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Refining the Policy for Timing of Kidney Transplant Waitlist Qualification.

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Journal

Transplantation direct, 3(8)

ISSN

2373-8731

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Publication Date

2017-08-01

DOI

10.1097/txd.0000000000000706

Peer reviewed

OPEN

Refining the Policy for Timing of Kidney Transplant Waitlist Qualification

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Background. Earlier qualification for the kidney transplant waitlist expedites transplant and is therefore associated with improved outcomes. U.S. Organ Procurement and Transplantation Network policies state that “measured or calculated creatinine clearance or glomerular filtration rate less than or equal to 20 mL/min” triggers waitlist time accrual. The choice of qualification method is somewhat arbitrary, and the policy implies that decline in renal function is monotonic. **Methods.** (1) We used survival analysis to quantify temporal differences in waitlist qualification by applying 3 kidney-function-estimating equations (Cockcroft-Gault, Modification of Diet in Renal Disease study, Chronic Kidney Disease Epidemiology Collaboration) to serial creatinine measurements from 3 patient cohorts: 1 of waitlisted patients at a major U.S. academic center and 2 national, multicenter cohorts of chronic kidney disease patients (African American Study of Kidney Disease and Hypertension, Modification of Diet in Renal Disease). (2) Survival analysis assessed whether requiring patients to demonstrate persistently reduced renal function on 2 occasions at least 90 days apart would meaningfully change qualification order. **Results.** On average, time to waitlist qualification would be delayed on the order of 1 to 2 years by using calculated creatinine clearance (per the Cockcroft-Gault equation). Compared with current policy, requiring demonstration of persistently reduced renal function delayed qualification by 0.6 to 2.1 years and caused 40% to 50% of patients to switch the order in which they qualify by 6 months or more. **Conclusions.** The kidney transplantation policies should be revised, such that timing of waitlist qualification is more standardized. We suggest that mention of using calculated creatinine clearance be dropped from the Organ Procurement and Transplantation Network policy wording and the units to quantify kidney function be changed to mL/min per 1.73 m². Some consideration should be given to whether requiring persistently reduced renal function would better identify patients most likely to benefit from earlier waitlist qualification.

(*Transplantation Direct* 2017;3: e195; doi: 10.1097/TXD.0000000000000706. Published online 11 July, 2017.)

Received 25 April 2017. Revision requested 17 May 2017.

Accepted 6 June 2017.

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This study was supported by NIH-NIDDK grants T32DK007219 (BJL) and K24DK92291 (CYH). Dr. Delgado's work is supported by the Department of Veterans Affairs, Clinical Science Research and Development Program under Career Development Award 1K2CX000527-01A2; her contribution is the result of work supported with the resources and the use of facilities at the San Francisco VA Medical Center.

The authors declare no conflicts of interest.

The AASK and MDRD studies were conducted by the AASK and MDRD Investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The data from the AASK and MDRD studies reported here were supplied by the NIDDK Central Repositories. This article was not prepared in collaboration with investigators of the AASK and MDRD studies and does not necessarily reflect the opinions or views of the AASK or MDRD studies, the NIDDK Central Repositories, or the NIDDK.

B.J.L. contributed to study concept/design and analysis/interpretation of results, acquired data for the study, wrote first draft of article, revised article based on

edits by other coauthors. C.E.M. contributed to the study design and analysis/interpretation of results, critically revised the article. B.G. contributed to the analysis of results and critically revised the article. S.C. contributed to the study concept/design and interpretation of results, and critically revised the article. I.E.A. contributed to the analysis of results and critically revised the article. C.D. acquired data for the study, contributed to interpretation of results, and critically revised the article. C.H. contributed to study concept/design and analysis/interpretation of results, acquired data for the study, and critically revised the article.

