The evaluation of kidney function in living kidney donor candidates

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Abstract

Living kidney donors incur a small increased risk of end-stage kidney disease (ESKD), of which pre-donation glomerular filtration rate (GFR) is an important determinant. As a result, kidney function assessment is central to the donor candidate evaluation and selection process. This article reviews the different methods of GFR assessment including estimated GFR, creatinine clearance and measured GFR, and the current guidelines on GFR thresholds for donor acceptance. Estimated GFR obtained using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation, while the best of estimating estimations, tends to underestimate and has limited accuracy, especially near normal GFR values. In the United States, the Organ Procurement and Transplantation Network policy on living donation mandates either measured GFR or creatinine clearance as part of evaluation. Measured GFR is considered the gold standard, although there is some variation in performance characteristics depending on the marker and technique used. Major limitations of creatinine clearance are dependency on accuracy of timed collection, and overestimation as a result of distal tubular creatinine secretion. GFR declines with healthy aging, and most international guidelines recommend use of age-adapted selection criteria. The 2017 Kidney Disease: Improving Global Outcomes Guideline for the Evaluation and Care of Living Kidney Donors diverges from other guidelines and recommends using absolute cut-off of <60 ml/min/1.73m$^2$ for exclusion and of ≥90 ml/min/1.73m$^2$ for acceptance, and determination of candidacy with intermediate GFR based on long-term ESKD risk. However, several concerns for this strategy exist, including inappropriate acceptance of younger candidates due to underestimation of risk, and exclusion of older candidates whose kidney function is in fact appropriate for age. Role of cystatin C and other newer biomarkers, as well as data on impact of pre-donation GFR on not just ESKD risk but also advanced chronic kidney disease risk and cardiovascular outcomes are needed.
Introduction
Living donor kidney transplantation is the best kidney replacement therapy option for eligible patients with end-stage kidney disease (ESKD), offering superior outcomes compared to deceased donor transplantation. Recognition of its benefits to recipients and to society has led to efforts to promote living donation at various levels: educating patients and healthcare providers, helping transplant candidates identify and approach potential donors, institution of kidney paired donation (KPD) programs, acceptance of medically complex candidates and navigating efficiency and financial barriers to donation. At the same time, ongoing success of the practice of living donation depends on ensuring the safety and good outcomes in living kidney donors, which ultimately relies on thorough evaluation and careful risk assessment before donation.

Overall approach to kidney evaluation in donor candidates
The traditional and widely used approach to the medical component of the evaluation involves assessment of individual variables related to 1) the current kidney health, including the glomerular filtration rate (GFR), proteinuria or albuminuria, and hematuria, and 2) the metabolic and cardiovascular risk factors such as hypertension, impaired glucose tolerance, obesity and smoking, and genetic risk factors such as family history of diabetes. GFR and proteinuria speak to the health of the kidney at the time of evaluation, which is relevant both for risk assessment of the donor candidate, and for assessment of nephron mass that will be available to the recipient via transplant. The systemic and genetic risk factors may or may not have a bearing on kidney function at the time of evaluation, but more importantly, are important to long-term donor outcomes after donation. In this context, our group conducted a national survey exploring practices regarding the use of different evaluation and selection strategies at transplant centers in the United States in recent years. Several criteria are sufficient for exclusion of donor candidates by themselves. For example, the survey showed that most programs exclude
candidates with GFR below 80 ml/min/1.73\(^2\), and two-thirds of programs exclude hypertensive candidates requiring two or more anti-hypertensive drugs. Other criteria are not considered absolute contraindications, but factor into the overall decision-making process. For instance, the decision to exclude candidates with prediabetes is frequently multifactorial, and several programs use less strict thresholds for older candidates. One frequently cited limitation of this approach is the lack of uniformity between transplant programs, which, however, is a difficult goal given the highly nuanced nature of the process, with strong emphasis on risk-benefit discussion and informed consent.

