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GFR Evaluation in Living Kidney Donor Candidates

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ABSTRACT

Evaluation of GFR, required in the evaluation of living kidney donor candidates, is now receiving increasing emphasis because recent data demonstrate increased risk of kidney disease after donation, including a small increase in the risk of kidney failure. The international guideline development group, Kidney Disease Improving Global Outcomes, recently published a comprehensive set of recommendations for living donor evaluation, with three recommendations regarding GFR. (*1*) Donor candidacy is evaluated in light of long-term risk, in which GFR is one of many factors. ESRD is considered a central outcome, and a method for estimating long-term risk of ESRD in donor candidates is described. (*2*) Two GFR thresholds are used for decision-making: a high threshold (≥90 ml/min per 1.73 m^2) to accept and a low threshold (<60 ml/min per 1.73 m^2) to decline, with 60–89 ml/min per 1.73 m^2 as an intermediate range in which the decision to accept or decline is made on the basis of factors in addition to GFR. (*3*) GFR is evaluated using several methods available at the transplant center, including estimating equations and clearance measurements. We review the rationale for the guideline recommendations, principles of GFR measurement and estimation, and our suggestions for implementation.

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Each year, nearly 5800 living donor kidney transplants are performed in the United States.[1] Evaluation of GFR is required as part of the donor evaluation and is now receiving increasing emphasis, as recent data from the general population demonstrate increased risks associated with reduced GFR, and data from kidney donors demonstrate increased risks of kidney disease after donation, including a small increase in the risk of kidney failure.[2–4] Selecting donors with minimal long-term risk of kidney failure is important to safeguard the practice of kidney donation, regardless of the degree to which it can be established that donation contributed to the risk of kidney failure. Equally important is respecting the donor candidates' autonomous decisions to seek the benefit and accept the risk of kidney donation. Balancing these objectives by transplant center clinicians requires careful consideration of multiple measures of health status of kidney donor candidates and the long-term consequences of kidney donation.

The international guideline development group, Kidney Disease Improving Global Outcomes (KDIGO), recently published a comprehensive set of recommendations for living donor evaluation on the basis of systematically collected evidence, where possible.[5] The guidelines are focused on donor safety, and exclude consideration of recipient outcomes on the basis of donor characteristics or implications for the number of living donors. The guidelines contain three recommendations regarding GFR (Table 1). The purpose of this review is to discuss the rationale for the guideline recommendations, principles of GFR measurement and estimation, and our suggestions for implementation.

EVALUATION OF DONOR CANDIDACY

KDIGO Framework for Decision-Making

The KDIGO recommendations are made on the basis of the principle that the evaluation of living donor candidates should include a comprehensive determination of risk to the donor, on the basis of simultaneous consideration of a composite profile of risk factors, rather than consideration of single risk factors in isolation as recommended in previous guidelines. Traditionally, donor candidates were advised that donating a kidney did not alter the lifetime risk of developing kidney disease if the remaining kidney was healthy at the time of donation. Recent data have led to reconsideration of this traditional advice. Although there are many outcomes to consider after kidney donation, KDIGO considered the long-term risk of developing kidney failure as central, and proposed a quantitative framework for medical evaluation and acceptance of donor candidates according to the donor candidate's estimated postdonation risk in relationship to the transplant center's threshold for acceptable risk (Figure 1). In this framework, the candidate's long-term postdonation risk is influenced by the combination of risks

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Table 1. KDIGO recommendations regarding GFR evaluation

Donor candidacy is evaluated in light of long-term risk, in which GFR is one of many factors. Each transplant center determines a threshold for acceptable risk to be applied to all donor candidates. Donor candidates with risk below the threshold are acceptable. Donor candidates with risk above the threshold are not acceptable. ESRD is considered a central outcome, and a method for estimating long-term risk of ESRD in donor candidates is described.
Two GFR thresholds are used for decision-making: a high threshold (≥90 ml/min per 1.73 m^2) to accept and a low threshold (<60 ml/min per 1.73 m^2) to decline, with 60–89 ml/min per 1.73 m^2 as an intermediate range in which the decision to accept or decline is on the basis of factors in addition to GFR.
GFR is evaluated using a variety of methods available at the transplant center, including estimating equations and clearance measurements. Two-stage testing is recommended. The initial test is eGFRcr. eGFRcys is an alternative initial test on the basis of an evaluation of likely non-GFR determinants of creatinine and cystatin C. Confirmatory tests include mGFR using clearance of exogenous filtration markers, mClcr using during a 24-hr urine collection, eGFRcr–cys, or repeat eGFRcr. A method for using eGFR to estimate the probability that mGFR is above or below a threshold is described.

conferred by his or her demographic and clinical characteristics at the time of evaluation plus the risk attributable to donation. The level of GFR is one of several clinical characteristics that determine the donor candidate's estimated risk.