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Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000706

Renal transplantation is the treatment of choice for end-stage renal disease. Compared with waitlisted, dialysis-dependent patients, transplanted patients have lower long-term mortality and increased life expectancy—by up to 10 years (depending on patient age and comorbidities)¹⁻⁴—and improved quality of life.⁵ Accounting for 11% of all deceased donor transplants in the United States from 2003 to 2012,⁶ preemptive kidney transplantation (ie, done before initiation of maintenance dialysis), is associated with an additional 26% to 31% reduction in mortality relative to non-preemptive transplant recipients, as well as lower rates of delayed graft function and graft failure.⁷

Observed mortality while accruing time on the transplant waitlist is high: recent estimates are 4% to 6% per year.⁸ Because timing of waitlist qualification affects the likelihood of preemptive transplantation, being placed on the waitlist earlier versus later has important clinical consequences. In addition, longer duration of pretransplant dialysis is associated with a progressive increase in patient death and graft loss posttransplant.⁹⁻¹² Yet over the last decade, 79% of deceased donor kidney transplant recipients were dialyzed for more than 2 years, and only 6% of deceased donor kidney transplant recipients were dialyzed for less than 1 year.⁶ Thus, even among non-preemptively transplanted patients, qualifying for the waitlist earlier reduces duration of pretransplant dialysis and may improve outcomes.

Therefore, factors that influence timing of waitlist qualification are important and deserve scrutiny. According to current U.S. Organ Procurement and Transplantation Network (OPTN) rules, patients with advanced chronic kidney disease (CKD) begin accruing time on the kidney transplant waitlist when renal function declines beyond a threshold defined as “measured or calculated creatinine clearance (CrCl) or glomerular filtration rate (GFR) less than or equal to 20 mL/min” (or when chronic maintenance dialysis is initiated).¹³

The Cockcroft-Gault equation estimates CrCl (in mL/min from serum creatinine, age, sex, and weight).¹⁴ Since 1999, the Cockcroft-Gault equation has been largely replaced in daily clinical practice (with the exception of medication dosing) by the Modification of Diet in Renal Disease (MDRD) study equation, which estimates GFR (in mL/min per 1.73 m² from serum creatinine, age, sex, and race).¹⁵ More recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (first published in 2009), which also estimates GFR (in mL/min per 1.73 m² using the same variables as the MDRD study equation), has been increasingly adopted in clinical practice.¹⁶

Prior studies have consistently shown that the Cockcroft-Gault equation overestimates renal function compared with the MDRD study and CKD-EPI equations in advanced CKD patients.¹⁷⁻²⁰ This fact is not surprising, because CrCl is systematically higher than GFR due to tubular secretion of creatinine.^{21,22} Therefore, using the Cockcroft-Gault equation may disadvantage patients for transplant waitlist qualification, but whether such a delay is clinically meaningful is unknown. Furthermore, by not requiring persistence of CrCl or estimated GFR (eGFR) being “ ≤ 20 mL/min” to begin waitlist time accrual, the current policy implicitly assumes that decline in renal function is monotonic. This concept had been a widely accepted paradigm of the natural history of renal disease progression, as formulated, for example, in a seminal article by Mitch et al²³ published in 1976 reporting that

for most patients, reciprocal serum-creatinine concentration declined linearly with time. However, recent studies demonstrate that estimated GFR trajectories among CKD patients are often not linear but instead vary between periods of rapid decline versus extended stability.²⁴

The goal of this study was to scrutinize the current OPTN policies for timing of kidney transplant waitlist qualification more closely, specifically for the approximately 20% of waitlisted patients who are listed preemptively (>57 000 patients from 2000 to 2009).²⁵ Given that calculated CrCl (by the Cockcroft-Gault equation) tends to overestimate renal function as compared with other creatinine-based renal-function equations (calculated GFR by the MDRD and CKD-EPI equations), we compared the equations' relative performance in 3 actual patient cohorts to assess whether the magnitude of difference in timing of waitlist qualification is clinically meaningful. We also examined the impact of requiring patients to demonstrate persistently low renal function to assess whether such a requirement may more appropriately prioritize which patients are in greater need for transplant. If choice of qualification method or incorrect assumption about the trajectory of renal function decline alters the timing of waitlist qualification by a large amount of time, the clinical implications are considerable for this patient population with high mortality risk.

