitration to avoid perceived conflicts of interest. i.e., Member from another department (Ethics) within the institution. | Please see prior similar comments and our responses above. |
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| 2. While I agree and embrace the concept that each transplant center should develop and communicate a quantitative threshold of 'acceptable risk' for each serious post-donation adverse outcome they wish to avoid, and the notion that this threshold should be both evidence-based and consensus-based, I think the suggestion that this should be consistent among centers within a region is a difficult concept to apply. This would, in effect, require programs align multiple facets of their programs to include the quality programs. It would necessitate common protocols, processes, and infrastructure to facilitate evaluation and measurement of the thresholds and outcomes. For example, not all centers perform stress tests on all donors, this would be one factor that might be taken into consideration in a predictive model, but if all centers do not evaluate patients in a similar fashion, the model would lack predictability. As more data emerge nationally, the threshold will become clear and will be both evidence-based and consensus-based. This will emerge without any effect introduced by practice variation from different centers as large numbers will provide the power. | Please see prior similar comments and our responses above. |

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| 3. Using a quantitative framework for donor candidate medical evaluation and acceptance centered on lifetime risk of kidney failure is an important recommendation. If possible, developing this concept more is key and this threshold should be the main driver of acceptance as it is difficult to predict how donation will affect the subsequent risk of kidney failure. | Please see prior similar comments and our responses above. |
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| 4. In table 2: Roles and responsibilities of participants in donor candidate identification, evaluation, care and follow-up. Would consider the addition of educating the donor candidate on the importance of post donation followup. Under the responsibilities for Donor/Donor Candidate Physician/Nephrologist, Donor Surgeon, nurse coordinator, and ILDA. | Please see prior similar comments and our responses above. |
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| It sounds good, but centers can't be responsible for long term care. Donors and the public may misunderstand this and expect too much from centers. | We believe the transplant program has a moral and professional obligation to coordinate a plan for follow-up of medical issues identified during the evaluation that resulted in a donor candidate being excluded, even if the program does not directly provide the care. Please see the public comments above calling for an expression of the importance of this obligation. |
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| Suggested changes underlined: | |
| 1.3.1: Healthcare providers for patients with kidney failure should offer <u>appropriately levelled</u> 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)* | This recommendation was removed from Ch.1 in streamlining the final document, but Table 2 in this chapter was retained and expanded to emphasize many of these themes. Please see Ch. 2 for detailed discussion of the information that should be included in education and informed consent, including treatment alternatives available to transplant candidates, and average expected outcomes. |

**Chapter 2: Informed Consent**

| COMMENT | RESPONSE |
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| I agree on all the points above since these statements are more of guided by sound ethical Principles, rather than evidence-based data. Those above mentioned should be HIGHLY RECOMMENDED even if not based on Research. | Thank you. |
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| 2.1, 2.2, 2.3: see comments in the previous section. | Thank you for the comments. Please see responses above. |
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| 2.3: Children, mentally challenged and substitute decision makers (incl. e.g., prisoners) can NEVER be accepted as organ donor. Organ donation under any possibility of emotional, social, situational pressure is unacceptable. | We appreciate the controversy on this issue. After due consideration, we retained the recommendation but revised it to read "*Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (e.g., children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review*." We expanded the supporting rationale discussing the considerations related to this topic, and added a Research Recommendation to "*Evaluate appropriate circumstances for and approaches to substitute decision making and use of surrogate consent, including definition of the necessary supporting ethical framework for particular scenarios*." |
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| 2.6: The donor HAS to agree to disclose his/her medical data to the recipient. The donor identity is not a question, as living donation or from any unknown donor (=removing kidney for an unknown recipient) is again unacceptable. It happens only in the case of organ trafficking could be interesting use of CKD-EPI to measure GFR in elderly patients. /sic/ | We revised the chapter and Table 1. to provide more detail on practices and privacy law restrictions related to sharing of personal health information between donors and recipients. |
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| 2.3: Using a substitute decision maker; does not look ethical. If the organ is in the body of a person who cannot make decision, ethically it is better to forget that organ. I was not convinced with the rationale. | Please see the prior similar comment and our response above. |

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| Included in point 2.4: A discovered misattributed biological relationship between the donor candidate and intended recipient (such as misattributed paternity in a father-child relationship) In my opinion this point, when discovered, should not be informed, as to do so can destroy the receptor family. It is enough to explain to the donor that he is not suitable as donor for the son. The family relation has to be preserved, for the good of the child. | We are not recommending what policy the transplant program should adopt. Rather, we recommend that the transplant program should develop a policy on the handling such information (which may include not disclosing the information to either party), and that this policy should be shared with donor candidates and recipients. |
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| The donor candidate must be older (according to the law in each country) (WHO) and in full possession of his/her mental, psychological and social skills, freely express in writing his/her will to be kidney donor, in front of an entity agreed by the country's legislation. Minors must be prevented always as also patient with some degree of mental, psychological or social disabilities to make this decision (Ref: Curr Transpl Rep 2015; 2: 29-34, Am J Transplant 2013; 13: 2713-2721; Clin Transplant 2011; 25: 185-190). | Please see the prior similar comment and our response above. |
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| I would love to see some enhanced language to support long-term donor follow-up in informed consent as well as potential to contribute to research and registry based studies. | Thank you. We have now strengthened related language in Ch.1, Ch.2 and Ch. 19. |
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| Regarding 2.5: the first reference cited in the overall draft of this report was by Thiessen et al. 2014; AJT regarding the involvement of donors in decision making when donors are marginal donor cases. It may be worthwhile to soften this policy item to consider the role of donors in making a case for their option of donating. | Thank you. We revised the Guideline text to emphasis the importance of shared decision making. |
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| Re: 2.7: this guideline should reference health literacy best practices and at the very minimum, recommend the use of teach back method which has been advocated by AHRQ and many other bodies (with evidence!) as a way of ascertaining comprehension. Also, 'understanding' should be phrased as 'comprehension'. | Thank you. We revised the text to emphasize that "*Optimal methods to assess understanding in living donor candidates are not well defined [37, 55], but general techniques for comprehension assessment may include use of "teach-back," in which patients are asked to "teach back" what they have learned during their visit.[73]* " which includes a reference to the AHRQ method. We also added mention of pilot testing of an |

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| | instrument developed by Dr. Gordon to assess comprehension during informed consent for living liver donation that provides a model for developing similar instruments for comprehension assessment in living kidney donor candidates. We also emphasize the need for more work in the leading Research Recommendation to "*Determine the best method to achieve informed consent from living kidney donor candidates, including what methods are most useful to impart information including risks and outcomes and what methods are most useful to assess comprehension."* We use the word "comprehension" intermittently through the revised text, along with the word "understanding" in places. |
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| Re: 2.10: the way this is stated makes it sound like no matter what, the donor's decision will be communicated to the recipient/others. I recommend softening this. Relatedly, the draft KDIGO report as it is written is unbalanced in its argument against the use of alibis. The report emphasizes the negative aspects but does not provide the positive aspects of protecting the potential donor from undue pressure or adverse effects on their relationship with the transplant candidate (recipient). I recommend rewriting this section so that it is more balanced. I know that empirical data are currently being collected on this topic - look for ATC abstracts - and the data should inform this policy. The matter of *how* information is disclosed has not been covered in this report. The LDCoP Consensus Conference which is cited in this report does discuss the importance of repetition and other adult learning evidence-based approaches to foster understanding that should be recommended. The topic of shared decision making should reference a key article on this: Gordon et al. AJT 2013;12(9):1149. I've also called for the standardization of the informed consent process for living donors - in reference 19 - it would be nice if you could cite ref 19 in this section. Competency is more than just age, but also health/mental health status. I recommend that the report states that the minimum age of majority varies by states, by transplant centers, and internationally. | Thank you. We clarified (softened) the wording as suggested. We also emphasize support by transplant programs to help donor candidates who decide not to proceed with donation (which includes help with communication to family members etc.). We added citation of the suggested article on shared decision making in this chapter and the AST LD-CoP. The revised text notes that "*Prior guidelines and policy statements have recommended that discussions be provided in a language that enables meaningful dialogue between the donor candidate and transplant program staff, using communication strategies and materials that are culturally sensitive.*[45, 47] *The information should also be presented in a sympathetic environment, using simple language, allowing time for questions, with information that is appropriate to a candidate's understanding and experience, at a pace determined by their needs.*[47] *Repetition of key information, and use of approaches that foster adult learning, are prudent.*[55] " |

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| 2.7: While I approve of the way this is written. I do not support mandating the use of the online risk assessment tool that seems to underlies other parts of these guidelines. | Thank you. We removed mention of the online risk assessment tool from this chapter. |
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| I can't agree that a transplant center 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). | Please see the prior similar comment and our response above. |
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| 2.3: Organ donation must never happen if the potential donor lacks the capacity to provide informed consent. Page 16: This includes a discussion about uncertainty in some long-term outcomes, when specific risks cannot be accurately quantified based on available data. Input: This includes an EXTENSIVE discussion that there is a huge lack in long-term data and that the longest studies followed their donors for less than two decades (see page7). The risks that cannot accurately be quantified need to be discussed in detail and (IMPORTANT) the negative outcomes that have recently been achieved need to be provided to the donor (Study 10, 11, 12). On page 20 it says: "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." The emotional role of a donor is a highly complex one. So far no measures have been taken on how to handle the disclosure of informed consent bearing this specific issue in mind. Because some potential donor may be more inclined to accept certain risks since the recipient seems to have the heavier burden to carry, there needs to be a focus on this fact and informed consent needs to be given with a strong emphasis on the negative possible outcomes and the life changes that might occur by this. This is also why the science of the real long term results on e.g. mortality or ESRD should be extensively discussed with the donor. | Thank you. Please see the prior similar comment and our response above. This chapter does not repeat the detail of the content of the outcomes was that information is covered in other chapter; rather we describe the process of informed consent. We updated the Research Recommendations to incorporate your valuable suggestion. |
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| I cannot envision any clinical context when a substitute decision make is required on behalf of a living donor. When such a situation arises, the candidate should be deferred. | Please see the prior similar comment and our response above. |
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| I do not approve on any exceptions not to use children and people who lacks capacity to make informed consent as living donors. Information on economic compensation and health insurances (both provided by health authorities and private) should be given. | Please see the prior similar comment and our response above. |
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| 2.5: In our work with potential living donors one of the major frustrations expressed has been failure by the center to respond to communication within a reasonable time frame. In one instance, it moved the potential donor to contact another center. To build a delay into the evaluation process and not inform the donor of it and the reasons for such a delay is patronizing, adds an element of distrust, and exposes the center to the charge of being uncaring. | Thank you. We removed this as a recommendation. In the text we simply make the point the donor candidate should have adequate time to make an informed decision (without mandating a delay). |
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| 2.3: Persons who are not able to give consent themselves cannot be donors. | Please see the prior similar comment and our response above. |
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| Under Information disclosed to the donor candidate: While a recommendation appears to be made that the donor should be notified if the intended recipient has health information that could impact the transplant outcome, in the end, it appears a recommendation is not made. In the interest of full disclosure, donors should be notified of specifics that could affect the outcome of a transplant in a premature or reckless manner. The nature of the kidney disease, when known, should be disclosed as some renal diseases like dense deposit disease, FSGS, and MPGN II have an accelerated recurrence resulting in early graft loss. And as in your example, donor candidates should know if the recipient lost a previously transplanted kidney due to medication non-adherence. In most cases, I would hope the issue of non-compliance has been addressed and this too can be and should be | Thank you. We revised the chapter and Table 1 to provide more detail on practices and privacy law restrictions related to sharing of personal health information between donors and recipients. We also added a Research Recommendation to "*Through focus groups and/or surveys, develop standardized criteria for circumstances under which intended recipients should be asked for permission to disclose certain personal health information to the living kidney donor candidate (such as loss of a prior graft due to medication non-adherence), so that donor candidates can make an informed decision about whether to proceed with donation or not. Develop standardized criteria for when donation and transplant should not proceed in the absence of disclosure, weighing considerations of privacy law, ethics, and the concerns of* |

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| shared with the donor. Knowledge of the potentially eminent and rapid graft loss is critical to informed consent as a donor may opt out if they realize the substantial risk they are accepting will only translate into a short lived benefit as a result of the disease or lack of conformity. This is not unlike the importance of discussing the differing risk and benefit of outcomes after compatible vs. incompatible transplantation. | *donor and recipient candidates*." |
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| In response to 2.5: We agree that 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." We recommend that when donor candidates are told of the anticipated timeline of donation, this should include any alteration or possible extension of the timeline due to "cooling off" periods or retesting for HIV or other infections for donors who are considered high-risk. We also recommend that donors be told of possible delays due to required behavioral modifications for donor candidates who are considered high-risk for the transmission of HIV or other diseases. Further, transplant centers that have a policy of not promptly returning communications with donor candidates in order to provide donor candidates more time for contemplation should disclose this to the candidates. | Thank you. Based on other comments, we removed "a cooling off" period as an explicit recommendation. In the text we simply make the point the donor candidate should have adequate time to make an informed decision (without mandating a delay). |
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| Recommend referencing Chapter 17, as there is overlap. Recommend adding language that the recipient candidate or any agent of the recipient candidate should not be present during some part of the donor's informed consent process. | Thank you. We now begin this section referring the reader to "*also refer to Chapter 1 for related discussions on the framework for decision-making and Chapter 18 on the ethical, legal, and policy framework of living donation."* Please note that the Policy chapter was renumbered from 17 to 18. We also recommend that "*Informed consent for donation should be obtained from the donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision*." |
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| Please see Chapter 1 for general comments. Chapter 2: In light of the discussion of risk calculation and risk thresholds in the Rationale for Chapter 1, it is surprising that there are no recommendations that centers | • We now clarify that informed consent must address "The processes of evaluation, donor acceptance, and follow-up" and provide details related to covering issues of the "processes of donor candidate |

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| communicate a need for long-term follow-up in living donors, either by the center or from the donor's personal health care providers. This would seem to be an important element for informed consent and for disclosure and understanding. Recommendation 2.5 states that centers should communicate "recommendations on need for follow-up care," but this seems potentially different than a specific recommendation stating that centers communicate unequivocally that donors should and must receive follow-up care. In this same recommendation, Living Donor Committee members questioned whether it should be stated more clearly that centers should inform donors of their need to obtain/maintain health insurance coverage. Recommendation 2.10 notes that the center should assist the donor in communicating a decision not to donate. However, it does not include the recommendation noted in the Rationale section, which is that "medical alibis" are discouraged. In fact, the paragraph in the Rationale section on this issue is somewhat unclear because it seems to be recommending that alibis not be used but then notes that there is controversy about teams assisting candidates with wording that includes factual medical findings which may or may not preclude donation. It is not clear whether this latter statement is saying that there is some sentiment that teams provide facts that may not preclude donation but are to be used as the medical alibi? Rewording here might be helpful. Evidence is cited in the Rationale section of the chapter. It is surprising, then, that all of the recommendations are ungraded. Perhaps there needs to be more explanation in the Preface or elsewhere in the document regarding the threshold that had to be met before something was graded. The Rationale section notes that the donor candidate should understand "the transplant center's policy about providing donation-related healthcare." However, it is unclear what "donation-related" would mean or how this would be explained to donors. It further suggests that the recommendations in Chapter 2 should be revised to indicate that centers should explain to donors what would and would not be considered donation-related. | • evaluation, candidacy determination, and follow-up" during informed consent.<br>• Revised recommendation 2.5 and Table 1 provides the framework for information disclosure to the donor candidate. The specific risk content is provided in other chapters.<br>• We improved the rationale discussing provision of a general statement regarding an "unsuitability to donate" to protect donors who wish to withdraw.<br>• We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document.<br>• We also corrected the "donation-related" healthcare wording in the Chapter. |
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| Good job. It seems to favor actual formal testing of donors, which I favor. Somewhere it should say that recipients have a right to know certain donor | • Thank you. We revised the chapter and Table 1. to provide more detail on practices and privacy law restrictions related to sharing of |

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| information and if donors refuse telling the recipient, the transplant will not go forward. I am not sure it exactly says that.<br>This section should require that an approximate predonation baseline risk of lifetime ESRD be understood by candidates, and they should hear the published risk multiples of 8-11-fold that are associated with donation. These were nicely derived and vigorously defended a year ago but now seem to be barely acknowledged and certainly minimized and deemphasized. This KDIGO manuscript is no exception. While predonation baseline risks are presented to the decimal point, the risk multiples are never stated clearly anywhere. Maybe they are not precisely known but can we not say they are approximately known and provide a number or range of numbers? I have not heard an explanation for this. It seems we have all agreed to just stop talking about them. They are now simply "unclear" or "debated." What happened? I hope we have not subliminally decided to provide donors with all possible good news but shield them from potentially bad news. | personal health information between donors and recipients.<br>• Revised recommendation 2.5 and Table 1 provides the framework for information disclosure to the donor candidate. The specific risk content is provided in other chapters.<br>• In Ch. 1 and Ch.2 we emphasize that the transplant program has the responsibility to disclose anticipated benefits and alternatives to the donor and recipient, anticipated risks and any uncertainty in these estimates to the donor candidate, tailored when possible for the characteristics of each donor candidate. |
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| This chapter deals with the process and issues of obtaining informed consent for living kidney donation. It addresses the transplant unit's responsibilities to donor consent in areas of donor capacity, understanding, voluntarism and the disclosure. | |
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| **Quality of Data for Recommendations:** | |
| · Data and discussion for recommendations is by necessity empiric and opinion based in content but is nevertheless well referenced in that setting. The variations are acknowledged and the discussion of issues is detailed. Some of the discussion leads to recommendations that have not been included (see below) | |
| · Wonder if ABOi should also be included as a choice in immunological incompatibility discussion on p20 which focuses only on KPD | Thank you. We include the following statement in Ch. 3: "*Donor candidates who are ABO or HLA incompatible with their intended recipient should be informed of expected patient and graft survival for paired kidney donation and incompatible transplantation compared with compatible living donor transplantation and deceased donor transplantation, as well as expected patient survival on dialysis, based on best available information*." |

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| **Agreement with recommendations and other suggestions** | |
| · All recommendations are 'not graded' level of evidence | |
| · Agree with statements but would suggest some rewording in following: | |
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| 2.3 may benefit from rewording to say 'if legally and ethically appropriate and in extraordinary circumstances' to ensure jurisdictional legal requirements are met (e.g., in most, children could not be considered as donors). | Thank you. Please see the prior similar comment and our response above. |
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| Also the wording in background "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." may provide better wording for recommendation | We revised the wording based on the feedback in several public comments. |
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| 2.5, pt 2: needs to be in context that there is also an expectation to respect recipient privacy - so should specify general not specific treatment options for recipient treatment alternatives can be provided. | Thank you. Throughout Ch. 2 we now emphasize that this discussion should be framed in general terms. |
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| For pt 7: request clarification for 'if it is a crime to receive valuable consideration' – is that not generally the case so why 'if' rather than 'it is a crime' | Thank you. Corrected. |
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| **Suggestions for additional recommendations** | |
| · Explicit statement that the donor should have their own advocate in transplant center with no conflict of interest with recipient is covered in data/discussion but would be worthy of a recommendation statement. | We discuss the function of Independent Living Donor Advocates in the rationale, but given the international perspective of the Guideline, note that 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. |
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| · Discussion on p20 of data/discussion that 'Interviewing the donor candidate without the intended recipient is important in the assessment of voluntarism' should also be a recommendation. | We added a recommendation that "*Informed consent for donation should be obtained from the donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision*." |

**CHAPTER 3: Compatibility Testing, Incompatible Living Donor Transplantation, and Paired Donation**

| COMMENT | RESPONSE |
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| 3.4: all donors should be typed for classical class I and II HLA Ag, not only for recipients with anti-HLA antibodies (which is obvious). Post-transplantation development of dnDSA requires full typing of the donor anyway. | We agree. We revised the recommendation to apply to all donor candidates. |
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| Why all of the recommendations here were not graded? I think these statements can be graded at least as Level 2. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |
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| 3.7: Paired kidney donation is not allowed in some countries. The item should add "if paired kidney donation is allowed". | We revised the recommendation to read "*Non-directed donor candidates should be informed of availability, risks and benefits of participating in kidney paired donation*." |
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| 3.6: The HLA-A, B, DR incompatibility has no negative influence, but those receiving grafts from donors older than 59 years have lower survival rates, as well as being a recipient woman, which is an independent risk factor (Ref: Transplantation 2010; 89: 694-701) | This recommendation statement refers to counseling related to ABO & HLA (ie, crossmatch or Luminex) incompatible transplantation - ie, risk related to preformed antibodies. The statement does not relate to outcomes according to the degree of HLA matching. The focus on incompatibility is explicitly stated. "HLA incompatible" is preferred to "crossmatch incompatible" because it encompasses positive Luminex as a form of incompatibility. |
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| 3.7: Although it depends on donor policies of each country, we can consider or implement the option of cross-donor (crossover donation or kidney paired exchange) as a national unified protocol, with an excellent selection of partners for this option, and also accept altruistic living donation, in order to help the long lists of recipients (Ref: JAMA 1956; 160: 277-82, Am J Med Genet 1998; 77: 412-4, Transplantation 2010; 89: 1496-503) 3.7b- Crossover donation as a national protocol should assure the exchange of organs, with | We discuss the growth of kidney paired donation internationally and the potential benefits in the rationale. |

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| clearly defined points and accepted by the different groups that make up the national transplant program guidelines. (Ref: JAMA 1956; 160: 277-82, Am J Med Genet 1998; 77: 412-4, Transplantation 2010; 89: 1496-503) | |
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| 3.8: Given the increasing demand for organs and the excellent results of living transplantation between genetically unrelated persons, it is legally permitted this type of conduct and procedure (Ref: Council of Europe Resolution CM / Res (2008) on transplantation of kidneys from living donors who are not genetically related to the recipient. | Thank you for your endorsement. |
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| I am pleased to see 3.3, 3.7, and 3.8 included which all have the potential to improve transplant access to larger numbers of patients. | Thank you for your endorsement. |
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| 3.7: Informed of the availability of paired kidney donation (if it's available by the center or government policies), and that participation. /sic/ | We agree. Please see the prior similar comment and our response above. |
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| Also for ABO and HLA incompatible transplantation , reliable local statistics are often lacking. | In streamlining the full guideline, moved all recommendations related to informed consent to Ch. 2., including a discussion of the outcomes available treatment options. In the rationale for this chapter, we removed the emphasis on local outcomes, which may not be available. |
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| Why “Not graded” can’t be replaced by expert opinion? | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |
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| 3.4: I support this for the donors of immunized patients but reformulation is needed. It seems that donor typing is not necessary for nonimmunized patients. All donors should be typed minimum of HLA- A, B, DRB1. Also non-immunized patients may develop antibodies shortly after transplantation and | We agree. Please see the prior similar comment and our response above. |