Using a risk threshold to guide decision-making to accept or decline donor candidates would ground transplant center decision-making in an objective, transparent, and defensible policy, and facilitate education of donor candidates. A risk threshold represents a quantitative expression of the acceptable balance of the objectives of assuring the safety and autonomy of living kidney donor candidates. KDIGO recommended that each transplant center should develop and communicate a quantitative threshold of acceptable risk, that this threshold can be both evidence-based and consensus-based. Once established, ideally the threshold should be applied consistently and transparently for all donor candidates evaluated at a center.

Decreased GFR and Risk in the General Population

It is now well accepted that decreased GFR in the general population is associated with a higher risk of complications of CKD, including death, cardiovascular disease, and ESRD, and the KDIGO 2012 CKD Guidelines define GFR<60 ml/min per 1.73 m^2 for 3 months or more as CKD.[6] A recent meta-analysis by Grams *et al.* estimated lifetime risk for ESRD in a low-risk subgroup of the general population similar to donor candidates on the basis of demographic and clinical characteristics.[7] Lifetime risk estimates varied by sex and race, but was lower at older age and higher GFR for all groups (Figure 2). For example, for eGFR≥90 ml/min per 1.73 m^2, estimated lifetime risk for white men and women was <1% at all ages, but exceeded 2% for black men and women aged <30 and 20 years, respectively. For eGFR of 60–89 ml/min per 1.73 m^2, estimated lifetime risk was higher but still <1% for those aged ≥60 years.

Decreased GFR and Risk after Kidney Donation

GFR declines after kidney donation because of the immediate loss of approximately 50% of renal mass. In the setting of health, there is rapid compensatory hyperfiltration leading to a net reduction in GFR of only 30% (25%–40%) after donation (decrement in GFR of 25–40 ml/min per 1.73 m^2).[8,9] Consequently, a person with a predonation GFR of ≥90 ml/min per 1.73 m^2 would be expected to have a 1-year postdonation GFR of >60 ml/min per 1.73 m^2.

With long-term follow-up, a substantial proportion of donors have larger reduction in GFR; however, there has been controversy about the clinical implications of decreased GFR after kidney donation.[10,11] Recent studies show an increased risk of complications associated with kidney disease after kidney donation, including hypertension, preeclampsia, hyperuricemia, gout, and hyperparathyroidism.[12–15] More importantly, two recent studies document a small but significant increase in absolute risk for ESRD within approximately 15 years after kidney donation compared with healthy nondonors: we calculated risk differences of 0.44% (0.5% versus 0.06%) in a Norwegian cohort[3] and 0.27% (0.31 versus 0.04 per 100 patient-years of follow-up) in a United States cohort.[4] Of note, because of the low absolute risk in healthy nondonors, small increases in absolute risk may translate to high relative risks. Grams *et al.* reported that the observed 15-year risk of ESRD after donation among kidney donors in the United States was from 3.5 to 5.3 times higher, depending on sex and race, than the estimated risk from the low-risk subgroup from the general population in the absence of donation.[7] However, all three studies are limited by selection of the comparison group, ascertainment of long-term follow-up, and assumptions in computation of risk estimates, and no data are available relating predonation GFR to long-term risk of ESRD after kidney donation.[16–18]

GFR THRESHOLDS

GFR as an Index of Kidney Function

The level of GFR is widely accepted as the best overall index of kidney function in health and disease. Normative levels of GFR are expressed per 1.73 m^2 because GFR is proportional to kidney size, which is proportional to body size. Indexing GFR to body surface area reduces the variability in GFR in healthy individuals, allowing communication of GFR thresholds for decision-making that can be applied to most donors across the usual distribution of body size; however, there is uncertainty about the