MATERIALS AND METHODS

The Cockcroft-Gault, MDRD study, and CKD-EPI equations have been previously described (SDC, <http://links.lww.com/TXD/A49>).¹⁴⁻¹⁶ We assessed the impact of using different renal function equations to determine waitlist qualification by applying the equations to serial creatinine measurements from 3 actual patient cohorts.

University of California, San Francisco Cohort

We examined patients from the University of California, San Francisco (UCSF) General Nephrology faculty practice who were placed on the UCSF adult kidney transplant waiting list from July 1, 1999, to June 30, 2012, and who had laboratory data in the UCSF electronic medical record (n = 224). The following data were extracted for each patient: serial serum creatinine measurements and serial body weights from the earliest available date in the UCSF electronic medical record through September 7, 2013 (the date our data were extracted), height, sex, and race (African American, white, or other). To remove serum creatinine values associated with potential acute kidney injury, values for which there was another creatinine measured within 1 week were excluded.²⁶ Of 224 patients in the total UCSF cohort, 9 patients were excluded because of missing body weights (precluding calculation of CrCl by Cockcroft-Gault), leaving 215 patients for analysis.

African American Study of Kidney Disease and Hypertension Cohort

African American Study of Kidney Disease and Hypertension (AASK) was an NIH-sponsored randomized controlled study of African American patients (n = 1094) with hypertensive CKD (GFR, 20-65 mL/min per 1.73 m² as measured by [¹²⁵I] iothalamate clearance) who were initially enrolled into “intensive” or “standard” blood pressure control groups (and assigned 1 of 3 antihypertensive drug classes) and

subsequently followed as a cohort.²⁷⁻²⁹ Because antihypertensive medication initiation at the time of enrollment caused acute changes in GFR,²⁷ only serial creatinine measurements during the chronic slope phase of the study were analyzed. Per the AASK protocol, creatinine was checked at 3 and 6 months postrandomization, and followed up every 6 months thereafter.²⁷ Of the 1094 patients in the AASK cohort, only 1059 had visits at 3 months postrandomization or later; 2 patients were subsequently excluded because of missing body weights; therefore, 1057 patients remained for analysis.

Modification of Diet in Renal Disease Cohort

The MDRD study was an NIH-sponsored randomized controlled study that evaluated the effect of dietary protein restriction and strict blood pressure control on progression of renal disease in 840 CKD patients (GFR <70 mL/min per 1.73 m² as measured by [¹²⁵I] iothalamate clearance).^{30,31} Similar to the AASK cohort, to avoid acute effects of antihypertensive medication initiation, we only examined serial creatinine measurements from the chronic slope phase of the study. Per the MDRD study protocol, creatinine was checked at 4 months postrandomization and then every 4 months thereafter.³¹ Seventeen patients did not have any serum creatinine measurements and were excluded from analysis, leaving 823 patients for analysis.

Statistical Analysis

For every patient in the 3 study populations, we applied the 3 creatinine-based equations (Cockcroft-Gault, MDRD study, and CKD-EPI) to calculate renal function (CrCl for Cockcroft-Gault, eGFR for MDRD study and CKD-EPI) for each creatinine measurement. The body weight used for the Cockcroft-Gault equation was the last weight measured on or before the date of creatinine measurement (ie, last value carried forward if not measured concurrently). For the few creatinine measurements where there were no prior or concurrent weights recorded, the first recorded weight was used. The date at which each patient's CrCl or eGFR fell to ≤ 20 mL/min ≤ 20 or 20 mL/min per 1.73 m² was determined for each equation. Although CrCl and eGFR and use different units, direct comparison is what is used under current OPTN policy.

