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Evaluation of Potential Living Kidney Donors

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1. Introduction

Renal transplantation is considered to be the treatment of choice for patients with ESRD. The incidence of ESRD is increasing, as a result of the increase in diabetes as well as other CKD causes. However the rise in ESRD is not matched by a rise in available kidneys for transplantation. As cadaveric kidneys have failed to meet the growing need for organs, attention has turned to organs from living donors [1].

2. History of living kidney donation and justification

2.1. First identical twin transplant

The first successful kidney transplant program was at The Peter Bent Brigham hospital in Boston. There, in December 1954, Dr. Joseph Murray performed the first successful kidney transplant between identical twins. The recipient's renal disease was presumably secondary to chronic glomerulonephritis. The opportunity of transplantation was suggested since the patient had a healthy twin brother. Cross skin grafting was performed between the 2 brothers and skin grafts survived for weeks establishing "genetic identity". Thirty days after the skin grafting, the transplant was performed; Dr. Hartwell Harrison removed the donor kidney, which was implanted in the recipient by Dr. Joseph Murray. The team performed seven more such transplants during the next four years. The patient died after eight years due to development of recurrent glomerulonephritis in the transplanted kidney [2-4].

2.2. Long-term survival of living kidney donor allografts

For recipients of a first deceased kidney in the United States, current 1-year patient and graft survival probabilities are about 95% and 88%, respectively. For recipients of a first living donor kidney, current 1-year patient and graft survival probabilities are 98% and 94%, respectively [5]. Improved immunosuppressive medications have decreased early acute

rejection. However, despite the improved short term survival, graft survival half-lives have increased only very little, but are almost two-fold higher in recipients of living donors than those in patients receiving a transplant from a deceased donor (ten years for deceased donors versus 20 years for living donors).[6] The slow improvement in long term survival is related in part to chronic allograft nephropathy (CAN) as well as the nephrotoxic effect of calcineurin inhibitors. Stronger immunosuppressive regimens lead to increased incidence of malignancies and infections that may alter renal function. Immunosuppressive medications can also have unfavorable effects on blood pressure, glycemic control and lipid levels that may also lead to worsening renal function.

According to the UNOS renal transplant registry, estimated cadaveric graft half-lives were 7.9 years for the 1988-1989 (2- year) cohort, 9.2 years for the 1994-1995 cohort, and 11.6 years for the 1998-1999 cohort, despite the concurrent greater use of organs from older and less optimal deceased donors. Estimated living donor graft half-lives were 12.5 years for the 1988-1989 cohort, 15.8 years for the 1994-1995 cohort, and 19.3 years for the 1998-1999 cohort [7].

Graft survival in living transplants may be favorably affected by the relatively low delayed graft function rates (4 % vs. 24 % in cadaveric transplants) [8].

2.3. Insufficient supply of cadaveric allografts, Limiting waitlist time

As the incidence of ESRD is rising, kidney transplantation has failed to keep pace. Despite all the efforts to increase deceased kidney donation, there is still a shortage of deceased kidneys leading to increasing times on the waiting list. This implies increased workload for the transplantation centers, to ensure that patients on the waitlist remain fit enough to be able to receive a transplant [5]. Efforts have been made to use deceased organs that might have formerly not been used. Examples of this are the increased use of Expanded Criteria Donor (ECD) kidneys as well as use of donation after cardiac death (DCD) organs [6].

This organ shortage has also created a number of ethical and social dilemmas that vary across different countries of the world. The prevalence of kidney transplant from living donors varies widely around the globe. Factors such as the availability of deceased donors, the role of the government, the attitude of local physicians towards the risks of living donation, the level of awareness and education about ESRD and transplantation among the general population all affect the rates of donation. The proportion of kidney transplant from living kidney donors is less than 15 % in most European countries, except for the United Kingdom, where it has reached 47% in the last few years [9]. This proportion is only 3.3% in Finland, 8% in France, 12% in Belgium, compared to 49.5% in the USA [10]. In Spain, efficient identification of deceased renal donors has kept the waiting time short and living donors account for less than 5% of all kidney transplants. In Japan, social and cultural barriers have limited deceased donor transplantation and living donors account for 80% of kidney transplants [11]. In other countries like Egypt and Pakistan, living donor kidney transplant is the sole method of transplant available.