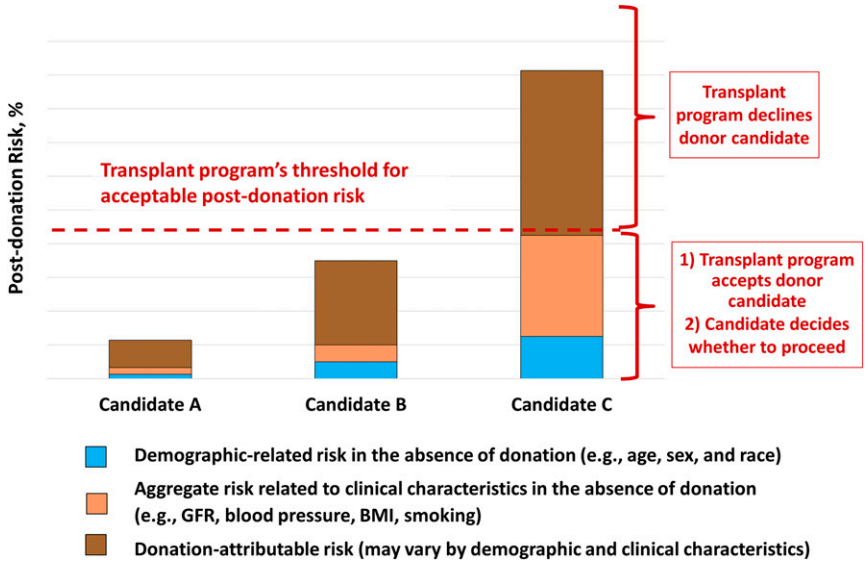

Figure 1. KDIGO proposed framework for a transplant center to accept or decline a donor candidate on the basis of a threshold of acceptable postdonation lifetime risk of kidney failure. A donor candidate's projected estimated lifetime risk is on the basis of their predonation demographic characteristics (blue bar) and clinical characteristics (orange bar), and their added risk attributable to donation (brown bar). The decision by the transplant center whether to accept or decline a donor candidate can be grounded upon on whether an individual's estimated projected postdonation lifetime risk is above or below threshold set by the transplant center (dotted line). Each transplant center may decide on its acceptable threshold for an important outcome and this threshold may vary across transplant centers, but to be fair, a transplant center should apply their same threshold to all donor candidates evaluated at that center. For example, candidate A would be accepted because the estimated projected postdonation risk for an important outcome is far below the threshold, candidate B would be accepted with caution because the estimated projected postdonation risk is close to the threshold, and candidate C would be declined because the estimated postdonation projected risk is far above the threshold. Reproduced from reference 5, with permission.

appropriateness of indexing by body surface area, especially at the extremes of body size.

Mean GFR in healthy young adult white individuals is approximately 125 ml/min per 1.73 m^2, with a wide range.[19] GFR is lower in older people, but the rate of decline over time is highly variable and the causes are not known. There is debate about whether the lower GFR in older people represents normal aging or disease.[20–23] There is some evidence that the normal level of GFR varies among ethnic groups.[24] Studies of kidney donor candidates report lower mean GFR, but the interpretation is limited by selection criteria and differences in GFR measurement methods[25,26]

In principle, GFR is the product of the number of nephrons (N) and the average single nephron GFR (SNGFR). Neither can be measured directly, but variation in either can cause variation in GFR. Variation in N is not well described, but it appears to be lower in people with CKD, older age, or a history of prematurity.[27,28] Variation in SNGFR may be affected by time of day, dietary protein intake, exercise, pregnancy, obesity, hyperglycemia, use of antihypertensive drugs, and surfeit or deficit of extracellular fluid, as well as chronic and acute kidney disease.

The KDIGO 2012 CKD Guidelines consider GFR in young men and women of ≥90 ml/min per 1.73 m^2 as normal or elevated.[6] GFR between 60 and 89 ml/min per 1.73 m^2 is considered to be decreased compared with the usual level for young adults, but does not meet the KDIGO criterion for the definition of CKD of <60 ml/min per 1.73 m^2 for 3 months.

KDIGO Recommendations

KDIGO recommended that GFR≥90 ml/min per 1.73 m^2 is acceptable for kidney donation and GFR<60 ml/min per 1.73 m^2 is not acceptable, whereas GFR of 60–89 ml/min per 1.73 m^2 is an intermediate range in which the decision should be individualized on the basis of age and other clinical factors in relation to the transplant center's acceptance risk threshold (Figure 3). These recommendations were not graded because the rationale is largely on the basis of extrapolation from studies not conducted in donors.

GFR EVALUATION METHODS

GFR Measurement and Estimation

GFR cannot be measured directly in humans; thus true GFR cannot be known with certainty. However, GFR can be assessed from clearance measurements or serum levels of filtration markers, exogenous or endogenous solutes that are mainly eliminated by glomerular filtration. Both measured GFR (mGFR) and eGFR are associated with error (bias and imprecision) in their determination (Table 2).

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, neither reabsorbed, secreted, synthesized, or metabolized by the tubules, and does not alter the function of the kidney. The classic method of Smith used urinary clearance of inulin, a 5200-D polymer of fructose, during a continuous intravenous infusion.[29] Inulin is difficult to use and not available in the United States, so alternative filtration markers have been proposed but all deviate from ideal behavior. Plasma clearance after a bolus intravenous infusion is simpler to perform, but may differ from urinary clearance because of nonequilibration across body fluid compartments and extrarenal elimination of the filtration marker. All clearance measurements are difficult to