Time-to-Waitlist-Qualification Analysis

We used survival analysis to quantify the differences in median time to waitlist qualification (ie, median time to ≤ 20) by equation for each cohort. Time to waitlist qualification was defined for the UCSF cohort as time from first available serum creatinine record for each patient in the UCSF electronic medical record. Time to waitlist qualification was defined for the AASK and MDRD cohorts as time from the first follow-up visit during the chronic-slope periods postrandomization. Patients who were not observed to qualify by 1 of the equations were censored for the analysis limited to that equation. Participants censored by all 3 equations were excluded from this analysis since the research question is not relevant to those persons (this situation occurred in 19 of 215 patients for UCSF cohort, 787 of 1057 patients for AASK cohort, 406 of 823 patients for MDRD cohort). That is, the purpose of our analysis was to compare *differences* between equations; patients who did not qualify by any equation would not contribute any information to this analysis, as the

outcome is not "survival time to waitlist qualification" in and of itself. For each cohort, Kaplan-Meier curves for time to waitlist qualification were constructed for each equation. The Kaplan-Meier method estimates cumulative incidence of an event (in this case, waitlist qualification) by splitting follow-up time into discrete periods and dividing the number of events by the number of at-risk individuals for each period.³² A Kaplan-Meier curve is a step function plotting cumulative incidence over follow-up time. Median time to event (point at which the KM curve crossed the 50% survival point) was then derived for each equation in each cohort (3 equations applied to 3 cohorts yielded 9 median times to event). Within each cohort, to compare median time to waitlist qualification across eGFR equations, we used bootstrapping³³ to generate *P* values and confidence intervals.

Persistently Low-Function Analysis

To assess whether requiring patients to demonstrate persistently low renal function would meaningfully change waitlist qualification, we compared time to qualification as defined by 2 different rules: (1) at first CKD-EPI-derived eGFR of 20 mL/min per 1.73 m² or less, regardless of subsequent measurements (current paradigm) and (2) at second CKD-EPI-derived eGFR of 20 mL/min per 1.73 m² or less given a prior eGFR of 20 mL/min per 1.73 m² or less at least 3 months before (akin to the definition of CKD³⁴). The start times, censoring rules, and patient cohorts were the same as described above. Kaplan-Meier curves for time to waitlist qualification were constructed for each cohort. To compare median time with waitlist qualification across rules for waitlisting, we used bootstrapping³³ to generate *P* values and confidence intervals. Within each cohort, we identified all instances where 2 patients switched the order in which they qualified for the waitlist by a magnitude of 6 months or more; the number of unique patients affected by these switches was noted for each cohort.

The study was conducted in accordance with the Declarations of Helsinki and Istanbul. The study design and methods were approved by the UCSF Institutional Review Board (IRB 12-10371), which waived the need for informed consent because the study involved no more than minimal risk to subjects. Analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS

Cohort Characteristics

Table 1 shows selected characteristics for the 3 cohorts studied. The AASK and MDRD cohorts have been described in detail previously.^{27,30} Of note, all patients in AASK were black, whereas the UCSF and MDRD cohorts were predominantly nonblack. For the UCSF cohort, the median MDRD study equation eGFR for the first creatinine measurement in the UCSF electronic medical record was 28.8 (interquartile range [IQR], 14.3-57.5) mL/min per 1.73 m². (The MDRD study equation was what was used by the UCSF Medical Center lab at the time the measurements were collected.) The median eGFRs (calculated using the MDRD study equation) at time of enrollment were 42.3 mL/min per 1.73 m² (IQR, 31.3-52.1 mL/min per 1.73 m²) for AASK and 32.7

TABLE 1.
Cohort characteristics

	UCSF (n = 224)	AASK ^a (n = 1094)	MDRD ^a (n = 840)
Mean age, y	47.0	54.6	51.5
Male sex, %	58.7	61.1	60.5
Race, %			
Nonblack	84.8	0.0	92.1
Black	15.2	100.0	7.9
Mean BMI, kg/m ²	27.4	30.6	27.1
Diagnosis of hypertension, %	80.9	100.0	86.2
Mean blood pressure, mm Hg			
Systolic	137.7	150.3	134.4
Diastolic	77.4	95.5	81.9
Diagnosis of diabetes mellitus, %	30.0	0.0	5.1 ^b
Median (IQR) serum Cr, mg/dL	2.1 (1.3-4.4)	1.8 (1.5-2.4)	2.1 (1.6-2.8)
Median (IQR) eGFR ^c , mL/min per 1.73 m ²	28.8 (14.3-57.5)	42.3 (31.3-52.1)	32.7 (24.1-43.1)

^a AASK and MDRD data from entire baseline cohort at time of randomization.