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| it is preferable to have donor tissue type to determine donor specificity of such antibodies. EFI standards require living donor typing in all situations. The typing of living donors must be verified before transplantation. | |
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| Recommend that 3.9 mention/ address bridge donation. | "Bridge donors" as a component of "Never Ending Altruistic Donor" (NEAD) chains. We did not include details on all the forms of kidney paired donation in this discussion due to length considerations, but include many informative references for the interested reader (as well as in related sections of Ch. 19: Policy), including recent studies and review articles. |
| | |
| Recommend that the KPD section, paragraph 4, specify that non-directed donors be informed about regional or national options. | We recommend that "*Non-directed donor candidates should be informed of availability, risks and benefits of participating in kidney paired donation*." In the rationale we expand that *"Non-directed donors (donor without an identified recipient) have the unique potential to expand the donor pool through chains of kidney exchanges.*[95]*"* |
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| Please see Chapter 1 for general comments. Chapter 3: It is not clear that Recommendation 3.8 should include the phrase, "to maximize utility of their gift." While it would be important to inform non-directed donor candidates of opportunities for donating into a chain or paired exchange program, the potential for undue pressure arises if they are advised that this form of donation is necessarily preferable or should be selected by the donor. We agree they need full education on all options, but the choice should be their own and they should not be advised regarding which choice is "best." | Thank you. We deleted the phrase from the recommendation statement. |
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| The document is very good and a great advance in living donor management. My comments are really limited to chapter three and I have attached this below with comments. Most of these come from my Histocompatibility background and reflect what we have done in Canada to support KPD but also align with many labs practices. I am attaching the guidelines (not restricted to living donation) that TTS sponsored that were published in 2013 (ref: Tait | Thank you for your comments and guidance. |

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| BD et al. Consensus guidelines on the testing and clinical management issues associated with HLA and Non-HLA antibodies in transplantation. Transplantation 95: 19, 2013)<br>I am happy to discuss further if you have any questions. Or if I can be of any help please let me know. Congratulations on an excellent document. | |
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| 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). RE: highlight above: Not sure what is meant by this statement | Thank you. We removed the recommendation as insufficiently clear. |
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| 3.3: *ABO subtype testing* should be included when donation is planned to recipients with anti-A antibodies. (Not Graded) anti-A antibodies.<br>RE: highlight above: Do you mean if ABO incompatible transplant is being considered?<br>Do you mean blood group A subtyping only? If so should be stated as such. | We revised the statement to read "*Blood group A* subtype testing should be included when donation is planned to recipients with anti-A antibodies." |
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| 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)<br>RE: highlight above: DRB1, DRB345, DQA1,DQB1, DPA1, DPB1: Would argue that should be done for all in donor and recipients to assess risk for de novo DSA. In Canada for KPD we mandate this. What does PRA>0 mean | We agree. Please see the prior similar comment and our response above. |
| Are you recommending any specific technology? In Canada for KPD we mandate cPRA derived from solid phase single antigen bead testing. | We revised the rationale to note *"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 or flow cytometry crossmatching and Luminex® (Bio-Rad Laboratories, Inc., Hercules, CA, US) assays to determine the history of sensitization,[86] and this testing should be current before proceeding with donor nephrectomy and living donor transplantation"* and included citation of a contemporary consensus guideline. |

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| 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)<br>RE: immunologically: 3.5, 3.6. 3.7 are confusing as "blood type or crossmatch incompatibility, HLA incompatible and immunologically incompatible are all terms used. I would suggest trying to be consistent with language | Thank you for pointing this out. We revised to "ABO or HLA incompatible". |
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| RE: availability- Is this universally available? | We revised the statement with the qualification "if regionally available" |
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| Guideline text: 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. | We agree. Please see the prior similar comment and our response above. |
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| RE: **DQ:** see previous comment | Thank you. We added DQ as suggested |
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| RE: 2nd highlight above ["presence"]: Should be reworded. All loci should be typed as HLA antibodies to HLA A B C etc have been associated with a higher incidence of graft loss? | Thank you. We revised to mention all loci as suggested. |
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| Guideline text: 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. RE: highlight above ["current"]: Would reword to see pre transplants immunological risk assessment should include solid phase antibody testing of current (within a month) and "peak/historic" sera. Antibody testing and cell based crossmatching by CDC and or Flow should be performed we ask | Thank you. We revised the rationale to state to mention these testing modalities, emphasizing that testing should be current before proceeding with donor nephrectomy and living donor transplantation. We also added citation of the consensus guidelines by Tait el al. |
| for flow but this can be worded to reflect international group (see ref Tait B et | |

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| al Transplantation 2013). | |
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| The overall quality of data is good to very good (not graded). | Thank you. |
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| No additional important publications were identified. | Thank you. |
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| **State whether we agree with the recommendations and or suggest alternative wording or alternative recommendations.** | |
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| Recommendation 3.2: ABO blood typing should be performed in duplicate. It seems obvious that this should be done "before" organ recovery. Please delete this obvious statement from the sentence. | While this wording may reflect an obvious requirement, we believe the wording is appropriate for the goal of ensuring safety. Unintentional ABO incompatible transplant events due to failure of testing protocols have occurred and are catastrophic. Care in ABO verification is an important component of quality assurance. |
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| Recommendation 3.4: suggest to state: "All donors should be HLA typed for class I/II antigens and not only those for recipients with anti-HLA antibodies" | We agree. Please see the prior similar comment and our response above. |

**Chapter 4: Pre-Operative Evaluation and Management**

| COMMENTS | RESPONSE |
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| On page 28 you say patients are "Advised to stop smoking" this is very vague; you need to say whether active smoking is an absolute or relative contraindication to live renal donation. | Smoking is addressed with parallel logic in the current chapter and in Ch. 11 (Predonation Metabolic and Lifestyle Risk Factors). We recommend smoking cessation for 4 weeks prior to donation due to peri-operative risks (11.15) and encourage long-term abstinence due to long-term risks of cancer, cardiopulmonary disease and ESRD. Given the prevalence of smoking worldwide and current practice variation, the Work Group determined that a universal statement to exclude active smokers is unlikely to be acceptable to the community (as reflected in other public comments below). Our approach supports disclosure of risks and shared decision making. |
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| I approve 4.2. Suspect there will be resistance to this policy. However, when used in framework of ESRD risk, I think it is effective. | Thank you for the feedback and understanding of our rationale. |
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| The guideline misses an important opportunity to streamline practice. What order should tests and evaluations be done to minimize cost and improve efficiency? | The Checklist in the Executive Summary provides a list of recommended items for the evaluation of living kidney donor candidates, that progresses in a logical order to facilitate efficient practice. |
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| As in Chapter 3, these statements can be labelled at least a Level 2, even if with little evidence. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |
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| It is important to rule out the presence of hidden malignancy. The work-up should include abdominal echography and search for occult blood in the stool. Mammography and PAP test in women and urological investigation in men should be recommended particularly in potential donors older than 50 years. | Cancer screening to reduce risks of transmission from donor recipients and to reduce risks of post-donation health complications is addressed in a designated chapter (Ch. 13) |

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| 4.2: Smoking should be totally banned in living donors, since mortality increases in the long-term donor (Ref: JAMA 2010; 303: 959-66). | Please see the response to the first comment on Recommendation 4.2 above. We cited the JAMA article mentioned by the Reviewer, and as well as a 2016 article relating smoking to long-term ESRD risk, in Ch. 11 focused on lifestyle and metabolic risk factors |
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| I would note that current UNOS policy requires assessment of coagulation testing for donors. | As no specific data are available on assessment of bleeding risk in the context of donor nephrectomy, we discussed and cited recent evidence-based guidelines on this topic in relation to general surgery in the rationale. We modified the rationale to note the current UNOS policy requirement for coagulation testing as well as the recommendation for performance in a prior living donor guideline. |
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| I am personally a non-smoker and approve 4.2. My experience with smoking people is, that lifelong abstinence will be a challenging issue for most donor candidates. | Thank you for the feedback and understanding of our rationale. |
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| 4.2 required, not advised. | Please see the response to the first comment on Recommendation 4.2 above. |
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| While I do understand the data regarding preoperative non-invasive cardiac testing, I would submit that we should have a higher standard for donors. Even young people can suffer from tachyarrythmias that can prove lethal when stressed. The real problem is that they may not be amenable to diagnosis unless under stress. As such, a stress electrocardiogram is in my opinion a useful adjunct. | The Work Group discussed the concept of a "higher standard" for donor screening at length. Ultimately, it was recognized that screening is not risk-free – screening can lead to false positive results and additional unnecessary testing, including invasive testing with serious risks such as angiography. All additional testing incurs costs, and can pose inconvenience to the donor candidate and prolong the evaluation. Thus, we chose to recommend adherence to the most current evidence-based guidelines for pre-operative evaluation as most clinically sound practice that serves the best interests of the donor candidate. |

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| Please see Chapter 1 for general comments. Chapter 4: Again, as noted earlier, it is unclear why both recommendations are ungraded. Particularly with regard to smoking cessation, it is well-known that smoking increases the risk of complications associated with surgery, and it is well-established that smoking leads to multiple long-term health problems. The latter area is one of the best-documented in medicine and public health. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. We did cite key evidence on the risks of smoking as well as the health benefits of smoking cessation in the current chapter and in Ch. 11. |
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| This chapter considers the general preoperative evaluation for donation surgery and risks of adverse outcomes from the general perspective. It excludes workup/evaluation of conditions which may affect renal/metabolic/vascular outcomes dealt with in subsequent chapters. | |
| **Quality of Data for Recommendations:** | |
| The rationale is a very general discussion and cites the lack of detailed data in the literature. The rates of perioperative complications is somewhat US centric except for a Norwegian study. However as complication rates quoted reflect other studies their inclusion may not add to the discussion. The specifics of 'major' and 'minor' complications from the studies are not detailed. Further the data is not referenced in recommendations. | The cited literature reflects recent available publications of peri-operative complications after donor nephrectomy, several of which were performed in the US. We revised the background to reflect the most recent literature at the time of final document assembly, clarified that "major" and "minor" complications relate to grading according to the Clavien system for surgical complications and provided a reference, and expanded the description of available study limitations and the need for prospective collection of granular clinical data on living donor perioperative outcomes. While these data to do not lead to a specific recommendation in this chapter, the data are relevant to a fundamental concept in the guideline Framework (Ch. 1) – specifically that the transplant program team should provide the donor candidate with individualized quantitative estimates of risks from kidney donation including perioperative risks, individualized to the extent possible based on available data, and with recognition of associated uncertainty. Last, we referred the reader to Ch. 17 for discussion of acceptable surgical approaches to donor nephrectomy and anticipated outcomes. |
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| Studies on smoking cessation are comprehensive and do lead to a recommendation. | Thank you. |

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| Other management areas re thrombotic risk, use of aspirin, cardiac evaluation are discussed but specific literature evidence is sparse. | |
| Agreement with recommendations and other suggestions | |
| · The 2 recommendations are at a 'not graded' level of evidence | |
| · Agree with these | Thank you for your review. |
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| **Suggestions for additional recommendations** | |
| · It may be appropriate to state the donor should be made aware of the incidence of complications and be assessed specifically for increased risk of these e.g., obesity or OCP for thrombosis, etc. | Ch.1 (Framework) includes the recommendation "*When possible, the transplant program should provide the donor candidate with individualized quantitative estimates of short-term and long-term risks from donation, including recognition of associated uncertainty, in a manner that is easily understood by donor candidates.* (1.11)" For integration purposes, we referenced this concept in the rationale of the current chapter. Ch.2 (Informed Consent) emphasizes that the content of informed consent must include discussion of anticipated medical, surgical, psychosocial and economic outcomes of donation. |

**Chapter 5: Kidney Function**

| COMMENT | RESPONSE |
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| You know that GFR declines with age, so I think it is illogical to declare a fixed value below which donation contra-indicated. You will know this is the approach the British Transplantation Society / Renal Association have taken, page 59 of their guidelines. | This issue is raised repeatedly and is answered here in full, and detailed in the revised rationale. The recommendations are not changed. The cause and magnitude of GFR decline in aging is not well described. The "reference" values for GFR by age are based on a small study of white men. Although GFR is generally lower in older than younger people, the variation is wide, and it is not possible to distinguish between age-related decline and disease-related decline, so we do not recommend using these values for decision-making regarding kidney donation. Using the lifetime risk approach, older people, even with lower GFR, have lower risk than younger people for future ESRD, which allows older donors to have acceptable lifetime risk with lower GFR than would be acceptable for younger donors. The lowest thresholds for older people in other guidelines are in the range of 60 ml/min/1.73 m2 which is the value that we have recommended an absolute exclusion to donation. |
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| The mGFR thresholds for accepting a donor should be age stratified and for young donors <age 30 years should be >75ml/min/1.73m$^2$, especially if the birth weight of the donor was <2.5kg. One size dies not fit all for the mGFR thresholds for donation. This is a serious issue. | • Regarding age, see the prior comment and our response above.<br>• We did not include a practice recommendation related to birth weight at this time, as reliable sources of birthweight information are often not available during the evaluation and precise risk relationships have not yet been defined, but we included birthweight as a potential novel risk factor warranting further study in the Research Recommendations. |
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| I am uncomfortable with relying on eGFR to clear a donor for surgery. I think these confirmatory tests should be mandatory. | There are many comments on this point and variation in opinion at this time, including that confirmatory tests are mandatory in the US at present. Both measured and estimated GFR are associated with error. In practice, many transplant programs have multiple ascertainments of GFR that must be reconciled. In some studies eGFR is more accurate than 24-hour urine creatinine clearances. The text has been revised and |

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| | we retained a recommendation for confirmatory tests, qualified by availability (5.4). |
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| 5.3: We recommend initial evaluation of GFR (screening) using estimated GFR from serum creatinine concentration (eGFRcr). (1B) In my experience, the estimated GFR is not always a good predictor of the real GFR measured with iothalamate clearance. I think that a transplant program should offer at least an iothalamate clearance determination to reduce the likelihood of erroneous estimations. I agree using eGFR in candidate donors only initially in referring centers, in order to estimate the GFR and select the most likely candidates for the recipient. | Please see the prior similar comment and our response above. |
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| The use of 15 year predictions is unhelpful and should be deleted. The conclusions over 15 years and lifetime are completely different. For example the 15-year cumulative risk is low for the 20-year old donor compared to the 50-year old donor, but the opposite conclusion is true when looking at lifetime risk. Which one should be communicated to the patient? The lifetime risks are low and are therefore in question. The population cumulative risk for ESRD is nearly 3% for white males age 20 who almost all have an excellent GFR and no albuminuria. More than 30% of patients will develop diabetes prior to death. This will have a significant impact on the development of ESRD and death especially in those who develop the disease relatively early. Those developing disease after age 65 will have much less incremental harm. I suspect that the 1.6% lifetime cumulative risk is for an individual who will never smoke, get fat, develop diabetes mellitus or hypertension. Not likely. Why is this included?? The study does not communicate incremental risk in absolute terms from donation-which is what needs to be communicated. I always tell patients that there is a risk of developing ESRD donation whether they donate or not and this risk can only go up after donation. There is no discussion about premature death which is certainly to occur in those developing CKD and dialysis. The Figures in the NEJM and in the guideline (Fig 5+6) are different. Use of a log scale is deceptive. Use a linear scale! The recommendations | The revisions related to this topic are described in the comments and responses to Ch.1 above. |

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| based on risk are inconsistent. The figures show that a healthy young black male or female has a higher risk of ESRD than a 50-year white male with diabetes mellitus. Yet diabetes mellitus is a contraindication. | |
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| We are forced to put too much emphasis on serum creatinine based indicators of GFR (or creatinine clearance) as indicators of normal or near normal renal function. GFR is not a fixed attribute, but a dynamic physiologically-regulated function that can range from 122 ml/min/1.73 $m^2$ in the daytime to 86 ml/min/1.73$m^2$ during the night. It can fluctuate ± 4 ml/min/1.73 $m^2$ throughout the waking hours. Consequently, one or two measurements of eGFR in a patient can be misleading as to the quality of renal function given the fact that GFR can be raised and lowered by dietary, pharmacologic, and physiologic factors. It is a poor "Gold Standard" for judging the integrity of renal function given the fact that the values can be held within the normal range by compensatory hyperfiltration. Given the increasing life expectancy of the past decades, we need a measure that will reflect the number of functioning nephrons in a prospective donor to avoid reducing, by uninephrectomy, their total below a threshold that might promote the development of ESRD later in life. The maximal concentration of urinary solutes in individuals on fixed solute and fluid loads offers an old-fashioned possibility to define a measure that reflects the integrated actions of blood flow, GFR and tubular function in humans. This (renal concentration test) or something similar would probably be much better than GFR in identifying the marginal cases in which GFR is borderline. The compensatory increase in GFR and kidney size following contralateral nephrectomy indicates that the body senses a deficit in renal function and acts to restore that function to a serviceable level. For relatively young donors who have high GFR values there is little loss of functioning nephrons to the aging process and it is reasonable to expect them to respond as described on page 38. By contrast, older donors with lower GFR levels within the normal range, aging has probably removed nephrons and compensatory hyperfiltration is maintaining the GFR to a certain degree; consequently the response to uninephrectomy will be less than in the younger donors and they will be at increased risk for developing ESRD as noted in Table 16. There is really no good evidence to prove this hypothesis, | The rationale has been modified to include more detail about physiologic influences on GFR, and appropriately, the recommendations in this guideline are more nuanced than in prior guidelines. Unfortunately, there is no alternative physiologic measure that is adequately studied and sufficiently standardized to include in addition or in place of GFR. |

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| yet common sense says that risk must be increased. It is important to identify those with reduced numbers of functioning nephrons and no measurement of GFR will suffice. Maximal concentration of urine would be one possibility to differentiate those with apparently “good” GFR’s due to compensation from normal. Urine concentration is a highly integrated function that depends on the normal function of cortical and medullary tubules; it accounts for one of the earliest signs of impaired renal function (nocturia) in patients with ostensibly normal GFR. It could be more sensitive that proteinuria as an early indicator of impaired renal function. | |
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| There are countries where actual GFR measurements are not available. Making its measurement an imperative makes it difficult and forces physicians to almost "living in the gray zone" to proceed without a mGFR. Once acting outside of the professional guidelines empowers professionals to act outside of the recommendations again, the next time. | We revised statement 5.4 to recommend that the approach to GFR confirmation considers test availability. Measured creatinine clearance (mClcr) is an option that should be available in any country practicing living donor kidney transplantation. |
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| The statement on page 34 (Chapter 5) paragraph 1, that: "mCLcr overstimates mGFR due to creatinine secretion" is not always true. One of the major limitations of 24hr urine creatinine clearence is its dependence on muscle mass and dietary protein intake(1). The increase in dietary protein is reported to increase the 24hr urine CrCl in healthy individuals (1), but may not in those with reduced renal functional reserve (2, 3). Consequently, the potential healthy donors with low protein intake may have erroneously low 24hr urine CrCl but should normalize with adequate protein intake. We have recently reported a case (article in press, Experimental and Clinical Transplantation) of a healthy kidney donor candidate, who had persistently low 24hr urine CrCl (55-60 ml/min) identified due to low dietary protein intake (0.5-0.6 g/kg) despite normal serum creatinine 0.7-0.8 mg/dl and completely normal rest of the work-up, but after her dietary protein intake was optimization (1g/Kg), her GFR normalized (110 and she was able to donate a kidney). One year post-nephrectomy, patient’s serum creatinine is stable at 1.1 mg/dL with no proteinuria. The above case highlights that 24hr urine CrCl may underestimate the true GFR in potential living kidney donors with low protein intake but otherwise with no chronic kidney disease. The | Our interpretation of the case that you described and in the references that you cited is that mGFR was low on a low protein diet and increased after increasing habitual protein intake. We have modified the rationale to include this point. We don't think you have specifically addressed the point of whether mClcr overestimated mGFR in your case. |

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| optimization of protein intake may correct the GFR estimate by 24hr urine CrCl in these donors. The authors of UpToDate in the chapter,'Evaluation of the living kidney donor and risk of donor nephrectomy' under the paragraph 'Renal Function" also mentions that the dietary intake of protein should be at least 1 g of protein per kg/body weight since a low-protein diet may decrease creatinine clearance by as much as 10 mL/min (4). Since the 24 hour urine creatinine clearance (24hr urine CrCl) is widely utilized for the measurement of GFR in potential kidney donors, it is important to mention its dependence on dietary protein intake and how a low dietary protein intake may lead to underestimation of the true GFR by CrCl. | |
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| I suggest to modify point 5.5. A separate function of kidneys should be assessed in ALL the potential donors either by radionuclides or contrast agents that are excreted by glomerular filtration (e.g., 99 mTc-DTPA). The kidney with lower function should be chosen for donation. It may be accepted if it contributes for at least 30-40% of total GFR in donors with GFR > 90 ml/min or >40% of total GFR in donors with GFR < 90 ml/min. | In practice, imaging of the kidney is performed using a filtration marker (iodinated contrast) to evaluate the vessels and kidney structure. However, in the absence of asymmetry of kidney size on imaging exam, the Work Group did not feel it was necessary to measure single kidney GFR. |
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| If mGFR not available at centre, what are the cut-offs for other GFR methods (eGFRcr, mClcr, eGFRcr-cy)? This should be clarified - before comfortable approving 5.6. | We did not feel that there was sufficient data to provide separate cut-off values for various GFR estimation or measurement methods. This is addressed in the rationale. |
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| mGFR of 90 ml/min may not be sufficient for an 18- or 20-yr old. An mGFR of 60 ml/min is too low for anyone but someone over the age of 75 or 80 and it would be wrong to imply that the transplant center can use its own risk threshold and accept a 40-yr old with a mGFR of 60. The threshold for acceptable minimal GFR should be varied according to age. | Please see the prior similar comment and our response above. |
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| The exclusion threshold of 60ml/min/1.73 $m^2$ is too low. The immediate effect of uni-nephrectomy would lead to a mGFR of 30ml/min/1.73 $m^2$. Assuming 20% recovery in the long term, the donor would be left with a | Please see the prior similar comment and our response above. |

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| mGFR of 40-45ml/min/1.73 $m^2$ at the expense of significant glomerular hyperfiltration. | |
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| 5.4: I would clarify the issue of the range of reliability of eGFRcr. I would point out that UNOS policy mandates an isotopic GFR or a GFR by 24-hour creatinine clearance. I think the KDIGO approach is more appropriate and the UNOS policy should be changed. I think centers should be the ones determining the GFR thresholds for donation. I realize that these are only guidelines. | Thank you. We revised statement 5.4 to recommend that the approach to GFR confirmation considers test availability. In the rationale we compare our recommendations to prior guidelines and policy requirements, including current UNOS policy. |
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| 5.7: the phase "the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold" is ambiguous in my opinion. What should be the attitude in new transplant centers especially with no prior centers in the country or region? | The revisions related to this topic are described in the comments and responses to Ch.1 above. |
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| 5.7: Urinary albumin excretion should also be a criteria for those patients with a GFR of 60-89 ml/min. | This guideline recommends measurement of urinary albumin as a requirement in all donors – please see Ch. 6 (Predonation Albuminuria) for detailed discussion of this topic. |
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| It is said on page 7 that uncertainty exists about the magnitude by which donation increases kidney failure risk and that three recent studies support that the risk of ESRD is higher compared to a healthy cohort. Also it is known that a GFR threshold might be unapplicable considering the diversity of donor ages. For a younger donor a threshold of 90/60ml GFR can be too low for a lifetime whereas it might be appropriate for a lot older donor. So donors age need to be taken into consideration when speaking of a threshold. And considering the latter studies revealing worse effects than expected, this threshold should be reviewed again and – in doubt – should be higher. | Please see the prior similar comment and our response above. |