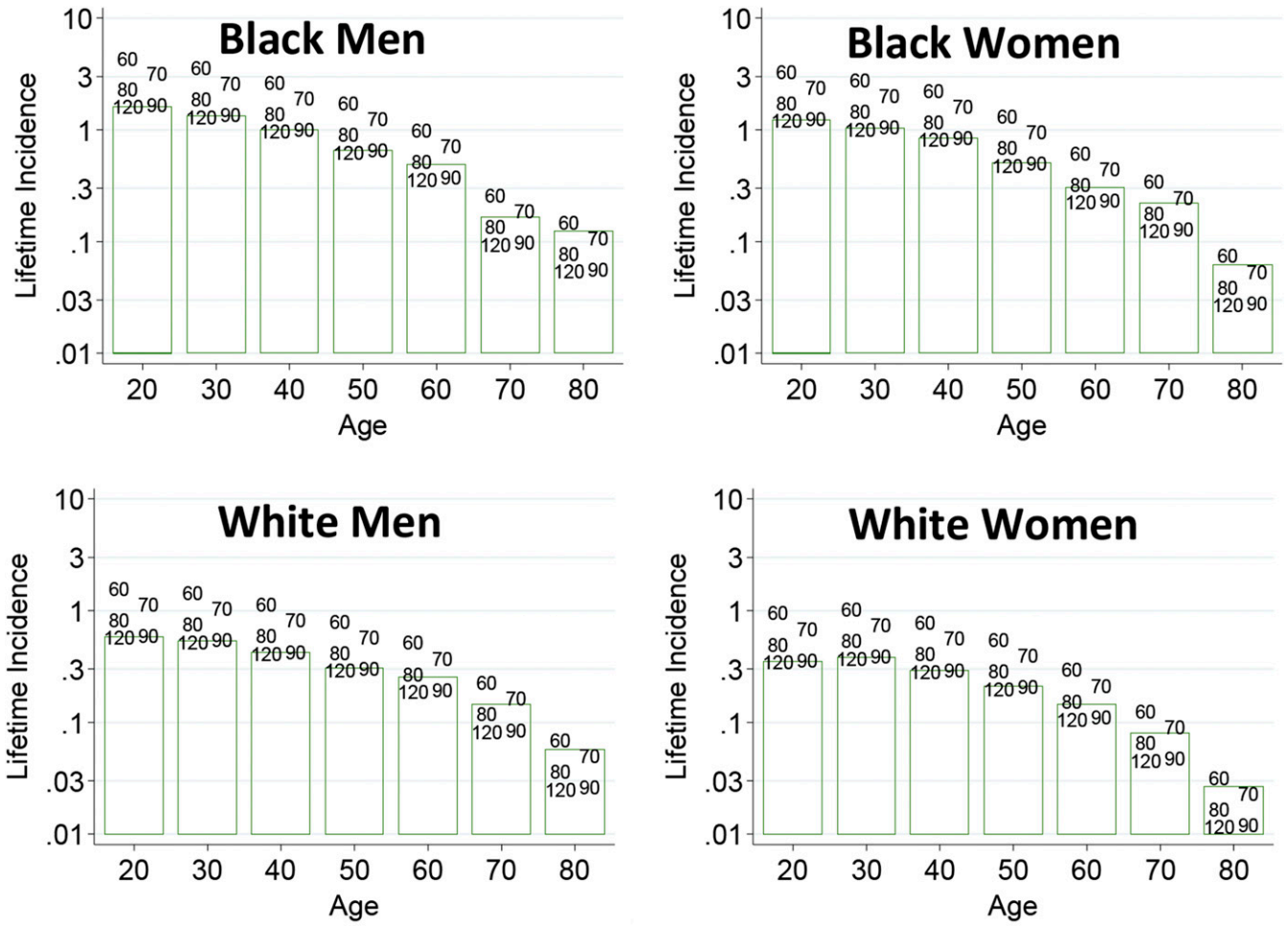

Figure 2. Estimated lifetime incidence (%) of ESRD in the United States according to baseline eGFR and demographic profile from the CKD-PC. The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min per 1.73 m^2 for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic BP 120 mmHg, urine albumin-to-creatinine ratio 4 mg/g [0.4 mg/mmol], body mass index 26 kg/m^2, and no diabetes mellitus or antihypertensive medication use. These were selected as being representative of recent living kidney donors in the United States where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are on the basis of data from nearly 5 million healthy persons identified from seven North American general population cohorts and a median cohort follow-up of 4–16 years, and calibrated to the incidence of ESRD in the low-risk population, and thus are likely imprecise. Reproduced from reference 5, on the basis of data from Grams *et al.*[7], with permission.

perform, leading to error in mGFR. A recent systematic review evaluated alternative methods in comparison to the classic procedure of Smith.[30] Of note, in this review, urinary creatinine clearance did not meet the criteria for accuracy because of large bias and imprecision.

