Evaluation of the Living Kidney Donor: Current Perspectives

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- Living kidney donation is increasing because of prolonged waiting times on the transplant list, as well as improved outcomes for recipients. In 2001, the number of living donors surpassed the number of deceased donors; this trend likely will continue with ever-increasing margins. Because of this increase, as well as changes in our society’s health, it is time to re-review the guidelines for selecting living kidney donors established by Kasiske et al in 1995. A conference will be held this year to review updated literature on medical conditions that impact on renal health. From this, new guidelines for the medical evaluation of living renal donors will be constructed. This review discusses information known to date on the outcomes of individuals undergoing unilateral nephrectomy, the impact of lifestyle on renal function in the setting of nephrectomy, and advancements in the detection of genetically transmitted renal diseases that impact on today’s decisions on living donation.


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INDEX WORDS: Living donor; kidney transplantation; evaluation.

Kidney transplantation improves longevity and quality of life compared with dialysis therapy in people with end-stage renal disease (ESRD). The long-term mortality rate among transplant recipients is 49% to 82% less than that for patients on the waiting list, depending on their comorbid medical conditions (Fig 1). Living donor transplantation improves survival more reproducibly than deceased donor transplantation because it more predictably results in preemptive transplantation (before dialysis therapy) (Fig 2). Preemptive transplantation may improve survival by limiting the cardiovascular risk associated with increasing years on dialysis therapy. Preemptive transplantation also is associated with improved long-term allograft survival and fewer episodes of rejection. Additionally, it enables scheduling transplantation at a time when the recipient is in optimal medical and psychological condition. Living donor transplantation further promotes access to transplantation for those without a living donor. Without increasing living donation, our transplant lists will continue to grow, dashed the hopes of many for a better life.

The growing need for kidney transplantation and better outcomes provided by living donation are focusing transplant center efforts on increasing living donation. With this refocus has come a change in the face of living donors. In the past, living donation meant donation by a sibling, parent, or, sometimes, a child (United Network for Organ Sharing/Organ Procurement and Transplantation Network [OPTN]). Now, living donation also means donation from a spouse, friend, acquaintance, or even a complete stranger. The advent of unrelated donation has increased living donation to the point that in the year 2001, for the first time ever, living donors were more numerous than deceased donors (Table 1). Because of this push for living donation, as well as variability in donor selection criteria noted around the globe, it again is time to review medical risks to living donors in the context of today’s medical advances, environment, and lifestyles. Variability in donor selection criteria exists for such medical characteristics as age, weight, level of renal function, amount of proteinuria, degree of hematuria, level of blood pressure (BP), and the evaluation performed in those with a history of nephrolithiasis and a strong familial history of diabetes. What thresholds for selection as a living donor should be accepted?

Evaluation of a living donor starts with education about the donation process and a screening history by the living donor coordinator. Often the prospective donor will be asked to supply a copy of their most recent history, physical, and laboratory examination to the transplant center. Early in the evaluation process, the donor’s blood type is ascertained to determine compatibility with
the recipient. If this information and the screening interview do not reveal issues that exclude donation, the prospective donor is asked to undergo a very complete history and physical examination (usually by a transplant nephrologist and surgeon), laboratory testing (including 24-hour urine tests), cross-matching, and, finally, renal imaging. The donor evaluation is completed with visits to the transplant social worker, psychologist, or psychiatrist. In some programs, a dietician and pharmacist also speak with the donor.

A cross-match is performed between the prospective donor and recipient to detect preformed antidonor antibodies that would cause early transplant failure. Tissue typing is performed to determine the degree of tissue matching and therefore the probability of long-term allograft acceptance. However, because both HLA laboratory testing and the complete medical evaluation are expensive and time-consuming, some centers have chosen to perform a screening cross-match first to rule out a donor before subjecting them to the entire evaluation, whereas others have continued with the medical evaluation, selected the healthiest donor, and then performed the cross-match and tissue typing. One approach saves on HLA laboratory expenses, and the other saves on medical evaluation charges. However, because of improved immunosuppressive effectiveness, a more recent approach is to not perform HLA typing at all. The only time these centers request tissue typing is if complete identity between the donor and recipient is possible or the recipient is sensitized. Even more changes in the use of HLA testing are on the way as advancements in renal transplantation make transplantation more easily achievable across previously contraindicated blood group–type barriers, from donors to whom the recipient is presensitized, and from species other than humans.11-14

During the medical evaluation, there is ongoing dialogue between the prospective donor and transplant team to ensure continued comfort with the decision to donate. Conversations are held to determine whether the donor understands the social and health implications of donation and whether there is evidence of coercion. This dialogue is the foundation of informed consent. Components of informed consent discussed with the donor include the impact of donation on their social and financial well-being, short-term morbidity and mortality directly related to the surgery, future risk for renal insufficiency and failure, risk for de novo medical problems on renal and overall health (ie, hypertension, diabetes), and risk for allograft failure in the recipient because of rejection, technical problems, recurrent disease, and/or comorbid medical problems.15,16

The degree of risk a donor is allowed to accept in the performance of donation is a topic of intense debate. Opinions vary from no allowable risk (ie, no transplantation) to allowing the donor to decide whether to donate irrespective of medical risks. Most transplant professionals believe the donor’s risk should lie somewhere between these extremes, and most believe that the risk assumed by the donor depends on the benefit of donation to the donor, ie, how their life will be enhanced if they donate. For instance, if a husband or wife donates to their spouse, their own quality of life may improve; therefore, more risk is accepted for the common benefit, whereas in the altruistic situation, there is no donor benefit other than the sense of helping someone in need, and even marginally increased medical
risks are not acceptable. However, this discussion is far from over as controversy permeates the issues of donor autonomy, reimbursement, and allowable medical risk. The final decision-making process about donation likely will never be final, but instead is a work in progress, a process that will always need to include input from our entire society and be updated with the arrival of new medical advances. Currently, a donor has complete independence to make a final decision on donation based on the perceived social or financial impact on their life. Likewise, a donor has the majority right to choose the limits of acceptable risk of graft loss of their kidney in the recipient. However, decisions regarding risk to their personal health classically have involved not only the donor, but also the donor advocate (nurse, physician, or social worker) and are the topic of the rest of this article. Discussion of

Table 1. Donors Recovered in the United States by Donor Type

<table>
<thead>
<tr>
<th>Year</th>
<th>Deceased</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>5,002</td>
<td>5,037</td>
<td>5,082</td>
<td>5,338</td>
<td>5,386</td>
<td>5,490</td>
<td>5,528</td>
<td>5,630</td>
</tr>
<tr>
<td>1996</td>
<td>3,376</td>
<td>3,652</td>
<td>3,918</td>
<td>4,372</td>
<td>4,612</td>
<td>5,411</td>
<td>6,001</td>
<td>6,233</td>
</tr>
</tbody>
</table>

Data from OPTN as of July 18, 2003. Available at www.optn.org.
personal health risk is especially important if the prospective living donor is a minor.\textsuperscript{15,16}

**SURGICAL RISK**

The real issue in living donation is how to make decisions about future donor safety using current medical data. Future medical risks can be broken down into surgical risks, lifestyle risks (smoking, obesity, and environmental exposure), risks associated specifically with reduced renal mass (unilateral nephrectomy or donor nephrectomy), risks for de novo medical illnesses associated with renal disease (autoimmunity, diabetes, vascular disease, and hypertension), and inherited risk for primary renal disease (polycystic renal disease and Alport’s disease). Although the information needed to predict future renal outcome is far from complete, scientific information as it currently stands provides guidance.

