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Personal Viewpoint

Estimating Risks of *De Novo* Kidney Diseases After Living Kidney Donation

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***De novo* postdonation renal diseases, such as glomerulonephritis or diabetic nephropathy, are infrequent and distinct from the loss of GFR at donation that all living kidney donors experience. Medical findings that increase risks of disease (e.g. microscopic hematuria, borderline hemoglobin A1C) often prompt donor refusal by centers. These risk factors are part of more comprehensive risks of low GFR and end-stage renal disease (ESRD) from kidney diseases in the general population that are equally relevant. Such data profile the ages of onset, rates of progression, prevalence and severity of loss of GFR from generically characterized kidney diseases. Kidney diseases typically begin in middle age and take decades to reach ESRD, at a median age of 64. Diabetes produces about half of yearly ESRD and even more lifetime near-ESRD. Such data predict that (1) 10- to 15-year studies will not capture the lifetime risks of postdonation ESRD; (2) normal young donors are at demonstrably higher risk than normal older candidates; (3) low-normal predonation GFRs become risk factors for ESRD when kidney diseases arise and (4) donor nephrectomy always increases individual risk. Such population-based risk data apply to all donor candidates and should be used to make acceptance standards and counseling more uniform and defensible.**

Keywords: Donor outcomes, donor risk, donor screening

Abbreviations: ESRD, end-stage renal disease; UNOS, United Network for Organ Sharing

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Introduction

Transplant centers often refuse candidates for living kidney donation with hematuria or increased diabetic risk because they are at increased risk of glomerulonephritis or diabetes, which may cause very low GFR or end-stage renal disease (ESRD) in the donor's lifetime (1–5). The risks of these diseases contribute to more comprehensive risks in the general population for low GFRs and ESRD from all kidney diseases. Such epidemiological data may not predict specific renal diagnoses like IgA nephropathy, but they profile outcomes that are meant to be addressed by the donor medical examination: the lifetime probability, ages of onset, rates of progression and severity of losses of GFR from kidney diseases that may arise after kidney donation. The health risks from loss of GFR at nephrectomy itself appear minimal (2,6). The further loss of GFR in the unfortunate few who develop *de novo* postdonation kidney diseases is a separate issue. This analysis presents renal epidemiological data in the general population, defends their relevance to donor risks, estimates risks and reinterprets current donor follow-up studies, suggests modifications to make donor exclusion standards more uniform and discusses the ethics involved. It suggests that the individual ''renal risks'' of currently acceptable donor candidates are markedly heterogeneous and sometimes unacceptably high.

Kidney Diseases in the US Population

In the general population, the lifetime probability of ESRD is about 3% for non-Blacks and fully 7–8% for Blacks (7–10). As presented in Table 1, only about 10% occurs by age 45; half occurs after age 64. Relatively more ESRD appears at younger ages in Blacks and is mostly nondiabetic (8). Just as only a fraction of individuals with hematuria will develop renal disease, only a fraction of most renal diseases will reach ESRD in a lifetime. Most will cause lesser decreases in GFR, beginning in middle age. As shown in Figure 1, the prevalence of a GFR < 30 mL/min/1.73 m^2 increases over sevenfold from ages 40 to 50, and increases again almost threefold to about 1% of the population by age 60 (7,8).

Type II diabetes causes almost half of all acquired, adult-onset ESRD (10) and causes even more chronic kidney disease, about 25% of which may go unrecognized as diabetic (11). The overall lifetime risk of self-reported diabetes in the general population is about 33% in males

Table 1: New-onset ESRD in the United States in 2011

Yearly incidence of ESRD by age, race and diagnosis	
Age	
0–19	1296
20–44	13 407
45–64	43 663
65–74	27 029
75+	29 936
Total	114 032 (28% Black)
Diagnosis	
Diabetes	50 335
Hypertension	32 510
Glomerulonephritis	7290
Cystic	2590
Urologic	1539
Other/missing	14 771/5027

Over 10 000 cases/year are attributed to all types of glomerulonephritis. The glomerulonephritides may also cause substantially more end-stage renal disease (ESRD) that is misattributed to primary hypertension (see text). From USRDS (10). Small inconsistencies arise from missing data.