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| I fundamentally disagree with any recommendations that promote eGFR use over mGFR using creatinine clearance methods. There are several reasons for this: | The recommendations do not promote the use of eGFR over mClcr; nonetheless there are several points on which we believe that the Reviewer's statements are not correct |
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| 1. All the current estimations were derived from populations with CKD and not explicitly validated in people with normal and near normal kidney function. | This is not correct. The development datasets for the 2009 CKD-EPI creatinine equation and the 2012 CKD-EPI cystatin C and creatinine-cystatin C equations included people without CKD |
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| 2. The calculators available on the web report eGFR as >60 ml/min/1.73 sq.m in individuals with normal renal function. None of these equations are sophisticated enough to be able to provide a more accurate measure. | This is not correct, there are many web-based calculators that report numeric values for eGFR >60 ml/min/1.73 m2. |
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| 3. Several, although smaller, studies comparing eGFR with mGFR in living donors reported the underperformance of the eGFR. I will be happy to provide the references. 4. mGFR using creatinine clearance is several times cheaper than the mGFR methods suggested by the KDIGO. It must be remembered that for every one successful kidney donor, several more individuals have to be screened and it is simply not financially viable for most transplant centers to resort to the expensive methods. | In the revised guideline we recommend that GFR confirmation may be performed using one or more different types of measurements, and recognize that confirmation choice may be influenced by practical constraints. Issues of accuracy of specific forms of testing are discussed in the supporting rationale, including the development of new web-based calculator to compute post-test probabilities for mGFR above or below threshold probabilities for decision-making based on eGFR. |
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| 5. 24-hour urine creatinine clearance: despite its mild overestimation - has been time tested for more than 5 decades of clinical practice. Besides, the overestimation in the majority of individuals is about 5% - not 15% as quoted in the guideline. If it were to be so unreliable as a test of renal function, it would have undoubtedly led to many adverse post-donation outcomes. Clearly clinical experience says otherwise. | In the revised guideline we recommend that GFR confirmation may be performed using one or more different types of measurements (including eGFR and mClcr), and recognize that choice of testing modality may be influenced by practical constraints. |
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| 6. The mGFR methods recommended by the KDIGO are not only expensive but require a certain amount of operator skill and experience. Unless those tests are being used on a routine basis and in reasonably high volumes, it is a certainty that the results would be just as unreliable as the radionuclide imaging or worse. This particular point is a significant one. At our institution, which is a very large one, we do not have any of the recommended mGFR methods and I suspect many others do not as well. | In the revised guideline we recommend that GFR confirmation may be performed using one or more different types of measurements (including eGFR and mClcr), and recognize that choice of testing modality may be influenced by practical constraints. |

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| 5.4.4: Consider add "or obtain mGFR or other methods to estimate GFR from other medical facilities" | This is unnecessary as recommendations have been rephrased to consider availability of testing modalities. |
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| 5.9: Consider add "In case that donor mGFR is higher than expected with/without increased kidney size, diabetes or pre-diabetes should be ruled out." | Ascertainment for diabetes or pre-diabetes is required for all donors, as discussed in detail in Ch 11. (Predonation Metabolic and Lifestyle Risk Factors). |
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| Every attempt should be made to get mGFR. | Based on the aggregate of public comments, we revised the guideline to recommend that GFR confirmation may be performed using one or more different types of measurements (including eGFR and mClcr), and recognize that choice of testing modality may be influenced by practical constraints. |
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| I strongly advice against using eGFR creatinine or creatinine clearance only. There are national and regional eGFR cystatin which may be used. | Please see the prior similar comment and our response above. |
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| The recommendation to use measured GFR (mGFR) using exogenous filtration markers and clearance calculations is a solid recommendation. That said, it may also be prudent to recommend assessment of individual kidney GFR as potential donors may not always reveal an asymmetry in kidney size but can have asymmetry in function. | Please see the prior similar comment and our response above. |
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| 5.7: The decision to approve donor candidates with a measured GFR of 75-89 ml/min/1.73m$^2$ should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. | We interpret this as a suggestion for a lower threshold of 75 vs. 60. We considered this, but some current practices allow donation with mGFR 60-74, so were concerned that this would be too restrictive as an absolute exclusion threshold. Instead, we recommend that the decision to approve donor candidates with GFR 60-89 ml/min/1.73 m2 should be individualized based on demographic and clinical profile in relation to the transplant program’s acceptable risk threshold. |

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| 5.8: Donor candidates with a mGFR of less than 75 ml/min/1.73 $m^2$ should be excluded from donation. | Please see the prior similar comment and our response above. |
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| Why give a mGFR of 60 ml/min/1.73$m^2$ as the lower limit for consideration? If you do so there would be a shift-drift to accepting donors with a low GFR and with the subsequent risk for these individuals to be in CKD 4! Accepting a low GFR irrespective of age? There are no data, no study and no evidence to accept such a low glomerular filtration rate, and it is also stated that this is "Not Graded". The data available today are from follow-up of donors who had a GFR pre-donation of a minimum of 80ml/min/1.73$m^2$. GFR decreases with older age, a decrease by approximately 1ml/min/year at the age of 50. Besides, there is a high probability that older people have a less renal reserve. Maybe the renal reserve is not as good at all at older age. As we have no reliable information on such a scenario, we should not allow us to accept unacceptable low GFR! T he information we have today seems to be true as long as we adhere to accepting donors with a minimum pre donation GFR of 80 ml/min/1.73$m^2$, allowing for some variance around 80ml/min/1.73$m^2$ for elderly donors (>70 years of age). Why should we allow living donors to live with a decreased renal function with a risk for renal osteodystrophy, anemia, cardiovascular morbidity and mortality? I think we should definitely not allow that! | Please see the prior similar comment and our response above. As described in the rationale, prior guidelines recommended 80 ml/min with specification of measurement method or indexing for BSA, leading to a wide range of acceptable mGFR for past donors. |
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| It is not acceptable that a kidney transplant center has not a mGFR method available. | Based on the aggregate of public comments including from practitioners when mGFR is not available, we revised the guideline to recommend that GFR confirmation may be performed using one or more different types of measurements based on availability. Measured creatinine clearance (mClcr) is an option that should be available in any country practicing living donor kidney transplantation. |
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| Recommend that age of the donor be included in an assessment of adequate GFR. For example, a GFR of 90 may be acceptable for a middle-aged donor, but may not be adequate for a 21 year-old donor; a GFR < 90 might be | Please see the prior similar comment and our response above. |

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| considered in a donor over age 60 whereas it would be unacceptable in a young donor. | |
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| Timed urine collection may be useful to assess kidney function in addition to mGFR. | We included measured creatinine clearance (mClcr) as an option for GFR confirmation and discuss considerations related to testing accuracy in the rationale. |
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| Please see Chapter 1 for general comments. Chapter 5: It is recommended that it be made clearer as to when the recommendations are being made based on data specific to only a few ethnicities (specifically white and black populations). While we support the recommendations in general, the authors should more clearly point out that their suggestion that eGFR can potentially replace measured GFR is based on data specific to whites and blacks and that it may not apply to those of Hispanic or Asian descent. This issue was likely considered in the preparation of the current document and, if so, it should be acknowledged in the document. While this point is also relevant to some of the other chapters, it is perhaps most important for Chapter 5. | The rationale includes more discussion about sources of error in eGFR using creatinine and using cystatin C, including the limitations of availability information on use among person of races other than black or white. |
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| If a kidney is going from a small person A to big person B, size-normalizing GFR for person A may make the kidney look better than it is. So in this way eGFR can mislead centers. Context. You imply a preference for precision in many of these criteria. As eGFR has a something like only a 90% chance of being within 30% of the right value, I am surprised you defer to it at any point. And it is worse than that in the range in which donors will usually be. CKD EPI only makes it a little better. Any center that can't do a creatinine clearance should fold its tents. If relative risks have taught us anything, it is that the lower immediate post-donation GFRs in donors increases long term risk. GFR is an ESRD risk factor across the normal range. Young donors with predonation GFRs of 90 may indeed be OK over a lifetime if they do not get ANY CKD in later life, but it will take very little CKD to put them on dialysis because they will have so little "renal reserve" (see editorials by other people besides me). The same risk arguments that prompt exclusion of | The rationale acknowledges these sources of imprecision in ascertainment of GFR, and for this reason we do not recommend a single threshold for accepting vs. denying donor candidates. |

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| donors with the lowest GFRs affect all GFRs and all candidates. As for renal asymmetry, the key point is how much GFR remains, not which kidney is taken. | |
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| The overall quality of data is good to very good and much of it is graded. | Thank you. We clarified that recommendations related to measurement of kidney function are based on physiological principles and recommendations for general clinical practice from KDIGO 2012 CKD guideline. |
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| No additional important publications were identified. | Thank you for your review. |
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| *State whether we agree with the recommendations and or suggest alternative wording or alternative recommendations* | |
| We do not agree with recommendation 5.7: "The decision to approve donor candidates with mGFR 60-89 ml/min/1.73 $m^2$ should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. (Not Graded)" This ungraded recommendation is too vague. Given that these guidelines will be used globally and in many developing countries we consider that this comment will allow many donors with inadequate renal function to be put at risk. The rationale for the GFR 60 ml/min/1.73$m^2$ cutoff seems to be that it is the cutoff the definition of CKD. This is too low a level as any donor would definitely meet the definition of CKD after donation. Our recommendation would be to raise the range for this recommendation to mGFR 75-89 ml/min/1.73$m^2$. This is still below the accepted cutoff of many experiences units. Our recommendation is the following: Recommendation 5.7 "The decision to approve donor candidates with mGFR 75-89 ml/min/1.73 m2 should be individualized based on the predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. (Not Graded)" | Please see the prior similar comment and our response above. |
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| This recommendation is the most important in this chapter and it is disappointing that there is no evidence to support it. There should be a research recommendation for this cutoff. | We added a Research Recommendation to "*Evaluate long term risks, including lifetime risk of ESRD, in living donor candidates and living donors according to predonation GFR*." |
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| 1. It is curious that there is no eGFR criteria when there are mGFR criteria given that 5.4 does not mandate mGFR? | Please see the prior similar comment and our response above. |
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| 2. More importantly, why is there nothing specific about conditions that would lead the eGFR to be "out of the range of reliability" ????? Should there not be something like if eGFR is 45-90 or something like that? | Thank you. We removed the unclear language. Additional information about factors that influence mGFR and eGFR were added to the rationale. |
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| 3. Also, most nephrologists have no idea what the accuracy and reproducibility of the Cr assay is at their center. | Please see the prior similar comment and our response above. |
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| Seems to me these recommendations could be vague to readers, and may be less helpful then they could be. | In the revised rationale we provide more details and compare our recommendations to prior guidelines. However, we also explain that more detailed guidance would not be evidence-based, noting, "*In contrast, our recommendations are more consistent with accepted measurement methods and thresholds in general clinical practice, and acknowledge that there is variation in GFR measurement methods and uncertainty in the appropriate threshold for decision-making to accept or decline donor candidates*." |
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| A statement should be made about potential donors who are vegetarian/vegan or have a low protein intake. These people will have a lower GFR but have a lower (non donation) risk of ESRD. It is possible that they have a lower risk of ESRD after donation due to greater GFR "reserve". They should not be denied donation based on a lower GFR. Give them a protein load and their GFR will go up! | The Work Group had separate email exchanges with Dr. Germain on this topic. The rationale has been modified to include variation in dietary protein intake as a cause of variation in mGFR. |
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| References:<br>1. Lew SW, Bosch JP. Effect of diet on creatinine clearance and excretion in young and elderly healthy subjects and in patients with renal disease. Journal of the American Society of Nephrology : JASN. 1991; 2: 856-65.<br>2. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. The American journal of medicine. 1983; 75: 943-50. | In the revised document, we have mentioned that diet affects measured GFR and cited references that provide more detail, but have not included these references specifically. |

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| 3. Rodriguez-Iturbe B, Herrera J, Marin C, Manalich R. Tubular stress test detects subclinical reduction in renal functioning mass. Kidney international. 2001; 59: 1094-102.<br>4. Pullman TN, Alving AS, Dern RJ, Landowne M. The influence of dietary protein intake on specific renal functions in normal man. J Lab Clin Med. 1954;44(2):320. | |
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| It seems a similar statement from a review by Dr. Levey would be good in the guidelines. Also I don't think much was said about older donors and what an acceptable eGFR is. It was discussed but I don't think there was a clear recommendation. Is the lower end of the 95% CI eGFR adjusted for age acceptable? | Please see the prior similar comment and our response above. |
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| "Measurement of creatinine clearance using timed (e.g., 24-hour) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, use of creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting). It is also useful for assessment of diet and nutritional status and need to start dialysis." (Manjunath G. Estimating the glomerular filtration rate. Postgraduate Medicine 110: 52, 2001) | The revised recommendations do not state that mClcr is preferred over eGFR, and we recommend an approach to confirming GFR using one or more measurements depending on availability, and discuss the accuracy and limitations of each test in the rationale. Notably, current US policy requires performance of an mGFR or mClcr in all living donor evaluations. |

**Chapter 6: Predonation Albuminuria**

| COMMENT | RESPONSE |
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| 6.2: Based on our national protocol we use 24-hour urine collection of protein and creatinine. The threshold is 200 mg proteinuria/day. The rationale behind suggestion of AER instead of proteinuria is very informative and necessary to help changing protocols (from my point of view). | Thank you |
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| 6.2: ACR is a surrogate. A 24-hour urine collection should be done to measure albuminuria in a potential donor. | We recommend albumin excretion rate (AER, mg/day) in a timed urine specimen as an appropriate strategy for ACR confirmation, but also recognize repeat ACR as an acceptable confirmatory approach based on concerns for practical constraints. |
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| Not clear if confirmation is only required for those who show elevated ACR in an untimed specimen. If that is the recommendation that may be insufficient. I agree that there is no data to inform us of the significance of non-albumin proteinuria but to dismiss it as having no relevance is shortsighted. At the very least patients should be counseled about the possibility that non-albumin proteinuria may have unknown long term consequences for kidney health. After all tubular diseases also lead to CKD - chronic tubulo-interstitial disease is an example. And these patients may manifest non-albumin proteinuria as the first sign of disease. And then there is the issue of light chains - surely the presence of monoclonal light chains in the urine are of concern. But we would not detect it if we did not screen for urine total protein or screen for light chains in every donor. | • We recommend confirmation of albuminuria in all donor candidates using AER or repeat ACR if AER cannot be obtained<br>• We expanded the discussion of non-albumin proteinuria in the rationale, but after due consideration, did not add measurement of non-albumin proteinuria as a recommendation. The Work Group had separate email exchanges with Dr. Thomas on this topic. |
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| 24 hours urines are cumbersome and prone to error. I believe that you should give an acceptable ACR (done twice) and only go to AER if the ACR is above threshold. I agree with the AER cut offs in 6.6 and 6.7 but for 6.5 you could give an acceptable ACR. | We recommend albumin excretion rate AER in a timed urine specimen as an appropriate strategy for ACR confirmation, but also recognize repeat ACR as an acceptable confirmatory approach based on concerns for practical constraints. Acceptance thresholds are defined in terms of AER as the gold standard. We also added a table |

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| | comparing values from measures of albuminuria and proteinuria from the 2012 KDIGO CKD guideline. |
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| I do not support the use of the online calculator to predict lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. 6.7: I think this should be a center derived value. | The revisions related to this topic are described in the comments and responses to Ch.1 above. |
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| AER 30-100 mg/d should be considered as an acceptable level for kidney donation (NOT GRADED) as well as > 100 mg/d. | There are several public comments about the AER threshold (>100 mg/d) for declining a donor candidate, some suggesting a higher and others suggesting a lower threshold. Since the risk relationship between albuminuria and ESRD, CVD and mortality appears continuous, there is bound to be disagreement about the precise threshold. We expanded the discussion in the rationale that allows for a threshold which is within the range of "moderately elevated" according to the 2012 KDIGO CKD guideline. We also revised the recommendation to refer to the transplant program's acceptance risk threshold. |
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| 6.6: Same comment as in 5.7. | The revisions related to this topic are described in the comments and responses to Ch.1 above. |
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| I would not accept microalbuminuric donors (alb 30-100 mg/d). It is not only the risk of ESRD, the overall risk of morbidity and mortality is high as well as the risk of perioperative complications. | Please see the prior similar comment and our response above. |
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| 6.7: Suggestion: Donor candidates with repeat urine AER > 100mg/d.... | We recommended confirmation for accepting the donor but not for declining the donor. |

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| We should not accept microalbuminuria (i.e., U-AER 3-30mg/d). There are several reports revealing an increased risk for cardiovascular morbidity in healthy people with microalbuminuria. Besides, microalbuminuria is an early sign of many renal diseases. Then, why accepting living kidney donors with a microalbuminuria? | Please see the prior similar comment and our response above. |
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| Re. 6.6: it is not only the risk for ESRD we should consider, but also the risk for cardiovascular burden and risk for cardiovascular morbidity/mortality. A living kidney donor should be a healthy man/woman and we should not contribute to give them risk factors for a poor outcome. Besides, there are several studies available now that reveals that kidney donors develop albuminuria in the long term follow-up. Microalbuminuria should not be accepted pre donation! | Please see the prior similar comment and our response above. |
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| Recommend clarification of what is considered an elevated ACR; any value above it should be confirmed with a timed urine collection. | We recommend albumin excretion rate AER in a timed urine specimen as an appropriate strategy for ACR confirmation, but also recognize repeat ACR as an acceptable confirmatory approach based on concerns for practical constraints. Acceptance thresholds are defined in terms of AER as the gold standard. We also added a table comparing values from measures of albuminuria and proteinuria from the 2012 KDIGO CKD guideline. |
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| Bottom of p 44: The average follow-up interval in the KDIGO study as a whole should be stated not just the range of median follow up intervals in the various cohorts. To me, the section as it now is written makes the average study interval seem longer than it was. Since these preliminary guidelines were published, the KDIGO study was published. With all due respect to the profession, most readers will take most of it on faith. The study was critiqued in a NEJM editorial. Even though you may well find it lacking, in fairness to the general reader these criticisms should be briefly noted. As one with some familiarity with this study, I still find this section hard to follow. I have no problem with excluding AERs of > 300 mg/day. I am not sure about the long-term absolute (not relative) risks of lower amounts of albuminuria. You seem | The revisions related to this topic are described in the comments and responses to Ch.1 above. |

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| to quote something that was not statistically significant as fact. These relatively strong risk associations could be peculiar to a relatively short term study interval in which microalbuminuria was caused by nascent, progressing glomerular diseases. I think that these extremely detailed recommendations about the risks of proteinuria seem to depend on one study and contrast with the more general recommendations made for other risk factors. | |
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| On page 46 I think you want to say in the first sentence of the last paragraph that there is concern about development of kidney disease that is specifically due to nephrectomy. Do the increases in AER after donation (nicely presented) mean that their risks of ESRD are increased? | We believe this is already addressed in the statement "*There is theoretical justification for concern about development of kidney disease after nephrectomy*." |
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| The overall quality of data is good to very good. | Thank you. |
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| No additional important publications were identified. | Thank you for your review. |
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| *State whether we agree with the recommendations and or suggest alternative wording or alternative recommendations.* | |
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| In essence we agree with the recommendations with the following caveat. In Recommendation 6.6 the comment "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)" is unlikely to be helpful to a large number of transplant nephrologists who are looking for guidance, especially in developing countries or those planning to set up programs. This suggests that the guidelines are useful only for those "evolved" programs that have such a threshold. | The revisions related to this topic are described in the comments and responses to Ch.1 above. |
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| If the group insists on this caveat, they should explain how to calculate this risk, what factors go into it, and so on. In the absence of such guidance, readers may come up with arbitrary threshold, which could actually be deleterious. We would recommend a more didactic recommendation be used e.g., "Candidates with AER 30-100 mg/d should not be used especially in young potential donors. Exceptions would be where the risk of ESRD has been assessed as not to exceed | The revisions related to this topic are described in the comments and responses to Ch.1 above. |

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| that of the age matched normal population." | |
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| UAE of 30-90 meets the criteria for stage 1 CKD. I do not believe stage 1 kidney disease is should be considered an acceptable risk especially if diabetic, obese or metabolic syndrome (with the proviso I stated in comment 2 and 3). There should be discussion of orthostatic proteinuria, this is likely an acceptable risk (or non-risk). Non albumin proteinuria also needs to be discussed. | • Please see the prior similar comment related to acceptance thresholds and our response above.<br>• We expanded discussion of non-albumin protein in rationale.<br>• We felt that the prevalence of postural proteinuria is probably too low, and the risks related to kidney donation were too uncertain, to include it in the discussion. |

**Chapter 7: Predonation Hematuria**

| COMMENT | RESPONSE |
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| This recommendation must define what microscopic hematuria is in men and women and what kind of tests (microscopy, dipstick, etc) be used to determine its presence or absence. | Given the controversies related to the definition of persistent microhematuria, we discussed the definition of the term and appropriate testing in the rationale: *"Persistent microscopic hematuria is most often defined as more than 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.*[156-159] *Consensus-based guidelines of the American Urological Association state that while a positive dipstick reading warrants microscopic examination to confirm the diagnosis of asymptomatic microhematuria, a positive dipstick alone does not define microhematuria, and evaluation should be based solely on findings from microscopic examination of urinary sediment.*[157] " This is similar to our approach in other chapters, wherein definitions of terms such as "prediabetes" are provided in the rationale (Ch. 11). This approach prevents the need to revise the guideline statements if definitions of clinical conditions are modified over time in other resources. |
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| 7.2 1: A timeline needs to be define for persistent hematuria (I would suggest 3 months) | We considered this, but found there is insufficient evidence and too much variability to provide that level of detail in the definition. Please see the prior comment on the definition of persistent microhematuria and our response above. |
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| 2. For evaluation of nephrolithiasis you should place a non-contrast CT scan not urography, and the 24 hr urine stone panel is not needed (this study should only be performed after the 3. second episode of lithiasis and 4 weeks after this, this is not a screening tool) | We clarified the recommendation to read “imaging” and then described radiologic modalities recommended by the American Urological Association in the rationale. |
| 4. Recommendations should be made to when to refer to a nephrologist for kidney biopsy | We simplified the recommendation to indicate that evaluate of persistent hematuria may include “Kidney biopsy to assess for glomerular disease (e.g. Thin Basement Membrane Nephropathy, IgA |

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| | Nephropathy, Alport syndrome).” We expand on signs of glomerular disease that may prompt kidney biopsy in the rationale, and added a proposed algorithm for sequential evaluation of microscopic hematuria in living kidney donor candidates. In general, lower risk and less expensive tests should be performed first, and at each step additional testing should only be performed if necessary |
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| 5. For evaluating glomerular disease a manual urinary sediment (perform by a nephrologist MUST be recommended). /sic/ | In the rationale text we discuss 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 on findings from microscopic examination of urinary sediment. We also added a paragraph discussing the limitations of a finding of dysmorphic RBCs on urinary sediment. |
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| 7.2: glomerular disease should be actively ruled out by renal biopsy only in case of (double-checked) confirmed dysmorphic hematuria or irreversible iso- or dysmorphic hematuria together proteinuria and/or renal function impairment. | Please see the response above regarding findings motivating kidney biopsy. We added a paragraph to the rationale discussing dysmorphic hematuria – while the presence of dysmorphic RBCs or cellular urinary casts can be helpful in directing the evaluation toward glomerular causes of hematuria, sensitivity and specificity are too variable to either firmly support the need for biopsy or to exclude the presence of underlying urologic processes |
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| Page 50: definition of hematuria in this guideline is a little wide in the field of kidney donation (microscopic evidence of >2-5 red blood cells per high-power). We can be on a more conservative side by defining as >2 or >3 to consider more potential donors for workup to be more conservative to protect the health of donors. | Given the controversies related to the definition of persistent microhematuria, we discussed definition of the term based on available literature in the rationale. Please see the prior similar comment and our response above. The Work Group discussed the concept of a "higher standard" for donor screening at length. Ultimately, it was recognized that screening is not risk-free – screening can lead to false positive results and additional unnecessary testing, including invasive testing with serious risks such as biopsies. All additional testing incurs costs, and can pose inconvenience to the donor candidate and prolong the evaluation. |