GFR can be estimated from serum levels of endogenous filtration markers without clearance measurements.[31] The serum level of an endogenous filtration marker is affected by factors other than GFR, including generation, renal tubular secretion and reabsorption, and extrarenal elimination, collectively known as non-GFR determinants. Estimating equations use easily measured clinical variables as surrogates for these unmeasured physiologic processes, and provide more accurate estimates than the serum level alone. However, the clinical variables can capture only the average relationship of the surrogates to some of these physiologic processes, leading to error compared with mGFR.

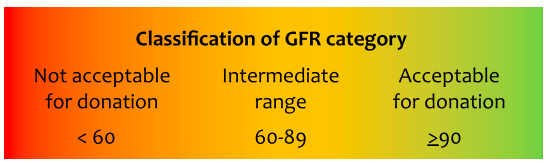

Figure 3. KDIGO classification of GFR categories and use in decision-making for donor candidates. Colors are blended together to signify that the threshold for decision-making is imprecise.

Table 2. GFR evaluation and assessment of living donor candidates

Tests	Use	Sources of Error
Estimates		
eGFRcr	Initial test Use standardized assays Use the CKD-EPI 2009 creatinine equation in North America, Europe, and Australia and other equations elsewhere if they are more accurate than CKD-EPI equation	Nonsteady state (acute kidney disease) Non-GFR determinants of serum creatinine (variation in muscle mass or diet), drug-induced inhibition of creatinine secretion (trimethoprim, cimetidine), extrarenal elimination Interference with creatinine assay
eGFRcys	Alternative initial test (can be obtained at the same time as eGFRcr) Use standardized assays and CKD-EPI 2012 cystatin C equation May be more accurate than eGFRcr in races other than black or white or in persons with alterations in muscle or diet	Nonsteady state (acute kidney disease) Non-GFR determinants of serum cystatin C (poorly understood) Incomplete standardization of assays
eGFRcr–cys	Confirmatory test (can be obtained at the same time as eGFRcr) More accurate than eGFRcr or eGFRcys Use standardized assays and CKD-EPI 2012 creatinine–cystatin C equation	Sources of error for eGFRcr and eGFRcys
Clearance measurements		
mGFR	Confirmatory test Most accurate[a] Methods not standardized and variation among methods Index to 1.73 m^2 body surface area	Physiologic variation in SNGFR Nonideal behavior of filtration markers Difficulty in performing clearance measurements
Measured creatinine clearance (mClcr)	Confirmatory test Index to 1.73 m^2 body surface area	Overestimation of mGFR (creatinine secretion) Incorrect timing or collection of urine
Assessments		
Assessment of GFR range (<60, 60–89, ≥90 ml/min per 1.73 m^2)	Use all measures and post-test probabilities to determine range rather than a single value Down-weight test results more likely to have error	Selection of pretest probabilities
Assessment of postdonation ESRD risk	Use numeric value for GFR in the risk calculator to obtain predonation risk of ESRD Add risk attributable to kidney donation Compare with transplant center threshold Be cautious with risk estimates near the transplant center threshold	Uncertainty in risk estimates

[a]Preferred: 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 99mTc-DTPA are preferred. Other methods, including imaging, are less accurate.[31] EDTA, ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid.

KDIGO Recommendations

The recommendations are on the basis of the KDIGO 2012 CKD Guidelines recommendation for general clinical practice,[6] because there is no evidence to suggest that kidney donors differ from other populations regarding these recommendations. The recommendations include expressing kidney function as GFR and not as serum creatinine concentration, and expressing GFR in ml/min per 1.73 m^2 rather than milliliter per minute. In addition, they include two-stage testing in all donor candidates (initial testing followed by confirmatory testing) and using the best available method at the transplant center to assess GFR of donor candidates, recognizing that more than one method may be available in many centers. The accuracy of various methods for measuring and estimating GFR are not known with sufficient certainty to define separate thresholds for each method.

eGFR on the basis of serum creatinine (eGFRcr) is the initial test. eGFRcr can be biased in people with very large or very small muscle mass, very high or very low meat intake, or race/ethnicity other than black (American or European) or white. In such candidates, eGFR on the basis of