and 39% in females, and is increased to about 50% in Hispanic or Black women. Only 2–3% of lifetime risk is manifest from ages 30 to 40 (1.2 million cases). At age 60 more than half of lifetime risk remains (12). Macroalbuminuria develops after about 15 years of diabetes, when GFR begins to be lost at about 40 mL/min/1.73 m^2 per decade (Table 2). About 30% of those who live long enough will develop ESRD (7,13,14). Over the last three decades, the prevalence of all stages of diabetic kidney disease has paralleled the increase in diabetes in the general population, despite advances in diabetic care (15,16). Aggressive nondiabetic diseases (with GFR < 60 mL/min/1.73 m^2, macroalbuminuria and hypertension) lose GFR at 39 mL/min/1.73 m^2 per decade, a rate similar to diabetic nephropathy (7). ESRD may be misattributed to primary hypertension in as many as 90% of Whites and may often be caused instead by various end-stage glomerulonephritides (17–19).

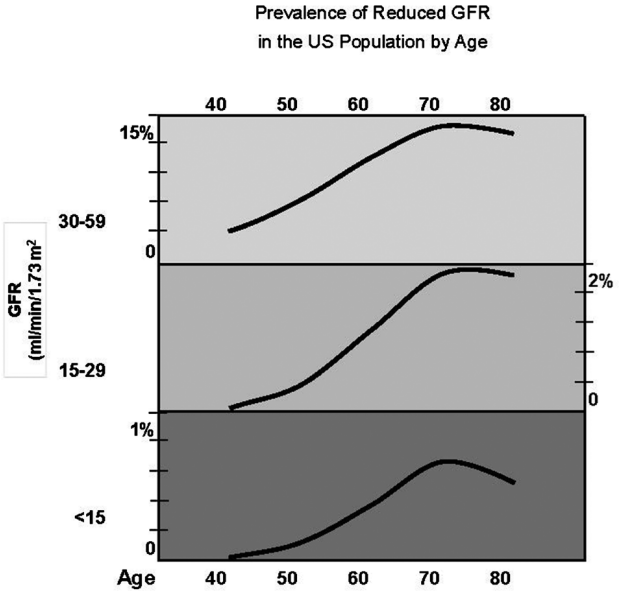

Figure 1: The progressively increasing prevalence of kidney diseases in the general population in middle age. Note different GFR scales for each group, as milder disease is more common than severe disease. Adapted from Hoerger et al (7).

Low-Normal GFRs Increase Risk When Kidney Diseases Develop

The general population consists of individuals with a spectrum of normal GFRs (20), at risk of developing renal diseases of varying severities at varying ages, with an average lifetime risk for ESRD of about 3%. As shown in Figure 2, when disease-driven losses of GFR begin, the baseline, ''premorbid'' GFR and the rate of disease-driven loss will determine when ESRD occurs (5,21). Disease-driven low GFRs are far more common than is ESRD in the general population, where the lifetime risk for a GFR < 30 mL/min/1.73 m^2 is 7–10%, or two to three times that of ESRD (7,8). All else equal, when ill-fated individuals with premorbid GFRs that were at the population average reach a lifetime GFR of <30 mL/min/1.73 m^2, those who had premorbid GFRs that were 30 mL/min/1.73 m^2 lower than average will have minimal kidney function and will have reached ESRD. The lower premorbid GFR increases the lifetime ESRD risk to more than two to three times that of the mean population value. Importantly, to keep overall risk the same, a GFR that is 30 mL/min/1.73 m^2 above the

Table 2: Average rates of loss of GFR in the general population for generically grouped renal diseases, with years to lose 40 mL/min/1.73 m^2 of GFR, which approximates the GFR often lost at kidney donation

Rates of loss of kidney function by disease category in the US population		
Disease	Loss of GFR[1] per decade	Years to lose 40 mL of GFR[1]
Normal	−06.5	61.5
Hypertension (HT)		
GFR[1] > 60	−7.2	57
GFR[1] < 60	−14	29
HT + macroalbuminuria		
GFR[1] > 60	−7.8	51
GFR[1] < 60	−39	10
Diabetes + macroalbuminuria		
GFR[1] > 60	−41	10
GFR[1] < 60	−52	7.7

Primary hypertension (without macroalbuminuria) causes relatively small losses. Adapted from Hoerger et al (7).
[1]GFR in mL/min/1.73 m^2.