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| | Thus, we chose to recommend adherence to the most current evidence-based guidelines as most clinically sound practice that serves the best interests of the donor candidate. |
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| Page 51: consideration of biopsy is putting another risk to potential donor (related /unrelated). What about to consider these potential donors as high risk in one statement to be on the safe side and having a statement of consulting with the donor that if continuation of evaluation is agreeable from his/her side. The bias that the reader gets is some hidden push to proceed with donation. | We modified recommendation 7.2 to clarify that testing "may include" certain components. A fundamental component of the Framework emphasizes that the donor candidate has "*the option to* ***confidentially withdraw from the evaluation or to decline to donate at any time*** *with the full support of the transplant program*." |
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| The statements above should be at least Level 2 recommendations. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |
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| A possible mistake in the text. Quotation #129: You can read "3/6 developed new onset proteinuria, 2/6 developed new onset proteinuria ??? I am not able to check the original paper. | Thank you. The citation was incorrectly linked, and has been corrected to: Gross O et al, Nephrol Dial Transplant 2009;24:1626-30. "3/6" means "3 of 6" and matches the notation uses to describe results from small series in other parts of this chapter |
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| The issue of dipstick positive hematuria (without microscopic hematuria) cannot be ignored. The AUA's guidelines focus on urological causes and do not take the unique case of the living donor. In some cases especially when the urine is very dilute, the dipstick reflects a high sensitivity for the detection of free Hb, greater than the sensitivity of microscopic detection of RBCs. This is not a false positive - meaning it is truly red cell derived heme. To argue that a full workup is not required here is again to neglect the possibility that such patients may have undetected renal disease. When it comes to living donors, we need to be concerned about the possibility of risk and the donor candidate should be counseled. | We revised that rationale to clarify that causes of a positive dipstick reading in the absence of red blood cells in the urine include hemoglobinuria, myoglobinuria, a dilute urine sample, or simply a false-positive test |
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| There needs to be explicit statement about thin basement membrane as 7.4 does not cover it adequately. | We expanded the discussion of Thin Basement Membrane Nephropathy in the rationale. |
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| This chapter is well thought out and informative. | Thank you for the review and feedback |
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| 7.4: is this a specific recommendation? Grade is not stated "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)" are standalone exclusion criteria. /sic/ | The recommendation statement was rewritten in a more actionable form: "*Donor candidates with IgA nephropathy should not donate*." |
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| I think you should also mention the value of genetic testing, particularly if the hematuria is familial. Outside the USA (where the costs are not covered by health insurance) genetic testing is increasingly available. Mutation screening within the type IV collagen genes is likely to give a positive result in around 50% of cases with unexplained hematuria and it would be very important to identify carriers of Alports, whether X-linked or autosomal recessive, as they are at increased risk of developing hypertension and renal impairment in later life and may not make ideal donors. (Flinter et al Arch Dis Child doi:10.1136/archdischild-2013-304827). There is some evidence, however, that if Alport's carriers are >45 years old and have normal blood pressure and no hematuria than they may be considered as suitable donors, with some reservations (Kashtan et al, 2009, Nephrol Dial Transplant ,24:1369-70 and Gross et al 2009 Nephrol Dial Transplant 24:1626-30) | Thank you for the comment. Please see Ch. 14 for a detailed discussion of genetic testing in the donor candidate. We added cross-referencing to Ch. 14 to this chapter. |
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| The cause of hematuria should be established by the diagnostic work-up before a decision of donation. | Please see our suggested algorithm for evaluating causes of hematuria before approving kidney donation. |
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| Has an indication for phase contrast microscopy been discussed? The presence of acanthocytes in the urine (>5%) should exclude an individual from kidney donation due to the very high likelyhood that glomerulonephritis is present (PMID 1921146). | We discuss factors that raise concern for glomerulnperhitis or familial kidney disease. We believe this specific statement would be hard to justify in the absence of any other clinical information (family history, urine protein, etc. |
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| Please see Chapter 1 for general comments. Chapter 7: It is surprising that all of the recommendations are ungraded. It seems likely that a reader/user of the document will fail to understand what evidence qualifies and what does not in terms of grading the recommendations. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |
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| I'd say an appropriately permissive and accurate section. The absolute ESRD risks of isolated microhematuria I think are low. Sometimes you can find donor candidates who have had it for 20 years and are still normal whose ESRD risks must be very low. | Thank you for the review and feedback |
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| The overall quality of data is good to very good (not graded). | Thank you for the review and feedback |
| No additional important publications were identified. | |
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| Recommendation 7.2: for glomerular disease preferably on at least two separate occasions, dysmorphic hematuria should be diagnosed. Renal biopsy can be considered in case of dysmorphic hematuria and/or proteinuria and/or renal function decline. | Please see the prior similar comment and our response above. |
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| Please add: “Potential donors with persistent glomerular hematuria should be excluded from donation”. | Thank you for the comment. After careful consideration, the Work Group defined selection criteria as:<br>• Donor candidates with hematuria from a reversible cause that resolves (such as a treated infection) may be acceptable for kidney donation.<br>• Individuals with IgA nephropathy should not donate.<br>Due to insufficient evidence, approval of donation in other circumstances is grounded on clinical judgement and informed |

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| | consent, including discussion of uncertainties in the available evidence |
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| I do not think it is defensible to state that isolated hematuria is not an acceptable risk but albuminuria. 30-90 is. What is the evidence for this? | Thank you for the comment. After careful consideration, the Work Group defined selection criteria as:<br>• Donor candidates with hematuria from a reversible cause that resolves (such as a treated infection) may be acceptable for kidney donation.<br>• Individuals with IgA nephropathy should not donate.<br>Due to insufficient evidence, approval of donation in other circumstances is grounded on clinical judgement and informed consent, including discussion of uncertainties in the available evidence |

**Chapter 8: Kidney Stones**

| COMMENTS | RESPONSE |
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| Any recommendations regarding turning down potential donors who have had 2 or more stones in the past or currently has a large stone burden on imaging? What about age of the donor? | We revised the recommendation to read: "*The acceptance of a donor candidate with prior or current kidney stones should be based on an assessment of stone recurrence risk and knowledge of the possible consequences of kidney stones after donation*." At the present time, it is difficult to say that one characteristic makes the recurrence quantitatively larger than another, and to make a clear decision regarding whether donation should proceed or not – in the revised rationale we discuss the challenges related to clinical prediction of stone recurrence. In the rationale we highlight that a frequent, recurrent stone history is a risk factor for more stones, as is kidney stones at a younger age. We also highlight that several prior guidelines recommend against donation in the presence of bilateral kidney stones. |
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| 8.8: unless the donor is found to have a metabolic abnormality, the only 'prophylactic treatment' that has ever been proven in studies is drinking more water. | Thank you. We added section on the prevention of kidney stones, and summarize prior evidence-based guidelines for the prevention of recurrent stones. |
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| All donors should dose the uric acid in the blood and urine prior to donation, independently if they have or not previous history of kidney stones. | Thank you. This is controversial. Some prior guidelines recommend measuring uric acid levels as standard, but others do not. Hyperuricemia could have implications for the risk of developing post-donation gout. We added a new chapter to the guideline discussing Hyperuricemia, Gout and Mineral and Bone Disease (Ch. 9) – please see this chapter for more details on the available evidence on this topic. |

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| At least an ultrasound can be used as a screening tool for presence of stones. | We chose not to be prescriptive on exactly what imaging should be performed. Some transplant programs perform a CT angiogram in all candidates prior to donation, which can also show the presence of stones. |
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| 8.4: I approve but would appreciate more quantitative information about what level of risk for recurrent stones, ESRD, etc. would define a decision not to proceed with donation. | Please see the new "Risk factors for recurrent stones" section in the Rationale. Unfortunately, the risk of recurrence after any single stone is difficult to predict, and to our knowledge there is no valid risk index / risk calculator for this (especially in donors). As a result, the decision to proceed with donation remains grounded on clinical judgement and informed consent, including discussion of uncertainties in the available evidence. We have emphasized several risk factors that may make it more or less likely for a kidney stone to reoccur. |
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| 8.3: I think it should be stated that a metabolic work-up for hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria should be performed. | Thank you. We added additional detail on the evaluation of donor candidates and donors with prior or current kidney stones, citing 2014 American Urological Association Guidelines. In this section we describe the testing you have outlined. |
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| This chapter has very general recommendations without guidance for risk assessment of patients with current stones or prior stones. | Please see the prior similar comments and our responses above. |
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| Recommend that a 24 hr urine collection be mentioned as part of the assessment of patients with current stones. | Thank you. We added mention of 24 hr urine collections in the description of the 2014 American Urological Association evidence-based guideline for the evaluation of adult patients with kidney stones |
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| Recommend adding additional citations. There are only 3 stone citations in the references (133-135); only 1 deals with donors. The authors might consider the following 2 papers: Thomas, S.M., Lam, N.N., et al. 2013. Risk of kidney stones | Thank you. We incorporated both these references into the rationale. |

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| with surgical intervention in living kidney donors. Am J Transplant 13:2935-2944; Lorenz, E.C., Lieske, J.C., et al. 2011. Clinical characteristics of potential kidney donors with asymptomatic kidney stones. Nephrol Dial Transplant 26:2695-2700. | |
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| In the USRDS database, the 5-year incidence of ESRD from stones is about 1,500 and the incidence of diabetic ESRD is about 250,000. I agree with a permissive approach. | Thank you. We described and cited prior studies reporting and association between prior kidney stones and ESRD to the rationale text of this chapter. |
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| The overall quality of data is good to very good (not graded). | Thank you. |
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| No additional important publications were identified. | Thank you for your review. |
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| *State whether we agree with the recommendations and or suggest alternative wording or alternative recommendations*. | |
| Recommendation 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. | We revised the recommendation to read: "*Donor candidates with prior or current kidney stones should be assessed for an underlying cause.*" |
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| Please add: "and associated risk factor for donation and/or underlying anatomical urological/renal abnormalities should be excluded". | Thank you. We did not include this in the recommendation, as we endeavored to keep the recommendation prose brief. However, we added detailed description of the 2014 American Urological Association evidence-based guideline for the evaluation of adult patients with kidney stones to the rationale. |
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| I'd suggest that potential donors at risk for renal calculi post-donation should live in areas with timely access to urologic care. Patients in remote or rural areas without easy access to urologic care should be discouraged from donating. | Thank you. Throughout the guideline we have emphasized the importance of ensuring access to any needed donation-related post-donation care. This concept applies to other health outcomes, and thus we close to feature this theme in global chapters such as the |

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| | Framework (Ch. 1) and Post-Donation Follow-up Care (Ch. 19). |
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| You might know that there is no nomogram or assessment tool that calculates a person's risk of recurrent stone formation (there should be – one day someone will do it). | Thank you. We added the need to develop such a tool to the Research Recommendations. |
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| We just go on intuition and findings on the metabolic testing when we are deciding if the risk of recurrent stones is too great or not. In the end, we are counting on prompt treatment of any obstructing stone to bail us out if the donor is unlucky and gets another stone. If prompt treatment is not going to be available then I think it's sensible to discourage donation. | We agree. Please see the prior similar comments and our responses above. |
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| A work up to evaluate the metabolic cause of the kidney stone should be done in all potential donors with a history of kidney stones. Both the person that donates and those that do not should have treatment accordingly. The number and frequency of stone formation should be a strong consideration for recommending donation. | We agree. Please see the prior similar comments and our responses above. |

**Chapter 9: Hyperuricemia, Gout and Mineral and Bone Disease**

- Chapter was written post-public comment – No Public Comments available

**Chapter 10: Predonation Blood Pressure**

| COMMENT | RESPONSE |
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| On page 3 you mention "masked hypertension", but it is confused, as this diagnosis will only be made if donors have ambulatory BP measurement despite acceptable office blood pressures. Either you need to say everyone needs ambulatory BP or you need to say will take risk of missing "masked hypertension", the latter I favor. PS You quote "The British Transplantation Society" guidelines, strictly I am afraid they are "The British Transplantation Society and Renal Association" guidelines - bit of a mouthful! | • Thank you. We added recognition that " *Masked hypertension cannot be identified in donor candidates in whom BP is measured by office readings alone, but the implications of requiring ABPM or home readings to screen for masked hypternsion in donor candidates (e.g., outcomes, cost, efficiency) are not defined.*<br>• We corrected the attribution to "The British Transplantation Society and Renal Association" |
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| On page 6 there is a reference missing (Ref) to do with BP treatment in European descent USA residents versus African descent USA residents. | Thank you. We added the references. |
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| Assuming the use of BP in framework ESRD risk, I agree with above. | We revised the recommendation to correspond to the final Framework language: " *The decision to approve donor candidates with hypertension should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance risk threshold*." |
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| I am not comfortable with using kidneys from donors with clear-cut elevations in BP above 140/90, treated or otherwise. There is simply not enough data from longitudinal experiences to prove that these donors will not experience an increase of ESRD as they move into the 9th and 10th decades of life. | We advocate that hypertensive candidates may be acceptable (not necessarily approved). The decision to approve donation in persons with hypertension should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance risk threshold. We describe a tool for grounding risk assessment in relation to ESRD in the Framework. |
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| 9.2 should be ABPM for all. (not graded) | Currently there is insufficient evidence to require universal ABPM in the donor candidate evaluation, and the requirement would pose barriers for centers or regions who have difficulty purchasing and |

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| | operating ABPM devices. We discuss the utility of ABPM if available in the rationale. |
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| 9.4 and who do not have evidence of end-organ damage, confirmed subclinical organ damage or risk factors for cardiovascular disease. Also 9.5 should add confirmed subclinical organ damage and cardiovascular risk factors (not graded). | The term "target organ" is defined in the literature and in our rational text; "confirmed subclinical" may be subjective. Cardiovascular risk factors (hypertension, smoking, lipids & demographic traits) were considered in development of the ESRD risk prediction model – please see Ch.1 and the rationale text of this chapter for more details. |
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| Page 3: Lifestyle modification, after follow-up of patents should be patients as health professional cannot guarantee that the donor sticks to his/her medications for HTN; it may be prudent to consider hypertensives on medication high risk for transplantation. In our national protocol they should be omitted. | • We revised the final counseling recommendation (10.5) in this chapter to read: "*Donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for hypertension and cardiovascular disease, including healthy diet, smoking abstinence, achievement of healthy body weight, and regular exercise according to guidelines for the general population. These measures should be initiated prior to donation and maintained lifelong*." We also dedicate a chapter to post-donation follow-up care (Ch.19).<br>• The ESRD risk model described in the Framework, as well as evidence assembled the independent Evidence Review Team (ERT), supports that some donor candidates with controlled hypertension may be acceptable donors based on risks of complications such as ESRD. |
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| I don't approve the first statement. The damage due to arterial hypertension is the same all over the world. In addition there is a possible "misundertanding" of this sentence. A missing quotation page 6 "hypertension control slows nephropathy progression in Europeans Americans [ref]"? | • We don't understand the comment.<br>• We added the missing reference. |
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| 9.2: Use of Ambulatory Blood Pressure Monitoring (ABPM) helps differentiate hypertensive '' White Coat '' and to clarify the true hypertensives (20-25%) (Ref | We discuss this topic in the "White coat hypertension" section of the rationale and cite the current references. |

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| O'Brien E. J Hypertens 2013; 31: 1731-1768, Chobanian, AV. Hypertension 2003; 42: 1206-1252, Stergiou, G. Hypertension 2014; 63: 675-682 | |
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| 9.4 The donor with mild to moderate hypertension, without other cardiovascular risk factors and preserved renal function should be accepted, as long as the micro albuminuria is <30 mg/g and no evidence of target organ damage present and be <50 years, since, as occurs in the general population, hypertension in the donor is associated with increased mortality in the medium term (Ref: Segev D. JAMA 2010; 303: 959-66). | Our recommendation considers the presence of target organ damage as an exclusion to donation. Rather than setting specific thresholds for individual additional risk factors such as age and albuminuria, we recommend an approach to integrated risk assessment as described in the Framework (Ch.1) and further elaborated upon in the rationale for this chapter. |
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| 9.5 Donor candidates with hypertension should be excluded from donation if evidence of end-organ damage present, proteinuria, ACR 30 mg/g, hematuria, difficult to control hypertension, retinopathy, left ventricular hypertrophy by echocardiogram or ECG, or GRF <60 ml/min/ 1.73 $m^2$. (Ref Chobanian, AV. Hypertension 2003; 42: 1206-1252) . | Please see our response to the similar comment above. |
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| Concerned about taking patients requiring more than one antihypertensive agent for BP control given potential for accelerated increase BP post-donation. Recognize lack of evidence at this time to support this. | The ESRD risk model described in the Framework, as well as evidence from the ERT, supports that some donor candidates with controlled hypertension may be acceptable donors based on risks of complications such as ESRD. Risk discrimination based on the number of antihypertensive agents is not available. |
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| The justification for two drugs as the cutoff is not apparent. The calculator does not distinguish the number of anti-hypertensive drugs when determining risk. I think it would prudent to use one drug as a cutoff until the risk can be better determined. | Please see the prior similar comment and our response above. |
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| In the absence of long-term outcome studies, I would be against accepting a donor with confirmed hypertension, even if controlled with one or two drugs. Such status is likely to be altered by uninephrectomy as well as aging. Let alone the possibility of treatment-noncompliance in an individual with a reduced GFR | The ESRD risk model described in the Framework, as well as evidence from the ERT, supports that some donor candidates with controlled hypertension may be acceptable donors based on risks of complications such as ESRD. |

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| The US Preventive Task force now recommends ABPM for the diagnosis of hypertension (Siu A. Ann Intern Med. 2015;163(10):778-786). I don't understand why this wise recommendation should not be applied to kidney donors!! | Please see the prior similar comment and our response above. |
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| 9.4: is there no consideration in hypertensive populations of African origin who have a high risk of CKD. | We recommend that "*The decision to approve donation in persons with hypertension should be individualized based* ***demographic*** *and clinical profile in relation to the transplant program's acceptance risk threshold*." Race is a critical demographic factor discussed in the rationale for this section and in the Framework (Ch. 1) for the assessment of long-term risks in relation to acceptance thresholds. |
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| 9.4: Asymptomatic organ damage should be evaluated such as LVH, etc. Control of BP with two drugs means the patient is most probably stage 2-3 hypertension when diagnosed and at high CV risk: So control with only one drug is better for donation. | A definition of target organ damage including LVH is provided in the rationale. |
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| 9.4: Comment on using one or two antihypertensive agents. Consider to be clear that each antihypertensive agent contain only 1 active antihypertensive drug (not a combination of 2 antihypertensive drugs in 1 pill). | Please see the prior similar comments and our response above. |
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| ABPM should be recommended in every living donor. | Please see the prior similar comments and our response above. |
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| Again! Where are the evidence to allow hypertension and such a statement "using one or two antihypertensive agents"? In the UK guidelines they refer to an abstract! And the study has never been published, at least as far as I have found. Blood pressure is mainly regulated by the kidneys, why then accept a | Please see the prior similar comments and our response above. |

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| disease/symptom that is a phenomenon of a kidney "malfunction"? Besides, hypertension has long been a very well known risk factor for cardiovascular morbidity and mortality. I can't see the rationale to accept living donors with a well-known risk factor for poor outcome, and we should not focus only on ESRD but also mortality and cardiovascular morbidity. We have not previously routinely accepted donors with hypertension, thus we have no data available on the magnitude of such a risk in the long term run and we should not make any statements allowing for such. As is written in "Evidence Regarding Pre-Donation Hypertension as a Risk Factor for Adverse Outcomes after Kidney Donation" – there are no such evidence favoring an acceptance of hypertension pre-donation –why then do? | |
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| Recommend including a statement: "as evidence emerges about risk of future renal dysfunction in particular at-risk groups (we have in mind African Americans,) this data should be incorporated into the donor evaluation and informed consent process." | Our Framework (Ch.1) and Informed Consent (Ch.2) section emphasize the importance of disclosure of risks and associated uncertainties. We also added Research Recommendations emphasizing the importance of continued efforts to improve the precision and granularity of long-term risk prediction. |
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| I believe there is a major omission here by not presenting the case that with proper screening essential hypertension is a weak risk factor for ESRD in the general population. I am not saying you have to endorse this view, just to present it fairly to the general reader. The data for blacks are certainly more complicated than for others. Here are a few references: | • Our recommendations are based on the independent Evidence Review and the model for long-term ESRD risk in healthy persons developed to support the Framework for this guideline.<br>• We also modified the rationale to state: "*Hypertension is a contributing cause of CKD in the general population, although in many cases, CKD may be the cause of hypertension*." |
| • Hoerger TJ, Wittenborn JS, Segel JE, et al. A Health Policy Model of CKD: 1. Model construction, assumptions, and validation of health consequences. Centers for Disease Control and Prevention CKD Initiative. Am J Kidney Dis. 2010;55:452-562. FINDS < 1 CC/ DECADE ADDITIONAL LOSS OF GFR<br>• Schlessinger SD, Tankersley MR, Curtis JJ. Clinical documentation of end-stage renal disease due to hypertension. Am J Kid Dis. 1994;23:655-660.<br>• Hsu C. Does non-malignant hypertension cause renal insufficiency? Evidence-based perspective. Curr Opin Nephrol Hyperten. 2002;11:267-272 | |

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| Again, the single, NEW KGIDO study is given a great deal of weight. With all respect, there are many other studies out there on this topic. Much hypertension in the KDIGO study may not have been so called essential hypertension but secondary to established nascent kidney diseases. | Our recommendations are informed by an independent systematic Evidence Review that queried evidence regarding the outcomes implications of hypertension in donors, and the modeling of ESRD risk in healthy persons in the general population performed by the CKD-Prognosis Consortium. The CKD-PC assembled evidence from 7 cohorts capturing data for nearly 5 million healthy persons. We agree the model has limitations, as expanded upon in the Framework chapter (Ch.1). We endorse use of the online prediction tool as part of the framework for decision making, but also recognize that application of the currently available online tool in the clinical setting at this time requires clinician insight and interpretation. |
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| 9.1: “Blood pressure should be measured prior to donation on at least two occasions” - would be helpful to suggest a minimum interval. Rhetorically - can it be 10 min? | At this time, there is insufficient evidence to recommend details for repeating blood pressure measurements during the evaluation. |
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| 9.4: Should include lifestyle measures. Should say “not more than two antihypertensive agents (one pill with FDC of two agents will count ad 2 agents)”, rather than “one or two antihypertensive agents” | We recommend that "*The decision to approve donation in persons with hypertension should be individualized based demographic and clinical profile in relation to the transplant center’s acceptance risk threshold*." As discussed in the Framework and in the rationale for this section, the ESRD prediction model constructed to support this guideline includes parameters for smoking and obesity as factors captured in large-population based cohorts. In 10.5 we emphasize the importance of counseling on lifestyle factors to address modifiable risk factors. |
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| 9.8: “several weeks” - Since the evidence is not great, please pick a suggested number, say 4 or 6 weeks. | At this time, there is insufficient evidence to recommend details of the timeframe for confirming blood pressure control. |
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| 9.9: why single out remaining kidney for end organ damage - it should be “end organ damage including kidney damage” | To streamline the recommendation statements, we moved the description of target organ to the rationale text. Consistent with your recommendation, we removed the phrase “remaining kidney”. |