More recently, the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Evaluation and Care of Living Kidney Donors provided a framework for acceptance of donor candidates according to their estimated post-donation risk of ESKD, in relation to the program’s pre-determined threshold for acceptable risk.\(^{11,12}\) This approach is performed through the following steps. First, ESKD risk in the absence of donation based on 10 demographic and health characteristics is estimated. The tool to do so was developed from a meta-analysis of 7 general population cohorts.\(^{13}\) Several limitations of this calculator have been discussed before.\(^{14}\) The second step involves assessment of the post-donation risk based on the relative risk associated with donation obtained in the study. The third and last step involves comparison of the post-donation risk estimate with the center’s pre-defined threshold of acceptable risk. If the post-donation risk exceeds the center’s threshold, the candidate is denied. If it is below the center’s threshold, the center accepts the candidate if the candidate is willing to proceed after learning the risks. Strengths of this approach include the simultaneous incorporation of multiple risk factors and the uniformity it lends to the evaluation process. Major limitations include 1) use of cohorts with relatively short follow up, which raise concern regarding underestimation of long-term risk (we do know that ESKD from diabetes and hypertension has delayed expression and increases exponentially over time\(^{15}\)), and 2) important missing variables, such as family history
of kidney disease, which still leave transplant providers to consider multiple additional risk factors, as they have always done. Notably, based on data available in the six large cohorts in the study of healthy non-donors, the calculator uses estimated GFR (eGFR) instead of measured GFR (mGFR) or creatinine clearance (CrCl). A few other calculators are also available. A post-donation ESKD risk calculator that was developed using the United Network for Organ Sharing (UNOS)/Scientific Registry of Transplant Recipients (SRTR) database included ‘first-degree biological relationship with the recipient,’ but did not incorporate a GFR measure, as pre-donation eGFR was not found to be predictive of ESKD in their exploratory models. This finding is counter-intuitive and contradicts previously published results from the same database where pre-donation eGFR was predictive of ESKD. Another study included donors from a single-center, with up to 40 years of follow up, and provided models for prediction of proteinuria and advanced chronic kidney disease (CKD).

**Importance of GFR assessment for donor candidate**

Regardless of the overall approach used, assessment of kidney function is crucial to the donor candidate evaluation process. Donor nephrectomy is followed by adaptive hyperfiltration to approximately 70% of pre-donation kidney function. If a donor goes on to develop progressive kidney disease e.g. diabetic nephropathy, by virtue of having lower GFR at the time of beginning of the disease process they would reach advanced CKD and ESRD sooner than if they had not donated a kidney, resulting in an increased risk of ESKD. Lower pre-donation GFR, which translates into lower post-donation GFR, has been shown to be a risk factor for ESKD in numerous studies. The study of US kidney donors between 1994 and 2016 found a hazard ratio of 0.89 for every 10 ml/min/1.73m² higher eGFR value. As an example, a CrCl of 85 ml/min/1.73m² in a 25-year old without any evidence of kidney disease as assessed by hematuria or proteinuria, is well below 2 standard deviations below mean for age for a 25-year old, and portends a 60% (1/(0.89^4)) higher risk of ESKD post donation compared to CrCl of
125 min/1.73m$^2$ for the same age. Additionally, ESKD is a rare event after kidney donation, but extrapolating from the above studies, it follows that the risk of advanced CKD and associated complications would be much higher in donors with lower pre-donation GFR.$^{18,19}$

In addition to donor safety, donor candidate GFR assessment is relevant when transplant candidates have the option of multiple donor candidates, as is often the case in KPD, or when multiple friends and family members offer to donate. The decision making is complex, as it involves HLA matching, vascular anatomy, CMV status etc., but donor kidney function is an important consideration in terms of ensuring the best recipient outcomes.$^{30,31}$

**Methods of GFR assessment**

Since the knowledge of pre-donation GFR is a key variable factoring into decision-making regarding selection of donors, this represents one of the relatively few scenarios in nephrology where accurate assessment of GFR is essential. The following methodologies are commonly used for measurement of GFR in donor candidates are:

1) **Estimated GFR (eGFR):** Several creatinine-based equations incorporate demographic and clinical variables, which serve as surrogates for the physiologic processes other than GFR that impact serum creatinine concentration e.g. creatinine generation and secretion. Of the commonly used creatinine-based equations (Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)), the 2009 CKD-EPI equation provides the least biased estimate at normal or mildly reduced GFR values, and has been recommended as the equation to calculate eGFR in living kidney donor candidates.$^{32}$ However, as illustrated in Figure 1, it lacks accuracy, especially in subjects with close to normal GFR. eGFR$_{Cr}$ differed from measured GFR (mGFR) by 30% or more of mGFR (a measure
frequently referred to as P$_{30}$) in 15.9% of the total population and in 11.7% of those with eGFR of at least 60 ml/min/1.73m$^2$.\textsuperscript{32} Therefore, in a candidate with mGFR of 100 ml/min/1.73m$^2$, there is a greater than 1 in 10 chance that this equation would estimate eGFR outside the 70 - 130 ml/min/1.73m$^2$ range. A study by Gaillard et al. underscored the concern that the 30% error in each direction is too wide in the context of living donor evaluation, in their retrospective study of 2733 donors. Accuracy with 10% (P$_{10}$) is a more relevant performance measure, and for eGFR$_{Cr}$ was only 50%.$^{33}$ In addition, eGFR$_{Cr}$ provides a slight underestimation, with median difference between mGFR and eGFR of 3.5 ml/min/1.73m$^2$.

Although less affected by muscle mass and diet, cystatin C by itself is not better at predicting GFR compared to creatinine.$^{34}$ The 2012 eGFR$_{Cr+CystatinC}$ equation that includes both these serum measurements fares better at estimating GFR than either alone, with only 2.3% of the eGFRs at or above 90 ml/min/1.73m$^2$ differing from mGFR by more than 30%, but still 16.2% differing by more than 20%. Similarly, only 5.3% of eGFRs between 60 and 89 ml/min/1.73m$^2$ differed from mGFR by more than 30% but 17.8% differed more than 20%.$^{35}$

While the average biases with these estimating equations are quite low, the departures from true GFR in individual cases can be quite significant. In this context, a few recent publications on prediction of mGFR based on eGFR are of interest. Huang et al suggested that if sufficiently high (or low), eGFR$_{Cr}$ alone, or sequential use of eGFR$_{Cr}$ followed by eGFR$_{Cr+CystatinC}$, could be used to confidently predict whether the mGFR was above (or below) thresholds commonly used for decision making.$^{36}$ The pretest probability and likelihood ratios used in this study were obtained from the NHANES and CKD-EPI study non-donor populations, and these computations were subsequently
validated in a study of living donors from France. The authors found that the calculator was highly sensitive in identifying all potential donors with an mGFR of <80 ml/min/1.73m²; however the specificity was low at 32%. In other words, the authors and several others have concluded that if the eGFR is high enough to confidently predict an adequate mGFR, mGFR or CrCl can be avoided, but due to low specificity, this threshold cannot be used to exclude candidates.

In addition, the use of a correction for race in the eGFR equation is highly controversial. Some hospitals across the US have already removed it from the equation; however this strategy further reduces the accuracy. Some others are reporting eGFR as a range, or associating the correction factor with “high muscle mass” but the performance of these strategies is untested. In an algorithm that relies on eGFR for decision making, removal of the correction factor for race from the eGFR equation could lead to inappropriate exclusion of some black candidates.

2) Measured GFR (mGFR): mGFR using an exogenous filtration marker is considered the gold standard for GFR assessment. Historically, inulin has been considered the perfect exogenous filtration markers as it is freely filtered in the glomerulus and is neither secreted nor reabsorbed in the kidney. However, it is used at very few centers worldwide and is not available in the US. Currently used methods for mGFR include chromium 51-labeled ethylenediaminetetraacetic (⁵¹Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol and iothalamate. The performance characteristics are generally better with renal clearance compared to plasma clearance methods. A systematic review showed that in reference to renal inulin clearance, the P₃₀ values for renal clearance of all four exogenous markers were greater than 90%. P₃₀ of plasma ⁵¹Cr-EDTA, iohexol and iothalamate measures are 82-86%, similar to that of eGFR₅₀ using the CKD-EPI
Due to ease of administration, plasma clearance methods are more popular than renal clearance methods, however, the accuracy is highly dependent on several factors including timing and number of samples drawn. In addition to the methodologic challenges, there are very few studies documenting normal mGFR values in healthy individuals from different age groups. Data on reference ranges for mGFR using inulin for different age groups from a Baltimore study published in 1950 is summarized in table 1. Notably, this study included only 9 to 12 adult males in each age group. A more recent study of 141 healthy kidney donors from the Mayo Clinic showed similar results. Various other studies provide demographic-specific reference ranges for iothalamate-mGFR obtained from healthy kidney donor populations.