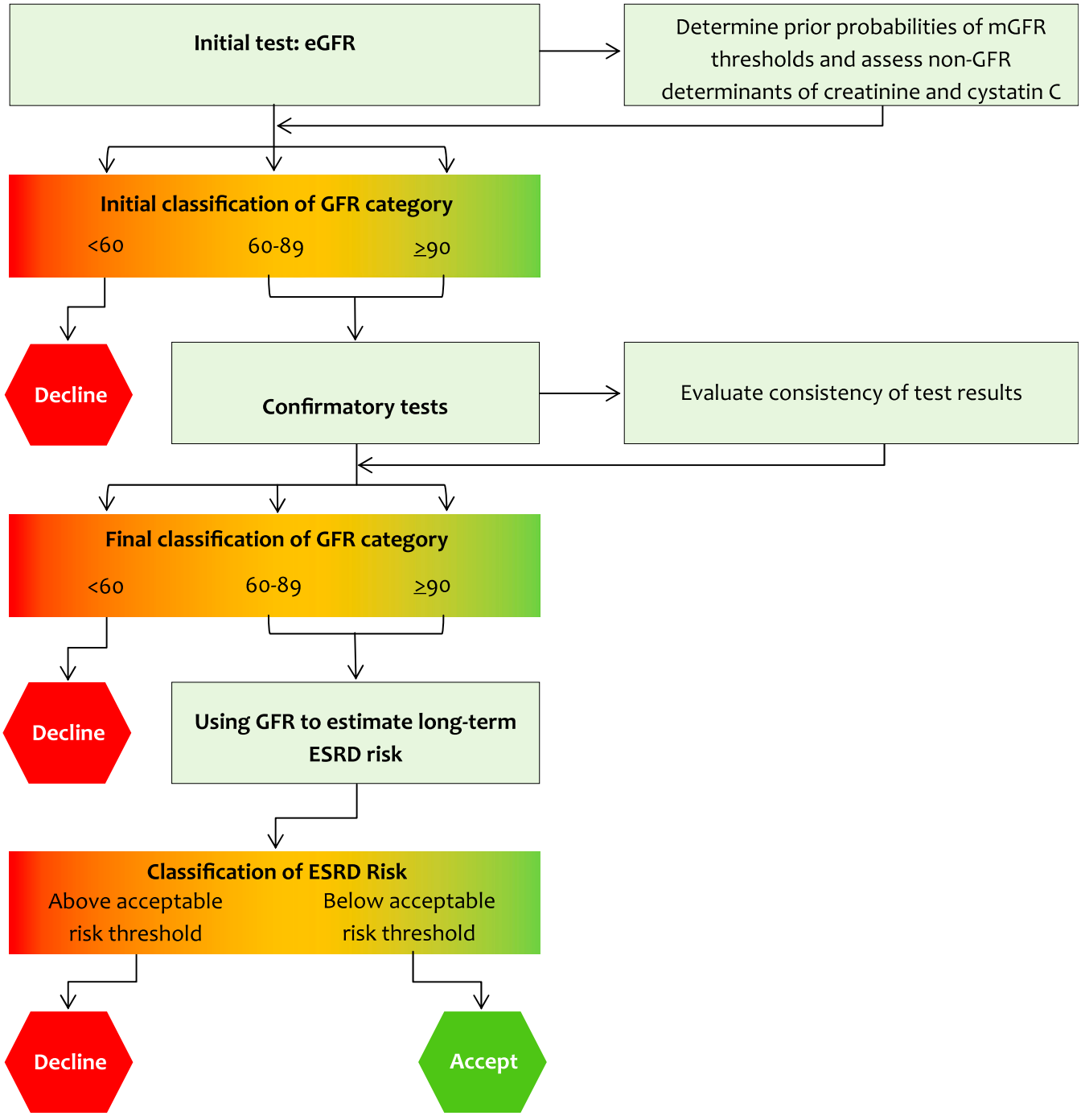

Figure 4. Implementation. Initial test: eGFRcr is the initial test in most candidates. eGFRcys may be the preferred initial test for candidates with variations in non-GFR determinants of serum creatinine, for example, variation in muscle mass or diet (Table 2). However, non GFR determinants of cystatin C are not as well understood as of creatinine. If differences between eGFRcr and eGFRcys are observed, the variation might be due to nonGFR determinants of either marker. Interpretation of eGFR should include consideration of the probability that mGFR is above or below threshold for decision-making (http://ckdepi.org/equations/donor-candidate-gfr-calculator/). Very high likelihood that mGFR is <60 ml/min per 1.73 m^2 is justification for a decision to decline without further consideration. Confirmatory tests: mGFR or mClcr are required in the United States. Elsewhere, eGFRcr–cys can be acceptable if mGFR or mClcr are not available and eGFRcys was not used as the initial test. Repeat eGFRcr can be acceptable if none of the other confirmatory tests are available, but is not preferred. Inconsistent test results suggest inaccuracy of one or more tests, which should be discarded or repeated. Very high likelihood that mGFR is <60 ml/min per 1.73 m^2 is justification for a decision to decline without further consideration. Using GFR to estimate long-term ESRD risk: Long-term estimated risk of ESRD is compared with the transplant center threshold for acceptable risk. Long-term risk in

serum cystatin C (eGFRcys) may be an alternative initial test. Serum creatinine and cystatin C assays should be traceable to international reference standards, and the CKD Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation and 2012 cystatin C equation should be used unless other equations have been shown to be more accurate. (Table 2). Both eGFRcr and eGFRcys are imprecise at high levels of GFR, so confirmatory testing is recommended for all donor candidates (Table 2).