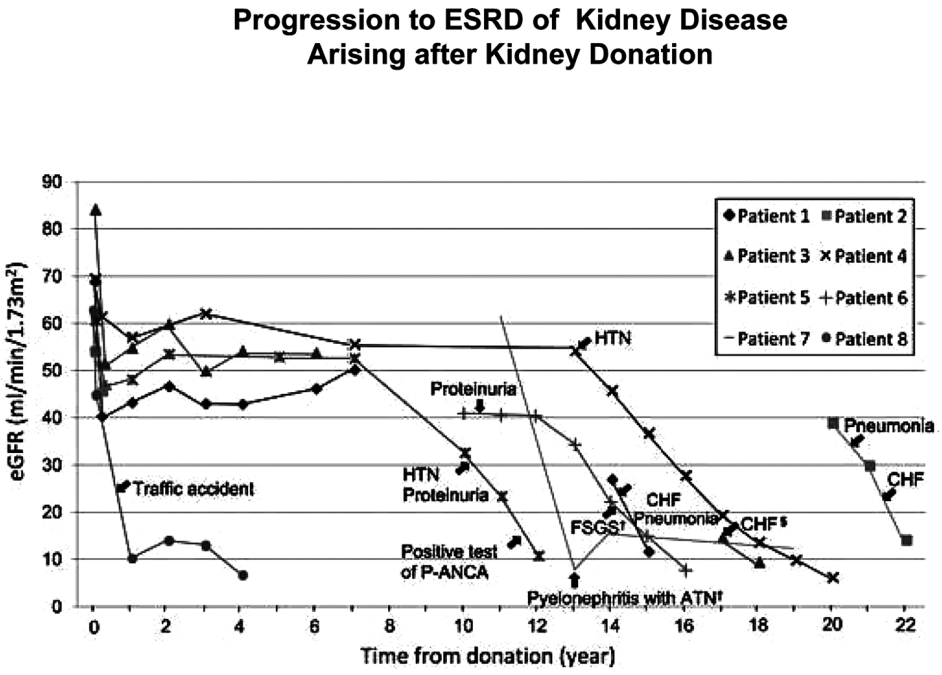

Figure 2: Eight cases of new-onset end-stage renal disease (ESRD) after donation. The time interval to ESRD can be seen to be a function ultimately of predonation GFR and the rate of loss of GFR from new-onset kidney disease. These examples would be among the earliest that would be predicted from population data. From Kido et al (5), with permission.

population mean will reciprocally lower the average lifetime ESRD risk to 1/2–1/3 of the group mean of about 3%. Predonation GFRs of 90–150 mL/min/1.73 m^2 would be reduced by about a third at donation, sacrificing about 30–50 mL/min/1.73 m^2, respectively. Therefore, sacrificing just 30 mL/min/1.73 m^2 of GFR would increase postdonation risk for ESRD twofold to threefold. Greater losses at donation would increase relative risk more.

Table 2 provides the average rates of losses of GFR in the general population from primary hypertension, diabetic nephropathy and proteinuric nondiabetic renal diseases. All else equal, if donation sacrificed 40 cc/min/1.73 m^2, postdonation diabetic nephropathy or other diseases that lost 40 mL/min/1.73 m^2 per decade would reach ESRD 10 years earlier because of donation. For less rapidly progressing disease, donation would make ESRD even more premature. Donation would similarly increase the lifetime chances of very low GFRs and earlier death (22). A possible effect of such premature mortality to reduce lifetime ESRD risk or time on dialysis attributable to donation is not formally addressed in this analysis but is an additional donor risk.

Why Older Candidates Are at Less Renal Risk

Because the prevalence of diabetes and overt renal diseases in the general population increases markedly with age, many ill-fated 55-year-old donor candidates will be excluded because they already have diabetes, overt diabetic nephropathy, nondiabetic kidney diseases or ESRD. Far fewer 25-year-old candidates will be excluded, as they will be four decades from the median onset of ESRD in the general population. Diabetes is uncommon before age 30 (12), and current donor exclusion protocols have not reduced postdonation diabetic risk (6,23,24). The risks of normal young candidates are closest to those of unselected individuals in the general population.

Centers currently exclude young and old candidates alike with GFRs below about 80 mL/min/1.73 m^2 (1–4,6). As shown in Figure 3, because GFRs normally decline with age (7,20), this threshold excludes about 30% of 55-year-old candidates with low-normal GFRs, that is those who have the least renal reserve and are at highest risk for ESRD when postdonation kidney diseases begin. But due to their higher normal range, only about 5% of 25-year-olds are excluded for a GFR < 80 mL/min/1.73 m^2. This is another way that current selection practices only remove the highest-risk older candidates.