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| *Rationale section should include the lessons from SPRINT, in particular the growing feeling that hypertension may not be a disease with a BP cutoff, but that the impact of BP may be a continuous variable, so **all donors** whether or not they have traditional hypertension, should receive counselling about BP control.* | We revised the counselling recommendation (10.5) to apply to all donor candidates. |
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| Repeated use of language like "decision should be individualised based on the predicted lifetime incidence of ESRD in relation to the transplant centre's acceptance threshold" is unlikely to be helpful to a large number of transplant nephrologists who are looking for guidance, especially in developing countries or those planning to set up programs. This suggests that the guidelines are useful only for those "evolved" programs that have such a threshold. | We revised the recommendation to read "*The decision to approve donation in persons with hypertension should be individualized based demographic and clinical profile in relation to the transplant program's acceptance risk threshold*." Chapter 1 provides a detailed discussion on how to apply consideration such as predicted ESRD risk within a Framework for acceptable risk. We also discuss limitations to currently available prediction tool, recommend important next steps for strengthening the evidence base, and recommend a process of consensus-building for acceptance thresholds. |
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| If the group insists on this caveat, they should explain how to calculate this risk, what factors go into it, and so on. In the absence of such guidance, renters may come up with arbitrary threshold, which could actually be deleterious. | Chapter 1 provides a detailed discussion of how to apply consideration such as predicted ESRD risk within a Framework for acceptable risk. We also discuss limitations to currently available prediction tool, recommend important next steps for strengthening the evidence base, and recommend a process of consensus-building for acceptance thresholds. |
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| Central BP measurements are readily available and correlate better with CV outcomes than even 24 hr ABPM. This should be discussed. | At this time, there is insufficient evidence to recommend central blood pressure in the donor evaluation, and recommending routine use would pose barriers for centers or regions who have difficulty purchasing and operating the devices. We added a Research Recommendation focused on defining the optimal strategies for measuring blood pressure during the donor evaluation. |

**Chapter 11: Predonation Metabolic and Lifestyle Risk Factors**

| COMMENT | RESPONSE |
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| Please consider the risk factors I summarized in my response to #11. | Unfortunately, we do not see your prior comment. However, we believe this chapter addresses a comprehensive set of metabolic and lifestyle risk factors to consider in the donor evaluation. |
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| Recommendations 'not graded'. No discussion/comment on other testing that is probably done, i.e., liver function tests. Not sure I missed this but how about hypercoaguable states and histories of DVT. Some centers routinely measure ANA, tests for myeloma/gammaglobulin level etcs. Arguably most of these have limited value but are being done routinely. | This chapter focuses on testing related to metabolic risk factors for accelerated GFR decline and atherosclerotic cardiovascular disease. Other testing is discussed by topic, such as in the chapter on general preoperative evaluation and management (Ch. 4). |
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| I am convinced that diabetes is at work in kidneys long before we see it in proteinuria or reduced GFR. | Thank you for the comment. |
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| All donors with previously prediabetes diagnosis should not be considered as organ donors. | Our recommendations are informed by an independent systematic Evidence Review that queried evidence on the outcomes implications of prediabetes in donors – evidence of adverse outcome warranting universal exclusion was not identified. Based on this evidence review and other public comments, we recommend that "*The decision to approve donor candidates with prediabetes or type 2 diabetes should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance threshold*." |
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| 10.3: (BMI ≥40 kg/$m^2$) should be excluded from donation. I was not convinced with the rationale. In my opinion previous guidelines were much more appropriate (BMI<30 or 35). Irrespective of metabolic syndrome. At least, we | Thank you. Based on public comments such as yours and review of the evidence, we removed a defined threshold for donor exclusion and revised the recommendation to read: "*Approval of donation in* |

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| know that perioperative events would be more. | *candidates with obesity and BMI >30 kg/m2 should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance thresholds*." Thresholds can include peri-operative and longer-term events. |
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| 10.4: The decision to approve donation in candidates with … predicted lifetime incidence of ESRD in relation to the transplant center's acceptance threshold. (Not Graded): Of note, obesity is not just a risk factor for kidney disease but risks of HTN and mortality are higher in obese. So, I think ESRD is not the only thread but attributed mortality risk should be added to the statement. As health professional concern is not just ESRD but sustained life. | We revised 11.3 to be more general about the risk thresholds used for decision making: "*The decision to approve donor candidates with obesity and BMI >30 kg/m2 should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance threshold.*" We also included the following in the rationale: "*Acceptance thresholds for donor candidate BMI can include peri-operative complications and long-term risks of ESRD and other complications as data become available*." |
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| 10.11: ….ESRD (or cardiovascular mortality due to diabetes) can be added. | We revised 11.3 to be more general about the risk thresholds used for decision making: "*The decision to approve donor candidates with obesity and BMI >30 kg/m2 should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance threshold.*" We also included the following in the rationale: "*Acceptance thresholds for donor candidate BMI can include peri-operative complications* ***and long-term risks of ESRD and other complications*** *as data become available*." |
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| 10.3: Severe obesity is a contraindication to donation due to higher surgical risk and development of chronic kidney disease in the long term; nevertheless, there is evidence of short term success in obese donors both from surgical as well as general points of view (Ref: Transplantation 2009; 88: 662-71) | As described in the rationale, the Evidence Review performed to support this guideline included 2 systematic reviews that examined peri-operative outcomes after donor nephrectomy according to BMI. |
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| 10.5: Donor candidates with a prior history of bariatric surgery should be assessed for risk of nephrocalcinosis by renal imaging and 24-hour urine supersaturation/stone profile, and may alter the absorption of some immunosuppressors (Refs: J Am Coll Surg 2010 Jul; 211 (1): 8-15; Cl J Am Soc Nephrol 2008; 3 (6): 1676; Nutr Clin Pract 2005; 20 (5): 517; Obes Surg 2005; 15 (2): 145. | This suggestion "may alter the absorption of some immunosuppressors" is relevant to transplant recipients, but not to donors, as donors do not receive immunosuppression. |

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| 10.11: should include not only prediabetes, but high risk individuals (race, family history, obesity) who do not yet have biochemical abnormalities and this should be captured in risk calculator. The fact that it is not captured is a significant shortcoming. The most common reason that I turn down young donors is their future diabetes risk. | The long-term ESRD risk model developed to support this guideline includes age, race and BMI. Family history information is not currently available in any large cohort capturing ESRD events, and we have noted this as a limitation in the framework (Ch. 1) and emphasized that risk may be higher than calculated in patients with additional risk factors. Although we do not specifically model the incidence of risk factors such as diabetes and hypertension, our projections incorporate the natural rate of disease development in a given subset of the population, thereby incorporating all disease pathways to ESRD. |
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| I would exclude persons with prediabetes. | We suggest that some prediabetic candidates may be acceptable as donors (not necessarily approved). The Evidence Review performed to inform this guideline does not support universal exclusion of prediabetic donor candidates. We recommend individualized risk assessment, counseling, and pursuit of more evidence. |
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| 10.11: Even though, the potential donors who have short predicted lifetime and prediabetes may be alive without progression of renal function to become end-stage renal disease (ESRD) after kidney donation, they may have unrecognized chronic kidney disease or other renal-related condition such as proteinuria which may not provide the optimal benefit for the recipients. Unless, the potential recipients have some barriers of kidney transplantation e.g., immunological barriers leading to difficulty in receiving acceptable matched organs, lack of dialysis access in ESRD, those potential donors should be accepted for kidney donation. | We suggest that some prediabetic candidates may be acceptable for donation (not necessarily approved). We recommend individualized risk assessment, counseling, and pursuit of more evidence. |
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| Recommend that 10.5 include a time component. A single kidney stone 1 year post- bariatric surgery is not the same as the same situation 10 years post-surgery. | 11.4 relates to active stones or stone risk factors in a candidate with a history of bariatric surgery. Please see Ch. 8 (Kidney Stones) for more details on the evaluation and acceptance of donor candidates |

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| | in relation to nephrolithiasis. |
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| Recommend that 10.11 strengthen components of work-up for potential live donors identified as 'pre-diabetic' so that all risk factors for diabetes (such as obesity) be corrected prior to donation. In addition, recommend that strong family history of late life type 2 DM be included as a consideration. | The long-term ESRD risk model developed to support this guideline includes 10 demographic and clinical risk factors. 11.1 emphasizes the importance of risk counseling and efforts to manage modifiable risk factors. |
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| Please see Chapter 1 for general comments. Chapter 10: It is surprising that recommendation 10.1 (regarding identification of metabolic and lifestyle risk factors) is ungraded, for reasons already noted in previous chapters: there would seem to be considerable evidence on this topic. The evidence may not be definitive but, given its presence, some grading would seem appropriate. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. The complete Evidence Review is also available as an Appendix and is summarized in a separate publication. |
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| Very informative first section. Since the later sections were written, the KDIGO study was criticized for being too short to measure diabetic risk. That is, by design, it could only include very early classic diabetic nephropathy, which could not have progressed to ESRD over the study interval. For this reason obesity was a surprisingly weak predictor of risk (going from BMI of 25 to 40 in a white 25-year old male on the website only changes lifetime risk from .49 to .65). The other general risk factors KDIGO uses are not recognized predictors of diabetes. For the benefit of the general reader to make up his or her mind, you might include these concerns in the final manuscript in a balanced fashion. You do not have to endorse them. In the end we all want and expect that this give and take will result in a better understanding of donor risk. You might also mention that some evidence suggests that we do not materially reduce diabetic risk by current donor selection and that diabetes typically takes a good 20-30 years to produce ESRD. A broader concern is that as in previous sections, general caution is advised when applying the KDIGO study conclusions and website algorithm, but it is not clear whether you want people to rely on them or not. With all due respect, some of the phrasing is ambivalent and almost legalistic and suggests maybe not. But the general reader might think that the study would not be so | Thank you for the thoughtful comments. Although the ESRD risk model described in the framework does not specifically model the incidence of risk factors such as diabetes and hypertension, our projections incorporate the natural rate of disease development in a given subset of the population, thereby incorporating all disease pathways to ESRD. We have revised the Framework chapter (Ch. 1) to move explicitly discuss the limitations of the model projections, including reference to your editorial. We believe the Framework and the risk assessment tool is an important step in advancing towards more empiric and defensible donor candidate evaluation and acceptance processes, centered on simultaneous consideration of multiple clinical factors relevant to ESRD risk. However, we also emphasize limitations and state that given the limitations, application in the clinical setting requires clinician insight and interpretation. We present the approach as a starting point, and advocate strongly for continued efforts to improve the precision, tailoring and generalizability of pre- and post-donation risk estimates. |

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| prominently featured and the website would not be making these detailed predictions unless they were thought to be substantially correct and to be used rather straightforwardly in donor counseling and selection. If you want people to do this you should say so. If you do not, you should clearly say that. | |
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| **Agreement with recommendations and other suggestions** | |
| 10.1: Should include excessive alcohol intake, and say "physical" inactivity. | • Alcohol intake is not mentioned as, in contrast to smoking, the relationship of alcohol use to atherosclerosis is complex (ie, moderate use may reduce risk), and there are is currently no strong evidence linking alcohol to GFR decline.<br>• The term "activity" was removed from the final streamlined recommendation statements. |
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| 10.3: Suggests they are excluded forever, should be tempered to suggest they can be re-evaluated once the weight is brought down. | Based on public comments such as yours and review of the evidence, we removed a defined threshold for donor exclusion and revised the recommendation to read: "*The decision to approve donor candidates with obesity and BMI >30 kg/m2 should be individualized based on demographic and clinical profile in relation to the transplant program's acceptance threshold*." At this time, there are insufficient data on the outcome implications of weight loss duration to support modifying the recommendation statement. We added the need to generate data on this topic as a Research Recommendation. |
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| 10.4: Should be brought in line with 10.1 to suggest race specific cutoff for obesity. For example - this cutoff is 25 for some Asian populations | We revised the final statement related to approval of obese donors (11.3) to recommend individualized decision-making based on demographic and clinical profile. Race is a key demographic trait as described in the rationale for this and other chapters. We emphasized the need for ongoing efforts to develop risk assessment tailored for demographic profile including age, sex and race in the Research Recommendations. |
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| 10.5: All will have some increase in oxaluria post bariatric surgery. Is there a definition for exclusion? | Hyperoxaluria is not a universal finding after bariatric surgery. There is currently insufficient evidence to ground a specific |

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| | exclusion threshold, but given the potential serious consequences of oxalosis after bariatric surgery, we believe the recommendation is warranted, understanding that clinical judgement is required. |
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| 10.6: “assess the stability of recent weight loss over one to several months” - Better to give an indicative reasonable number, i.e. 4 or 6… | At this time, there are insufficient data on the outcome implications of weight loss duration to support modifying the recommendation statement. We added the need to generate data on this topic as a Research Recommendation. |
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| The comment about encouraging smokers to quit is too vague, you need to go onto say what is guidance if still smoking. On page 67 you say "while donation may not increase the risk related to a given factor" so why do you consider it? You may as well rule out people who participate in "risky sports" like say SCUBA diving. I think dyslipidemia falls into that category. I am unconvinced uninephrectomy materially alters the impact on cardiovascular risk of dyslipidemias, and so I do not think we should be measuring lipids/cholesterol. Page 71 you say "diabetic persons should generally be excluded from kidney donation" this is useless!! What on earth is this sentence supposed to mean? | • In Ch.4 (Pre-Operative Evaluation) we recommend smoking cessation for 4 weeks prior to donation to reduce peri-operative risks and encourage long-term abstinence to reduce long-term risks (e.g, cancer, cardiopulmonary disease and ESRD). Given the prevalence of smoking worldwide and current practice variation, the work group felt that a universal statement to exclude active smokers is unlikely to be acceptable to the community. Our approach supports disclosure of risks and shared decision making.<br>• We consider factors that contribute to the baseline risk of ESRD and cardiovascular mortality as relevant to donor risk assessment, even if donation may not modify the risk contributed by a given factor. Dyslipidemia was explored in relation to ESRD in the development of the ESRD prediction tool, and as discussed, was found to not be a significant risk factor. However, as dyslipidemia is clearly a modifiable risk factor for atherosclerosis, we believe assessment of lipid status is relevant to a comprehensive donor evaluation, risk assessment, and counseling on long-term health promotion.<br>• As described in the rationale, some programs have allowed donation from "low risk" diabetic persons (e.g., elderly, with less remaining years of expected lifetime for developing complications). Consistent with a theme of comprehensive risk factor assessment, we revised the final recommendation to read: “*The decision to approve donor candidates with prediabetes or type 2 diabetes should be individualized based on demographic and clinical profile in* |

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| | *relation to the transplant program's acceptance threshold.*." |
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| Severe needs to be defined. Is there a threshold for medication like hypertension? Should abnormalities be treated before acceptance. These guidelines are too vague on this. | We agree with ambiguity and deleted the word "severe" from the statement. |
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| Even though technically these are modifiable risk factors, should not proceed with donation when at high risk. | Our recommendations are centered on individualized risk assessment considering comprehensive demographic and clinical profile, and exclusion when risk exceeds acceptance thresholds. |
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| 10.14: Please clarify what is "severe" | We agree with ambiguity and deleted the word "severe" from the statement. |
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| Healthy lifestyle should be recommended in all potential donors (regardless of HTN) and explained how this can likely mitigate the added risk of donation for ESRD. Diet (salt and animal protein restriction) in particular may be beneficial. | We agree, and include several recommendations regarding counseling to promote healthy lifestyle in the guideline, including 11.1 in this chapter. In Ch. 10, we also recommend that "*Donor candidates should be counseled on lifestyle interventions to address modifiable risk factors for hypertension and cardiovascular disease, including healthy diet, smoking abstinence, achievement of healthy body weight, and regular exercise according to guidelines for the general population. These measures should be initiated prior to donation and maintained lifelong."* |

**Chapter 12: Preventing Infection Transmission**

| COMMENTS | RESPONSE |
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| What is not covered:<br>1. The fact that HCV infection is now an easy to cure disease. This has a major impact on kidney transplantation, both for living donor related and cadaveric donors. You have the option, waiting time permitting, to treat the donor and/or the recipient prior transplantation. This approach may increase the costs, but in the long-term you will save a lot. Treating before NTX has the advantage, that one has not to care about DDI's. The only study you quote deals with SOF/LDV, which is suboptimal for patients with impaired kidney function. Current published data (none after NTX!!!) indicate that combinations of protease inhibitors with NS5$ Inhibitors (i.e., Grazoprevir+Elbasvir, C-Surfer Study, Zeuzem et al, Ann Int.Medicine 2015; Zepatier TM; Paritaprevir/r+Ombitasvir+Dasabuvir (Ruby Study; VIEKIRA PACK) are effective and safe in CKD. | In the rationale, we state that the availability of new HCV antiviral medications such as interferon-free regimens may change the acceptability of transplantation from HCV+ donors. However, we believe it is premature to recommend transplantation from HCV+ living donors outside of research protocols, and emphasize the need for studies of safety and cost-effectiveness. Long-term health outcomes including recurrence risk after these new treatments are not defined, especially in the context of organ donors whose long-term health may be impacted by GFR reduction from donor nephrectomy. We added reference to the 2015 Ann Intern Med article describing short-term outcomes related to a protease inhibitor/NS5A inhibitor regimen, as recommended. Finally, in the Research Recommendations, we emphasize the need for studies 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. |
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| 2.The two most important risk factors for HCV Infection are not mentioned: a. Blood Tx before 1992; b. iv Drug abuse; c. Tattos. The sexual transmission occurs rarely and is not a real problem, the respective statements are overdone. | Recommendations for HCV, HBV and HIV screening have been issued by a number of organizations and evolved over the years. We chose to focus on the 2013 US PHS guidelines because these are the most current, were adapted specifically for the context of organ donation and have been publicly vetted for this application. The 2013 US PHS guidelines have replaced use of prior CDC guidelines in US transplant and donation policies. Based on the Reviewer's comments, we added mention of additional HCV risk factors identified by the US Centers for Disease Control (CDC) for the general public (not specific to organ donation), including: persistently abnormal alanine aminotransferase (ALT) levels, receipt of blood transfusion or blood components before 1992, receipt of clotting factor concentrates produced before 1987, recognized exposure among healthcare workers, and children born from HCV+ |

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| | mothers. Please note that tattoos are not included in the current list of risk factors recognized by the CDC. Please also note that testing for HCV is recommended for all donor candidates. Thus, behavioral risk factor assessment is used to inform pre-test probability for interpretation of microbiological test results and to guide counseling to avoid infection after testing, not to determine which donor candidates should be tested. |
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| When molecular testing of HIV, HBV and HCV is available, and can be performed close to the time of transplant, and individual risks of transmission can be calculated to account for infection in the window period, what is the added benefit of determining from history the likelihood of infection? | Behavioral risk factor assessment can be used to inform pre-test probability for interpretation of microbiological test results and to guide counseling to avoid infection after testing. Despite the apparent redundancy, a case of unexpected HIV transmission from a living donor occurred in the US when a new infection was acquired from high risk behavior after initial screening. The behavior history is an additional safeguard, as endorsed by the US PHS guidelines for organ donors. We added this rationale including the application to counseling to the supporting text: "*Living donor candidates with behaviors associated with an increased risk of acquiring HIV, HBV or HCV identified during evaluation should receive individualized counseling on specific strategies to prevent exposure to these viruses during the time period prior to donation surgery*." |
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| 11.3: Microbiological screening should be performed …following pathogens: The following first 5 pathogens are viruses. The wording of microbiological may not be appropriate. | We considered the terminology in preparing the section. As "microbiology" is defined as "a branch of biology dealing with microscopic forms of life", "microscopic" is defined as "able to be seen only through a microscope", and viral particles can be seen with an electron microscope, we chose the term "microbiological" as a suitable term to encompass all pathogens discussed in this chapter. |
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| Spelling error to be corrected: Chapter 11, page 83 Table #4 Treponema pallidum- Read Rapid Plasma Reagin for Rapid Plasma Regain (Syphilis) | Thank you. We corrected the spelling error. |

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| I am not sure that living donors with HepBs Ag should be considered. I am also not sure that living donors with chronic Chagas disease should be considered as donors given the relatively high incidence of cardiomyopathy and the limited ability of anti Trypanosomal therapy to affect the course of Chagas cardiomiopathy. | • Transplantation of kidneys from HBsAg+ donors to HBsAg+ recipients or recipients with HBV protective immunity has been described as, similar to any form of increased-risk transplantation, a possible strategy to increase transplant options and avoid the high morbidity and mortality of dialysis. We do not endorse the practice without careful consideration, and emphasize the need for informed consent of the recipient, possible anti-viral HBV treatment of the recipient and post-transplant monitoring. We also added the need for more study of the outcomes of this practice to the Research Recommendations.<br>• We agree with the need for caution in consideration of kidney transplantation from donors with Chagas disease. Our recommendations are based on review of available transmission data by recent transplant work groups – we summarize these data and agree with the prior recommendations for individualized consideration. Recipients must be informed of the need for participation in close monitoring and therapeutic intervention 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. |
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| We agree that "[l]iving donor donor candidates with behaviors associated with an increased risk… should receive individualized counseling on specific strategies to prevent exposure to these viruses during the time period prior to surgery." We recommend donors should be told how they may be asked to modify their behavior to reduce the risk of disease transmission before evaluation begins. Because some donor candidates who are considered "high-risk" may not realize they may be eligible to serve as a living donor, we encourage KDIGO to recommend that transplant centers describe how they treat high-risk donor candidates on their website. | Thank you for the comment and agreement with the importance of behavioral risk factor screening and counseling. After due consideration, we did not feel that disseminating lists of high-risk behaviors on websites would be particularly helpful. Discussions on these sensitive topics are best handled in a confidential conversation with trained professionals, and lists may serve to deter inquires by candidates who may ultimately be suitable to donate after careful evaluation and counseling. As emphasized in our Framework chapter (Ch. 1), programs should be transparent and consistent about evaluation practices once an evaluation begins. |

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| Agreement with recommendations and other suggestions | |
| 11.1: There is an internal contradiction in this statement: ALL vs USPHS instrument, which includes much more than the three conditions. Importantly, this being a global guideline document, use of such US specific recommendations is not appropriate. Parts of this are anyway ridiculous: Box 1 suggests asking donors "Have you been on hemodialysis in the preceding 12 months?"! | The US PHS instrument is designed to assess risk of 3 specific pathogens, HIV, HBV and HCV. While this guideline was developed in the US, the risk factors are not US-specific and are appropriate for an international audience. We do agree that the question related to hemodialysis exposure would be unlikely to be answered yes by a person being evaluated as a living donor candidate, but could be possible such as in the case of management of resolved acute kidney injury. Further, UNOS auditors in the US require use of the instrument in intact form, and a simple answer of "No" should not be burdensome to donor candidates. |
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| 11.2: Similarly, Box 2 really localises these guidelines to US. Might be more appropriate to suggest all program develop screening protocols for infections screening in consultation with their local infectious disease/public health specialists. | While the risk factor list adapted in Table 2 was developed by the UNOS Disease Transmission Advisory Committee (DTAC), the assessment of geographic, occupational, seasonal, hobby-related, and animal exposures is not US-specific. We believe enumerating these consideration is more helpful to transplant programs internationally than recommending consultation with local public health specialists - programs without resources may fail to develop any relevant policies. |
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| 11.4: Again, imposes too great a burden by bringing in US-specific recommendations and specifying infections in a global guidelines. Also ignores the fact that new/emerging infections other than the ones listed might need to be included from time to time. The recommendation should be practical and realistic - somewhat similar to the suggestion for #11.2 that "protocols should be developed and revised as needed in consultation with their local infectious disease/public health specialists" | The infections listed in 12.4 (Mycobacterium tuberculosis, Strongyloides, Trypanosoma cruzi, West Nile virus, Histoplasmosis, Coccidiomycosis) are not US-specific concerns and some in fact have higher prevalence and potential impacts in other countries. We chose to focus on these pathogens as the implications for potential transmission through organ donation are recognized in the transplant community, as discussed in detail in the supporting rationale. Table 3 provides a comprehensive list of recognized organ-derived infections that is internationally relevant. We do agree on the importance of responsiveness to new/emerging infections, and added the following recommendations: " *Transplant programs should develop protocols to screen donor candidates for emerging infections in consultation with local public health* |