Transplantation increases the survival of patients with renal failure when compared to dialysis. One study of United States Renal Data System (USRDS) data compared outcomes

in patients on the transplant waiting list (who were continuing to receive dialysis) versus those who had received a kidney transplant. It found that, after 3 to 4 years of follow-up, transplantation reduced the risk of death overall by 68 % [1]. Transplantation conferred a survival benefit in almost all subgroups. In addition, over the long term, it is more cost-efficient than dialysis. Thus, transplantation remains the optimal therapy for patients with ESRD [5].

3. Team approach to donor selection and evaluation

3.1. Medical

3.1.1. Amsterdam Forum Guidelines

In April 2004, renal transplant physicians and surgeons met in Amsterdam, The Netherlands, for the International Forum on the Care of the Live Kidney Donor. The participants included over 100 experts in transplantation from more than 40 countries [12]. The main purpose of this forum was to develop an international consensus on the standards of care for the living kidney donor and to emphasize the concern of the transplant community for the welfare of the donor. It also formed an alliance with the World Health Organization (WHO) to implement these standards of care, in continuation to the Madrid WHO conference on organ donation and transplantation that was held in October 2003. The forum emphasized the low operative risk of renal transplantation that has a perioperative mortality rate of 0.03% [13]. It also stressed the importance of long-term safety of this procedure noting the absence of accelerated loss of renal function and lack of appearance of hypertension in healthy donors post nephrectomy. The forum elaborated in detail about the acceptance criteria of donors with hypertension, obesity, dyslipidemia, low-normal renal function, hematuria, proteinuria, stone disease and other factors.

3.1.2. General medical evaluation and informed consent

The medical evaluation starts with a general assessment that includes a detailed history and physical examination, age appropriate medical screening, and a determination of contraindications to kidney donation such as active malignancy, active infection, transmissible conditions among other conditions that will be discussed in detail below.

Elements of the living donor evaluation vary across different transplant centers. Some of the major components of the general medical evaluation are outlined in table 1 [14].

Donor age:

Almost all transplant centers preclude individuals younger than 18 years old from donating and consider the age of 18–21 years as a relative contraindication to donation. Young donors with even what seems like mild or borderline risk factors should be evaluated more stringently as they have many years ahead of them to potentially develop medical conditions that may harm the remaining kidney such as diabetes and hypertension [14]. In fact, the OPTN (**Organ Procurement and Transplantation Network**) data showed that most

<p>Blood group, HLA typing, crossmatch</p> <p>Urinalysis and urine culture</p> <p>24 hour urine collection for protein and creatinine clearance</p> <p>CBC, Prothrombin time, Partial thromboplastin time</p> <p>Comprehensive metabolic panel (electrolytes, albumin, alkaline phosphatase, transaminases, Calcium, phosphorus, bilirubin)</p> <p>Infectious screen: HIV, hepatitis B and C, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, RPR, tuberculosis (PPD, quantiferon) and if indicated, screen for toxoplasma, trypanosoma, malaria, West Nile.</p> <p>Human chorionic gonadotropin quantitative pregnancy test in women younger than 55 years</p> <p>Fasting blood glucose and lipid profile</p> <p>Hemoglobin A1c, glucose tolerance test as clinically indicated</p> <p>ECG, CXR</p> <p>Echocardiography, cardiac stress testing if clinically indicated</p> <p>Age appropriate cancer screening: mammogram, pap smear for women PSA for men colonoscopy</p> <p>Renal imaging: CT angiogram or Magnetic resonance angiogram</p>

Table 1. Living donor medical evaluation [14]

of the donors who were later listed on the transplant list donated between the ages of 18 and 34 years and developed ESRD more than 15 years after donating [15]. In a 2007 survey of US transplant centers, 21% of the centers list the age of 65 as an upper limit to exclude donation, while 60% don't set an upper age limit for donation [16]. Donation from well selected older donors (>60 years old) appears to be safe and has good short and long term outcomes. Well selected older donors have no difference in perioperative outcomes when compared to younger donors [17,18].

Informed consent:

Living donor transplantation creates a conflict between the duty to do no harm and the duty to respect the donor's autonomy [19]. A fundamental part of the donor evaluation is informed consent. The elements of the informed consent process include a careful assessment of the donor's capacity to make medical decisions and understand the information provided. The donor should be informed in detail about:

- the different elements of the donor evaluation process
- the surgical procedure and the recovery period
- the potential medical or psychosocial risks to the donor
- the short and long-term follow-up care requirements
- the quality of life after donation
- the availability of alternative treatments for the transplant recipient
- the recipient's risks, recurrent disease, and chances for survival

- national and center-specific outcomes for recipients and living donors
- the possibility that the donor's medical evaluation could reveal conditions that the transplant program must report to governmental authorities, such as infection with the human immunodeficiency virus
- the possibility that future health problems related to the donation may not be covered by the donor's insurance and the ability to obtain health disability or life insurance may be affected
- the donor's right to opt out of donation at any time during the donation process.

