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Strategies for assessing GFR and albuminuria in the living kidney donor evaluation

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Abstract

Purpose of review—The international guideline development group Kidney Disease Improving Global Outcomes (KDIGO) recently published a comprehensive set of recommendations for living donor evaluation which contains a new framework for decision making in the evaluation of kidney donor candidates.

Recent Findings—The guidelines recommend that decisions to accept or decline a candidate donor should be based on incorporation of multiple sources of information pertaining to the donor candidate's likelihood of serious adverse outcomes after donation. Two central components of assessment of risk are glomerular filtration rate (GFR) and albuminuria. We describe strategies for clinical decision making in assessment of GFR and albuminuria in the evaluation of living kidney donor candidates. Our premise is that all measurements will contain error; no single test result should lead to a decision to accept or decline a donor candidate.

Summary—A structured approach to use of information from multiple sources (e.g. estimated and measured GFR, estimated and measured albuminuria) aids in test interpretation and can lead to increased accuracy of testing and efficiency of evaluation strategies.

Keywords

kidney donor candidate; glomerular filtration rate; albuminuria; ESRD risk

Introduction

Kidney Disease Improving Global Outcomes (KDIGO) published a clinical practice guideline for evaluation of living kidney donor candidates in 2017.[1] A central goal of this new guideline is to facilitate individualized and quantitative estimates of perioperative and long-term post-donation risk using “consistent, transparent and defensible decision-making”,

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based on evidence where available. The framework for the KDIGO donor guideline is that decisions to accept or to decline a candidate donor should be based on incorporation of multiple sources of information pertaining to the donor candidate's likelihood of serious adverse outcomes after donation. Two central components of the overall risk assessment are glomerular filtration rate (GFR) and albuminuria - both are used to detect the presence of kidney disease and are critical parameters in the assessment of long term risk of adverse outcomes after donation.

Our goal in this review is to describe strategies for clinical decision making in the evaluation of GFR and albuminuria in living kidney donor candidates. To do so, we first review background and physiology related to GFR and albuminuria and the recommendations from the KDIGO 2012 chronic kidney disease (CKD) guideline pertaining to the methods of assessment of these parameters and thresholds for definition of CKD.[2] We next review the recommendations from the KDIGO donor guidelines for the assessment of GFR and albuminuria. Finally, we provide our perspective on how these recommendations could be used to increase the efficiency of the evaluation of kidney donor candidates, while ensuring a rigorous and accurate assessment of the level of GFR and albuminuria. Our premise is that all measurements have some form of error - some errors are systematic while others are random - thus no single test result should lead to a decision to accept or decline a donor candidate. Use of information from multiple sources aids in interpretation of these tests and can lead to increased efficiency and accuracy of testing and evaluation strategies.

Assessment of GFR

GFR - what is GFR and what are normal GFR levels

Glomerular filtration is the physiological process of creating an ultrafiltrate of blood as it flows through the glomerular capillaries.[3, 4] The GFR is the best overall assessment of kidney function due to the associations of decreased GFR with alterations in kidney structure and complications related to CKD. In the general population as well as in patients with CKD, decreased GFR is associated with a higher risk of kidney failure, cardiovascular disease and death.[5]

GFR is not measured directly in humans; thus “true” GFR cannot be known with certainty. GFR can be assessed from clearance measurements (measured GFR [mGFR]) or serum levels of endogenous filtration markers (estimated GFR [eGFR]) (Table 1). These measurements provide an assessment of the total GFR, which is the sum of the number of individual nephrons (N) multiplied by the average of the single nephron GFR (SNGFR). Reduction in N vs reduction in SNGFR cannot be differentiated in humans; clinically, we attempt to distinguish between these factors by clinical history and laboratory evaluation.

The mean GFR in healthy young white adults is approximately 125 mL/min/1.73 m²; however, GFR in healthy persons varies substantially such that normal GFR in young men and women is greater than 90 mL/min/1.73 m², GFR less than 60 mL/min/1.73 m² is considered low in adults of any age, and GFR between 60 and 89 mL/min/1.73 m² is considered to be decreased compared to the usual level for young adults.[6, 2] Adjusting GFR to body surface area (BSA) reduces the variability in GFR in healthy individuals,

allowing for use of GFR thresholds for clinical decision-making and donor selection that can be applied to most people across the usual distribution of body size.