3) Creatinine clearance (CrCl): Given the cost, resource and time intensiveness, and lack of availability of mGFR methods, many centers in the US rely on timed CrCl for assessment of GFR. This is in accordance with the OPTN policy on living donation which requires either mGFR or CrCl as part of evaluation of living donor candidates. Due to distal secretion of creatinine, CrCl overestimates GFR by 10-20%, creating a positive bias. One major limitation of this method is the susceptibility to error due to inaccurate urine collections. Traditionally, the accuracy of urine collection is assessed by comparing the measured creatinine excretion rate to the expected creatinine excretion rate of 20-25 mg/kg in men and 15 to 20 mg/kg in women. This does not account for several important determinants of endogenous creatinine generation, such as age and race. Ix et al. developed and validated two equations that provide a more refined assessment of expected creatinine excretion rate by incorporating age, race and serum phosphorous levels (if available) in addition to gender and body weight. In one study
from our group, we identified that using the equations developed by Ix et al, a substantially higher proportion of urine collections are accurate, including 42.6% which would be deemed inaccurate, mostly under-collections, using the conventional gender- and weight-based methodology. Additionally, using the average of eGFR\textsubscript{Cr} and mGFR assessed against urinary iothalamate clearance essentially eliminated the bias in measurement; however the accuracy as assessed by \( P_{10} \) and \( P_{30} \) measures was still modest. This study provided data on mGFR, eGFR\textsubscript{Cr}, CrCl and average of eGFR\textsubscript{Cr} and CrCl from a population of otherwise healthy living donor candidates, which can serve as a reference in clinical practice (Table 2).

The currently available major guidelines are summarized in Table 3. While they vary in their recommendation to use different methods, when it comes to mGFR, none provide any details on regarding choice of exogenous marker or choice of protocol use.

**GFR based donor selection criteria**

GFR declines with age. Using body surface area (BSA)-adjusted GFR values two standard deviations below mean for age as a threshold under which candidates are deemed ineligible appears to be a reasonable way to ensure that the actual donors have kidney function within a healthy range. In the example of the 25-year old man with GFR of 85 ml/min/1.73m\(^2\), that is below two standard deviations for age. The absence of hematuria, proteinuria and hypertension should not necessarily be considered benign and may be related to an unmeasured risk factor such as preterm birth, which is associated with lower nephron mass and consequent risk of CKD. These are variables not traditionally assessed during evaluation and relevant information may not be reliably available.

A potential barrier to implementation of a strategy based on two standard deviations below mean for age is that most guidelines do not provide method-specific GFR cut-offs. In fact, as discussed above, there are significant differences in performance
characteristics of GFR measured using exogenous filtration marker depending on the marker, methodology (plasma vs. renal clearance) and protocol used \textsuperscript{41}, and none of the major guidelines make a recommendation on the preferred technique, or provide method-specific criteria. Due to these limitations, two standard deviations below mean for age, measured by any methodology, should not be considered an absolute cut-off below which donation must be excluded, but rather as a way to assess whether the donor's kidney function is within the expected range for age or not.