Surgical risk to the living donor today usually means risk associated with a laparoscopic nephrectomy.\textsuperscript{20-22} This technique has been credited with increasing living donation rates because of smaller incisions, diminished pain, and shorter hospital stays.\textsuperscript{20-22} Surgical risk associated with this procedure, as with most surgical procedures, is determined by the cardiopulmonary health of the donor. Mortality from the procedure is low (0.03\%) because the donor medical evaluation excludes anyone with significant cardiopulmonary disease. However, deaths have occurred and are reported to be caused by pulmonary emboli, infection, and bleeding.\textsuperscript{23,24} Serious donor morbidity has been described in up to 3\% of donors, varying according to type of donor nephrectomy (open versus laparoscopic) and surgeon experience.\textsuperscript{23,24} Although there may be instances in which transplant centers have not disclosed donor deaths or complications, no reports have yet been published to confirm this claim.

**RISKS OF SMOKING, OBESITY, AND HYPERTENSION**

Smoking and obesity impact on renal function, protein excretion, and the development of renal cell and other cancers.\textsuperscript{25-27} Although the overall prevalence of smoking in the United States is declining, new adolescent smokers are increasing, risking the long-term health of many prospective donors (www.cdc.gov/tobacco/research_data/youth/initfact.htm). Furthermore, smoking also has been associated with increased development of systemic lupus erythematosus in African-American women.\textsuperscript{28}

Obesity and its associated complications (eg, diabetes and vascular disease) are increasing rapidly in the United States.\textsuperscript{29-33} More than 60\% of the adult population in the United States is categorized as overweight (body mass index [BMI] $> 25$), with 27\% classified as obese (BMI $> 30$).\textsuperscript{34,35} In concert with early smoking and increased weight, rates of renal cell cancer also are increasing.\textsuperscript{25,36} This increase is caused not only by lifestyle changes, but also by environmental exposures to such chemicals as organic solvents.\textsuperscript{37-39} Thus, it is increasingly possible that a smoker who is overweight and exposed to organic solvents will present for donation. Therefore, it is likely that more prospective donors will be at increased risk for proteinuria, hypertension, diabetes, and cancer compared with donors from previous years. Studies detailing information supporting the renal risks of smoking, hypertension, hyperglycemia, environmental exposures, and obesity are discussed next.

Population studies have shown that smoking, obesity, high BP, and elevated blood glucose levels are associated with increased risk for proteinuria.\textsuperscript{26,27,40-43} The development of proteinuria signals a marked increased risk to develop renal failure. The association of proteinuria with ESRD has been studied most extensively by Iseki et al\textsuperscript{41} in Okinawa. These investigators screened 106,177 adults older than 20 years between 1983 and 1984 by means of dipstick urinalysis, blood testing, and BP measurement. Repeated testing was performed, and renal outcomes were determined after 17 years. Figures 3 and 4 show the relationship between dipstick-detectable urinary protein and the development of ESRD.\textsuperscript{40,41} Also important to the development of ESRD was screening BP; the BP of those developing ESRD was higher than that in patients who did not develop ESRD (143.9/86.8 versus 130.2/78.7 mm Hg; $P < 0.001$). Causes of ESRD in those who started dialysis therapy and survived longer than 1 month were chronic glomerulonephritis (48.8\%), diabetes (23.8\%), nephrosclerosis (13.1\%), polycystic kidney disease (PKKD; 2.9\%), systemic lupus erythematosus (1.4\%), and other (10\%).
Tozawa et al.\textsuperscript{26} evaluated the development of proteinuria during 2 years in 5,403 men and women in Japan. In 1997, study subjects had no protein detected on urine dipstick and a serum creatinine level less than 1.2 mg/dL (\(<106 \mu\text{mol/L}\)) in men and less than 1.0 mg/dL (\(<88.4 \mu\text{mol/L}\)) in women. Twenty-one percent of study subjects had hypertension, and 5.1% had diabetes.\textsuperscript{26} Their weight, smoking habits, and BP were recorded. In 1999, these same individuals were revisited and underwent the same evaluation. Proteinuria had developed in 5.8%. The development of proteinuria was predicted by the 1997 BP, blood glucose level, smoking history, and BMI. Number of cigarettes smoked per day was associated with increased risk for proteinuria (\(P = 0.04\)). After removing those with hypertension (BP > 140/90 mm Hg) and diabetes at initial evaluation from the analysis, relative risk (RRs) for developing proteinuria were 1.4 (\(P = 0.08\)) for smoking and 1.45 (\(P = 0.002\)) for obesity. RRs for developing proteinuria in those

### Table 1: Cumulative Incidence of ESRD by Baseline Results for Proteinuria

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Number of Screened</th>
<th>Number of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>86,253</td>
<td>185</td>
</tr>
<tr>
<td>±</td>
<td>10,000</td>
<td>38</td>
</tr>
<tr>
<td>+</td>
<td>4007</td>
<td>55</td>
</tr>
<tr>
<td>2+</td>
<td>1072</td>
<td>76</td>
</tr>
<tr>
<td>≥3+</td>
<td>357</td>
<td>55</td>
</tr>
</tbody>
</table>

Proteinuria and the rise of developing end-stage renal disease. Kidney Int 63:1468-1474, 2003.\textsuperscript{41} Published by Blackwell Publishing Ltd.
with hypertension (BP ≥ 140/90 mm Hg) were 2.28 for men and 1.56 for women (P = 0.001). The RR for developing proteinuria in the presence of diabetes was 2.28 (P < 0.0001).

Briganti et al.43 evaluated the risk for proteinuria and renal impairment in a population-based cross-sectional study of 11,247 healthy Australian adults. Participants underwent a physical examination that included BP measurement, anthropometry, and laboratory testing, including a fasting glucose level, 75-g oral glucose tolerance test, creatinine measurement, and urinalysis. A total of 4,516 participants were without hypertension, diabetes, or impaired fasting glucose levels. Of these individuals, 3.4% had an estimated calculated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m², and 1.1% excreted more than 250 mg/d of protein. A systolic BP of 131.5 mm Hg or higher and a 2-hour glucose level greater than 126 mg/dL (6.99 mmol/L) were associated with a significant increased risk for proteinuria and renal impairment. Smoking in men was significantly associated with proteinuria (RR, 3.59; confidence interval, 1.27 to 10.09). There was an association between number of pack-years smoked and GFR; GFR decreased 3.2 mL/min/1.73 m² for each 10 pack-years among current smokers, more in men than in women.