Measured GFR

The “gold standard” for the measurement of GFR is urinary clearance of an ideal filtration marker, defined as substance that is freely filtered at the glomerulus, is neither reabsorbed, secreted, synthesized, or metabolized by the tubules, and for exogenous markers, does not alter the function of the kidney.[7] Inulin meets the requirements of an ideal filtration marker. This method is not affected by patient characteristics other than kidney function. To simplify the measurement, many alternative filtration markers and clearance methods have been proposed, but all filtration markers deviate from ideal behavior and clearance measurements are difficult to perform; thus, values for measured GFR usually contain an element of error, which differentiates measured GFR (mGFR) from true GFR (Table 1).[8] In a recent systematic review, urinary creatinine clearance did not meet the criteria for accuracy due to large systematic bias and imprecision likely related to collection errors, suggesting that despite its widespread use, creatinine clearance has limitations in the assessment of GFR in routine outpatient settings.[9] That review and other studies suggest that iothexol clearance is lower and iothalamate clearance is higher than inulin clearance, especially at higher levels of GFR which is especially important in donor candidate evaluation.[10, 11, 4]

Estimated GFR

GFR can be estimated from serum levels of endogenous filtration markers. The serum levels of an endogenous filtration marker are determined not only by the level of GFR, but also by non-GFR determinants (generation, renal tubular secretion and reabsorption, and extra-renal elimination) (Table 1). These physiological processes are generally not measured, so estimating equations use easily measured clinical variables as surrogates. The equations provide more accurate estimates than the serum level alone, but the estimates capture only the average relationship of the surrogates to the unmeasured physiological processes of the population used in the development of the equation, a potential source of error when applied elsewhere.

The most commonly used endogenous filtration marker for GFR estimation is creatinine. Creatinine-based estimating equations include age, sex, race or weight as surrogates for creatinine generation from muscle mass or diet.[12] People with extremes of muscle mass and dietary intake, who are malnourished or have a reduction in muscle mass from illness or amputation, are likely to have large differences between measured and estimated GFR_{cr}.

Cystatin C is an alternative endogenous filtration marker that is less influenced by muscle and diet than creatinine. Potential nonGFR determinants of lower eGFR_{cys} include older age, male gender, greater fat mass, diabetes, smoking status, higher C-reactive protein and white blood cell count, lower serum albumin, higher urine protein, hypothyroidism, certain malignancies, and use of glucocorticoids.[13-16] eGFR based on cystatin C (eGFR_{cys}) is not more accurate than eGFR_{cr}, but eGFR based on both markers (eGFR_{cr-cys}) is more precise than either alone.[17, 18] Although a standardized reference material for cystatin C

is now available, considerable variation remains among cystatin C assays, limiting its use. [19]

Assessment of Albuminuria

Albuminuria: what is it and what are the normal levels?

Albuminuria is a marker of glomerular damage, and the most commonly used marker of kidney damage. In both the general population and in patients with CKD, higher albuminuria is associated with a higher risk of kidney failure, cardiovascular disease and death.[2] For some donors, other forms of kidney damage might be highly relevant in their assessment, e.g. cysts in those with family history of polycystic kidney disease or hematuria in those with a family history of hereditary nephritis. However, even in such patients, albuminuria provides important information on the severity of kidney disease and risk of kidney failure, cardiovascular disease and death, and therefore remains a key parameter in the evaluation of all living kidney donor candidates.

Normal urine contains a variety of proteins, including filtered serum proteins and proteins derived from the kidney and urinary tract.[20] The glomerular capillary wall hinders the passage of albumin and other large serum proteins into Bowman's space. Larger body size, upright posture, exercise, fever and activation of the renin-angiotensin system are associated with higher albumin excretion, and there is significant diurnal and day-to-day variation, with repeated measurements showing day to day variability of approximately 30% [21]. Albumin is the largest component of total protein in the blood. Therefore when there is disruption of the glomerular wall, albumin is the most abundant component of total protein found in the urine. The rationale for preferring measurement of albumin to total protein as a marker of kidney damage is that methods for quantifying total albumin, but not total urine protein, can be standardized, although the process of albumin standardization is still being refined. Hereafter, we will refer to albumin when discussing measurement issues, but the same issues relate to urine total protein.