Re-Interpreting Postdonation Follow-Up Studies

The ostensibly benign results of current postdonation follow-up studies (6,25) are what would be predicted from

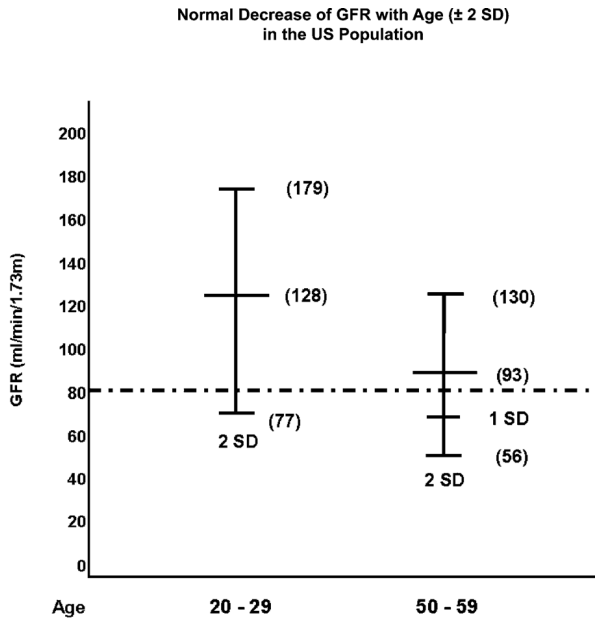

Figure 3: Representative normal ranges for GFR for males aged 20–29 and 50–59. Values for females may be slightly lower. As discussed in the text, a lower limit for acceptable kidney donation of 80 mL/min/1.73 m^2 excludes more low-normal older candidates, who will be at highest risk for end-stage renal disease should postdonation kidney diseases arise. Adapted from National Kidney Foundation KDOQI Clinical Practice Guidelines (20).

renal disease epidemiology in the general population. Little postdonation risk would be demonstrated in studies averaging 10–15 years (6,25), except in Blacks. Normal middle-aged donors will be at low lifetime risk; younger donors would take decades to acquire significant numbers of *de novo* kidney diseases that would gradually progress to ESRD. Steady state may not be reached for a much longer time. However, postdonation studies do begin to show ESRD in Caucasians at median intervals of 22 and 19 years, respectively (6,26), consistent with predictions of ''delayed risk.'' In a multiracial study of 194 former US donors who developed ESRD and were themselves waitlisted for transplantation from 1/96 to 2/09, half of the ESRD occurred over 20 years after donation (27). Those who were under age 35 at donation produced 66% of the ESRD. In 1986, 23 years before the study ended, there were less than 1000 United Network for Organ Sharing (UNOS) living donors under 35 (28). As that number was increasing linearly, about two-thirds of the ESRD came from perhaps 5% of the 100 000 individuals who had donated during the study period. A conventional risk analysis would include all 100 000 donors in the risk denominator (6,23,26), suggesting a low ''population risk'' when expressed as ESRD/patient/year, but obscuring the high late-onset risks of the subset of youngest donors. About 10% of donors would have been Black (1), virtually all normal at donation. Blacks accounted for 40% of the overall 20% of donor ESRD that developed by 10 years postdonation, strikingly consistent with the four- to fivefold increased incidence of ESRD in young Blacks in the general population (8).

Although in any reasonable analysis, most donors will do well, 10- to 15-year donor follow-up studies do not allow time for the likely onset of *de novo* kidney diseases and their slow progression to ESRD. A study end point of ''population risk'' as ESRD/patient/year is not appropriate, as both the general population and postdonation cohorts consist of Black and young individuals who are higher-risk and lower-risk, normal middle-aged people. The relevant parameter is lifetime renal risk, which currently must be estimated from epidemiological data in the general population. Similarly, the increased long-term mortality associated with donation suggested by a recent study (26) may not be best expressed as a ''population risk,'' as it should be greatest after several decades in young donors with the lowest predonation GFRs.