mGFR using an exogenous filtration marker is the most accurate confirmatory test. These methods are not standardized, however, and there is variation across them. Furthermore, mGFR is not available in all centers, so alternatives are acceptable. Measured creatinine clearance (mClcr) is not as accurate as mGFR. It overestimates mGFR because of creatinine secretion, with the magnitude of overestimation exceeding 15% at normal GFR, and is prone to error because of inaccurate urine collections. In principle, all transplant centers can perform mClcr, however, it may be difficult in some donor candidates because of logistical difficulties in collecting or transporting a timed urine collection. eGFR on the basis of serum creatinine and cystatin C (eGFRcr–cys) using the CKD-EPI 2012 creatinine–cystatin C equation can be used as a confirmatory test. In general, using two filtration markers improves precision of GFR estimates compared with using either marker alone; thus eGFRcr–cys is generally recommended over eGFRcr or eGFRcys.[32,33] Repeat eGFRcr can be used if no other confirmatory tests are available, but this is not our preference (Table 2).

COMPARISON TO PREVIOUS GUIDELINES

Some previous guidelines recommend a GFR threshold of ≥80 ml/min (not adjusted for body surface area), on the basis of the level of GFR in the donor that was associated with the best outcomes in the recipient, not the donor.[34] Other guidelines recommend a GFR threshold within two SDs of normal for age and sex, although standardized reference values have not been developed.[35] In general, the guidelines do not specify the GFR measurement method to be used or whether the threshold value should be adjusted for body surface area. A 2007 survey of practices by transplant centers in the United States revealed that approximately 90% of centers used mClcr, whereas the other 10% of centers used the clearance of an exogenous filtration marker, and that approximately 67% of transplant centers used a threshold of ≥80 ml/min to accept donors, whereas 25% used a threshold on the basis of age and sex.[36] In contrast, the KDIGO recommendations are more consistent with accepted measurement methods and thresholds used 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. Although the recommended threshold values for decision-making (mGFR ≥90 and <60 ml/min per 1.73 m^2) are probably higher and lower, respectively, than used by most centers at this time, the intermediate range (mGFR of 60–89 ml/min per 1.73 m^2) would generally include a mClcr of 80 ml/min as well as previously recommended age and sex thresholds for mGFR.

IMPLEMENTATION

The purpose of GFR evaluation in kidney donor candidates is to detect chronic or acute kidney disease. In patients with kidney disease, reduction in N is hypothesized to be the cause of reduction in true GFR. Because donor candidates are selected by the absence of self-reported disease, factors other than kidney disease are more likely causes of reduced GFR, such as physiologic variation in SNGFR, GFR measurement error, and deviation in non-GFR determinants of serum levels of endogenous filtration markers (Table 2). Because all measures are accompanied by error, results from estimates and clearance measures may not be concordant for assessment of the GFR compared with the threshold. Our approach is to use the information from all measures to determine a likely range for true GFR for decision-making (Figure 4).

Assessment of GFR Range

In the United States, performance of a clearance measurement is required for GFR evaluation. In our experience, it is helpful to interpret clearance measurements in light of eGFR. Despite the well recognized imprecision of eGFR at higher levels, it can provide substantial information to estimate the probability that mGFR is above or below the thresholds for decision-making.[37] For example, the pretest probabilities (without knowledge of eGFRcr) for mGFR thresholds of interest can be computed using data from National Health and Nutrition Examination Surveys, and the post-test probabilities (with knowledge of eGFRcr) can be computed using categorical likelihood ratios for eGFRcr using the CKD-EPI equation. Very high post-test probabilities provide reassurance that mGFR is above the threshold, whereas very low post-test probabilities provide reassurance that mGFR is below the threshold. If serum cystatin C is available, eGFRcr–cys can be computed, and post-test probabilities for mGFR thresholds can be recomputed by substituting post-test probabilities from eGFRcr as pretest probabilities and substituting categorical likelihood ratios for eGFRcr–cys to compute post-test probabilities. A web-based calculator

the absence of donation can be computed from demographic and clinical characteristics, including GFR (http://www.transplantmodels.com/esrdrisk/). Additional risk attributable to donation is likely to be 3.5–5.2 times higher than risk in the absence of donation depending on sex and race, but there is substantial uncertainty, especially in younger donor candidates, and we suggest caution in decision-making. Postdonation risk above the threshold is justification for a decision to decline. Candidates with risk below the threshold can make their own decision whether to donate. Colors are blended together to signify that the threshold for decision-making is imprecise.

has been developed to compute post-test probabilities for mGFR above or below various threshold probabilities (http://ckdepi.org/equations/donor-candidate-gfr-calculator/).[38]

Consistency among measures provides confidence that true GFR is above or below the mGFR thresholds for decision-making. If measures are not consistent, an evaluation of the likely sources of error can suggest which measure is more likely to be correct. For example, a lower eGFRcr and eGFRcr–cys but higher eGFRcys, mClcr, and mGFR suggests increased creatinine generation rather than low true GFR. A higher eGFRcr, eGFRcr–cys, and mGFR but lower mClcr suggests an incomplete 24-hour urine collection. A higher eGFRcr, eGFRcr–cys, and mClcr but lower mGFR suggests a GFR measurement error.