Lhotta et al.42 examined renal biopsy specimens for vascular abnormalities and correlated the findings with the patient’s smoking status (107 biopsies). The proportion of patients with partially or totally sclerotic glomeruli and extent of glomerulosclerosis were similar among smokers, ex-smokers, ever-smokers, and nonsmokers. However, the proportion of patients with myointimal hyperplasia of interlobular arteries was twice as high in smokers, ex-smokers, and ever-smokers compared with nonsmokers. The difference between never-smokers and ever-smokers was statistically significant (P < 0.01). Thus, informed consent of the living donor includes discussions of lifestyle risk and should include education about exercise, smoking, dietary choices, and targeted weights. The impact of microalbuminuria and renal impairment (GFR < 60 mL/min) on the development of cardiovascular disease also needs to be discussed with the prospective donor.44-46

<table>
<thead>
<tr>
<th>Table 2. Cause of Renal Disease Leading to Nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baudoin et al.</strong> (n = 111)</td>
</tr>
<tr>
<td>Cause</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Wilm’s tumor</td>
</tr>
<tr>
<td>Renal calculi</td>
</tr>
<tr>
<td>Perirenal abscess</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Renal dysplasia</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
</tbody>
</table>

**RENAL FUNCTION AFTER UNILATERAL NEPHRECTOMY FOR MEDICAL INDICATIONS**

The risk of nephrectomy on future renal function has been evaluated in the setting of uninephrectomy for unilateral renal disease, as well as renal donation. The risk of uninephrectomy for unilateral renal disease on future renal function recently was evaluated by Praga et al.27 Seventy-three patients were reviewed 1 or more years after a uninephrectomy (Table 2). At surgery, they had a normal remaining kidney and normal serum creatinine level and were without proteinuria, diabetes, liver disease, or chronic infection. At study, subjects could be divided into 2 groups, those who developed proteinuria (protein, 0.6 to 13.5 g/d) and renal insufficiency (1.4 mg/dL [123.76 μmol/L]; creatinine clearance < 70 mL/min/1.73 m²) and those who retained normal renal function without proteinuria. The preoperative characteristic that determined the development of proteinuria and renal insufficiency was BMI. The probability of proteinuria was 60% in obese subjects (BMI ≥ 30) 10 years after nephrectomy and 92% at 20 years. This compared with 7% and 23% for those with a BMI at surgery of less than 30, respectively. Renal impairment was seen in 65% of obese compared with 9% of normal subjects 20 years after nephrectomy.

**UNILATERAL NEPHRECTOMY IN CHILDREN**

The impact of unilateral nephrectomy on long-term renal function in children was evaluated retrospectively by Baudoin et al.47 Children underwent nephrectomy for unilateral renal disease; the remaining kidney was “without re-
ported damage” (Table 2). At surgery, children had no proteinuria and a normal serum creatinine level. Follow-up ranged from 7.1 to 51.9 years; 111 of 224 qualifying subjects were evaluated. Evaluation included inulin and para-aminohippurate clearances. The study concluded that children generally did well after nephrectomy, with long-term GFRs remaining around 75% to 80% of that expected with 2 kidneys. Effective renal plasma flow (ERPF) was an average of 30% greater than the normal single (2-kidney) kidney value. However, after 25 years with 1 kidney, some subjects showed a slight, but significant, decline in renal function, slight increase in serum creatinine level, and increase in protein excretion compared with those fewer than 25 years from surgery (Table 3). Twenty-three percent of children seen in follow-up had detectable albuminuria (albumin > 30 mg/dL), and 6 patients excreted more than 250 mg/d of albumin. There was no discussion of de novo medical illnesses that would affect renal function.

**UNILATERAL NEPHRECTOMY IN TYPE 2 DIABETES**

Silveiro et al investigated the impact of unilateral nephrectomy in patients with type 2 diabetes of at least 1 years’ duration. They compared renal function and proteinuria in subjects with (n = 20; duration of diabetes, 8.5 ± 7 years) and without diabetes (n = 17) undergoing unilateral nephrectomy with renal outcome in patients with type 2 diabetes with 2 kidneys (n = 184; duration of diabetes, 10 ± 7 years). All groups were matched for age. Single- and 2-kidney patients with diabetes also were matched for sex and BMI. Those undergoing nephrectomy were at least 5 years (mean, 23 ± 17 years) from surgery, and smoking prevalence was not different between the groups. At the time of nephrectomy, serum creatinine level was less than 1.2 g/dL (<106 μmol/L) and urine was negative for protein by dipstick.

At follow-up, more subjects with diabetes who underwent nephrectomy showed microalbuminuria (40% versus 17.6%; P = 0.03) and macroalbuminuria (30% versus 6%; P = 0.03) than those without diabetes. They also showed more microalbuminuria than subjects with diabetes and 2 kidneys (40% versus 20%; P = 0.03). Microalbuminuria was noted an average of 23 ± 18.4 years after surgery in subjects with diabetes compared with 43.5 ± 23.2 years in those without diabetes. Onset of albuminuria was as early as 5 years after nephrectomy in patients with diabetes, but most often after 30 years in those without diabetes. When evaluating subjects based on time after nephrectomy, all subjects with a single kidney, diabetes, and more than 25 years from surgery had albuminuria. Even so, renal function at the time of study was not significantly different between nephrectomized subjects regardless of whether they had diabetes. Furthermore, comparing those with diabetes and a single kidney with those with diabetes and 2 kidneys, the prevalence of such chronic complications of diabetes as retinopathy (54% versus 76%), peripheral neuropathy (23% versus 54%), and macro-vascular disease (31% versus 28%) was similar in this small study in which duration of diabetes at study was an average of 10 years. The conclusion to be drawn is as follows: nephrectomy in an individual with diabetes, normal renal function, and no dipstick-identifiable proteinuria results in good short-term outcome. However, with time, increasing proteinuria is common, and this may

<table>
<thead>
<tr>
<th>Interval After Nephrectomy (y)</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>ERPF (mL/min/1.73 m²)</th>
<th>Plasma Creatinine (mg/dL)</th>
<th>Urine Albumin Excretion (mg/d/1.73 m²)</th>
<th>Urine Protein Excretion (mg/d/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 (n = 62)</td>
<td>90 ± 14</td>
<td>478 ± 97</td>
<td>0.84 ± 0.17</td>
<td>25 ± 43</td>
<td>60 ± 82</td>
</tr>
<tr>
<td>≥25 (n = 49)</td>
<td>82 ± 19*</td>
<td>393 ± 93*</td>
<td>0.92 ± 0.25*</td>
<td>124 ± 336*</td>
<td>309 ± 681*</td>
</tr>
</tbody>
</table>

NOTE. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.
*P < 0.05, 25 or greater years compared with less than 25 years (Student’s t-test).
Data from Baudoin et al.
ultimately increase risk for renal disease and cardiovascular events.