Modifying Donor Acceptance Practices

At high risk would be a normal 25-year-old Caucasian male candidate with a predonation GFR of 85 mL/min/1.73 m^2. Other young candidates with the population average GFR of 128 mL/min/1.73 m^2 (Figure 3) and the population average 3% lifetime chance of ESRD would have to acquire significant kidney disease to lower GFR by 43 mL/min/1.73 m^2, to his predonation baseline. His predonation risk for ESRD is increased from the population average of 3% to about the 33% lifetime risk in the general population of reaching a lifetime GFR of 45 mL/min/1.73 m^2 (i.e. almost the 43 mL/min/1.73 m^2 that he is below the population mean) (8). Donation itself would decrease GFR to about 60 mL/min/1.73 m^2 and a lifetime ESRD risk of over 50% (8). Starting at 60 mL/min/1.73 m^2, normal, age-related losses alone could well produce late-life ESRD (7,20). The approximately 30 mL/min/1.73 m^2 of GFR lost with donation would be equal to losses from about 7.5 years of diabetic or aggressive nondiabetic kidney diseases (Table 2). ESRD would not likely occur for decades, but donation would have caused it to occur at least 7.5 years sooner.

At least half of this young donor's lifetime ESRD risk before or after age 64 would be from diabetic nephropathy (Table 1). As discussed above, the lifetime risk of diabetes of 27% for White men gradually decreases to a residual risk of 17% by age 60 (12), and predonation screening or advances in diabetic medical management may not reduce postdonation risks. Diabetes that developed at age 40 would produce ESRD at perhaps age 65–70 in about a third of patients who lived that long (13,14).

A normal 55-year-old candidate will not have the kidney diseases that will be present in many other ill-fated individuals in his age group. As disease is unlikely to begin *and reach* ESRD by age 64, the median age of onset for ESRD in the general population, his lifetime risk of 3% is

halved. Because of the long prodrome for diabetic ESRD, he is very unlikely to develop postdonation diabetes soon enough to produce ESRD by the end of a normal lifetime, so the risk is halved again. As discussed above, excluding predonation GFRs < 80 mL/min/1.73 m^2 decreases renal risk even more in the remaining 55-year-old candidates. These risk differentials would triple if only the young donor were Black. If the older candidate were already diabetic, particularly with microalbuminuria, such a marked reduction in risk could not be predicted. Microalbuminuria in otherwise normal individuals is not uncommon (20) and is associated with a continuum of increasing risk that extends well into the normal range and increases renal risk far less (7,21).

With these examples in mind, a center that wished to accept only the lowest risk donors would accept only non-Black, normal, middle-aged candidates. A center that accepted a normal 25-year-old could not justify refusing 55-year-olds with many epidemiologically less risky typical donor abnormalities, who would be at lower absolute risk than the young candidate. Accepting any young Black candidates would seem to set an unacceptably permissive risk threshold for other donor subgroups (23).

To correct the largest imbalances, centers might consider (1) refusing Black candidates under age 35, (2) refusing other donors under age 35 with below-median GFRs and all but the lowest diabetic risk and/or (3) accepting more older donors with abnormalities such as nephrolithiasis, increased diabetic risk or hypertension. As with our current exclusion standards, somewhat arbitrary ''cutoffs'' would be applied to a continuum of risk. Even if centers did all these things, the inability to exclude young candidates who would go on to develop diabetic and nondiabetic kidney diseases might well put them at higher risk than normal 55-year-olds. A feasible goal of future 10- to 15-year follow-up studies might be to see whether tighter exclusion protocols can reduce the incidence of postdonation diabetes in young candidates, which is critically important to their lifetime renal risk.

The overall benign interpretations of current postdonation outcome data have seemed to validate current donor selection practices (6,25,27). But if centers agreed that the long-term risks of currently acceptable donors were markedly heterogeneous and sometimes quite high, selection practices should change. Centers could not knowingly countenance very high risks for Blacks, high risks for other young candidates, and only allow much lower risks for willing middle-aged individuals. They could not explain to a 55-year-old father with a medical abnormality that predicts a small increase in absolute renal risk why he is an unacceptable donor, but his normal 25-year-old son—with a much higher lifetime risk—is not. Transplant ethicists should help centers understand that finding donor candidates medically normal is neither ethically mandated nor necessarily a predictor of a low or reasonably uniform risk. In the final analysis, donors are not benefitted if they do not know their real risks, and when they do not, their consent should not count as informed consent.

Response to Potential Problems With This Analysis

(1) ''Average'' renal population outcomes in two-kidney individuals are used to estimate long-term postdonation individual outcomes

Most medical counseling involves a somewhat imprecise application of ''average'' risks to individuals, for example, when discussing perioperative complications. Predonation ESRD risk estimates will be inexact and—depending on the donor—may be formulated as ''about'' 0.5%, 3% or 7%, etc., which will be ''about'' doubled, tripled, etc. by donation. Currently donors are told only that their renal risks are ''small,'' ''nil'' or ''unknown'' (1). Epidemiological risk estimates will be debated and refined by centers, but the alternative of not incorporating them at all in donor risk formulations is more problematic.