The mean value for albumin excretion rate (AER) is 5-10 mg per day in young adults and generally rises with age. AER greater than 30 mg/d generally reflects an alteration in structure of one or more layers of the glomerular capillary wall and is considered moderately increased, and AER greater than 300 mg/d is considered severely increased. [2]

Measured and estimated albuminuria

Accurate assessment of albumin excretion rate requires collection of a timed urine specimen, which is inconvenient and can be inaccurate due to errors in timing, incomplete bladder emptying, incomplete collections and spills (Table 1). For these reasons, albuminuria is generally assessed from untimed "spot" urine samples using albumin to creatinine ratio (ACR). The rationale for preferring ACR to albumin concentration is that use of the ratio overcomes variation in urine concentration and dilution. The 2012 KDIGO CKD guideline therefore recommends that clinical laboratories measure creatinine when albumin is requested in spot urine samples, and express the results as ACR in addition to albumin concentration. An early morning sample is preferred, as it minimizes variation due to diurnal

variation in albumin excretion. Indexing urine albumin by urine creatinine introduces variation by creatinine generation, however, and some investigators have proposed estimating creatinine excretion rate (CER) and multiplying this quantity by ACR to estimate AER.[22] Irrespective of the collection method, day to day variability in urine albumin is high.

KDIGO Recommendations for Evaluation of GFR and Albuminuria in Living Kidney Donor Candidates

Overall approach

The ultimate goal of the living donor evaluation is to assess the donor candidate's perioperative and long term risk for adverse outcomes after donation in comparison to the transplant center's threshold to accept. The 2016 KDIGO living donor guideline recommends incorporation of multiple sources of information to make this assessment of risk. For long-term risk, the guidelines recommend focusing the discussion on risk for chronic kidney failure requiring treatment with dialysis or transplantation [end-stage renal disease (ESRD)] as the critical adverse outcome. For key parameters such as GFR and albuminuria, the guideline recommends two thresholds - one to accept and one to decline the candidate. In the intermediate range between the two thresholds, decisions individualized are based on a profile of demographic and clinical factors affecting the candidate's long term risk for adverse outcomes.

Prediction of ESRD risk

Prior to the evidence review conducted by the guideline work group, two studies had documented a small increase in absolute ESRD risk within approximately 15 years after kidney donation compared to healthy non-donors - risk differences of 0.44% (0.5% vs. 0.06%) in Norwegian donors[23] and 0.27% (0.31 vs. 0.04 per 100 patient-years of follow-up) in US donors.[24] However, these studies did not provide information on ESRD risk in relation to baseline characteristics of the donor. As part of the guideline process, the CKD Prognosis Consortium developed a method to project 15-year and lifetime risks of ESRD in the absence of donation, based on a meta-analysis of nearly 5 million healthy persons identified from low risk subgroups of 7 general population cohorts who are similar to kidney donor candidates.[25] Compared to the risk in these healthy people, the observed risk for ESRD in US donors was 3.5 to 5.3 times higher depending on sex and race. An online tool is available which can be used to project ESRD risk in individual donors in the absence of donation based on age, sex, race, GFR, ACR, diabetes, smoking, blood pressure, hypertensive treatment and body mass index (<http://www.transplantmodels.com/esdrisk/> and for details of its use, see Box 1). For any value of eGFR or urine ACR, 15-year risk is higher in older compared to younger people, while life-time risk is lower for older compared to younger people.

Assessment of GFR

Box 2 includes the key recommendations from the 2017 KDIGO guideline on evaluation of GFR in the living kidney donor candidate.

Assessment—The guideline recommends initial assessment based on eGFR_{cr} and confirmation using one or more of the following measurements depending on their availability: measured GFR from clearance of exogenous filtration markers, measured creatinine clearance, estimated GFR from cystatin C in combination with creatinine, or repeated estimated GFR from creatinine. For GFR estimates, the guideline recommends and using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for eGFR_{cr}, eGFR_{cys} and eGFR_{cr-cys} unless other equations have been shown to be more accurate than the CKD-EPI equations.

Thresholds to accept or decline donor candidates—The guideline recommends that GFR > 90 ml/min per 1.73m² is acceptable and whereas candidates with GFR < 60 ml/min per 1.73m² should not donate. The guideline suggests that the decision to approve donor candidates with GFR 60-89 ml/min/1.73 m² should be individualized based on age and other clinical factors in relation to the transplant center's acceptable risk threshold, including projected ESRD risk. The rationale for these thresholds is based on accepted GFR thresholds in the general population and risk associated with decreased GFR.

Albuminuria

Box 3 includes the key recommendations from the 2017 KDIGO guideline for the evaluation of albuminuria in the living kidney donor candidate.