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| | *specialists*." We also added a brief description of emerging infections to the rationale text. We emphasize the importance of developing and validating risk assessment questionnaires and protocols for living donor-derived infections, considering behavioral, occupational, hobby-related, geographic (including country/region specific) and seasonal exposures as an important Research Recommendation. |
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| Box 2: Recommendation for MTB screening and prophylaxis as stated is debatable, not fact-based and unlikely to be practised. General population prevalence of a positive TST or IGRA is high, indicated past infection in endemic countries and nor really an increased risk of disease transmission. | Our recommendations related to MTB were drawn from consensus based recommendations of several major transplant organizations, including the UNOS DTAC, the American Society of Transplantation, Canadian Society of Transplantation, and The Transplantation Society, and Spanish Society of Infectious Diseases and Clinical Microbiology. |
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| **Suggestions for additional recommendations** | |
| Screening for strongyloidosis should take place in all "Born in or lived in tropical / subtropical countries with substandard sanitation" is - to put it mildly - not based on evidence. | We describe the source of the recommendation as *consensus-based* recommendations of the 2013 American Society of Transplantation Infectious Diseases Community of Practice workgroup and the OPTN/UNOS Disease Transmission Advisory Committee (DTAC). Of note, the World Health Organization reinforces these epidemiologic risk factors, stating that Strongyloidiasis is linked to a lack of sanitation and risk is increased occur where there is poverty, while the pathogen has almost disappeared in countries where sanitation and human waste disposal have improved (references added to the rationale). We also note in the rationale that Strongyloidiasis has occurred in most countries with the exception of Canada, Japan and Northern Europe. |
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| Histoplasma - Antibody may be positive in someone with a remote exposure only. | We propose the antibody test as a screening option, and urine or serum antigen testing for confirmation. |
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| HCV - Donors from high endemicity areas should be screened only by NAT. Asking for antibody also will raise cost of screening. | Our recommendation is consistent with the 2013 US PHS guideline, which recommends that all potential living donors should be tested for both anti-HCV Ab and for HCV RNA by NAT. |

**Chapter 13: Cancer Screening**

| COMMENTS | RESPONSE |
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| Persons with renal cell cc should be excluded. | The Work Group considered the scope of available international experience on this topic. Multiple cases of back table excision of small renal cell carcinomas after donor nephrectomy, followed by use of the kidney for transplantation, have been reported with acceptable outcomes for the donor and recipient – a recent UNOS DTAC report concluded that "*the literature is virtually unanimous in suggesting that kidneys with small, solitary, well differentiated RCC may be usable for transplantation provided the lesion itself is completely resected*" (Am J Transpl 2011; 11:1140). We concluded that the decision to proceed with donation in a person with suspected kidney cancer based on predonation imaging should by individualized, considering 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. Programs still have the opportunity to determine that the risks are not acceptable in their practice. Finally, we added the need for systematic monitoring of long-term donor and recipient outcomes in the case of kidney transplantation from living donors with small (T1a) renal cell carcinoma as a Research Recommendation to better inform guidance for when donation and transplantation may or may not be acceptable. |
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| 12.1: Donor candidates should undergone cancer: → undergo | This comment appears truncated in the submission site. |
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| The guidelines are appropriate but I am wondering whether to add some information about the interval between cancer and potential donation. As an example, what to do with a woman who received mastectomy for cancer 20 years ago? | The cited risk classification includes some information on timing based on the source information including cancer registry reports, published literature, and data submitted to the OPTN. For example, treated non-CNS malignancy >=5 yrs. prior with >99% probably of |

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| | cure is considered low risk, while treated non-CNS malignancy >=5 yrs. prior with 90-99% cure probability is considered "intermediate" risk. At this time, any history of breast cancer stage 1 or higher is considered "high risk" for disease transmission. We revised the rationale to emphasize that this classification scheme should be updated with new information as data become available. |
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| 12.1: It is important to accept the classification of risk transmission of a neoplasm derived from the donor into six categories, since it is easy to apply in order to define the acceptance or rejection of the donor (Ref Ann Transplant 2004; 9: 53-56, Am J Transplant 2011 11 : 1140-1147. | Thank you for the comment. The most recent 6-level classification scheme defined in Am J Transpl 20111; 11:1140 is presented in the rationale for this chapter and informs the acceptance criteria for donor candidates with a past history of cancer (13.6). |
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| I am not sure that the risks of transmission or recurrence can be as accurately quantified as this statement implies. | This classification provides a framework that can be updated with improved supporting information as data become available. In the rationale we explain that the 6-level classification scheme for risk of donor-derived cancer transmission is based on cancer registry reports, published literature, and data submitted to the OPTN. We revised the rationale to state that this classification scheme should be updated with new information as data become available. We also added a statement that consideration of living donation from a person with a history of treated cancer should include consultation with the donor candidate's oncologist to confirm that individual case factors are associated with "low" (<1%) risks of both recurrence and disease transmission, and that long-term surveillance will not require frequent imaging that may limited by reduced GFR (e.g. CT scans with iodinated contrast or MRI scans requiring gadolinium). |
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| 12.1: not all countries have clinical practice guidelines for cancer screening, so I think some basics need to be stated. | We added the statement that transplant programs in countries without national clinical practices guidelines can refer to guidance from other countries most similar to their population, and provided links to current examples. |

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| 12.2: 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. If the tumor leads to nephrectomy (not 'partial nephrectomy'!), this kidney cannot be transplanted, and the contralateral cannot be transplanted either? I am afraid I do not understand this sentence. | The assumption is that the decision for total nephrectomy would be driven by the individual's desire to serve as a kidney donor, not the size or stage or the tumor. As discussed in the rationale, while partial (rather than complete) nephrectomy is often the treatment of 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 predonation 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. |
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| The section on cancer screening to reduce the risks of transmission is relatively brief. As the authors have implied there is very little evidence that can be used to develop guidelines. However the recommendations seem reasonable based on common sense rather than data. | Thank you for your review and support. |
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| **Suggestions for additional recommendations** | |
| Our recommendation is that the existence of the Notify Library should be made known to readers. It is a WHO initiative to promote vigilance and surveillance. The Notify Library is an open access database of published didactic cases of adverse occurrences arising with medical products of human origin including transplants (www.notifylibrary.org). In particular it is a comprehensive database of disease transmission including malignancy, from donors to recipients. It is useful source to access data regarding malignancy transmission. | Thank you for the comment. Our leading Research Recommendation in the chapter is to better define the incidence of donor-derived disease transmission according to cancer type, clinical features and duration since treatment, through improved monitoring and reporting. We added a statement that efforts such as the "Notify Project", a consortium of global experts who gather didactic information on documented types of adverse outcomes in transplantation to identify general principles supporting detection and investigation, should be supported and expanded. We included the URL for the project. |

**Chapter 14: Evaluation of Genetic Renal Disease**

| COMMENTS | RESPONSE |
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| For ApoL1 risk, I would recommend that age be used as a determinant to decide whether to test or not test. The lifetime risk of CKD progression would be very high for a young donor with ApoL1 risk variant. Even if the potential AA donor has no FH of renal disease, consideration should be still be given for ApoL1 testing. | • Thank you. We revised the recommendation to read: "*Apolipoprotein L1 (APOL1) genotyping may be offered in donor candidates with sub-Saharan African ancestors. Donor candidates should be informed that having 2 APOL1 allele risk variants increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified*."<br>• We describe the current state of evidence related to the outcome implications of APOL1 genotyping in the rationale, and added the sentence: " *The implications of having 2 risk alleles likely differ in younger vs. older donor candidates...*"<br>• We also include "*Define the role APOL1 genotyping in the evaluation donor candidates of sub-Saharan African ancestry*" as a Research Recommendation. |
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| I believe that the data supports the conclusion that ALL potential donors for kidney transplants should undergo testing for high risk APOL1 alleles and if two risk alleles are present that they should be advised not to donate. | • Thank you. We revised the recommendation to read: "*"Apolipoprotein L1 (APOL1) genotyping may be offered in donor candidates with sub-Saharan African ancestors. Donor candidates should be informed that having 2 APOL1 allele risk variants increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified."*<br>• We describe the current state of evidence related to the outcome implications of APOL1 genotyping in the rationale, and added the sentence: " *The implications of having 2 risk alleles likely differ in younger vs. older donor candidates, and whether the genetically related intended recipient has the same alleles. The implications of having 2 risk alleles may also be influenced by the results of renal function testing done at the time of donor candidate evaluation.*"<br>We also include "*Define the role APOL1 genotyping in the evaluation* |

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| | *donor candidates of sub-Saharan African ancestry*" as a Research Recommendation. |
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| 13.9: Young (16-40) potential donors with any renal cysts should undergo genetic testing before being considered as donors. | After consultation with a number of experts, the Work Group concluded that genetic testing is imperfect – i.e. genetic testing can confirm the presence of the condition, but absence of an identified mutation does not definitely exclude ADPKD, given not all mutations are identified by currently available testing (imperfect sensitivity). We refer to imaging criteria that reliably exclude the presence of ADPKD, in the presence of family history. In the rationale we provide several more details about genetic testing. In our recommendations we state that "*Donor candidates with a family history of ADPKD in a first-degree relative may be acceptable for donation if they meet age-specific imaging or genetic testing criteria that reliably excludes ADPKD.*" |
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| 13.10: It is unclear whether ApoL1 alleles put donors at risk if there is no clinical evidence of renal disease at the time of donation. | Please see the prior similar comments and our response above. We incorporated your suggestion in the rationale to note that the implications of having 2 risk alleles likely differs in younger versus older donor candidates, and may be influenced by the results of renal function testing done at the time of evaluation. |
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| 13.10: clear risk study are needed with influence on various factors as compared with APOL1 genotyping (BMI, other genes) | We agree, and emphasize the need for future study in the Research Recommendations. |
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| We restricted ourselves to the general recommendations and did not thoroughly screen the disease specific recommendations. Some of the suggestions refer to the text that is not in bold in the document, they are listed last. | Thank you for your review. |
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| 13.1: The donor family history should be more general than just kidney disease. Just as examples: HNF1B, COL4A1 (also COL4A3-5), and INF2 have pleiotropic effects that can be missed when only enquiring about kidney disease. All first and second degree relatives should be part of the family history. | • Thank you. To incorporate your comment while avoiding barriers to execution (i.e. a need ask about all the possible extra-renal manifestations of kidney disease in the absence of knowledge of the presence of a genetic kidney disease), we revised recommendation 14.1 to read: " *Donor candidates should be asked about their family history of kidney disease, and when present, the type of disease, time of onset, and extra-renal manifestations associated with the disease.*"<br>• We also emphasized the extra-renal manifestations of several of the genetic diseases in the revised rationale.<br>• In terms of first vs. second degree relatives, we focused on first degree relatives when specification was necessary - i.e. imaging criteria for ADPKD. |
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| 13.2: we propose an addition: "....evaluation team. EARLY AGE OF ONSET OF RENAL DISEASE, EXTRARENAL MANIFESTATIONS IN THE RECIPIENT AND POSITIVE FAMILY HISTORY (FOR RENAL AND/OR EXTRARENAL DISEASES) ARE CLUES FOR A GENETIC CAUSE AND SHOULD EACH SEPARATELY LEAD TO GETTING THE GENETIC DIAGNOSTIC WORK-UP IN THE RECIPIENT UP-TO-STANDARD BEFORE ACCEPTING A RELATIVE AS DONOR CANDIDATE." | We are aiming to minimize the length of the recommendation statements themselves. In accord with your comment, we added the following to the rationale: " *All donor candidates should be asked detailed questions about a possible family history of hereditary kidney disease, and all reasonable measures should be taken by health professionals caring for the intended recipient to determine the cause of kidney failure in the setting of possible hereditary kidney disease. With permission of the intended recipient, information about the intended recipient's cause of kidney failure should be reviewed carefully by the donor evaluation team and shared with the donor candidate."* |
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| 13.9: We propose an addition, after the last line (imaging criteria for ADPKD): "WHEN IN DOUBT, CONSIDER GENETIC TESTING IN RECIPIENT AND DONOR (SEQUENTIALLY)." Suggestions for not-bolded text: | • We are aiming to minimize the length of the recommendation statements themselves. However, we improved the description of ADPKD testing in the rationale section, which incorporates this suggestion.<br>• The comment also has implications for the APOL1 genotyping section, where we added the statement: "*The implications of having 2 risk alleles likely differs in younger versus older donor candidates, and whether the genetically related intended recipient has the same alleles*." |

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| 1) Introductory paragraph We propose an addition: ".... from becoming a kidney donor. LONGTERM FOLLOW-UP DATA HOWEVER ARE OFTEN NOT AVAILABLE IN LITERATURE." | We added this statement to the rationale text. |
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| 2) First paragraph of Rationale We propose an addition: "...genetic cause of kidney disease. DIAGNOSTIC GENE PANEL SEQUENCING FOR SETS OF GENES KNOWN TO CAUSE MENDELIAN END STAGE RENAL DISEASE IS AVAILABLE IN SOME FIRST WORLD COUNTRIES AND CAN OFTEN BE REQUESTED FROM ABROAD. THIS TYPE OF DIAGNOSTICS SHOULD SERIOUSLY BE CONSIDERED WHEN AVAILABLE. ALSO, THE RECENT LITERATURE SHOWS VARIABLE EXPRESSION OF KNOWN GENES PLAYING A ROLE (e.g., PAX2 in FSGS (Barua M, Stellacci E, Stella L, et al. Mutations in PAX2 associate with adult-onset FSGS. J Am Soc Nephrol. 2014 Sep;25(9):1942-53.)) IN KIDNEY DISEASE. THIS IN ITSELF IS AN ARGUMENT FOR LIBERAL GENETIC TESTING (WHEN AVAILABLE) IN RECIPIENTS. THIS TYPE OF WORK-UP CALLS FOR CLOSE COLLABORATION WITH A CLINICAL GENETICIST. | We felt the current evidence base was insufficient to make this statement in the rationale. However, we added the need to "*fevelop better strategies and tools to screen donor candidates for genetic kidney diseases that consider the accuracy, efficiency and costs of testing, including assessment of targeted gene panels for known mutations implicated in kidney diseases*" as a Research Recommendation. |
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| 3) page 103, third paragraph ".... is currently imperfect or evolving...." : I don't quite understand this text; for Mendelian renal disease, which one is most worried about in this context, very sensitive tests are widely available in the first world, culminating in gene panel sequencing of a sizeable number of genes available in some countries, open to requests from abroad. | As above, we felt the evidence base was insufficient to make this statement in the rationale at this time. We appreciate the field of genetic diagnostics is rapidly changing, and the evidence to support this approach could become stronger in the near future. We simplified this paragraph in the rationale to avoid misrepresentation of current capabilities. |
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| I don't approve the 13.9 statement. In the clinical situations of ADPKD described I do think that a genetic test should be performed. | There are varying opinions on this topic, as expressed in other public comments above. Our recommends do not preclude genetic testing in these scenarios. In the rationale we describe current limitations of genetic testing. Based on the balance of comments and discussion with Genetics experts, we revised the rationale to be less prescriptive regarding which tests should be performed to reliably rule out ADPKD in a candidate who is younger than 40 years old. In our recommendations we state that "*Donor candidates with a family history of ADPKD in a first-degree relative may be acceptable for donation if they meet age-specific imaging or genetic testing criteria* |

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| | *that reliably excludes ADPKD*." |
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| 13.9: The number of less than five simple renal cysts between 16-40 years of age in one kidney or in combination can lead to ambiguities. ADPKD criteria with the use of ultrasound are: From 15-39 years, less than three simple cysts in one kidney or in combination -sensitivity 82%, specificity 96%. From 40-59 years, two or more cysts in each kidney. Sensitivity 90%, specificity 100% . Older than 60 years: over four kidney cysts, 100% sensitivity and specificity (Ref: J Am Soc Nephrol 2009; 20 (1): 205, J Am Soc Nephrol 2015 Mar; 26 (3): 746-53. | In the initial public review version of the guideline we presented MRI criteria. Based on the balance of comments and discussion with Genetics experts, we revised the rationale to be less prescriptive regarding which tests should be performed to reliably rule out ADPKD in a candidate who is younger than 40 years old. Please see prior similar comments and our responses above. |
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| It is important to acknowledge that in a significant fraction of cases the cause of ESRD in a transplant candidate is not known. When a biologically related individual is donating, the possibility of undiagnosed genetic kidney disease must be entertained. It is insufficient to say that donating when a candidate has a first degree relative with genetic kidney disease should be carefully assessed on a case-by-case basis. It would be better to say that donating when a candidate has a first degree relative with kidney disease that is genetic or of unknown etiology should be carefully assessed on a case-by-case basis. | This is an excellent point. Recommendation 14.2 was revised to read: "*When the intended recipient is genetically related to the donor candidate, the cause of the intended recipient's kidney failure should be determined whenever possible. The intended recipient should consent to share this medical information with the donor evaluation team, and with the donor candidate if it could affect the decision to donate*." We also emphasized this point in the rationale. |
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| I would like to see more extensive discussion of the issue of APOL 1 genotyping in all candidates of African descent. | We expanded the background information related to APOL1 genotyping, while at the same time being mindful of the word count for this section and for the overall guideline. |
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| In the case of a young potential donor (e.g. 16-22 yrs) with some cysts in his/her kidneys (though less than 5), I would have some perplexity in accepting him/her as the donor for an ADPKD relative recipient. In this case at least a genetic test should be performed | Please see prior similar comments and our responses above. |

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| Age 30-39 years with no cysts on ultrasound should undergo MRI Imaging to exclude ADPKD.<br>Age < 30 years with less than five cysts on MRI should undergo a genetic testing to rule out ADPKD (see publication: Kanaan N, Devuyst O, Pirson Y: Nature Reviews Nephrology 2014) | Thank you for these important comments. We now cite your review. Given the balance of comments and current controversies, we are less prescriptive regarding the exact testing that should be performed to reliably rule out ADPKD in a patient who is younger than 40 years old. |
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| 13.10: If a donor candidate is of native African ancestry and has a first degree relative with non-diabetic kidney disease, consideration should be given to genotype testing 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. | Based on the balance of comments we revised the recommendation to read: "*Apolipoprotein L1 (APOL1) genotyping may be offered in donor candidates with sub-Saharan African ancestors. Donor candidates should be informed that having 2 APOL1 allele risk variants increases the lifetime risk of kidney failure but that the precise kidney failure risk for an affected individual after donation cannot currently be quantified*." We also clarify that genotyping is relevant to those with sub-Saharan African ancestors. |
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| Recommend that 13.3 reads that 'most' genetic kidney diseases in the donor should preclude donation. We advise that regardless of the genetic disease, IF it is the same one leading to kidney failure in the intended, related recipient, then it should preclude donation. | Thank you. Based on other comments we removed this recommendation, as it was thought to be self-evident. We did add a recommendation that incorporates your comment: "Donor candidates found to have a genetic kidney disease should not donate. " |
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| Recommend that 13.9 address the fact that PKD 2 presents later than PKD 1; imaging criteria may be different for ruling out PKD in a young potential donor with family history of PKD 2. | Thank you. We added the following statement to the rationale: "*Kidney disease from PKD2 presents later in life than PKD1*." |
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| I think you should include a few lines about of nephropathic cystinosis. Nephropathic cystinosis is a rare disease, inherited autosomal recessive, caused by defective transport of the amino acid cystine out of lysosomes, by mutations. in CTNS gene. Kidney transplantation in patients with infantile cystinosis corrects kidney failure and prolongs survival, the donor parenchymal | Thank you for this suggestion. To be pragmatic, we limited the chapter to more common (although often still rare) genetic diseases. Covering all possible genetic diseases was not feasible. |

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| cells are not homozygous for the genetic defect and are therefore able to transport cystine from the lysosomes. Kidney transplant does not prevent extrarenal damage. The patients require therapy with bitartrate cysteamine | |
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| Pei et al reported 2011 that MRI has not been validated for ADKPD exclusion in studies yet. “However, MRI likely will detect both small, simple cysts and small cysts that arise from ADPKD. Therefore, until its diagnostic utility has been evaluated formally as in ultrasonography, it should not be used as the initial imaging modality for diagnosis of ADPKD." Not to speak using it as an exclusion instrument. Furthermore the donor (at least every donor under 30) should be informed that a genetic testing might give the highest safety (especially if linkage analysis can be performed - large family). Also donors over 30 should be given detailed information that ADPKD cannot be ruled out by 100% but always a little less percentage. | Thank you. Given the balance of comments and current controversies, we are less prescriptive regarding the exact testing that should be performed to reliably rule out ADPKD in a patient who is younger than 40 years old. Ultrasound criteria cited are reliable for ruling out ADPKD in candidates 40 years of age and older. |
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| Overall the section on the evaluation of genetic renal disease in kidney donor candidates is comprehensive and well written. It covers the areas of evaluation of the kidney donor, general advice re: donation to a relative with genetic renal disease, the role of counselling and genetic testing as well as advice for specific genetic diseases. | Thank you for your review and support. |
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| Agreement with recommendations and other suggestions | |
| At the moment it is difficult to give comprehensive advice about how to investigate such donors and the role of genetic testing is in a state of flux with implementation of new high throughput technologies such as deep sequencing and whole genome sequencing. Hence for some genetic diseases the advice offered may change in the near future. This fact ought to be acknowledged in the text. | We now acknowledge this in the rationale: " *With advances in genetic medicine and the implications of new risk alleles such as APOL1, there is likely to be rapidly evolving knowledge that may influence future donor candidate evaluations. However, at this time the testing for several genetic conditions is imperfect.*" In the Research Recommendations, we emphasize the need to: “*develop better strategies and tools to screen donor candidates for genetic kidney diseases that consider the accuracy, efficiency and costs of testing, including assessment of targeted gene panels for known mutations implicated in kidney diseases*.” |

| **Suggestions for additional recommendations** | |
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| Regarding advice re: aHUS. We agree there is a high risk of recurrence in the recipient and there is a risk of developing the disease in the donor. However the advice offered is vague. We recommend that the risk ought to be highlighted in the summary as:<br>13.11: atypical HUS. There is a risk that the genetically related donor may subsequently develop HUS after donation and there is a high risk of recurrent disease in the recipient. Therefore an evaluation of the specific risks need to be taken into careful consideration when assessing such a donor. | For several genetic diseases, including Fabry disease, Alport syndrome, familial FSGS, hereditary interstitial nephritis and atypical HUS, we restricted our suggestions to the rationale, rather than as formal recommendations, given limitations of the evidence for donor candidate evaluation. The rationale text notes that current genetic testing is imperfect in ruling out the presence of aHUS in a donor candidate even when the mutation is known in the recipient. For these reasons some suggest never to proceed with living kidney donation in the setting of a recipient with aHUS. Others suggest assessing whether a donor candidate shares a genetic susceptibility factor to HUS to determine whether or not they may be a suitable donor. |