It seems safest to assume that uninephrectomy does not make the courses of common kidney diseases more benign. Indeed, hematuria and prediabetes in donor candidates are considered postdonation risk factors because of their deleterious outcomes in the two-kidney population. An individual's lifetime renal risks may not depend greatly on whether a given GFR is supplied by one kidney or two. Postdonation studies suggest the same risks of diabetes and hypertension, the same risks of early ESRD in Blacks and the same delayed onset of ESRD in non-Black donors that are seen in the general population.

Some studies using single-point creatinine-based estimates suggest slightly increasing postdonation GFRs long term, after the initial 30–33% decrease. However, in one such study, sequential isotope clearances decreased, with a projected difference between the two methodologies of 32 cc over 40 years (6). Even if nephrectomy somehow ameliorated the postdonation losses of GFR that are seen in the general population with age or disease, the major differences in relative risk in currently acceptable candidates would remain. This topic deserves further study, as do the effects of ''hyperfiltration'' (high single-nephron GFRs) in the absence of overt disease in former donors and in the general population.

Renal diseases and ESRD will likely be decades away for the youngest, highest-risk candidates, leaving ample time for changes in disease epidemiology and medical practices to decrease risks. However, in the general population, diabetes is becoming more prevalent, improvements in management have not decreased its renal risks (15,29) and retrospective data analysis may underestimate them (7,8,12). These factors can be acknowledged in a balanced fashion to donor candidates.

Table 3: Counseling normal non-Black 25-year-olds about postdonation renal risks

This risk information is for the average person. Your experience after donation could be somewhat better or worse, but you should know what usually happens to most people.
With average kidney function now, you have about a 3% chance of kidney failure in your lifetime.
If your level of kidney function now (your GFR) is high normal (or low normal) now, that decreases (or increases) your chances of future kidney failure.
Your testing is normal now, but that will not decrease your risk a great deal for kidney failure 30–50 years from now, when you are most likely to develop it.
Future diabetes is responsible for about half of your risk of kidney disease, especially if it develops from ages 30 to 50. Keeping your weight normal will reduce diabetic risk, but capable people often are not able to do this.
Changes in medical care might reduce these risks, but it is safest to assume that they will remain about the same.
Donation will double or triple your predonation risk of kidney failure. If you are unlucky enough to develop kidney failure in later life, it will likely happen at least 10 years earlier because of donation.
Many centers strongly feel that normal candidates for kidney donation have little risk and would reject someone with the above risks. We think that these risks are real, but involve kidney problems that you might have when you are much older.
Now repeat back to me what I have told you.

These ''transitional'' suggestions acknowledge present practices but illustrate discussion of approximate renal risks. Changing donor counseling and selection practices is advocated in the text.

(2) This analysis summarizes what we already do

Currently, transplant centers exclude candidates largely because of medical findings outside the normal range that might predict an increased risk of kidney disease (4). Centers have not formally incorporated the epidemiological risks associated with donor age, low-normal GFR, race or even different donor medical abnormalities themselves (1–4,30). Despite the fact that diabetes may cause more postdonation ESRD than all other renal diseases combined, center tolerance of diabetic risk is currently ''quite variable'' (1,3). Urolithiasis is common in the general population but causes about 0.5% as much ESRD as does diabetes (10). The renal risks in the general population of primary hypertension may be overstated (7,17,18). In many programs, an asymptomatic kidney stone or a blood pressure of 145/95 would threaten or exclude donation. But only if two donor candidates were very similar, for example, 55-year-old Caucasians with GFRs of 110 mL/min/1.73 m^2, would these differences determine a slightly greater absolute renal risk for the afflicted individual. Among many candidates, the difference in risk from *entirely normal* epidemiological factors will far outweigh those differences. Table 3 outlines a ''transitional'' approach to donor counseling while this analysis is considered.

When plausible doubt has been raised about the risks of living kidney donation, we are mandated to proceed cautiously (30). Population data provide new insights into the risks of normal and abnormal donor candidates alike, risks that are as real as those of an abnormal urinalysis. The transplant profession should now consider this more comprehensive approach to donor risk estimation to improve the defensible selection of living kidney donors, to which we are all committed.

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Disclosure

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