In some patients, it may be difficult to perform a clearance measurement. A recent study suggested that eGFR may be sufficiently accurate for decision-making without the need for mGFR or mClcr in many donor candidates.[36] In that study, 53% of recent donors in the United States had eGFR sufficiently high to provide a ≥95% post-test probability that mGFR was ≥90 ml/min per 1.73 m^2. Another study confirming this finding in donor candidates has been reported.[39] Future studies should address prediction accuracy among racial and ethnic groups for whom the accuracy of eGFR is less certain (*e.g.*, nonblack, nonwhite persons).

Assessment of ESRD Risk

Our approach to assessment of ESRD risk is to first estimate the long-term risk in the absence of donation using demographic and clinical characteristics of the donor, including GFR, and then to estimate the additional risk attributable to donation. Grams *et al.* developed a web-based calculator to estimate the 15-year and lifetime risks of ESRD on the basis of these characteristics in the absence of kidney donation (http://www.transplantmodels.com/esrdrisk/).[40] The risk attributable to kidney donation is not well defined. KDIGO suggests multiplying the estimated risk by the observed relative risk of kidney failure attributable to donation (3.5–5.3, depending on sex and race) to estimate the risk after donation. As an example, if the transplant center's accepted threshold for lifetime risk of ESRD is <5%, then a donor candidate with a lifetime estimated risk of >1% in the absence of donation would have an estimated lifetime risk as high as 3.5%–5.3%, which is near or above the threshold and would not be accepted, whereas a donor candidate with a lower risk would be accepted. There are several limitations of this approach, including lack of inclusion of biologic and household relatedness with ESRD as possible prediction variables.[16] In addition, as described in the KDIGO Guidelines, there is substantial uncertainty in long-term risk estimates, especially for younger candidates in whom it is difficult to predict whether they will develop the conditions that confer higher risk for ESRD. Nevertheless, as is stated in the KDIGO Guidelines, this model and approach is a reasonable starting point, but cautioned that the use of such tools require clinician insight, and transplant centers and donor candidates may consider other factors in their acceptance criteria for living kidney donation in addition to quantitative risk estimates. KDIGO recommended that quantifying donation-attributable relative risk for a given clinical profile and incorporating updated estimates into the online tool should be a leading priority for future research.

Implications

Using this approach, older donor age would be associated with lower estimated lifetime risk, justifying consideration of older donor candidates, although GFR may be lower than in younger donors. Older donors may be especially appropriate for the growing number of older recipient candidates who may benefit from transplantation of a kidney despite a lower GFR.[41] In principle, the decision whether or not the donor candidate is appropriate for the recipient should made by the recipient evaluation team after the decision that the donor is acceptable based on the criteria discussed above. In fact, the principle of matching donor kidney estimated survival to recipient candidate estimated survival is the foundation of current United States policy for allocation of deceased donor kidneys.[42,43] On the other hand, younger donor age would be associated with higher estimated lifetime risk despite higher GFR, and we suggest caution in consideration of younger donor candidates, who have been traditionally been favored over older candidates. The higher risk of ESRD in young black donor candidates poses a special problem because of the disproportionate number of blacks with ESRD.

In conclusion, the KDIGO Guidelines are an advance over previous guidelines. The framework for decision-making provides an explicit objective approach to balance donor safety and autonomy partly on the basis of the donor candidate's level of GFR. The use of a higher and lower GFR threshold for decision-making allows more flexibility than a single threshold. The recommendations for GFR evaluation are on the basis of principles of GFR measurement and estimation that underlie evaluation in the general population and can be implemented by practical strategies using available online tools. Implementation of these guidelines may lead to substantial changes in living donor transplantation.

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DISCLOSURES

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Tufts Medical Center, John Hopkins University and Metabolon Inc have a collaboration agreement to develop a product to estimate GFR from a panel of markers. L.A.I. reports funding to Tufts Medical Center for research and contracts with the National Institutes of Health, National Kidney Foundation, Pharmalink AB, Gilead Sciences, Otsuka, and has a provisional patent (filed August 15, 2014 by Coresh, Inker, and Levey, Precise estimation of glomerular filtration rate from multiple biomarkers, patent no. PCT/US2015/044567). The technology is not licensed in whole or in part to any company. Tufts Medical Center, John Hopkins University, and Metabolon Inc. have a collaboration agreement to develop a product to estimate GFR from a panel of markers.

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