^b Noninsulin-dependent diabetic nephropathy; excluded insulin-dependent diabetes.

^c Calculated using MDRD study equation.

mL/min per 1.73 m² (IQR, 24.1-43.1 mL/min per 1.73 m²) for the MDRD cohort.

Time-to-Waitlist Qualification Analysis

Among patients for whom at least 1 equation yielded an observed qualification date (UCSF, n = 196; AASK, n = 270; MDRD, n = 417), the magnitudes of time difference between qualification dates generated by survival analyses are shown in Table 2. The MDRD study and CKD-EPI equations gave similar waitlist qualification dates, but Cockcroft-Gault consistently disadvantaged patients. The difference in median time to waitlist qualification (not median time on the waitlist) for the Cockcroft-Gault equation as compared with the MDRD study equation was 715.5 days (1.96 years) *later* for the UCSF cohort, 711 days (1.95 years) *later* for the AASK cohort, and 466 days (1.28 years) *later* for the MDRD cohort. In other words, on average, time to waitlist qualification would be delayed on the order of 1 to 2 years by using calculated CrCl rather than calculated GFR. Between the MDRD study equation and CKD-EPI equation, on the other hand, differences in median times to waitlist qualification were all less than 1 month for all cohorts.

Persistently Low-Function Analysis

Survival analyses assessing timing of waitlist qualification under an alternative rule requiring patients to demonstrate eGFR ≤20 mL/min per 1.73 m² on 2 occurrences at least

3 months apart as compared with current policies are shown in Table 3. Using the CKD-EPI equation, requiring demonstration of persistently low renal function delayed median time to waitlist qualification by 770 days (2.1 years), 539 days (1.5 years), and 234 days (0.6 years) in the UCSF, AASK, and MDRD cohorts, respectively. Furthermore, changing to rule 2 delayed waitlist qualification by at least 6 months in a large majority of the patients: 181 (92.3%) of 196 UCSF cohort patients, 247 (91.5%) of 270 AASK cohort patients, and 366 (87.8%) of 417 MDRD cohort patients. In addition, implementing such an alternative rule caused a significant number of patients to switch the order in which they would qualify. 53.1% of UCSF cohort patients switched positions with at least 1 other patient by 6 months or more; the alternative rule similarly affected 47.8% of the AASK cohort and 40.5% of the MDRD cohort.

DISCUSSION

The U.S. Department of Health and Human Services' "Final Rule" establishing a regulatory framework for the OPTN states that the goal of organ allocation is to balance "utility and equity" using "objective and measurable medical criteria" for individuals to be added to organ transplant waiting lists.³⁵ This study suggests that there is room for improvement in how we determine when patients should qualify for the kidney transplant waitlist.

We show that choice of method to determine waitlist eligibility led to clinically significant differences in qualification time when applied to 3 diverse patient cohorts: a cohort of waitlisted patients at 1 major U.S. academic center and 2 national, multicenter study cohorts of CKD patients, 1 with only African Americans, and the other with predominantly whites. On average, calculated CrCl (by the Cockcroft-Gault equation) disadvantaged patients as compared with calculated GFR (by the MDRD study and CKD-EPI equations) on the order of 1 to 2 years, which is notable given median wait times of 1.4 to 3.3 years (depending on geographic location) for deceased donor transplant in the United States.³⁶

Prior papers in academic journals have shown that Cockcroft-Gault-calculated CrCl tends to overestimate renal function as compared with MDRD study- or CKD-EPI-calculated eGFR.¹⁷⁻²⁰ We have illustrated these mathematical relationships further based on computational analysis as described in **Methods**, **SDC**, <http://links.lww.com/TXD/A49>.