Along this line of reasoning, all major guidelines, including those from the British Transplantation Society (BTS), the European Renal Best Practice (ERBP) and the Canadian Society of Transplantation (CST), incorporate age-specific criteria (Table 3). \textsuperscript{52-54} The one major exception is the 2017 KDIGO guideline that recommends use of fixed cut-offs of 60 ml/min/1.73m\textsuperscript{2} for exclusion, and of 90 ml/min/1.73m\textsuperscript{2} for acceptance. Between the two cut-offs, it recommends individual risk assessment based on a calculator that incorporates several demographic and clinical variables, including age. These thresholds conveniently align with the GFR criteria in the KDIGO CKD classification. \textsuperscript{55} However, the disconnect from age raises concerns that young individuals with low GFR for age may be allowed to proceed to donation based on their low ESKD risk estimates, which are likely to be underestimated, and that older individuals with GFR less than 90 ml/min/1.73m\textsuperscript{2} may be inappropriately considered suboptimal candidates for donation. An analysis of 2007 donors from France showed that one-third of them had GFR less than 90 ml/min/1.73m\textsuperscript{2}. As expected, donors with lower GFR were older. The lifetime renal reserve i.e. pre-donation GFR/ expected number of remaining years of life, as well as the magnitude of mGFR decrease was similar in the three groups based on the baseline GFR i.e. \textless 80, 80-89.9, and \textgreater=90 ml/min/1.73m\textsuperscript{2}. The authors concluded that the decision to accept candidates with GFR less than 90 ml/min/1.73m\textsuperscript{2} is closely tied to age and is reasonable for the older individuals. \textsuperscript{56} In another analysis, the same group of investigators found that use of fixed
GFR criteria led to substantial misclassification of donor candidates. These discussions parallel the literature on GFR decline with healthy aging in the general population, and the suggestion to amend CKD definitions to include age-specific criteria to allow for earlier diagnosis in the young, and prevent over-diagnosis and over-treatment in the elderly.

Assessment of donor kidney function using BSA-adjusted and age-adapted criteria is paramount to ensuring donor safety. At the same time, assessment of absolute GFR of the transplanted kidney is important from the recipient point of view. A GFR of 100 ml/min/1.73m$^2$ from a donor with BSA of 1.50m$^2$ represents an absolute GFR of 86.7 ml/min, which means approximately 43.4 ml/min will be available to the recipient after transplantation. The same GFR of 100 ml/min/1.73m$^2$ from a donor with BSA of 2.00m$^2$ represents an absolute GFR of 115.6 ml/min, which translates into 57.6 ml/min GFR for the recipient. In the recipient context, not surprisingly, higher absolute donor GFR is associated with better kidney function after transplantation. The commonly used cut-off of 80 ml/min likely comes from an older study evaluating outcomes in the recipient. However, in the case of elderly donor recipient candidates, absolute GFR<80 ml/min, if adequate from donor standpoint, may still yield adequate kidney function for the recipient, and better outcomes compared to dialysis.

**Conclusion**

Evaluation of each living donor candidate is highly intricate, and decision-making relies heavily on education and informed consent. Assessment of kidney health is central to the evaluation process. It incorporates several variables including GFR, proteinuria, hematuria, cysts, stones, and genetics, including family history of kidney disease and ApoL1 genotype in candidates of African ancestry. This review focuses purely on the GFR assessment. mGFR using an exogenous filtration marker provides the most accurate assessment of kidney function, although variation depending on the marker and technique used certainly exists. While the best of the
creatinine-based estimating equations, the accuracy of the CKD-EPI equation alone, especially with near-normal kidney function, is suboptimal. CrCl is known to overestimate GFR, and is highly dependent on the accuracy of timed urine specimens. Average of eGFR_{Cr} and CrCl, two measures of kidney function already available at most centers in the US, improves the overall bias but accuracy is still modest. Most guidelines recommend use of criteria calibrated for age, which is consistent with our understanding of kidney function decline with healthy aging. We agree with using GFR cut-offs 2 standard deviations below mean for age, below which donor candidates are excluded, as a reasonable measure to ensure adequate kidney function. The living donor kidney population is a unique population in which accurate assessment of kidney function is important, and in this context, the role of newer biomarkers, including but not limited to cystatin C, needs to be explored. Additionally, long-term data on not just ESKD risk but also CKD and cardiovascular outcomes in relation to various pre-donation risk factors is also important, especially as more and more medically complex candidates are proceeding to donation.
Disclosures

N. Garg reports to following: Honoraria: CareDx; Scientific Advisor or Membership: BMC Nephrology Associate Editor, Advisory Board for CareDx. E. Poggio reports the following: Consultancy Agreements: Renalytix; Honoraria: CareDx; Novartis, Reata. D. Mandelbrot reports the following: Scientific Advisor or Membership: CareDx, CSL Behring.

Funding

DAM is the recipient of an unrestricted research grant from the Virginia Lee Cook Foundation, which supported this study.