**UNILATERAL NEPHRECTOMY FOR TRAUMA**

Narkun-Burgess et al.\(^49\) examined the consequences of uninephrectomy because of trauma in World War II in US Army personnel. Records for US Army field hospital admissions were reviewed for a diagnosis of uninephrectomy in field hospitals between 1942 and 1945. Of 495 personnel so treated, 473 patients were found to have files in the Veterans Administration Beneficiary Identification and Records Locator Subsystem, and the files of 163 personnel were obtained. Personnel were considered eligible for study if nephrectomy was performed for trauma, there was no history of hypertension or renal disease, and there were no additional injuries that would predispose to renal disease. Sixty-two subjects remained for study. Twenty-eight patients had died, 2 subjects could not be found, and 32 living subjects were contacted and invited to participate in the study.

Twenty-eight subjects agreed to participate and were referred to a local physician, who obtained medical histories and performed physical examinations. Urinalyses were performed, and measurements of serum urea nitrogen and creatinine and urine protein and creatinine (from 24-hour urine collections) were determined by commercial or hospital laboratories. Study subjects were all men, the majority were of European ancestry, average age at nephrectomy was 25 ± 4 years, and average time after nephrectomy at follow-up was 45 years. Renal function in living subjects is listed in Table 4. Average serum creatinine value and prevalence of hypertension were similar in study subjects compared with those observed in men of the same age in the Second National Health and Nutrition Examination Survey study.\(^50\) The condition of the remnant kidney in 17 of 28 deceased subjects was good, determined by review of autopsy reports and reports of urinalyses and serum creatinine measurements performed within 2 years of death. Six subjects were reported to have abnormal renal function at the time of death. Death was attributed to renal failure in only 1 subject. No subject was recorded to have been or be on dialysis therapy. Renal dysfunction was attributed to type 2 diabetes, obstruction, atherosclerosis, congestive heart failure, and pyelonephritis. The mortality rate of veterans during the 45 years of follow-up was the same regardless of whether or not they underwent unilateral nephrectomy in the field (Fig 5).

In summary, uninephrectomy performed for unilateral renal disease may result in increased protein excretion and decreased renal function in the remaining kidney during the long term. However, the extent of renal impairment and timing depends on underlying medical illness and, in many instances, the development of new medical conditions (hypertension, diabetes, vascular disease, and glomerulonephritis) not present at the time of surgery. Renal dysfunction develops earlier in those who are obese, smoke, have hypertension, or have abnormal glucose metabolism. To date, no increased occurrence of ESRD or mortality has been reported in patients with normal renal function at the time of nephrectomy up to the limits of study follow-up. However, the possibility that longer term studies may find such an association must be considered because microalbuminuria is a risk factor for the development of peripheral and coronary vascular disease.\(^44,45\)

### Table 4. Kidney Function After Unilateral Nephrectomy in World War II

<table>
<thead>
<tr>
<th>Subject</th>
<th>NHANES II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69 (65-81)</td>
</tr>
<tr>
<td>Time after nephrectomy (y)</td>
<td>45 (44-47)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>75 (37-168)</td>
</tr>
<tr>
<td>Urinary protein (mg/d)</td>
<td>146 (&lt;6-535)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19/28 (68%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8/28 (29%)</td>
</tr>
</tbody>
</table>

**NOTE.** To convert serum creatinine in mg/dl to \(\mu\)mol/L multiply by 88.4; creatinine clearance in mL/min to mL/s, multiply by 0.01667.


Data from Narkun-Burgess et al.\(^49\)

**UNILATERAL NEPHRECTOMY FOR LIVING DONATION**

The risk for developing renal disease and renal failure and risk for death have been evaluated in several studies after living renal donation. These studies showed that the situation of living donors followed up for more than 20 years appears
similar to that of subjects discussed previously, although these individuals were even healthier, with less risk for contralateral renal disease at the time of nephrectomy. The largest of these long-term studies is from the University of Minnesota, with the most recent published in 2002. Ramcharan and Matas identified 773 individuals who donated a kidney between 1963 and 1979. They were able to locate information on 464 individuals; 84 patients had died, and 3 patients were on dialysis therapy at the time of death. The surviving 380 donors were contacted and asked to fill out a survey and undergo physical examination, urinalysis, and serum creatinine measurement. Of this group, 124 patients said they had no kidney problems, but did not participate in the study; 380 donors were contacted and asked to fill out a survey and undergo physical examination, urinalysis, and serum creatinine measurement. Of this group, 124 patients said they had no kidney problems, but did not participate in the study; 198 of those who participated had donated 20 to 29 years earlier; and 58 had donated greater than 30 years before the survey. Serum creatinine levels were available in 74 persons who donated 20 to 29 years before the study and 29 persons who donated more than 30 years before the study. Mean creatinine values were 1.2 ± 0.04 mg/dL (106 ± 3.5 µmol/L) in the 20-to-29-year group and 1.3 ± 0.1 mg/dL (115 ± 8.8 µmol/L) in the longer-than-30-year group. Proteinuria rates were 11% and 5%, respectively; most were 1+ on dipstick. Hypertension was apparent in 36% and 38%, respectively. The incidence of hypertension was no different than that reported in a population study published in 1995. After donation, 19 of 250 responding donors developed diabetes; 9 of these donors (47%) had a negative family history for diabetes. Five of the responding donors had a serum creatinine level greater than 1.7 mg/dL (>150 µmol/L); 2 donors had developed ESRD and undergone transplantation.

Overall, the prevalence of ESRD in the donor population was 5 of 464 donors, or 1% (2 living donors had received renal transplants, 3 of the 84 donors who had died were on dialysis therapy at the time of death), slightly greater than the national rate of 0.03% (US Renal Data System [USRDS]; www.usrds.org/adr.htm).

An earlier study from 1992 by Najarian et al. also from the University of Minnesota, compared renal function, BP, and proteinuria in 57 donors from 20 to 30 years after nephrectomy with that in 67 siblings. Average age at study was 61 years in donors and 58 years in siblings. There were no differences in mean serum creatinine levels, proteinuria, or hypertension between donors and their siblings. Average serum creatinine level was 1.1 mg/dL (97.2 µmol/L), average BP was 130/80 mm Hg in both groups, 32% of donors versus 44% of siblings were administered antihypertensive medications, and 23% of donors and 22% of siblings showed proteinuria. None of the donors (n = 15) had died of kidney disease. The investigators concluded there was no difference in renal risk in donors compared with other family members.