Assessment—The guideline recommends that proteinuria should be assessed as albuminuria. Spot urine samples to measure albumin to creatinine ratio should be used as an initial test followed by confirmation in all candidates using AER in a timed urine collection or a second spot urine sample if a timed urine collected cannot be obtained.[26]

Thresholds to accept or decline donor candidates—The guideline recommends that urine AER < 30 mg/day should be considered as an acceptable level for kidney donation, while donor candidates with urine AER >100 mg/day should not donate. The decision to approve donor candidates with AER 30-100 mg/day should be individualized based on age and other clinical factors in relation to the transplant center's acceptance risk threshold, included projected ESRD risk. The rationale for these thresholds is based on accepted albuminuria thresholds in the general population and risk associated with increased albuminuria.

Our Perspective: Implementation

Assessment

Greater reliance on estimated GFR—The advantages of creatinine to estimate GFR are that it is inexpensive, widely available, and has a precise and standardized assay. Cystatin C assays are less widely available and are more variable, but nevertheless are easier to obtain than a clearance measurement. We propose that in selected patients with careful use of eGFR, it would be possible to make accurate decisions as to the level of mGFR without a clearance measurement. The key challenge to the use of eGFR in donor candidates is the greater error at higher levels of GFR in donor candidates compared to patients with kidney

disease. We recently showed that eGFR may be useful in evaluation of donor candidates despite this greater error. Using pretest probabilities from the National Health and Nutrition Examination Survey for mGFR thresholds based on age, sex and race, and likelihood ratios for eGFRcr and eGFRcr-cys categories versus mGFR thresholds, we computed the post-test probability that mGFR for a donor candidate is above or below the threshold for decision making.[27] This method was validated in a separate cohort.[28] Table 2 shows how this information can be used to make decisions to accept or decline a donor candidate based on the eGFR or to require further evaluation with a clearance measurement. An online tool is available at <http://ckdepi.org/equations/donor-candidate-gfr-calculator/>. Future studies should address prediction accuracy among racial and ethnic groups for whom the accuracy of eGFR is less certain (e.g., non-black, non-white persons). In the United States, clearance measurements (Clcr or mGFR) are required by Organ Procurement and Transplantation (OPTN) policy for all donor candidates at the present time [29], but we suggest that regulatory agencies might reconsider their policies in selected patients.

Lesser reliance on timed urine collections—Currently, timed urine collections are widely used for measurement of creatinine clearance as the confirmatory test for GFR and for measurement of AER as the confirmatory test for albuminuria. In our view, this practice is cumbersome and may lead to greater errors compared to eGFR and urine ACR. Although there are methods to assess the completeness of a urine collection by comparing the measured creatinine excretion to expected creatinine excretion, there is a wide range for expected values leading to uncertainty about the accuracy of urine collections.[30, 31]

Although a clearance measurement is required by OPTN policy for donor evaluation in the US, a timed urine collection for AER is not required. In countries where clearances are required for assessment of GFR, an efficient strategy might be to omit timed urine collections and to rely on mGFR using clearance of an exogenous filtration marker and urine ACR. In countries where clearance measures are not required for assessment of GFR, transplant centers could take the approach of obtaining eGFRcr, eGFRcr-cys and urine ACR prior to a candidate donor's visit to the center. If the posttest probability that mGFR is greater than the threshold for decision making is extremely high, and if urine ACR is very low, then these tests could simply be repeated for confirmation without mGFR, mClcr or AER. Alternatively, donor candidates with a very high post-test probability that mGFR is < 60 ml/min per 1.73m² or with high urine ACR could be excluded and saved the inefficiency of a complete evaluation. Donor candidates with eGFR or urine ACR in intermediate ranges would require confirmatory tests with mGFR, mClcr or urine AER. Determining eGFR and urine ACR in advance of the visit to the transplant centers allows planning for confirmatory tests.

“Triangulation” on the true GFR – use of multiple methods for cross-verification—All tests are measured with error and therefore values from any test, even the reference standard, should be interpreted in context of this understanding (Table 1). Using multiple methods to assess GFR, rather than relying on one method as the “truth”, allows for consideration of the presence of systematic and random errors that may be present in both

estimated and measured GFR. We first provide two examples and then discuss our approach to use of results from multiple methods.