Author Contributions

N Garg: Conceptualization; Writing - original draft; Writing - review and editing

E Poggio: Writing - review and editing

D Mandelbrot: Conceptualization; Writing - review and editing
References


Table 1: Measured GFR using Inulin in Healthy Adult **Males** According to Age.\(^\text{29}\)

<table>
<thead>
<tr>
<th>Age</th>
<th>Insulin Clearance, mean ± SD (ml/min/1.73m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>123 ± 16</td>
</tr>
<tr>
<td>30-39</td>
<td>115 ± 11</td>
</tr>
<tr>
<td>40-49</td>
<td>121 ± 23</td>
</tr>
<tr>
<td>50-59</td>
<td>99 ± 15</td>
</tr>
<tr>
<td>60-69</td>
<td>96 ± 26</td>
</tr>
<tr>
<td>70-79</td>
<td>89 ± 20</td>
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<tr>
<td>80-89</td>
<td>65 ± 20</td>
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</table>
Table 2: mGFR, CrCl, eGFR and average of CrCl and mGFR, by age, adapted from reference 61

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>mGFR, mean ± SD</th>
<th>CrCl, mean ± SD</th>
<th>eGFR, mean ± SD</th>
<th>Average of CrCl and eGFR, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>769</td>
<td>103 ± 16</td>
<td>106 ± 18</td>
<td>98 ± 16</td>
<td>103 ± 16</td>
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<tr>
<td>18-30</td>
<td>133</td>
<td>109 ± 14</td>
<td>108 ± 19</td>
<td>110 ± 16</td>
<td>109 ± 16</td>
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<tr>
<td>31-40</td>
<td>209</td>
<td>107 ± 17</td>
<td>108 ± 20</td>
<td>103 ± 16</td>
<td>104 ± 18</td>
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<tr>
<td>41-50</td>
<td>246</td>
<td>103 ± 18</td>
<td>106 ± 18</td>
<td>96 ± 14</td>
<td>101 ± 15</td>
</tr>
<tr>
<td>&gt;50</td>
<td>181</td>
<td>94 ± 15</td>
<td>98 ± 16</td>
<td>89 ± 15</td>
<td>97 ± 17</td>
</tr>
<tr>
<td>Guideline</td>
<td>GFR assessment</td>
<td>GFR-based criteria</td>
<td></td>
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<td>------------------------------------------------</td>
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<tr>
<td>British Transplantation Society (2018)</td>
<td>mGFR in everyone after initial screening using eGFR</td>
<td>Provides age and gender-specific GFR criteria</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| KDIGO (2017)                                  | eGFR, followed by confirmation with mGFR, CrCl or eGFR                       | - Donor candidates with GFR ≥ 90 ml/min/m² should be considered acceptable, and those with GFR ≤ 60 ml/min/m² should be excluded.  
  - Decision to approve donor candidates with GFR 60-89 ml/min/m² should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold |
| OPTN (2021)                                   | mGFR or 24-hour CrCl                                                          | No specific recommendations provided                                                                                                                                                                 |
| Canadian KPD Protocol (2015)                  | eGFR on two separate occasions, followed by 24-hour CrCl on two separate occasions or mGFR | Provides age-specific criteria                                                                                                                                                                         |
| European Renal Best Practice (ERBP) (2013)    | eGFR; mGFR when more exact knowledge of GFR is needed or where is doubt regarding the accuracy of eGFR. | Recommends age-dependent GFR cutoffs, such that the GFR of the remaining kidney will be > 37.5 ml/min/1.73m² at the time the donor reaches age 80. |
| Caring for Australians and New Zealanders with Kidney Impairment (CARI) (2010) | eGFR, at least on two separate occasions or CrCl; mGFR if there is doubt regarding the accuracy or eGFR or CrCl | Recommends against accepting kidneys from donors with GFR<80ml/min/1.73m²                                                                                                                                |
| Amsterdam forum (2005)                         | eGFR or CrCl; mGFR may be used in cases of borderline GFR determination      | GFR<80ml/min or body-surface area-adjusted GFR below two standard deviations below normal based on age and gender generally preclude donation.  
  Additionally noted successful transplantation from some, usually elderly living donors with GFR as low as 65-70 ml/min, indicating a need for individualization in donors with GFR<80ml/min/1.73m². |