Fehrman-Ekholm et al. analyzed actual survival and causes of death in 430 living donors and compared it with expected survival in the general Swedish population. The expected donor cohort mortality rates were calculated from age, sex, and calendar year-specific (1964 to 1992) mortality rates for the general population. Donors had a 20-year survival rate of 85% compared with an expected rate of 66% (Fig 6). No donor death was reported from renal disease; most deaths were caused by cardiovascular disease. Twenty years after donation, one third of donors were hypertensive, and 1% had proteinuria with protein excretion greater than 1 g/d.

![Figure 5](image.png)
ESRD IN LIVING DONORS

A more specific analysis of the development of ESRD in living donors was performed by Ellison et al.\textsuperscript{54} The OPTN database was used to determine the number of renal waitlist candidates who previously had been living donors. A total of 56 living donors were identified who subsequently had been listed for deceased donor kidney transplantation, 36 were donors before the inception of the OPTN waiting list in 1987. Thus, the estimated incidence of ESRD in living donors since 1987 is 0.04%, the incident rate of ESRD in the general US population is 0.03% (USRDS 2001 Annual Data Report). However, it should be remembered that this study represents the selected group of former living donors who were listed for transplantation; there likely are others who developed ESRD and were not listed. Furthermore, because the study did not fully capture the years before the establishment of the OPTN registry, data from this era likely are incomplete.

Therefore, unilateral donor or medically necessary nephrectomy appears to result in maintained renal function during 20 to 30 years if the subject has normal renal function, no hypertension, and no proteinuria at the time of nephrectomy. However, there appears to be an increased risk for hypertension and mild proteinuria and some increased risk for developing renal insufficiency, beginning about 20 to 25 years after surgery. To further define the very long-term risk of donor nephrectomy, 40- to 60-year prospective studies comparing contemporary subjects undergoing unilateral nephrectomy with those not undergoing nephrectomy are needed. This is particularly important for children who desire to donate. Currently, individuals with 1 kidney should be encouraged to have regular medical follow-up, exercise, and maintain a relatively normal weight and BP.

RISK FOR RENAL DYSFUNCTION IN THE SETTING OF SYSTEMIC ILLNESS

Hypertension

The process of informed consent includes assessment of the donor’s renal risk caused by the presence of or propensity to develop medical illness known to negatively impact on renal function. Such diseases include hypertension, hepatitis C and B, diabetes, nephrolithiasis, fibromuscular dysplasia (FMD), and sickle cell trait. Unilateral nephrectomy in donors with borderline or known hypertension was evaluated by Torres et al\textsuperscript{55} in 1987. They evaluated donors greater than 10 years from surgery at the Mayo Clinic. Of 144 qualifying donors, 5 donors had died, 39 donors could not be found or refused follow-up, and 100 donors participated in the long-term evaluation study. The 5 deceased do-
nors died of nonrenal diseases. One of 100 participants was found to have light chain nephropathy and was excluded from the study, leaving 99 final participants. Hypertension was defined as a BP greater than 160/95 mm Hg. At donation, 22% had borderline hypertension, whereas 4% had definite hypertension; none was administered antihypertensive medications. At follow-up, 14% had borderline hypertension and 21% had definite hypertension; 16 of 19 patients were administered antihypertensive medications. At follow-up, 14% had borderline hypertension and 21% had definite hypertension; none was administered antihypertensive medications. At follow-up, 14% had borderline hypertension and 21% had definite hypertension; none was administered antihypertensive medications. At follow-up, 14% had borderline hypertension and 21% had definite hypertension; none was administered antihypertensive medications.

Hepatitis C and B

Other medical issues that need to be addressed more fully in the setting of living donation in-
include risk for developing renal disease in patients with hepatitis and risk for developing diabetes, especially in those with a positive family history. Chronic hepatitis C virus (HCV) and B virus infections are associated with many extrahepatic manifestations. Up to 74% of individuals chronically infected with HCV will manifest extrahepatic symptoms or signs. In a single-center study of 1,614 patients at their first visit for HCV care by Cacoub et al., 40% had cryoglobulins, 10% had antinuclear antibodies, and 3% had an elevated serum creatinine level. Renal diseases, such as membranoproliferative glomerulonephritis and membranous nephropathy, are well-known complications of HCV infection. Furthermore, HCV infection is associated with an increased risk for hepatocellular carcinoma and cirrhosis and may be associated with the development of diabetes and lymphoproliferative disorders. Hepatitis B virus infection is associated with the development of polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis, hepatic failure, and hepatocellular carcinoma. Given these risks, living kidney donation by an individual with chronic viral hepatitis is not justified.

**Type 2 Diabetes**

Accurately determining who will develop type 2 diabetes is difficult. Obesity, ethnicity, and a positive family history increase risk, but more

---

**Table 5. Hypertensive Living Renal Donors**

<table>
<thead>
<tr>
<th></th>
<th>Before Nephrectomy</th>
<th>6-12 mo After Nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>No. of patients</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>Clinic systolic BP (mm Hg)</td>
<td>123 ± 2</td>
<td>150 ± 2</td>
</tr>
<tr>
<td>Clinic diastolic BP (mm Hg)</td>
<td>74 ± 1</td>
<td>89 ± 2</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.5 ± 0.1</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dyne s/cm⁵)</td>
<td>1991 ± 55</td>
<td>2392 ± 198</td>
</tr>
<tr>
<td>Iothalamate clearance (mL/min)</td>
<td>98 ± 3</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>Microalbuminuria (µg/d)</td>
<td>11.3 ± 5</td>
<td>9.5 ± 1</td>
</tr>
</tbody>
</table>

Data from Textor et al.
specific testing is needed to reliably identify those who will develop the disease. Recent work has shown that the most predictive studies appear to be fasting blood glucose and insulin levels, together with 2-hour oral glucose tolerance test glucose and insulin levels. The most accurate methods detect both insulin resistance and insulin-secretory dysfunction. For women, a careful obstetrical history also is helpful because up to 35% of women with previous gestational diabetes develop type 2 diabetes by 15 years after delivery. Additionally, inflammatory responses predicted by the cytokine genotypes of tumor necrosis factor-α, interleukin-1β, and interleukin-6 have been implicated in the pathogenesis of and risk for type 2 diabetes. Importantly, diet and exercise programs have been shown to modify the risk for and onset of diabetes in persons with increased risk and those with established glucose intolerance, making early identification of risk essential. However, even with the evident progress described, definitive guidelines detailing how best to evaluate the risk for diabetes are not available. The transplant community urges the American Diabetes Association, international diabetes associations, and concerned physicians to join in an effort to compile clinically useful guidelines for predicting and avoiding future type 2 diabetes so that the transplant community can more safely advise prospective renal donors.