Until recently, the United Network for Organ Sharing policy on kidney transplant allocation defined the threshold for waitlist eligibility as "measured (actual urinary collection) CrCl level or calculated GFR (Cockcroft-Gault or other reliable formula) less than or equal to 20 mL/min."³⁷ Our results support the decision to remove explicit mention of the

TABLE 2.
Median time (95% CI) in years to waitlist qualification by equation

	Cockcroft-Gault	MDRD	CKD-EPI	Difference: Cockcroft-Gault vs MDRD	Difference: MDRD vs CKD-EPI
UCSF cohort	2.93 (1.50-4.32)	0.97 (0.24-2.29)	1.04 (0.31-2.38)	1.96 (0.87, 2.83), P < 0.0001	-0.07 (-0.50 to 0.17), P = 0.63
AASK cohort	3.20 (2.72-3.70)	1.25 (0.83-1.70)	1.23 (0.80-1.42)	1.95 (1.51-2.43), P < 0.0001	0.02 (-0.06 to 0.36), P = 0.39
MDRD cohort	1.58 (1.34-2.01)	0.30 (0, 0.35)	0.33 (0, 0.37)	1.28 (1.04-1.69), P < 0.0001	-0.03 (-0.33 to 0.00), P = 0.18

Time to waitlist qualification was defined for the UCSF cohort as time from first available serum creatinine record for each patient and for the AASK and MDRD cohorts as time from first follow-up visit after 3 months and 4 months postrandomization, respectively.

^a Censored.

TABLE 3.
Effect of requiring persistently low renal function

	Difference in medians (95% CI) between rule 1 and rule 2, y	Percentage of patients delayed by ≥ 6 mo	Percentage of patients involved with ≥ 1 switch (≥ 6 mo) in qualification order
UCSF cohort	2.1 (1.2-3.2) ^a	92.3%	53.1%
AASK cohort	1.5 (1.0-1.7) ^a	91.5%	47.8%
MDRD cohort	0.6 (0.4-0.7) ^a	87.8%	40.5%

Time to waitlist qualification was defined as in Table 2. eGFR was calculated using the CKD-EPI equation. Rule 1 reflects current policy (qualification after a single eGFR ≤ 20 mL/min per 1.73 m²). Rule 2 requires patients to demonstrate eGFR ≤ 20 mL/min per 1.73 m² on 2 occurrences at least 3 months apart.

^a $P < 0.0001$.

Cockcroft-Gault equation as was done in the most recent policy revision in April 2017, thus removing any possible appearance of implicit endorsement of this equation over others. However, current policy still mentions calculated CrCl as a method for determining eligibility, and the Cockcroft-Gault is the only equation in common use for this purpose. We therefore suggest that calculated CrCl should be eliminated from the rules. This reasoning is especially compelling since relatively few transplant centers are likely still using calculated CrCl after widespread adoption of automatic reporting of eGFR (by the MDRD study or CKD-EPI equations) with serum creatinine measurements.

More broadly speaking, current policy wording is problematic in its apparent premise that CrCl and GFR are interchangeable. Although we do not have an actual data set in which CKD patients underwent direct measures of CrCl and GFR repeatedly over time, it is likely that using measured CrCl versus measured GFR will also disadvantage patients to a similar degree (ie, 1-2 years) as our analyses of using calculated CrCl versus calculated GFR, because it is well known that CrCl is higher than GFR due to tubular secretion of CrCl.

Further potential improvements in the policy language may include eliminating mischaracterization of eGFR as being expressed in “mL/min.” In this context of discussing units of measurements, perhaps it should be made explicit that if CrCl were to be measured, the output should be expressed in mL/min per 1.73 m² (adjusted for body surface area), just like for GFR, to reduce inconsistency and enhance fairness.