First, discordance in results between estimated GFR from creatinine and cystatin C enables detection of variation in non-GFR determinants as a source of error in one or both estimates. For example, patient A in Table 3 is a body builder. High muscle mass is suggested by history and confirmed by a high creatinine excretion compared to other people of his age, race and sex, and would lead to an estimated GFR that underestimates his true GFR. Measurement of cystatin C and computation of eGFR_{cys} and eGFR_{cr-cys} could be performed to verify the decreased eGFR_{cr}. If divergence between the results is found, we would presume that in this patient eGFR_{cr} is not accurate; eGFR_{cr} and eGFR_{cr-cys} should not be used and eGFR_{cys} should be used as the initial test. Second, even reference methods may have measurement error. Patient B in Table 3 shows an extreme example wherein creatinine clearance was inaccurate because urine collection was incomplete due to a spill, as suggested by the very low creatinine excretion. However, often this history is not captured. In those cases, cross verification across methods provides support for the source of error.

In our donor evaluations, we use results from multiple methods to assess true GFR and albuminuria levels through cross verification. We request that donor candidates begin a 24 hour urine collection the day prior to their visit and complete it upon arrival at our center. We measure serum creatinine and cystatin C, as well as urine albumin, total protein and creatinine at this initial visit. We compute the post-test probabilities for eGFR_{cr} and eGFR_{cr-cys}, and the mClcr and albumin and total protein excretion rate.

For GFR evaluation, if the post test probabilities of eGFR_{cr-cys} for mGFR > 90 ml/min per 1.73m² or < 60 ml/min per 1.73m² are sufficiently high (95%) and if mClcr is consistent, we consider the evaluation for GFR to be complete, and assign a GFR category of < 60, 60-89 or ≥ 90 ml/min per 1.73m². If the results are inconsistent, we consider possible reasons for the inconsistency (differences in expected creatinine excretion, non-GFR determinants of creatinine and cystatin C) and consider eliminating the inconsistent value from consideration, repeating the measurement, or measuring GFR using an exogenous marker. Although the 2017 KDIGO guideline suggests that repeat eGFR_{cr} could be acceptable confirmation, we do not prefer this approach because it addresses imprecision due to variability in eGFR but does not address bias due to non-GFR determinants of serum creatinine.

For albuminuria evaluation, we compare ratios of albumin and total protein to creatinine in spot urine samples and excretion rates in the timed urine collections and base decisions on consistency of measures. However, if assessment of measured clearances were not required, and a method were available for determining post-test probabilities for urine AER from ACR, we would consider reliance on urine ACR for decision making, with repeat testing to determine consistency. At present, post-test probabilities for AER above or below thresholds for decision making are not available, but in principle could be computed from pre-test probabilities and measures of ACR, as discussed for GFR evaluation.

Thresholds to accept or decline donor candidates

Due to normal biological variability, the range for both GFR and albuminuria considered to be normal can overlap with the range considered to reflect disease. In kidney disease, reduction in the number of nephrons (N) is hypothesized as the reason for a decrease in true GFR. Because of pre-evaluation screening, donor candidates have a low pretest probability of kidney disease, a lower level of GFR is more likely related to a decrease in SNGFR, errors in GFR measurement, or non-GFR determinants of endogenous filtration markers than a reduction in nephron number. Similarly, increase in albuminuria in donor candidates is often more likely to be due to physiologic variability and measurement error rather than increased glomerular permeability. Repeating even the initial tests, eGFRcr and urine ACR can help to differentiate transient decreased GFR or increased albuminuria from persistent changes.

Donor candidates' clinical characteristics provide a clue to the probability of kidney disease. In Table 3, we show the clinical data for two candidate donors, patients C and D. Both are 60 year-old women with a GFR of 60-89 ml/min per 1.73m². Patient C has been extremely healthy with no medical problems or vascular risk factors. Her albuminuria is 4 mg/day. In contrast, patient D has a history of hypertension and smoking, and has higher levels of albuminuria. While we would assess her GFR to be the same, it is more likely that patient D's GFR is lower due to decreased nephron number from kidney disease. Concurrent with this, she has a higher risk for development of ESRD than Patient C. We would consider patient C potentially acceptable as a donor candidate, but would decline Patient D.

Our Perspective: Caveats

Prediction of ESRD Risk in the Donor

The risk projection tool provides a quantitative estimate of ESRD risk without donation using clinical variables that were widely available in general population cohorts. However, other clinical information might be relevant for ESRD risk, including family history. In the Norwegian study of ESRD risk post donation, all of the nine donors who developed ESRD had family history of ESRD, and seven of the nine had primary kidney disease. The current inability to quantify the impact of family history on ESRD risk but should be discussed with donor candidates, particularly younger candidates. Given limitations, application of the currently available online tool in the clinical setting at this time requires clinician insight and interpretation.