**Nephrolithiasis**

Unilateral nephrectomy in patients with nephrolithiasis is fraught with concern over the possibility of recurrent stones, prolonged obstruction in a single kidney, and infection. One study specifically addressing this issue was performed by Lee et al. Fifty patients were followed up for 5 or more years after unilateral nephrectomy. All subjects had a normal contralateral kidney, no proteinuria, and normal serum creatinine level at nephrectomy. Thirty percent of patients had recurrent stones, 2 patients developed acute reversible anuria, and 1 patient had proteinuria and progressive renal failure 47 months after nephrectomy. Average number of recurrent stones per patient was 2.1, and average time to recurrence was 31.1 months. Patients with metabolic stone disease had a greater recurrence rate; 37% compared with 13% in those with infection as the cause of stone formation. Thus, during 5 to 6 years, renal function remained relatively stable, and patients with metabolic reasons for nephrolithiasis developed recurrent stones more frequently. Because of the continued formation of stones in a significant number of patients undergoing nephrectomy and the associated risk for anuria, nephrectomy in patients with nephrolithiasis for the purpose of donation needs to be undertaken very carefully. Prospective donors should have a complete evaluation for the cause of stone formation, be capable of following the medical treatment regimen, and consider participation in an ongoing study of such donors through the University of Chicago (mjosephs@medicine.bsd.uchicago.edu).

**Renovascular Disease**

Renovascular disease is detected by means of arteriographic imaging in up to 10% of persons undergoing donor evaluation. FMD is found in an average of 2% to 4% of prospective donors and has been noted in up to 7%. Indudhara et al. followed up 19 living donors who had FMD. A total of 37 individuals with FMD had been considered for donation, but 18 persons were rejected because of disease severity or the availability of another donor. Donors were older than those who did not donate (50.5 compared with 44.7 years) and had less severe disease; only 1 patient had bilateral disease. At a median follow-up of 4.5 years (range, 2 months to 12 years), no donor had hypertension, increased serum creatinine level compared with in-hospital postoperative value, or abnormal proteinuria. Radionuclide renal scintigraphy with determination of ERPF showed ERPF to be 29% greater than that for normal single kidneys. Of 18 patients not undergoing nephrectomy, 11 patients were contacted, and none had developed hypertension, proteinuria, or an abnormal serum creatinine level. This study concluded that an evaluation for bilateral and distal branch disease should be performed before donor nephrectomy in an individual with FMD, and donors with severe and diffuse disease should not be selected for donation. Age of the prospective donor also should be considered, with outcome in donors older than 50 years seemingly more predictable and benign than that in younger donors.
Sickle Cell Trait

Sickle cell trait may be associated with abnormal urinary concentrating ability and hematuria. Also present can be defects in urinary acidification and potassium excretion and, uncommonly, papillary necrosis, acute renal failure, or renal medullary carcinoma.93-99 Even so, donor nephrectomy in patients with sickle cell trait has been performed for years, but formal studies evaluating long-term outcome have not been published. Discussions with centers frequently performing transplantations with organs from such donors have not shown increased concern for these donors compared with those without sickle cell trait. However, prospective donors with sickle cell trait would be benefited by a review from centers with a large experience.

RENA L ASSESSMENT

Orthostatic Proteinuria

Mild proteinuria discovered during a living donor medical evaluation often leads to a search for orthostatic proteinuria. The implications of orthostatic proteinuria have been studied most extensive by Springberg et al.100 These investigators evaluated the long-term renal outcome of orthostatic proteinuria in young men. At initial evaluation, all subjects showed fixed and reproducible orthostatic protein excretion. No patient had a history of urological disease, systemic illness, or impaired kidney function. All had normal findings on excretory urography. Biopsies were performed, and specimens were adequate for analysis in 51 of 64 patients. Subtle alterations in glomerular architecture were found in 23 specimens (45%), and definite morphological evidence of renal disease was found in 4 specimens (8%).101,102

Follow-up evaluations were performed 5, 10, and 20 years after the original examination; 36 of the original patients returned for the 20-year visit at an average age of 38 years (range, 37 to 44 years). Seven patients (18%) either had hypertension at follow-up or a history of hypertension. The prevalence of qualitative proteinuria over time is shown in Fig 9. Proteinuria declined to undetectable levels in most participants by 20 years. In addition, creatinine clearance values were followed up and were normal at 20 years in all patients, although a decline within the normal range was seen in 4 patients. Patients lost to follow-up were not identified on rosters of ESRD. No relation was detected between the initial presence or absence of renal histological changes and subsequent clinical observations. Therefore, protein excretion only in the upright position appears to be a benign condition. However, that some patients have changes on renal biopsy and some patients show a mild decline in renal function (6%; 4 of 64 patients; age, ≤44 years) indicates the need to evaluate these individuals carefully before supporting them as donor candidates. It could be argued that patients with persistent orthostatic proteinuria would best be served by an evaluation of their renal histological state before agreeing to donate.

GFR

Methods used to determine donor GFR vary among transplant centers, as does level of renal function deemed acceptable for donation. Most centers use 24-hour creatinine clearance as the determinant of renal function, whereas a few other centers use radionuclide or inulin clearance methods.7-9 The threshold GFR accepted by most
centers for living donation is 80 mL/min/1.73 m\(^2\), although up to 21.1% would accept a creatinine clearance as low as 60 mL/min/1.73 m\(^2\), and 2.4% would accept a creatinine clearance of 40 mL/min/1.73 m\(^2\).

Difficulties encountered with renal function assessment stem from the inaccuracy of 24-hour urine collections, as well as the influence of diet, age, and exercise on glomerular filtration. GFR is increased by protein intake, may be decreased in vegetarians, and may decrease slightly during exercise. GFR declines by approximately 10 mL/min/1.73 m\(^2\) for every decade after age 40 years.\(^{57,103}\) Inulin, an uncharged polymer of fructose, is the most ideal substance to measure GFR. It is filtered freely at the glomerulus and not reabsorbed, secreted, synthesized, or metabolized by the tubules. However, inulin infusions are not practical; therefore, alternative markers have been established. Table 6 lists available methods for GFR determination. Both method of assessment and level accepted for donation need more thorough study. Discussions about this subject perhaps should be framed within the context of the new National Kidney Foundation–Kidney Disease Outcomes Quality Initiative guidelines.\(^{103,104}\)

### FAMILIAL RENAL DISEASE

The possibility of developing primary renal disease is the final health discussion of living donor informed consent. Those with family histories of primary renal diseases known to be genetically transmitted, such as PCKD, need to be evaluated to the point at which there is no chance that the donor is at risk for the disease. For many other primary renal diseases, the extent of genetic contribution to disease development has not been fully elucidated. Diseases awaiting genetic characterization include immunoglobulin A (IgA) nephropathy, systemic lupus erythematosus, and hemolytic uremic syndrome.\(^{105-115}\) Some