Notably, these issues are also relevant to other areas in transplant medicine. For example, the United Network for Organ Sharing Board recently approved a new simultaneous liver-kidney policy which includes the following language: “Candidates who are 18 years or older when registered on the liver waiting list are eligible to receive both a liver and a kidney from the same deceased donor when the candidate is registered on the waiting list for both organs and meets at least 1 of the criteria according to Table 9–11 below... At the time of registration on the kidney waiting list, that the candidate’s most recent measured or calculated creatinine clearance (CrCl) or GFR is less than or equal to 30 mL/min.”³⁸

In addition to stimulating these types of discussions, we hope that our analyses will provoke further examination regarding the underlying disease-model assumption behind the OPTN’s rule qualifying patients based on a single reading that is not obviously due to acute kidney injury. Because GFR decline is not linear and monotonic,²⁴ requiring only a single estimate of low renal function among non-dialysis-dependent patients may be suboptimal for identifying when patients should qualify for the waitlist. In the cohorts studied,

requiring patients to demonstrate CKD-EPI-derived eGFR of 20 mL/min per 1.73 m² or less on 2 occurrences at least 3 months apart delayed median time to qualification on the order of 0.6 to 2.1 years, and a large majority (85-95%) of each cohort was delayed by 6 months or more. More important clinically, requiring demonstration of persistently low renal function caused a substantial number (approximately 40-50%) of patients to switch the order in which they qualify by 6 months or more. Although requiring demonstration of low renal function on multiple measurements may not benefit an individual patient, at a societal level, appropriately prioritizing patients with sustained low renal function for deceased donor transplant would better manage the imbalance between kidney supply and demand. The large number of patients who switched the order in which they qualify suggests that there is room for improvement regarding the order in which patients should be added to the waitlist.

A strength of this study is the use of 3 different cohorts. The UCSF cohort, although small (most waitlisted patients at UCSF are not from the faculty practice), demonstrates the applicability of our findings to patients who were placed on the transplant waitlist locally. Because these patients were not enrolled in a structured research study, the frequency of serum creatinine checks mimics how patients are monitored before qualifying for the transplant waitlist in actual clinical practice. Our use of the other 2 multicenter research cohorts with different racial compositions supports the generalizability of our results to the broader population.

Limitations of our study include that some serum creatinine measurements were obtained before the era of more uniform creatinine calibration to isotope dilution mass spectrometry-traceable references. However, because each creatinine measurement was used for each equation within the same person, the lack of standardization for older creatinine measurements should not have significantly biased our results, which focus on within-person comparisons of waitlist-qualification timing. The start date of our analyses is somewhat arbitrary—but the emphasis is on the differences in the median times to qualification and not the median times themselves. We were limited in our ability to perform subgroup analyses by demographics because the UCSF cohort was relatively small and the AASK and MDRD cohorts were largely racially homogeneous (all African-American for AASK, predominantly white for MDRD). However, our computational analysis (Figure S1, SDC, <http://links.lww.com/TXD/A49>) suggests that both black and nonblack races and both men and women were similarly affected. Finally, we were not able to evaluate every possible way to begin accruing time on the waitlist because we did not have directly measured GFR (eg, assessed by exogenously

injected filtration markers) or CrCl (eg, determined by 24-hour urine collection).

To conclude, we do acknowledge that there are very legitimate reasons for the OPTN not to dictate specific medical practice and that programs should have some latitude on defining their best measure for kidney function. However, we suggest that the OPTN policy language be changed to “measured CrCl or estimated GFR less than or equal to 20 mL/min per 1.73 m²” rather than “measured or calculated CrCl or GFR less than or equal to 20 mL/min.” In other words, we suggest that calculated CrCl be dropped because it disadvantages patients, and most centers do not use that method anyway. We also suggest that measured CrCl be quantified as mL/min per 1.73 m² rather than mL/min to promote fair comparison to GFR values. Finally, we believe that some consideration should be given to whether requiring persistently reduced renal function will identify patients most likely to benefit from earlier qualification for the kidney transplant waitlist and hence expedited kidney transplant.

ACKNOWLEDGMENTS

The authors thank Peter P. Reese, MD, MSCE, for helpful discussions, and Joseph J. Lee, PhD, for statistical discussions.