**Chapter 15: Pregnancy**

| COMMENTS | RESPONSE |
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| 14.5: may be acceptable for donation, provided a transplant center after reviewing the nature of this hypertension BUT the candidate's post-donation long-term risk of ESRD is NOT low. | Thank you. We revised the recommendation to read: "Female donor candidates with a history of a hypertensive disorder during pregnancy (including preeclampsia) or gestational diabetes may be acceptable for donation, provided the candidate's long-term post-donation risks are acceptable." |
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| If the recipient is a relative to the young females donor, screening has to be performed if there is any familiar cause of the kidney disease. It has to be expressed to any young female, that later her own child might need a kidney. | Please see the Ch. 13 for a detailed discussion of the evaluation of genetic kidney disease. Any person who serves as kidney donor will not have the opportunity to donate again in the future; a young woman seeking to donate may be attempting to give to her own child. |
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| I thank the work of this committee on the progress made in thinking about pregnancy and living donation, including in quantifying risk. The conversation still has a long way to go in practice but this is a great start. | Thank you very much for your review and comments. |
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| 14.3 Not approve: Women who are pregnant, or may be pregnant, should not be investigated for living donation. So the recommendation does not apply. | Thank for the comment – the feedback illustrates that we did not communicate as intended. We revised the recommendation to read: " *Local guidelines should be followed to confirm the absence of pregnancy before performing radiologic tests, including abdominal computed tomography (with iodinated contrast) or nuclear medicine GFR testing."* |
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| 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. "simply" should be removed as it suggests minimal risk and biases the | Thank you. We revised the wording of this recommendation for clarity, and also rephrased this recommendation based on other feedback received, to read: "*Women should not be excluded from* |

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| question. You could use "only" or "exclusively". | *donation solely because they desire to have children after donation*." |
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| One think that needs to be take into consideration and that needs to be full included in the informed consent is the fact that as many as 70-90% of pregnant women experience dilatation of the right kidney. This can lead to endangerment of the kidney function as there is no contralateral organ. There are published case reports and also in our association were this kidney dilatation led to an emergency Caesarian or a premature birthday just in order to save the remaining kidney from further damage. Actually it should only be allowed (if at all) to donate the right kidney since this is the one which suffers from dilatation in most of the cases. With a kidney dilatation the infection risk is higher, potentially putting mother's kidney and child in danger. This potential danger to the kidney is well known but hardly ever recognized of transplant centers. This needs to be included in the guidelines! Even if a pigtail/JJ stent is inserted it still carries the danger of premature birth and infection. Either way potential donors need to be fully informed about this risk. | Thank you for this comment. There is a dearth of information on this topic. In our Research Recommendations, we prioritized that we need to understand whether the risk of complications in post-donation pregnancies vary according to the side of the donated kidney. We also highlight your important point here, that pregnancy may be associated with ureteral obstruction and dilatation, particularly of the right kidney. We expanded the rationale text to note that pregnancy may be associated with ureteral obstruction and dilation, particularly of the right kidney. In the recent retrospective study of pregnancy outcomes after donation in Canada, only 16% of women donated their right kidney, with too few patients to perform meaningful analyses on the basis of this characteristic. |
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| This chapter concerns living donors and pregnancy – examining both potential risk of donation to future pregnancies and also the impact of past pregnancy histories on donation risks and on outcomes of subsequent pregnancies. Quality of Data for Recommendations: · The recommendations are all at a level of 'not graded' · Quality of data in rationale section is comprehensive in a relatively data poor area of practice. · No additional publications identified that have not been cited | Thank you for your review and comments |
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| Agreement with recommendations and other suggestions: | |
| · Agree with recommendations except the one regarding performance of CT scans in workup if pregnant (or potentially pregnant) - The recommendation is potentially open to misinterpretation in current wording and would be better left out – current wording suggests this may be a reasonable/expected scenario in workup of donors – clearly not the case | Thank you. Please see prior similar comment and our response above. We have clarified the wording of this recommendation. |

| **Suggestions for additional recommendations:** | |
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| · Rationale does cite literature supporting increased incidence of hypertension and preeclampsia in post-donation pregnancies but this does not get to recommendation list – would suggest that 'donors are made aware of these risks' should be a recommendation (even if qualifying the case cohort based nature of such studies). | We agree with the importance of sharing current outcome information with donor candidates. Recommendation 15.9 states: " *We suggest that women with childbearing potential be counselled about the effects donation may have on future pregnancies, including the possibility of a greater likelihood of being diagnosed with gestational hypertension or preeclampsia. (2C)"* |
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| · The issue of assessment of suitability for donation in the female donor of childbearing potential is a common clinical decision making scenario in transplantation. Practice varies and should not depend on biases of individual units/clinicians and should be standardized by consensus guidelines may be worth saying this in recommendation or rationale sections. | Thank you for the comment. The objective of the current chapter is to provide recommendations to help standardize evaluation, selection and counseling, and to explain the state of available evidence grounding these recommendations. We also provide recommendations for further research to help improve future guidance for clinical practice. |

**Chapter 16: Psychosocial Evaluation**

| COMMENTS | RESPONSE |
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| I think the implication that all donors would benefit from face to face psychosocial evaluation has no evidence to support it. In resource poor health care economies (like the UK!!) it will be a delay and disincentive to live donor programs, which is not what we want. | We acknowledge in the rationale that currently there is a lack of strong evidence or concrete guidance for many aspects of the psychosocial evaluation, and thus our recommendations reflect opinion. Of note, as reflects in the public comments, there is also range of public opinions, including those who advocate for specific credentials of individuals performing the psychosocial evaluation. The Work Group considered practicalities, but deems the psychosocial evaluation to be equally important as the medical evaluation. Telephone screening may be a first step, but we believe the primary psychosocial evaluation should be conducted in person as an opportunity to capture important non-verbal communication. In-person evaluation has been recommended in prior reports, as referenced in the rationale. |
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| 15.5: I do not believe financial incentives are either immoral or should be considered as a negative factor of donation. In Iran for example people donate and the State pays a fee for the donor. I personally see no reason why donation should be discouraged when it could help a poor person to get out of "the poverty rut". This is strictly an item of social, cultural acceptance or rejection. | Please see Chapter 18 focused on Policy Considerations. Our recommendations are consistent with the Declaration of Istanbul, which condemns the *illegal* sale of organs. We note the debate on the acceptability of legalized incentives. |
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| Should 15.3 include review of information about programs and policies specific to living donors (such as priority on deceased donor list, living donor advocacy and support groups, etc?) | Review of these topics with the donor candidate are described in Ch. 2 (Informed Consent). |
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| We are pleased to see that POSITIVE impacts, including good psychosocial outcomes are included in the following. Please ensure and expand where applicable. | Thank you for the comment. |

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| 15.3: 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. | |
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| Under the rationale discussion there appears to be an incomplete sentence structure. In the third paragraph, the sentence on: In which setting should the evaluation be performed? We believe the main psychosocial evaluation should be conducted as a face-to-face interview, as has also been recommended in several prior reports. | Thank you. We corrected the sentence as suggested. |
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| We strongly encourage evaluating non-directed donors in the same manner as other donors and agree with KDIGO on their position. | Thank you for the comment. |
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| Recommend that 15.1 clarify appropriate licensing/ training credential of the nurse - psychiatric RN vs NP. | The Work Group believes that the psychosocial evaluation is as important as the medical evaluation, and advocates for performance by a trained profession experienced in the psychosocial dimensions of living kidney donation and transplantation. However, there is insufficient evidence to define requirements for specific licensing. Further, licensing/credentialing may vary regionally, and overly prescriptive language may introduce barriers to practice. |
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| Please see Chapter 1 for general comments. Chapter 15: The recommendations are generally well-reasoned. However, an important exception is the potential exclusion item in Recommendation 15.5 about active substance abuse/dependence that affects decision-making. The wording gives the impression that it is satisfactory for a donor candidate to have a diagnosis of active substance abuse/dependence, as long as it does not affect decision-making or put the donor at risk above a center's threshold. It would seem to be a poor recommendation to be saying, essentially, that substance | We agree that the terms "abuse/dependence" imply problematic behaviors. We removed the qualifying phrase from the description of contraindications to donation (now listed in Table 2) and explained the concern in the rationale. The term "active" allows for an intervention to resolve the exclusion. |

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| abuse/dependence is otherwise acceptable for living donor candidates. It is strongly suggested that this wording be modified. | |
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| Questions again arise concerning what level of evidence is needed before a recommendation moves from ungraded to some level of grading. In many instances, it would seem that at least "we suggest" recommendations should be possible. For example, there would seem to now be a preponderance of evidence that donors do incur financial costs and need to be informed of this likelihood, and it needs to be discussed during the evaluation so that donors can adequately consider it and prepare. | We added a Methods Chapter with details of these processes to the guideline document. The complete Evidence Review is also available as an Appendix and is summarized in a separate publication. Herein we recommend assessment of the donor candidate's preparation for possible financial impacts of donation. Ch. 2 provides recommended content for Informed Consent, and includes disclosure of economic risks. |
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| Recommendation 15.1, noting that the psychosocial evaluation should "ideally" be performed with the donor candidate alone, also seems potentially problematic because it is inconsistent with the evidence that is cited in the Rationale, which notes reasons why at least part of the evaluation might benefit from having another individual present. "Ideally" seems like an odd choice of words because it is a value statement and does not clearly provide a roadmap for centers—perhaps it would be better to strike the term altogether, or use an alternative such as stating that "at least some portions of the evaluation should be performed with the donor candidate in the absence of …" | We agree and modified the statement as suggested. |
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| Page 113: "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)." There is absolutely no reason why those important issues mentioned here are OPTIONAL (Donor candidates CAN be informed)! They HAVE TO be informed about those possible and reported consequences of donation. It is well known in the transplant community that there is a huge lack of valid long term studies on donors, still some report a decline in health in certain issues (e.g., fatigue, reduced physical stamina, reduced vitality, higher rates of depression). Hence it is of utmost importance to be as detailed as | The word "can" was replaced by "should", to read: "*Donor candidates should also be informed that some people experience psychosocial difficulties after donation…*" |

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| possible about any possible future risk - at least for juridical reasons, not to speak of ethical reasons. | |
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| The informed consent also needs to include the lack of knowledge about long term consequences and the donor needs to be made aware of the fact that in hardly any study the donors were compared to a healthy cohort. Hence a bias might have occurred evaluating the real risks for the donor. The possible decline in vitality (or fatigue issues) must be an emphasized issue during informed consent as it has been mentioned in different studies, but never been examined on its own. Paralleling the fatigue issues in kidney recipients that have just recently been described in several studies. This has hardly been recognized before because fatigue or loss of physical stamina has been underreported also in those studies. Not to speak of donor studies. But - well known from cancer patients - very often reduced vitality appears to be the biggest problem in daily life for those patients. There should be no doubt that potential donors need to have (ethically and juridically obvious) the most detailed and best informed consent possible. If there is nescience/ignorance about the pathogenesis of reduced vitality this must not mean that it is not mentioned to the potential donor. There is a lack of knowledge about the pathogenesis of fatigue in many diseases, but there is (mostly) an awareness that it is causing trouble in the patients daily life. Hence the word "CAN"need to be exchanged for "SHALL" and more Information should be given about this issue within the guideline! | The rationale text for this section summarizes the results of an independent Evidence Review that queried existing literature on psychosocial outcomes after donation. Accompanying detailed evidence tables are provided, reflecting the metrics included in the source studies. We also summarized the findings of a systematic review and large cohort study published after completion of the independent evidence report. The recent systematic review by Wirken et al (Am J Transplant 2015) did report on fatigue, and we added a summary of the findings to the rationale text. |
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| The overall quality of data is good to very good (not graded). | Thank you. |
| No additional important publications were identified. | |
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| *State whether we agree with the recommendations and or suggest alternative wording or alternative recommendations:* | |
| In particular we agree with the recommendation that all potential donor should undergo a psychosocial evaluation prior to being accepted as a donor. | Thank you for the comment |

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| This chapter begins by outlining the many functions of the psychosocial evaluation. The functions listed are: is the donor psychologically suitable; addressing any donor concerns, ensure that the psychological risks and benefits of donation are disclosed and understood by the potential donor and develop a tailored plan to support the donor throughout the donation process and beyond. | |
| There are various tasks outlined here,<br>ü acute listening to evaluate the psychological state of the donor (suitability)<br>ü dealing with the anxieties (e.g. health, financial) of the donor (addressing concerns)<br>ü information giving (risks and benefits)<br>ü planning (tailored plan)<br>These tasks in my opinion call for different skills. The key skill is acute and active listening to evaluate the suitability of the donor. This calls for specialist training which is acknowledged by the document. | Thank you for the comment. We moved evaluation elements to a table, and added headers for evaluation tasks similar to the suggested themes. |
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| *Evaluation and Pre-Donation Counselling* | |
| As outlined this is comprehensive. | Thank you. |
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| 15.1: The one issue I would raise is the use of the word 'counselling'. Counselling is a generic term that can mean different things to different people, therefore, it is open to misunderstanding. I would suggest using 'psychological support' rather than the word counselling. | Thank you. Although we use “Counselling” as a header in many chapters, given the unique connotations in the content of psychosocial evaluation, we revised the header to “Disclosures and Support”. |
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| 15.4: I agree there should be no difference in the evaluation for related or non-related donors. | Thank you |
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| *Psychosocial Acceptance Criteria for Donation* | |
| 15.5: Comprehensive list which covers the main issues relevant to donation. | Thank you |
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| *Follow-up Support* | |

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| 15.6: I would underline the importance of follow-up. It is essential to offer follow-up psychological care to the donor. Issues (as outlined on p.112/3) - depression, anxiety, concerns about health, etc. need to be monitored after donation. It is unacceptable that following successful donation the donor is not offered continued psychological support should any issues arise. There seems little point when transplant is successful to have a donor who is left psychologically damaged post-donation. | We revised the statement to emphasize that support should be available both before and after donation. |
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| Comments on rationale (p.111/115) | |
| *Overview of prior guidelines* | |
| KDIGO raise the concern that each transplant centre develops its own criteria for psychological evaluation. There is no consensus or guidelines in operation across transplant centres. Transplant centres should be encouraged to come together to develop appropriate guidelines for the provision of psychological assessment of potential donors. | We agree with the need for efforts to strengthen the evidence base and consensus building, and have emphasized these issues as priorities in the Research Recommendations. |
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| *Should all donors have a psychological evaluation?* | |
| Absolutely. I agree with KDIGO that a psychological assessment should be mandatory for every potential donor. | Thank you |
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| *Who should perform the psychological evaluation?* | |
| The key point here is that whoever does the psychological evaluation must have the requisite skills and abilities. | Thank you. We emphasize the need for appropriate experience in the recommendation statement and expand upon qualifications of requisite training, knowledge and skill in the rationale. |
| | |
| *What psychological criteria preclude donation?* | |
| The report outlines the reasons why donation may not be accepted from a donor. Once again the provision of psychological care must be robust and be available to the donor whether the donor proceeds or not. A donor who is not deemed appropriate to donate should be supported in the aftermath of the decision. The provision of ongoing psychological support is essential to address whatever issues arise because of their inability to donate. | Thank you for the comment. We revised the recommendation statement to emphasize that support should be available both before and after donation. The transplant program should assist donor candidates and donors in receiving needed psychosocial support or psychiatric help before and after donation. We also expanded the rationale text to describe the difficulties that may be experienced by excluded donor candidates, and the need for |

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| | transplant programs to be aware of these difficulties and assist the candidate in receiving psychosocial support or psychiatric help if needed. |
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| *What should donor candidates be told about their likely psychosocial outcomes after donation?* | |
| While due consideration should be given to the individual, in principle donors should be appraised of the possible psychological outcomes following donation. Not to do so can lead to unnecessary anxiety in the donor. | We agree and emphasize the need for such education in the recommendations and Table 1. |
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| *How do we support donors when the recipient or donor outcome is poor?* | |
| The document underlines the importance of follow-up psychological support particularly in cases where the outcome is poor. This in my view is essential especially should the transplant fail or not achieve the expectation of the donor and recipient. | We expanded the discussion of "poor outcomes" to include outcomes that do not meet expectations. |
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| *Key Points* | |
| • standardise the guidelines across transplant centres for the psychological evaluation | We emphasized this point in the Research Recommendations |
| • have the necessary staff with the requisite skills to conduct the evaluation | We agree and emphasize in this point in the recommendations and rationale. |
| • use the words 'psychological support' in preference to the word 'counselling' (see 15.1) | Please see the prior comment and response above. We revised the header from “Counselling” to “Disclosures and Support”. |

**Chapter 17: Acceptable Surgical Approaches for Donor Nephrectomy**

| COMMENTS | RESPONSE |
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| Page 117 you say "bilateral FMD CONSIDERED as contra-indication" this is misleading if you think is an absolute contraindication suggest just say "bilateral FMD is an absolute contraindication" | KDIGO recommendations are phrased as actionable rather than declarative statements. We revised the recommendation to read: *"A donor candidate with atherosclerotic renal artery disease or fibromuscular dysplasia involving the orifices of both renal arteries should not donate."* |
| | |
| Page 122 you mention novel surgical modalities - I am not sure why, but if you are going to then you should include retrieval via a natural orifice | Thank you for the comment. These modalities are mentioned to emphasize the current limited experience and lack of robust safety and outcomes data, and thus to emphasize that these procedures should only be performed by surgeons with adequate training and experience, and after informed consent. We added mention of natural orifice transluminal nephrectomies to the recommendation statement and rationale text. |
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| I agree with all comments. | Thank you for your review and comments. |
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| 16.10: Under such circumstances, the donor should be decline. | Please see the discussion of donation from persons with high grade Bosniak cysts or small (T1a) renal cell carcinoma in Ch. 13 (Cancer Screening). For better alignment with supporting rationale text, all recommendation statements related to the implications of renal cysts for donation were moved to Ch. 13. |
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| 16.8: We routinely do not accept kidney donor with small cyst. | Because simple (Bosniak I) renal cysts are not associated with increased risk of complications, organ dysfunction or cancer, the Work Group did not consider simple cysts to be a contraindication to kidney donation. For better alignment with supporting rationale test, all recommendation statements related to the implications of |

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| | renal cysts for donation were moved to Ch. 13. |
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| ASTS now has developed certification for laparoscopic nephrectomy. We can specify more objective details of who is considered a "trained or experienced surgeon". Renal functional test (GFR study) should be considered case-by-case. | • We added a research recommendation to *"determine the optimal training and experience levels necessary to define proficiency with donor nephrectomy techniques."*<br>• The concept of case-by-case consideration is now addressed in recommendation 5.9 as: "*When asymmetry in GFR, parenchymal abnormalities, vascular abnormalities, or urological abnormalities are present but do not preclude donation, the more severely affected kidney should be used for donation*." To minimize redundancy, we attempted to avoid providing similar recommendations in different chapters. |
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| Please see Chapter 1 for general comments. Chapter 16: The literature cited in relation to robotic nephrectomy in the Rationale section is not complete (see 2013 review by I. Tzvetanov, World J Surg). There appears to be a lack of recognition that many US centers are routinely performing living donor nephrectomies at the current time. While Recommendation 16.4 seems generally appropriate, it is not clear why which would be an ungraded recommendation based on the fact that evidence does exist on the issue. | • The section on robotic nephrectomy was not supported by a systematic review; rather, representative articles identified by the Work Group were cited. Thank you for the additional reference – we cited this article in the revised rationale.<br>• We added a Methods Chapter with details of these processes to the guideline document. The complete Evidence Review is also available as an Appendix and is summarized in a separate publication. |
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| It was disappointing to find that the amount and level of data supporting the current surgical approaches to live kidney donation is very meager. | In the Research Recommendations we emphasize the need for "*prospective collection of granular clinical data on living donor peri-operative outcomes in representative samples (i.e., not limited to experienced programs with a limited number of surgeons), including capture of surgical approach and side of nephrectomy."* |
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| Agreement with recommendations and other suggestions: | |

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| Overall we agreed with the recommendations although we felt that recommendation 16.3 needed to be qualified. Since this document has global reach and the standard of care and equipment may vary considerably we felt it was not wise to mandate laproscopic nephrectomy in centers where laproscopic surgery was not routine. Also we recommended a modification to the grading of Bosniak Cysts in recommendation 16.9. Our recommended changes to the wording of the recommendations were as follows (changes underlined): | |
| 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 some circumstances, such as for donors with extensive previous surgery and/or adhesions and for sites where laparoscopy is not routine, open nephrectomy (flank or laparotomy) may be justified. (*2D*) | Thank you for the comment. We revised the statement to read "*However, in some circumstances, such as donors with extensive previous surgery and/or adhesions, and centers where laparoscopy is not routinely performed, open nephrectomy (flank or laparotomy) may be acceptable*." |
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| 16.9: Use of live donor kidneys with Bosniak 2F 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 2F or higher cysts should not be left in the donor. *(Not Graded)* | For better alignment with supporting rationale, all recommendation statements related to the implications of renal cysts for donation were moved to Ch. 13. The final recommendations read:<br>• *" Donation of kidneys with Bosniak II renal cysts should proceed only after assessment for the presence of solid components, septations, and calcifications on the preoperative computed tomography scan (or magnetic resonance imaging) to avoid accidental transplantation of a kidney with cystic renal cell carcinoma. (13.4)*<br>• *Donor candidates with high grade Bosniak renal cysts (III or higher) or small (T1a) renal cell carcinoma curable by nephrectomy may be acceptable for donation on a case-by-case basis. (13.5)* |

**Chapter 18: Ethical, Legal and Policy Considerations**

| PUBLIC COMMENT | Response |
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| I approve all statements, but donor cost must be cut off. | Thank you for the comment. In the rationale we emphasize that initiatives to remove financial disincentives to kidney donation are acceptable as an issue of justice. We recommend that "*Donor candidates should be informed of the availability of legitimate financial assistance for expenses from evaluation and donation*" (18.8). |
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| The last point is of paramount importance. | Thank you for the comment. |
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| Autonomy should be respected within a socioeconomic framework. Cases were does exist a great economic disparity between the donor and recipient must be cautiously investigated by a skilled team. /sic/ | Our leading recommendation in the Framework Chapter (Ch. 1) is that the donor candidate's willingness to donate a kidney voluntarily without undue pressure should be verified (1.1). In the Ch. 2 (Informed Consent) we recommend that required disclosures during the informed consent process should include disclosing if it is a crime to receive any valuable consideration (money, property) for donation (Table 2). |
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| I'm supportive of 17.5 if it happens in a standardized way that also doesn't unfairly advantage or disadvantage patients at a particular center. | We revised recommendation 18.5 to read: " *Transplant candidates should be assisted in identifying living donor candidates, as long as these efforts respect donor autonomy and do not exert undue pressure to donate."* The distinction focuses on the need to help transplant candidates access existing resources (as opposed to the connation to directly seeking donors for the center's patients). The revised recommendation also implies assistance can come from a variety of sources, including governmental and non-profit entities dedicated to improving the health outcomes of patients with kidney failure. |