### Table 6. Measurement of GFR

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine</td>
<td>Random blood sample</td>
<td>Simple, but inaccurate, especially with mild renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced with low muscle mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased after cooked meal meal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affected by some drugs that alter tubular secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affected by drug influences on creatinine assays</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>24-Hour urine collection with blood sample</td>
<td>Urine collections unreliable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overestimates GFR due to tubular secretion of creatinine especially at lower GFR</td>
</tr>
<tr>
<td>Estimated creatinine clearance; Cockroft-Gault formula</td>
<td>Random blood sample</td>
<td>Drugs may affect creatinine assays</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoids urine collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More accurate than plasma creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Underestimates creatinine clearance in obesity</td>
</tr>
<tr>
<td>Estimated GFR; Modification of Diet in Renal Disease study equation</td>
<td>Random blood sample</td>
<td>Overestimates on low-protein diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoids urine collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Better estimation of GFR than creatinine clearance or Cockroft-Gault formula</td>
</tr>
<tr>
<td>Plasma clearance techniques</td>
<td>Single IV or SQ injection and at least 2 timed blood samples</td>
<td>Best approximation to true GFR</td>
</tr>
<tr>
<td>Isotopic; (^{125})I-iodothalamate; (^{51})Cr-EDTA; (^{99})mTc-DTPA; nonisotopic; iodothalamate, iohexol</td>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May use radioisotopes</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{125}\)I, iodine 125; \(^{51}\)Cr, chromium 51; \(^{99}\)mTc-DTPA, technetium 99m pentetate; IV, intravenous; SQ, subcutaneous.

Data from Johnson and Feehally.\(^{143}\)
forms of focal segmental glomerulosclerosis have been biochemically and genetically characterized. Other forms await characterization or are a consequence of hemodynamic and flow influences on podocyte function. One of the syndromes in which the structural abnormality has been definitively identified, but genetic polymorphisms and heterogeneity of clinical presentation have made prediction of renal risk difficult, is Alport’s syndrome.  

**Basement Membrane Disease**

Alport’s syndrome, or “hereditary nephritis,” is the most completely characterized basement membrane abnormality leading to ESRD. Alport’s syndrome is caused by an aberration of the α5 chain of type IV collagen (COL) that, in most patients, results in a lack of detectable COL4A3, COL4A4, and COL4A5 in the glomerular basement membrane. Instead, embryonic COL (COL4A1, COL4A1, and COL4A2) is present and results initially in thinning and then splitting of the glomerular basement membrane. Additionally, genomic abnormalities in the other chains of type IV collagen, α3 and 4, also have been found to cause thinning of the glomerular basement membrane and be associated with clinical renal disease. Furthermore, it also is theoretically possible that abnormalities of other basement membrane proteins (eg, laminin) could contribute to the phenotype of glomerular basement membrane disease.  

Classic teaching has conveyed that non–X-linked Alport’s thin basement membrane disease, such as benign familial hematuria, follows a benign course. However, several investigators provided evidence that the presence of thin basement membranes associated with benign familial or sporadic hematuria may denote risk for progressive renal disease. Nieuwhof et al reported on a subset of subjects with microscopic hematuria in a prospective epidemiological study of idiopathic glomerular disease. General study participants were 16 to 65 years old and did not show extrarenal symptoms or have a known familial history of renal disease. Biopsies were performed for the presence of hematuria, nephrotic-range proteinuria, or renal insufficiency. Within this study were subjects with greater than 6 months of microscopic hematuria. Of those with microscopic hematuria, 19 individuals had biopsy-proven thin basement membrane disease, 27 patients had IgA nephropathy, and 24 patients had normal renal histological characteristics. Subjects were all normotensive and without renal insufficiency at study entry. Renal biopsy had been performed within 2 years of identification of hematuria, and follow-up encompassed a median of 12 years (range, 9 to 15 years). None of the subjects with thin basement membrane disease had hearing or ophthalmologic abnormalities. At the end of follow-up, the incidence of hypertension in patients with thin basement membrane disease exceeded that of healthy controls (35% versus 8%; Table 7). Renal function in subjects with thin basement membrane disease, measured by inulin clearance at follow-up, was reduced in 3 of the 7 patients studied, all older than 50 years (Table 7). Furthermore, there was an increased presence of renal failure in older family members of individuals with thin basement membrane disease compared with those with IgA nephropathy and normal renal biopsy results ($P = 0.019$).  

Liapis et al studied renal pathological characteristics and COL α3 to α5 (IV) expression in 16 patients who presented with overlapping signs between thin basement membrane disease and Alport’s nephritis. All patients presented with hematuria, 11 patients also had proteinuria, 9 of 16 patients had premature glomerulosclerosis, and 12 patients did not have classic Alport’s nephritis because COL α3 to α5 of COL IV expression was present. Many of the 12 subjects with the thin basement membrane variant had hypertension and proteinuria, and 4 subjects had renal insufficiency, including 1 subject who had donated to a daughter with ESRD.  

Auwardt et al reviewed records of patients with thin basement membrane disease ($n = 71$) and IgA nephropathy ($n = 31$) identified from the ledger of renal biopsies performed during 15 years at their hospital. Patients with thin basement membrane disease had no family history of Alport’s syndrome or familial deafness. At presentation, patients with thin basement membrane disease had hematuria (42%), proteinuria (42%), or both (24%), and 5 of 71 patients (7%) had a serum creatinine level greater than 1.3 mg/dL (115 μmol/L). Most patients with IgA nephropathy had both proteinuria and hematuria (71%). At a median follow-up of 4 years for thin basement
membrane disease (n = 61) and 6 years for IgA nephropathy (n = 31), proteinuria increased in 5% of patients with thin basement membrane disease and 10% of patients with IgA nephropathy; renal function remained stable in patients with thin basement membrane disease, but decreased in those with IgA nephropathy. Other investigators have reported the development of ESRD in individuals with thin basement membrane disease.125,130

Inheritance of glomerular basement membrane disease is X-linked in classic Alport’s disease and heterogeneous (autosomal dominant or autosomal recessive) for COL4A4/COL4A3-related disease.122 As investigation into the biochemistry and genetics of Alport’s type lesions proceeds, it is becoming apparent that abnormalities of COL IV show significant phenotypic heterogeneity when it comes to renal functional outcome. Much of the variability appears to be caused by the type of mutation present (nonsense, missense, reading-frame shifts, large deletions, splice variants, exon skipping).121,122 Thus, clinical presentation and the appearance of the glomerular basement membrane on electron microscopy are insufficient to help determine risk for renal failure. Although progressive renal disease may be predicted partially by the type of gene mutation, the difficulty developing genetic tests that would predict clinical outcome stems from the difficulty testing for the large number of scattered mutations that have been identified in COL4A3, COL4A4, and COL4A5 genes.121,122