Outcomes of CKD in the donor other than ESRD

There is growing data to support that lower GFR is associated with increased risks of other complications such as high blood pressure, albuminuria, gout and preeclampsia, although quantified absolute risks for complications have been small.[32-35] The 2017 KDIGO living donor guideline evidence review team found that the evidence was not consistent across all studies, and that some studies were poor quality, indicating the need for further studies. In addition, one study of approximately 3500 US donors showed that over approximately 25 years, 36% had eGFR < 60 ml/min per 1.73 m² (corresponding to CKD stage 3 or worse) and 2.6% had eGFRcr <30 ml/min per 1.73 m² (corresponding to CKD stage 4 or worse).

While the importance of CKD stage 3 after kidney donation is debated[36], there is little debate that CKD stage 4 is associated with higher risk for adverse events and requires heightened medical attention. We anticipate that accepting donors with lower GFR prior to donation will lead to higher risk of complications, and we suggest ongoing study of subsequent outcomes. Some donor candidates might accept increased risk, but current knowledge of the quantifiable risks should be provided as part informed consent.

Outcomes in the recipient

The 2017 KDIGO living donor guideline focuses on the donor and does not consider the impact of donor characteristics on recipient outcomes. For example, our patient C in Table 3 is an extremely healthy 60 year-old woman with GFR of 60-89 ml/min per 1.73m², and has a low predicted 15 year and lifetime risk for ESRD. The donor may be acceptable because she has a low risk for development of adverse outcomes from donation, but she may not be the best donor for a particular recipient. In this example, this donor might be more appropriate for a similarly aged woman of the same height, but less appropriate for a tall young male. We recommend that there should be an explicit assessment by the recipient's teams of the appropriateness each kidney donor candidate, or for minimum standards in the case of donor exchange participation.

Conclusions

Living kidney donation is a vital treatment options for patients with kidney failure. The 2017 KDIGO living donor guideline provides a helpful framework for individualized and quantifiable decision making which should facilitate transplant center's ability to communicate risks and benefits to the candidate donor and make decisions to accept or decline a candidate donor. In our view, given this framework and understanding of appropriate diagnostic test interpretation, the efficiency of the donor evaluation can be improved, while ensuring the rigour and accuracy of the evaluation.

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Box 1**Use of prediction tool to estimate ESRD risk pre-donation and post donation**

1. Use the online tool (<http://www.transplantmodels.com/esdrisk/>) to estimate the projected lifetime risk of kidney failure in the absence of donation according to baseline demographic and clinical characteristics considered in the online tool.
2. Multiply the projected pre-donation risk by the best available estimate for donation attributable risk obtains the projected post-donation risk. For example, Grams et al report a relative risk of 3.5 to 5.3 for 15-year ESRD risk, according to sex and race.
3. Compare the quantitative projected estimate to the center's post-donation threshold of acceptable risk.
4. Exercise caution when there is concern that the individual has risk factors not captured in the online tool (e.g., familial or genetic risk).

Box 2**Key KDIGO Donor Guideline Recommendations for GFR Evaluation in Kidney Donor Candidates****Measurement**

5.1: Express kidney function as glomerular filtration rate (GFR) and not as serum creatinine concentration.

5.2: Express GFR in mL/min/1.73m² rather than mL/min.

5.3: Estimate glomerular filtration rate (GFR) from serum creatinine (eGFR_{cr}) for initial assessment following recommendations from the KDIGO 2012 CKD guideline.

5.4: Confirm GFR using one or more of the following measurements depending on their availability:

5.4.1: Measured GFR (mGFR) using an exogenous filtration marker, preferably urinary or plasma clearance of inulin, urinary or plasma clearance of iothalamate, urinary or plasma clearance of ⁵¹Cr-EDTA, urinary or plasma clearance of iohexol, and urinary clearance of ^{99m}Tc-DTPA

5.4.2: Measured creatinine clearance (mCl_{cr})

5.4.3: Estimated GFR from the combination of serum creatinine and cystatin C (eGFR_{cr-cys}) following recommendations from the KDIGO 2012 CKD guideline

5.4.4: Repeat estimated GFR from serum creatinine (eGFR_{Cr})

5.5: If there are parenchymal, vascular or urological abnormalities or asymmetry of kidney size on medical imaging, assess individual kidney GFR by using radionuclides or contrast agents that are excreted by glomerular filtration (e.g., ^{99m}Tc-DTPA).