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| RE: 17.3: do not say 'potential risks' because the word 'risk' already encompasses potentiality. Re: research proposal #1 - imminent death donation was tabled by the UNOS Board. It thus may be premature to include it here. Re: research proposal #2 - the way this is written is unclear. There is too much being stated in one bullet. | • Thank you. The statement was removed from the streamlined recommendations, as the concept is addressed in other chapters.<br>• The concept of surrogate consent is now addressed in the Research Recommendations of Ch.2 as "*Evaluate appropriate circumstances for and approaches to substitute decision making and use of surrogate consent, including definition of the necessary supporting ethical framework for particular scenarios*." "Imminent death donation" is encompassed within this broader framing. |
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| I don't think transplant teams should be expected to advocate for legal changes. I don't think transplant centers have a responsibility to advocate for policy changes. | The recommendation relates to advocacy in circumstances when *local laws impede the ethical practice of living donation*. As illustrated in other comments, many members of the public consider advocacy for modifying public policies that disadvantage donors as central to transplant practice. We did revise the wording of all recommendations in this chapter from a focus on the transplant program to more generic wording, such that the entity of action may include other groups such as governmental and non-profit entities dedicated to improving the health outcomes of patients with kidney failure and organ donors. |
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| 17.7: I think this should be on a case by case basis and not specific center policy. | While case by case considerations apply to individual donor candidate acceptance, some programs will not consider any donors identified by public solicitations. This recommendation relates to upfront disclosure of whether candidates identified by such processes can be considered at the program. |
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| Local differences in the National Health Services could play some relevant role in these issue. This should be underlined. | This chapter was introduced with the principle that laws and regulations may vary across jurisdictions and governing or regulatory bodies, and that living kidney donation must be practiced within the local regulatory framework. |

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| These comments are in response to 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.<br>We strongly support increasing public awareness, education and the removal of disincentives in living kidney donation by all transplant centers. We find this practice to be universally avoided due to fear associated with the appearance of donor coercion. We ask KDIGO guidelines to encourage transplant centers to increase public awareness and education, improve evaluation procedures and remove donor disincentives as a "duty" of practice, by clarifying their professional efforts in these areas are urgently needed and therefore will not be construed as a conflict of interest or coercion. We believe that public awareness, education, donor advocacy and the evaluation of kidney donors will not expand or improve without transplant center participation. | Thank you for the appreciation of the importance of this recommendation. |
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| 17.4: we recommend that the list of appropriate strategies be amended to include “home-based education” and “educational programs that include donor and recipient candidates’ families and social circles." Our pilot program Connect to Transplant will test the efficacy of home visits performed outside the clinical setting, staffed by volunteer living donors and managed by a community nonprofit. Until CMS covers the cost of home education, the efficacy of them should be part of any outreach campaign, including to local nonprofits who may want to take this on. | For succinctness, we removed the word "public" from "education", to broadly encompass educational efforts. In the rationale text we expand the definition of education to include public, clinic-based, and home-based education, and include citation of published randomized controlled trials of educational interventions. |
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| 17.11: As in Israel, a living donor should be allowed to designate a single family member to receive priority on the deceased donor allocation system or transplant waitlist. Israel’s program needs to be evaluated for how many donors would have declined without this safeguard in place. | Thank you for the comment. We added mention of the Israeli system to the rationale, and highlighted the need for study of the impact of this priority on the national allocation system and on attitudes and concerns about living donation. |

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| We agree that transplant centers should work to increase awareness and understanding of living donation. In light of successful trials of transplant education programs that incorporate home visits (Ismail, Luchtenburg and Tinman, 2014; Rodrigue et al, 2007) as well as promising pilots that utilize donors champions (Garonzik-Wang et al, 2012), we recommend that the list of appropriate strategies be amended to include “home-based education” and “educational programs that include donor and recipient candidates’ families and social circles." This is in response to 17.4. | Thank you for the endorsement of the recommendation. For succinctness, we removed the word "public" from "education", to broadly encompass educational efforts. In the rationale we expand the definition of education to include public, clinic-based, and home-based education, and include citation of published randomized controlled trials of educational interventions. The rationale cites all the publications noted by the Reviewer. We also expanded the rationale text to note that effective strategies may include participation of family and friends of the transplant candidate to increase knowledge and awareness of living donation within the patient's social network. |
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| We strongly endorse 17.11 on the need for living donor priority on the transplant waitlist. Further, we endorse the principle that in cases where a family member of a living donor develops ESRD subsequent to the donation, that a living donor be allowed to designate a single family member to receive priority on the deceased donor allocation system or transplant waitlist. This practice has been successfully implemented in Israel and would prevent situations where non-directed donors are unable to donate to a family member due to previously donating anonymously. It would also reduce situations where a donor candidate might hesitate to donate to “save” a kidney for a currently healthy child or spouse. This is in response to 17.11. | Thank you for the endorsement of the recommendation. We added mention of the Israeli system to the rationale, and highlighted the need for study of the impact of this priority on the national allocation system and on attitudes and concerns about living donation. |
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| AAKP strongly endorses that living donors not be excluded from receiving health benefits by any insurance carrier regardless of whether chronic kidney disease (CKD) or any other donor-related disease develops. | In the rationale we emphasize that initiatives to remove financial disincentives to kidney donation are acceptable as an issue of justice. We also revised recommendation 18.2 to encompass policies beyond law (e.g., insurance policies). We also added description of the 2016 Living Donor Protection Act, which is designed to prohibit discrimination based on an individual's status as a living organ donor in the offering, issuance, cancellation, coverage, price, or any other condition of a life insurance policy, disability insurance policy, or long-term care insurance policy. |

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| Recommend that this chapter include reference to the informed consent chapter (2). | We added cross-referencing to both Ch. 1 and Ch. 2 to the start of this chapter. |
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| Recommend adding language that the recipient candidate or any agent of the recipient candidate should not be present during some part of the donor's informed consent process. | We added cross-referencing to both Ch. 1 and Ch. 2 to the start of this chapter. Recommendation 1.1 states "*The donor candidate's willingness to donate a kidney voluntarily without undue pressure should be verified*." Recommendation 2.1 states: "*Informed consent for donation should be obtained from the living donor candidate in the absence of the intended recipient, family members and other persons who could influence the donation decision*." We did not repeat the concept in the recommendations for Ch. 18 to minimize redundancies. |
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| Please see Chapter 1 for general comments. Chapter 17: Recommendation 17.9 should be amended to note that donors participating in paired donation should be informed about the center's policy on contact not only with the recipient but with the other donor(s) involved in the exchange. In addition, it is not clear why the wording would be limited to paired exchange since the possibility for other more elaborate chains of exchange is likely as well. This would pertain to any recommendation in the document that concerned "paired" donation. The Rationale section states that "laws to regulate donation include…" We suggest that this be modified to state that "laws…include, but are not limited to" because there are other U.S. state laws (for example) such as tax credits, employee (often government) time off, etc. Alternatively, the document could note that there are also laws that support donors in connection with non-medical costs and time off from employment. These laws also affect the regulation/occurrence of donation. A problematic section of the Rationale is the section on "Financial Support for Living Donors." It addresses two extremely different issues—different in ethical, legal and practical terms. We strongly suggest that the section be divided into a section on issues of reimbursements for donor out-of-pocket costs and the removal of economic disincentives, and a section on financial incentives and valuable consideration in living donation. | • We revised 18.9 to read: "*Non-directed donors and donors participating in exchanges should be informed of the transplant program's policy on contact with the recipient and other exchange participants at all stages in the donation process*."<br>• We added the phrase "not limited to" to the rationale, as suggested.<br>• We also added the following sentence to the rationale: "*Other relevant laws and policies relevant to donor protections include insurability criteria related to donation status, state tax credits for donation-related expenses, and access to medical leave after donation*", and added a description of the new Living Donor Protection Act introduced for consideration in the US.<br>• We divided the rationale related to financial issues according to the recommended sub-heading. |

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| The one glaring omission from the document is the lack of mention of pediatric donors which we strongly feel ought to be excluded as donors and that there should be a strong recommendation stating this – perhaps in chapter 17. | This topic is controversial and public opinions are conflicting. We respect the view of TTS, but ultimately the Work Group decided that there are exceptional cases that warrant individualized decision making. We revised recommendation 2.3 to read: "*Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (e.g., children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review*." |
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| Agreement with recommendations and other suggestions: | |
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| Regarding recommendation 17.11: we do not agree that a specific recommendation be made that: "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." Whilst we have no objection to such a measure being adopted by jurisdictions we feel the rationale for such measure is not strong. Furthermore they may be circumstances e.g., (non-compliance) which would make it difficult to justify such a priority. The rationale for this recommendation not discussed at all in the text. To our knowledge there is no data to support such a recommendation and hence we commend that it not be included. Whilst we acknowledge that this is a practice in some countries, in others it is not. | While there is not international consensus on this topic, the view that prior living donors should be given access priority is strongly held in some countries as an ethical protection against future risks related to their gift. The precedent of some priority for prior living donors in the US is long-standing; further, while we did not go into these details in the rationale, there have been recent debates in the US about whether the current priority is enough to afford sufficient protection (living donors are not placed at the "top of the list" and some vulnerable groups such as highly sensitized candidates have higher priority). Transplant candidacy is always determined on a case-by-case basis, and a prior living donor could have medical or psychosocial contraindications to transplantation, like any patient – such considerations and clinical judgement are not precluded by the current allocation priority. Other reviewers advocated for additional policies such as extension of priority to family members of living donors, as currently occurs in Israel. While we did not include a recommendation for broad adoption of this unique system, we described it, the supporting motivation, and the need for more study in the rationale text. |

| Suggestions for additional recommendations: | |
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| A major omission in this chapter is the lack of any mention of pediatric donors. Whilst the use of pediatric donors is banned in many countries, it is not in others. In light of recent data suggesting that it is difficult to quantify the long-term risk in young donors we believe a strong statement needs to be included that pediatric donors should not be used. | This topic is controversial and public opinions are conflicting. We respect the view of TTS, but ultimately the Work Group decided that there are exceptional cases that warrant individualized decision making. We revised recommendation 2.3 to read: "*Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (e.g., children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review*." |

**Chapter 19: Post-Donation Follow-up Care**

| PUBLIC COMMENT | REPONSE |
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| I suggest that: respect to the follow up in the first year post-transplant, the visit and medical practice /should be/: in the first month, weekly, then until to the 1st year, bi-monthly or quarterly. | We agree that early post-donation care will include more frequent contacts – early post-donation follow-up care after donor nephrectomy is routinely practiced as part of post-operative care. In contrast, long-term follow-up practices have been controversial due to concerns for financial and time burdens on both donors and centers. We clarified that the topic of longer-term follow-up is the focus of this chapter. Based on the comments, we revised 19.2 to include the phrase "at least annually". |
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| Long-term follow up of renal donors is not optimum. Policy should state that when a person sacrifices 50% of their nephrons to save a life, they are owed a lifetime of surveillance to protect residual function. | The topic of longer-term follow-up has raised controversies regarding financial and time burdens on both centers and donors. In the first section of the rationale for this chapter we emphasize the ethical principles and clinical needs that justify a commitment to post-donation follow-up by both centers and donors, as endorsed by international consensus. |
| | |
| Loss of 50% of GFR means that the solute and fluid loads of the past will be laid before the remaining kidney forcing it to enlarge to a greater extent than if the solute load was reduced to more nearly match the remaining number of nephrons. Evidence indicates that glomerular hyperfiltration, together with elevated protein, salt, and potential proton intake may harm a normal complement of nephrons in an otherwise normal person. These factors may have an even greater effect to harm reduced numbers of nephrons. | In Ch.1 (Framework) and Ch.5 (Renal Function) we discuss current knowledge of the implications of kidney donation for post-donation renal function. |
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| Evaluate diet history in prospective donor to determine the extent to which they may exceed recommended levels of protein, salt, lipids, and protons. | In Ch. 10 (Hypertension) and Ch.11 (Metabolic & Lifestyle Risk Factors) we recommend assessment of dietary history as part of the donor evaluation. In the current chapter we further emphasize a recommendation to review and promote healthy lifestyle practices including regular exercise, healthy dietary habits, and avoidance of smoking at least annually after donation (19.2). |

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| Devise and evaluate diets for prospective donors that limit the potentially harmful components and couple this with intensive dietary counseling for as long as it takes to reduce the patient's solute loads to levels potentially less harmful than the diet ingested preceding donation. | In Ch. 10 (Hypertension) and Ch.11 (Metabolic & Lifestyle Risk Factors) we recommend we recommend assessment counseling on healthy lifestyle both before and after donation. In the current chapter we further emphasize a recommendation to review and promote healthy lifestyle practices including regular exercise, healthy dietary habits, and avoidance of smoking at least annually after donation (19.2). Finally, we also recommend that: "*Donors should receive age-appropriate healthcare maintenance, and management of clinical conditions and health risk factors according to clinical practice guidelines for the regional population*." (19.4) |
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| 18.1 and 18.2, 18.5, 18.6: The continued follow-up of donors by the transplant program may not be necessary in a country with universal health care. The information to donors to obtain appropriate follow-up with their primary care physician may be adequate. | We agree that follow-up testing may be performed by a primary care provider, and discuss this in the rationale. We expanded this discussion to state: "*Because donors in many countries report regular follow-up with a primary provider,[523] donor follow-up and care may be appropriately performed by a primary care provider to preserve convenience for the donor. However, communication of follow-up information back to the transplant center is necessary for centers to be aware of the health status of their donors, to comply with reporting mandates (when applicable), and to direct additional care if needed."* |
| | |
| 18.3: This information should only be reported to national registries with the donor's informed consent. | Thank you for the comment. Based on the balance of comments and controversies about the resource requirements for registries, we removed registry reporting from the recommendation statements of Ch. 19, and reserve discussion of international experience with registries for the rationale. In addition, please note that Ch. 2 (Informed Consent, Table 2) states that that the informed consent should include disclosure of *"the program's recommendations for follow-up care…The program's need to collect ongoing personal health information after donation…"* |

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| 18.7: This seems somewhat intrusive. It may be acceptable with donor consent for future contact from the program. | Thank you. We removed this statements from the recommendations. We added a Research Recommendation to "*Examine electronic tools such as websites or portals to maintain contact with donors, facilitate data collection, and provide messaging to disseminate educational information to donors*." |
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| All donors should estimate your uric acid rates in both the blood and urine before and after the donation, especially those whose family history reports kidney lithiasis. There are good reasons to believe with the reduction of the number of nephrons, there may be uric acid accumulation in the blood. | We agree there is emerging data on the impacts of kidney donation on serum uric levels and gout risk, and added Ch. 9 (Hyperuricemia, Gout and Mineral and Bone Disease) post-public comment, wherein these data are now reviewed. Based on available data, the absolute impact on gout risk appears small (e.g., 1.4% at 8 yr). Given the uncertain benefit vs risk ratio for treating asymptomatic hyperuricemia, we do not include uric levels as a routine laboratory study necessary for the follow-up of all living donors, but we agree the topic warrants ongoing attention, as articulated in the Research Recommendations in Ch. 9. |
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| 18.2: I would suggest to include in the recommendation the equation to be used for estimating GFR, and an urinary sediment should be part of annual evaluation of kidney donors not just albuminuria. | Thank you for the comment. After careful consideration, we opined that there is insufficient evidence to support utility of a urinalysis in addition to serum creatinine testing with GFR (eGFR) estimation and evaluation for albuminuria (although we appreciate that many programs include as part of post-donation follow-up). Our recommendations are grounded on the 2012 KDIGO CKD guidelines, which emphasize monitoring based on eGFR and albuminuria. |
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| 18.1: The risk of ESRD in the US in a cohort of 52,998 kidney donors, compared with 4,933,314 healthy patients over a period of 4-16 years and then projected to 15 years, was 3.5 to 5.3% more for the donors tan non-donors (0.24%) (Ref N Engl J Med. November 6, 2015) | The cited study was performed to support the current guideline, and we review it in detail in Ch.1 (Framework) and throughout other sections of the guideline. |

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| 18.3, 18.7, 18.8 are difficult to do logistically for many centers, and in part depend on the geographic spread of the program and available resources to carry out these recommendations. I agree with them, but think they will be hard for many centers to implement. | Thank you for the feedback. Based on such comments, we removed these concepts from the recommendation statements, and discuss registries and models for integrated follow-up, education and communication in the rationale and Research Recommendations. |
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| 18.8: May be difficult in practice to do this but it is a good idea. How to define "important" might be problematic, for example should centers try to contact female donors about the risks of preeclampsia? | Thank you for the feedback. Based on such comments, we removed these concepts from the recommendation statements, and discuss models for integrated follow-up, education and communication in the rationale and Research Recommendations. |
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| We hold special interest in the following areas: | |
| 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. *In countries where registries do not exist, they should be created and maintained. | Thank you for the comment. Based on the balance of comments and controversies about the resource requirements for registries, we removed registry reporting from the recommendation statements of Ch. 19, and reserve discussion of international experience with registries for the rationale. |
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| 18.4: Donors who develop hypertension or CKD should receive appropriate medical treatment for these conditions according to clinical practice guidelines for the conditions. * By offering donors an opt-in health insurance program, essential follow up and data collection and analysis will help donors maintain their health (as close to the level they held when going into this process) as well as provide a system to collect data to help future donors. | We understand and appreciate the arguments in favor of provision of insurance to uninsured living donors. The topic is controversial, as some consider it a form of incentive or valuable consideration. The availability of resources such as universal healthcare also varies across countries. The Work Group felt the most practical approach is to provide recommendations for the content of follow-up and allow programs to structure follow-up processes within the framework of their local healthcare systems and available resources. |
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| 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. *Registries should make this process easier. | Thank you for the comment. Based on the balance of comments and controversies about the resource requirements for registries, we removed registry reporting from the recommendation statements of Ch. 19, and reserve discussion of international experience with registries for the rationale. |

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| Under Rationale: within the body of the discussion of rationale, last paragraph on page 131: 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), I would consider adding to avoiding potentially nephrotoxic exposures avoiding intravenous contrast with CT scans and if absolutely necessary and unavoidable, would recommend IV hydration with HCO solution and administration of Mucomyst to mitigate potential nephrogenic insult from contrast. | Thank you for the comment. The risk of contrast nephropathy varies with level of kidney function; given the low contrast volume administered with a single CT scan, we believe this clinical issue can be evaluated on a case by case basis. The exposures highlighted as specific examples were chosen as more likely to be chronic. |
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| Periodic follow up of live donors after donation should be mandatory with a frequency as determined by the discretion of the managing physician. | We revised recommendation 19.2 to read: "The following should be performed *at least annually* post-donation…"We also recommend that "*Donors should be monitored for CKD, and those meeting criteria for CKD should be managed according to the 2012 KDIGO CKD Guideline. (19.3),"* which specifies testing intervals according to clinical status. More frequent assessments may be appropriate on a case-by-case basis. |
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| The cost of the follow-up of a living donor must be taken by the community. | Please see Ch. 18 (Policy) for a discussion of "Financial Support for Living Donors and Removal of Economic Disincentives." In the current chapter, we provide recommendations for the content of follow-up and encourage programs to structure follow-up processes within the framework of their local healthcare systems and available resources. |
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| Please see Chapter 1 for general comments. Chapter 18: as noted for earlier chapters, there would seem to be evidence that should be relevant to grading at least some of the recommendations, rather than having them all appear as ungraded. | We added a Methods Chapter describing details of the formal evidence review and grading processes to the guideline document. |

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| With regard to Recommendation 18.1, it would seem that if centers are recommended to monitor these parameters, then specific recommendations are needed regarding the assessments that should be used (e.g., for health status and well-being). It would not be appropriate for centers to choose unvalidated measures for these constructs, any more than it would be appropriate to use inadequate measures of the other elements in the recommendation. | Thank for you for the comment. After extended considering (including communication with Dr. Dew) we retained the original phrase "well-being", in part due to concerns for interpretation and thresholds of quality of life metrics. We expanded the rationale text to note: "*Guidelines for metric thresholds indicating presence of an impairment to prompt more attention by the clinician are not specifically defined in donors, but could be based on existing test standards (e.g., scores below 0.50 SD of the normative mean on the "Short Form" (SF) class of measure, SF36, 12, or 8).*" |
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| In general, the Rationale section gives the impression that the transplant center should have prime responsibility for donor follow-up. It would be important to either justify this position, as opposed to a position that follow-up should be a shared responsibility with other health care providers (e.g., the donor's primary care provider). | We expanded the rationale to clarify: "*Because donors in many countries report regular follow-up with a primary provider,[523] donor follow-up and care may be appropriately performed by a primary care provider to preserve convenience for the donor. However, communication of follow-up information back to the transplant center is necessary for centers to be aware of the health status of their donors, to comply with reporting mandates (when applicable), and to direct additional care if needed.*" |
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| In addition, we recommend considering revisions to the wording of Recommendation 18.8. Whether "reasonable" efforts are sufficient depends on the information and on how one defines "reasonable." If it is information about an outcome that a donor could head off with certain follow-up care, for example, it would seem appropriate for centers to more aggressively attempt to reach donors. Thus, it seems as though the wording should be revised to note that transplant centers should use their best judgment with recognition that the level of effort should depend on the type of long-term outcome and whether follow-up treatment could aid the donor in avoiding the outcome. | Thank you for the feedback. Based on such comments, we removed these concepts from the recommendation statements, and discuss registries and models for integrated follow-up, education and communication in the rationale and Research Recommendations. |
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| Donors should be encouraged to report any change in physical Stamina/vitality or if they tire more easily. This fatigue issue is well known in CKD III onward patients and recent studies found out that there is a huge prevalence of fatigue within the recipient groups. Since it is known that fatigue issues stay mostly underreported, donors should be encouraged to mention any problems here. | In Ch. 16 (Psychosocial Evaluation) we review current evidence on quality of life measures in living donors, including the results of the formal Evidence Review performed to support this guideline, which included psychosocial impacts of kidney donation. Among the cited evidence, a recent systematic review (Wirken at el, Am J Tranpl 2015) of 34 prospective studies of post-donation health-related quality-of- |

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| | life (HRQoL) (1990 to 2014) found that, after mild reductions early after nephrectomy, HRQoL returned to baseline or was slightly reduced by 3 to 12 months, particularly for ***fatigue*****,** but was still comparable with general population norms. |
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| Good section. Do you want to say that the center is not responsible for follow up care? It is a sort of harsh truth, but true. We tell our donors that. | • We expanded the rationale to clarify: "*Because donors in many countries report regular follow-up with a primary provider,[523] donor follow-up and care may be appropriately performed by a primary care provider to preserve convenience for the donor. However, communication of follow-up information back to the transplant center is necessary for centers to be aware of the health status of their donors, to comply with reporting mandates (when applicable), and to direct additional care if needed."*<br>• Please note that Ch. 2 (Informed Consent) states that that the Informed Consent should include disclosure of "t*he program's recommendations for follow-up care, including the likely timing and financial impacts of care and.... The program's policy about providing care to the donor following evaluation and donation.*" |
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| Overall this chapter is well written and provides concise and practical information for the nephrologist or primary care giver who is responsible for donor follow up. The chapter is comprehensive and well referenced. | Thank you for your review and supportive feedback. |
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| Agreement with recommendations and other suggestions: | |
| We are in agreement with the recommendations as outlined. We would suggest that a comment be included that it is the transplanting centre responsibility to ensure that the donor is referred to an appropriate health care professional for follow up (either nephrologist or primary care giver). If the transplanting centre is primarily a surgical department or a national/regional referral centre they may not be in a position to provide this care themselves. | • Thank you for the comment. We expanded the rationale to clarify: "*Because donors in many countries report regular follow-up with a primary provider,[523] donor follow-up and care may be appropriately performed by a primary care provider to preserve convenience for the donor. However, communication of follow-up information back to the transplant center is necessary for centers to be aware of the health status of their donors, to comply with reporting mandates (when applicable), and to direct additional care if needed."* |

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| | • Please note that Ch. 2 (Informed Consent) states that that the Informed Consent should include disclosure of "t*he program's recommendations for follow-up care, including the likely timing and financial impacts of care and.... The program's policy about providing care to the donor following evaluation and donation."* |