The frequency with which a transplant program may be faced with evaluation of a prospective donor with hematuria and thin basement membranes is outlined in 2 studies. Iseki et al40,41 reported microscopic hematuria in a mass screening study in Japan in 4% of adult men and 10% of adult women. Thin glomerular basement membranes have been found in up to 7% to 9% of donor kidney transplant biopsy specimens from reportedly healthy individuals.131,132 Currently, one approach to prospective donors with hematuria and thin basement membrane disease might be to limit selection to those with apparently the least risk; those older than 50 years with predictable family histories of disease and normal func-

Table 7. Characteristics of Patients With Microscopic Hematuria and at Follow-Up and Renal Function in Patients Older Than 50 Years With Thin Basement Membrane Disease

<table>
<thead>
<tr>
<th></th>
<th>TBM</th>
<th>IgA</th>
<th>Normal Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with microscopic hematuria</td>
<td>No. of patients</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>No. of patients with primary relatives with ESRD</td>
<td>6/89</td>
<td>1/129</td>
</tr>
<tr>
<td></td>
<td>Mean age at presentation (y)</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Isolated hematuria</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Hematuria‡</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Proteinuria glomeruli with FSGS at biopsy (%)</td>
<td>13.5 ± 17</td>
<td>3.1 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>GBM thickness (nm)</td>
<td>191 ± 28</td>
<td>345 ± 55</td>
</tr>
<tr>
<td>Characteristics at follow-up</td>
<td>No. of patients followed up</td>
<td>17 (2 died, cancer)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>New hypertension</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Increased protein</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Increased creatinine to &gt; 1.5 mg/dL</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>TBM disease renal function in those &gt;50 years</td>
<td>TBM</td>
<td>Aged-Matched Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR insulin clearance* (mL/min/1.73 m²)</td>
<td>64, 79, 79</td>
<td>97 ± 13</td>
</tr>
<tr>
<td></td>
<td>ERPF (mL/min/1.73 m²)</td>
<td>&lt;357</td>
<td>404 ± 59</td>
</tr>
</tbody>
</table>

NOTE. Values expressed as number of patients or mean ± SD. To convert serum creatinine in mg/dL to µmol/L multiply by 88.4.

Abbreviations: TBM, thin basement membrane; FSGS, focal sequential glomerular sclerosis; GBM, glomerular basement membrane.

*Each of the individuals older than 50 years who underwent GFR testing. GFR in normotensive individuals without hypertension was normal.

Data from Nieuwhof et al.124
Table 8. Ultrasound Identification of ADPKD in Individuals Younger Than 30 Years and 30 Years or Older At Risk

<table>
<thead>
<tr>
<th></th>
<th>ADPKD Type I</th>
<th>ADPKD Type II</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &lt; 30 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients at risk</td>
<td>146</td>
<td>15</td>
<td>161</td>
</tr>
<tr>
<td>ADPKD-positive linkage</td>
<td>84</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>False-negative US</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>False-positive US</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Sensitivity (%)</td>
<td>95</td>
<td>67</td>
<td>93</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Patients ≥ 30 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients at risk</td>
<td>139</td>
<td>19</td>
<td>158</td>
</tr>
<tr>
<td>ADPKD-positive linkage</td>
<td>98</td>
<td>14</td>
<td>112</td>
</tr>
<tr>
<td>False-negative US</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>False-positive US</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Data from Nicolau et al.133

Table 8. Ultrasound Identification of ADPKD in Individuals Younger Than 30 Years and 30 Years or Older At Risk

In kindreds with Alport’s syndrome, the carriers have thin glomerular basement membranes and a phenotype similar to that in patients with benign familial hematuria. For this reason, the boundary between Alport’s syndrome and benign familial hematuria has become increasingly vague. More rigorous evaluation of individuals with isolated hematuria by biochemical, genetic, and functional (hyperfiltration) analysis over time needs to be undertaken before proclaiming that individuals at any age with thin glomerular basement membranes are completely safe for renal donation.

**PCKD**

Testing in prospective donors at risk for PCKD must be 100% accurate to prevent selection of an individual with the disease. Multiple familial studies using genetic identification of the disease by linkage analysis in concert with ultrasound (US) examinations have shown the sensitivity of US to be 100% in individuals at risk who are 30 years or older. However, sensitivity is less in those younger than 30 years (Table 8).133 The same rigorous comparison of computed tomography (CT) and magnetic resonance imaging (MRI) with linkage studies has not been performed; however, resolution of CT and MRI for small cystic structures is better than for US.134 Although technology is continually changing, on average, US can detect cysts of 1.0 cm, CT with intravenous contrast can detect cysts of 0.5 cm, and heavily T2-weighted MRI can detect cysts of 0.3 cm in diameter. Therefore, when possible, linkage analysis should be performed in prospective donors at risk who are younger than 30 years; however, if genetic testing is not a possibility, CT and/or MRI may provide better sensitivity than US. In the near future, more specific gene tests for the diagnosis of PCKD may be available.135-139

**SUMMARY**

Informed consent of a living donor includes providing information about social risk, surgical risk, renal risk, and, most importantly, donor survival. Determination of future health risk includes a medical evaluation focused on the donor’s lifestyle risk factors, as well as those related to uninephrectomy, possible future medical illnesses, and primary renal disease. The opportunity to convert a donor to a healthy lifestyle (smoking cessation and weight reduction) should not be missed, and encouragement should be given for routine medical follow-up. Crucial to the safe future of living donation is a national study of long-term outcomes of renal donation. Such a study needs to be established soon and funded in perpetuity to answer the still-lingering question of what characteristics (medical, lifestyle) before unilateral nephrectomy predict future renal failure. Our society owes this to persons who are considering such a courageous act as living donation.

**CONCLUSION**

Living donation provides the gift of life. The price of donation is the summation of benefit to the recipient and risk to the donor. As the need for organ transplantation grows, we must make sure that risk to the donor is not overlooked during the tally of financial benefit to society and quality of life to the recipient. Increasing donation should not mean increasing risk to the donor; instead, it should mean minimal long-term risk to the donor while maintaining the huge benefit to the recipient and society. Within this year, 2 conferences will convene to discuss medical issues that could potentially impact on donor health. Current data about future renal risks predicted by such physical findings as weight and
BP, such laboratory values as low-density lipoprotein cholesterol and fasting blood glucose levels, and such family histories as that for diabetes will be reviewed at this conference. A standard of care will be proposed in which medical data firmly support risk of specific medical characteristics, and guidelines will be suggested for when the information is less clear. Outlines for future studies will be formatted, and a timeline for future updates to the standards and guidelines will be generated. This conference will convene 8 years after the original in-depth analysis by Kasiske and Bia,140 Kasiske et al.,141 and Bia et al. Instead of occurring at arbitrary time points, criteria used to evaluate living donors should be reviewed continually in the light of information provided from long-term follow-up of living donors, as well as new advances in medical science. The transplant community needs to ensure that to the best of medical ability, donors enjoy long healthy lives free of dialysis therapy and transplantation.

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