Selection

5.6: GFR ≥ 90 mL/min/1.73m² should be considered as an acceptable level of kidney function for kidney donation.

5.7: The decision to approve donor candidates with GFR 60-89 mL/min/1.73 m² should be individualized based on age and other clinical factors in relation to the transplant center's acceptable risk threshold.

5.8: Candidates with GFR <60mL/min/1.73 m² should not donate

5.9: When asymmetry in GFR, parenchymal abnormalities, vascular abnormalities, or urological abnormalities are present but do not preclude donation, use the more severely affected kidney for donation

Counseling

5.10: We suggest that donor candidates be informed that the risk of someday developing kidney failure needing treatment with dialysis or transplantation is slightly higher as a result of donation; however, average absolute (15yr) post-donation risk remains low

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Box 3**Key KDIGO Donor Guideline Recommendations for Albuminuria Evaluation in Kidney Donor Candidates****Measurement**

- 6.1: Measure proteinuria as albuminuria, not total urine protein
- 6.2: Initial evaluation of albuminuria (screening) should use urine albumin creatinine ratio (ACR) in a random (untimed) urine specimen.
- 6.3: Confirmation of albuminuria should be obtained using:
 - 6.3.1: Albumin excretion rate (AER, mg/day) in a timed urine specimen
 - 6.3.2: Repeat ACR if AER cannot be obtained

Criteria for Acceptable Pre-Donation Albuminuria

- 6.4 Urine AER <30 mg/day should be considered as an acceptable level for kidney donation
- 6.5 The decision to approve donor candidates with AER 30-100 mg/day should be individualized based on age and other clinical factors in relation to the transplant center's acceptance risk threshold.
- 6.6 Donor candidates with urine ACR >100 mg/day should not donate

Table 1
Methods to assess GFR and albuminuria and their limitations

	Description	Limitation
True GFR (tGFR)	Average value over 1-2 days	Hypothetical
Measured GFR (mGFR)	Urinary or plasma clearance of exogenous filtration marker	Biological variation Inconvenience Non-ideal behavior of markers Variation among assays Measurement error
Measured creatinine clearance (mClcr)	Urinary clearance of creatinine	Biological variation Inconvenience Tubular secretion of creatinine Urine collection errors
Estimated GFR (eGFR)	Equations based on serum levels of endogenous filtration markers	Non-GFR determinants of markers Variation among assays
Albumin excretion rate (AER)	Urine albumin measurement in timed urine collection, usually 24 hours	Inconvenience Variation among assays Measurement error
Albumin to creatinine ratio (ACR)	Urine albumin divided by urine creatinine in spot urine sample	Biological variation Variation in urine collection methods Variation in creatinine excretion based on body size Variation among assays

Non GFR determinants for creatinine include: generation [differences in muscle mass (body building, amputation, muscle wasting), protein intake (including creatine supplements)]; tubular secretion [decreased by drug-induced inhibition of secretion (trimethoprim, cimetidine, fenofibrate)]; extra renal elimination [decreased by inhibition of gut creatininase by antibiotics]

Non GFR determinants for cystatin C include: thyroid abnormalities, glucocorticoid excess, and fat mass, inflammation, smoking, urine protein
 Errors in eGFR_{cr} are smaller than in either eGFR_{cr} or eGFR_{cys}, related to lesser influence of non-GFR determinants of two filtration markers when both are used compared to when either is used alone.

Table 2
Examples of using eGFR as initial test for 50 year old white women using sequential testing with eGFRcr and eGFRcr-cys in hypothetical transplant program

Patient 1: 50 year old white woman with higher GFR.			
Example	A	B	C
Pre-test probability of mGFR 90	64%	64%	64%
eGFRcr value	110	95	95
Post-test probability of mGFR 90	98%	89%	89%
Transplant center decision	<i>Accept without confirmatory test</i>	<i>Require confirmatory test</i>	<i>Require confirmatory test</i>
eGFRcr-cys value	NA	95	75
Post-test probability of mGFR 90		99%	89%
Transplant center decision		<i>Accept without mGFR test</i>	<i>Require mGFR test</i>
Patient 2: 50 year old white woman with lower GFR			
Example	D	E	F
Pre-test probability of mGFR < 60	6%	6%	6%
eGFRcr value	25	40	40
Post-test probability of mGFR < 60	96%	63%	63%
	<i>Reject without confirmatory test</i>	<i>Require confirmatory test</i>	<i>Require confirmatory test</i>
eGFRcr-cys value	NA	40	50
Post-test probability of mGFR < 60		98%	84%
Transplant center decision		<i>Reject without mGFR test</i>	<i>Require mGFR test</i>