REFERENCES

- Port FK, Wolfe RA, Mauger EA, et al. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. *JAMA*. 1993; 270:1339–1343.
- Rabbat CG, Thorpe KE, Russell JD, et al. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in Ontario, Canada. *J Am Soc Nephrol*. 2000;11:917–922.
- Schnuelle P, Lorenz D, Trede M, et al. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. *J Am Soc Nephrol*. 1998;9:2135–2141.
- Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341:1725–1730.
- Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int*. 1996;50:235–242.
- Jay CL, Dean PG, Helmick RA, et al. Reassessing preemptive kidney transplantation in the United States: are we making progress? *Transplantation*. 2016;100:1120–1127.
- Kasiske BL, Snyder JJ, Matas AJ, et al. Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol*. 2002;13: 1358–1364.
- Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2013 Annual Data Report: kidney. *Am J Transplant*. 2015;15(Suppl 2):1–34.
- Cosio FG, Almir A, Yim S, et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. *Kidney Int*. 1998;53:767–772.
- Goldfarb-Rumyantzev A, Hurdle JF, Scandling J, et al. Duration of end-stage renal disease and kidney transplant outcome. *Nephrol Dial Transplant*. 2005;20:167–175.
- Helanterä I, Salmela K, Källönen L, et al. Pretransplant dialysis duration and risk of death after kidney transplantation in the current era. *Transplantation*. 2014;98:458–464.
- Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. *Kidney Int*. 2000;58:1311–1317.
- Organ Procurement and Transplantation Network. Policy 8.3: Kidney Allocation Points. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_08. Updated July 1 2017.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
- Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; 130:461–470.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
- Froissart M, Rossert J, Jacquot C, et al. Predictive performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol*. 2005;16:763–773.
- Evans M, van Stralen KJ, Schon S, et al. Glomerular filtration rate-estimating equations for patients with advanced chronic kidney disease. *Nephrol Dial Transplant*. 2013;28:2518–2526.
- Poggio ED, Wang X, Greene T, et al. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol*. 2005; 16:459–466.
- Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*. 2010;363:609–619.
- Bauer JH, Brooks CS, Burch RN. Clinical appraisal of creatinine clearance as a measurement of glomerular filtration rate. *Am J Kidney Dis*. 1982;2: 337–346.
- Shemesh O, Golbetz H, Kriss JP, et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 1985;28:830–838.
- Mitch WE, Walser M, Buffington GA, et al. A simple method of estimating progression of chronic renal failure. *Lancet*. 1976;2:1326–1328.
- Li L, Astor BC, Lewis J, et al. Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis*. 2012;59:504–512.
- Fissell RB, Srinivas T, Fatica R, et al. Preemptive renal transplant candidate survival, access to care, and renal function at listing. *Nephrol Dial Transplant*. 2012;27:3321–3329.
- Hsu CY, Bates DW, Kuperman GJ, et al. Relationship between hematocrit and renal function in men and women. *Kidney Int*. 2001;59:725–731.
- Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285:2719–2728.
- Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363: 918–929.
- Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421–2431.
- Greene T, Bourgoignie JJ, Habwe V, et al. Baseline characteristics in the Modification of Diet in Renal Disease study. *J Am Soc Nephrol*. 1993;4: 1221–1236.
- Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994; 330:877–884.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
- Vittinghoff E, Glidden DV, Shiboski SC, et al. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. 2nd ed. New York, NY: Springer; 2012.
- Levin ASP, Bilous RW, Coresh J, et al. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl*. 2013;3:19–62.
- US Government Publishing Office. §121.8 Allocation of organs. https://www.ecfr.gov/cgi-bin/text-idx?SID=bb60e0a7222f4086a88c31211cac77d1&mc=true&node=pt42.1.121&rgn=div5#se42.1.121_18. Updated June 8, 2017.
- Davis AE, Mehrotra S, McElroy LM, et al. The extent and predictors of waiting time geographic disparity in kidney transplantation in the United States. *Transplantation*. 2014;97:1049–1057.
- Organ Procurement and Transplantation Network. Policy 8.4: Waiting Time. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_08. Updated July 1 2017. Accessed July 12 2015.
- Organ Procurement and Transplantation Network. 9.7.B Liver-Kidney Candidate Eligibility for Candidates 18 Years or Older. https://optn.transplant.hrsa.gov/media/1888/kidney_policynotice_slk_201606.pdf. Published January 25 2016.