Scenarios for clinical decision-making presented at a hypothetical transplant program that has the following policies: 1) Decisions may be based on eGFRcr and eGFRcr-cys if the post-test probabilities of mGFR below or above a threshold are 95%. 2) eGFRcr done first, followed by eGFRcr-cys and clearance measurement only performed in those with post test probabilities < 95%. 3) mGFR 90 ml/min per 1.73 m² is acceptable for donation, while mGFR < 60 ml/min per 1.73 m² is not acceptable.

In the top panel, the clinical decision to be made is if the candidate donor be accepted without the use of confirmatory tests (eGFRcr-cys or measured GFR). In the bottom panel, the clinical decision to be made is if the candidate donor can be rejected without use of confirmatory tests (eGFRcr-cys or mGFR).

For use of eGFRcr-cys as a confirmatory test, the post-test probability from the eGFRcr becomes the pre-test probability for eGFRcr-cys. Confirmatory testing is not required if post-test probability based on eGFRcr is 95%. mGFR testing is not required if post-test probability is 95%.

Pretest probabilities were based on data from the National Health and Nutrition Examination Survey, but can be modified for a specific candidate donor. Categorical likelihood ratios were computed from data from the CKD-EPI Collaboration equations.

Units of GFR are ml/min per 1.73 m².

Table 3
Assessment of GFR and AER range in four hypothetical candidate donors

Test	Patient A 45 year old African American man	Patient B 45 year old white woman	Patient C 60 year old white woman	Patient D 60 year old white woman
	“Mr Body builder”	“Ms Clumsy”	“Ms Healthy”	“Ms Subclinical vascular risk factors”
Test results				
Estimates				
eGFR _{Cr} value	72 54% <i>PTP > 90</i>	95 89%	75 49%	75 49%
eGFR _{Cys} value	95 85% <i>PTP > 90</i>	95 98%	80 54%	80 54%
ACR	2	20	4	80
24 hour urine collections				
Creatinine clearance, ml/min per 1.73 m ²	120	75	85	85
Albumin excretion rate, mg/day	4	10	4	80
Creatinine excretion rate, mg/day (expected)[31]	2400 (1600)	500 (1000)	1000 (1000)	1000 (1000)
Measured GFR from iohexol clearance, ml/min per 1.73 m ²	94	90	75	75
Assessments				
Assessment of GFR range	> 90	> 90	60-89	60-89
Assessment of albuminuria range	< 30	< 30	< 30	30-60
Estimation pre donation ESRD risk[25]	0.42% 15 years 1.02% lifetime	0.11% 15 years 0.40% lifetime	0.09% 15 years 0.34% lifetime	1.10% 15 years 1.99% lifetime
Comments				
	Test results are inconsistent. In body builders, high creatinine excretion will falsely lower both eGFR _{Cr} and ACR. The 24	Test results are inconsistent. On questioning, the patient reported spilling the urine collection. This was suggested	Test results are consistent and show intermediate range for GFR and low range of	Test results are consistent and show intermediate range for GFR and ACR. Candidate is at

Test	Patient A 45 year old African American man	Patient B 45 year old white woman	Patient C 60 year old white woman	Patient D 60 year old white woman
	“Mr Body builder” <i>hour creatinine excretion confirms high creatinine excretion, and therefore eGFR and ACR will not be considered. Candidate is at low risk for ESRD. Acceptable for donation</i>	“Ms Clumsy” <i>by creatinine excretion that was lower than expected for age and weight. This will falsely lower mClcr and AER, and therefore mClcr and AER will not be considered. Candidate is at low risk for ESRD. Acceptable for donation</i>	“Ms Healthy” <i>albuminuria. Candidate is at low risk for ESRD. Acceptable for donation</i>	“Ms Subclinical vascular risk factors” <i>higher risk for ESRD. Not acceptable for donation</i>

eGFR_{Cr}, estimated GFR from creatinine; eGFR_{Cys}, estimated GFR from cystatin C; PTP, post test probability for measured GFR greater than 90 ml/min per 1.73 m², mCrCl, measured creatinine clearance