(adapted from The living donor advocate: a team approach to educate, evaluate, and manage donors across the continuum [20])

3.1.3. Hypertension

Hypertension (HTN) has been considered as a risk factor for chronic kidney disease (CKD). Screening for hypertension in a potential donor includes blood pressure (BP) measurement on three separate occasions [12]. Other experts advocate the use of ambulatory blood pressure monitoring (ABPM) [21].

Hypertension, defined by JNC7 as Systolic BP > 140 mm and/or Diastolic BP > 90 mm Hg or an average daytime blood pressure > 135/85 on ABPM, is a relative contraindication for renal transplantation. Most renal transplant centers exclude potential donors with BP greater than 140/90 by ABPM from donation. The prospective donor should have a mean awake BP less than 135/85 mm Hg and a BP less than 120/75 mm Hg when asleep.

On the other hand, the association of HTN with CKD has been argued in other studies. The RHEDY Study examined 1856 patients with primary HTN, with an average age of 47 years. Microalbuminuria and macroalbuminuria were detected, respectively, in 22.7 and 0.7% of the entire population. Systolic BP and abdominal obesity were two important determinants of microalbuminuria. However, only 5.2% of patients had simultaneously albuminuria and a reduced estimated GFR, implying a weak relation to one another [22].

Renal outcomes of kidney donors who were hypertensive at baseline were found to be favorable in some studies. Gil Thiel reported 18 donors who were hypertensive at the time of nephrectomy. The renal function, assessed by the creatinine clearance, of the 18 donors who were hypertensive at nephrectomy, was no different than the 75 normotensive donors [23]. In a report from Stegall from the Mayo clinic, 24 donors had hypertension, as defined by awake ABPM > 135/85 mm Hg and/or office BP > 140/90 mm Hg before donation. Hypertensive donors were older (53.4 vs. 41.4 years, $P < .0001$). The GFR (determined by iothalamate clearance) of the 24 hypertensive donors was not statistically different than 150 normotensive donors prior to nephrectomy or at 1 year postdonation. None of the subjects had albuminuria [24].

The following consensus guidelines regarding hypertensive donors were adopted at the Amsterdam Forum on the Care of the Live Kidney Donor [12]:

- Patients with a BP > 140/90 mmHg by ABPM are generally not acceptable as donors.

- BP should preferably be measured by ABPM, particularly among older donors (≥ 50 years and/or those with high office BP readings).
- Some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, $GFR \geq 80$ mL/min/1.73m², and urinary albumin excretion < 30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
- In cases with borderline high BP, and/or abnormalities suggesting cardiomegaly, or left ventricular hypertrophy on chest radiograph or electrocardiogram, an echocardiogram may be considered to evaluate for cardiac hypertrophy.

Patients with borderline BP and/or easily controlled hypertension can be considered for donation if they meet the following criteria [12]:

- more than 50 years of age
- not African American
- urine albumin excretion < 30 mg/day
- no signs of end organ damage
- $GFR > 80$ mL/min/1.73m²

3.1.4. Nephrolithiasis

Nephrolithiasis affects 12% of the population and is increasing in prevalence [25]. The routine evaluation of kidney donor should include screening for kidney stones. The risk of kidney donation in a stone former includes the risk of stone recurrence and development of obstructive uropathy as well as urinary tract infections that may lead to worsening kidney function. Most stones are calcium containing stones, and carry a 50% recurrence risk at 5-10 years [26]. Patients with nephrolithiasis should be screened for metabolic abnormalities that predispose to stone formation.

Burgher et al conducted a retrospective evaluation of 300 male patients, 62.8 years old on average, who were followed for a mean of 3.26 years for asymptomatic renal calculi. Mean stone diameter was 10.8mm. 77% of patients experienced disease progression, with 26% requiring surgical intervention. Stone size, blood and urine uric acid level were associated with increased risk of growth. Small (< 4 mm), non uric acid, upper-pole calculi in patients with normal metabolic profile had the slowest progression [25].

After unilateral nephrectomy for pyelonephritis in patients with stone disease, the overall risk for stone recurrence is about 30% over a mean follow up of 5 years. In this study, the kidney function remained normal over the 5 year follow up period [27].

According to the Amsterdam forum,[12] an asymptomatic potential donor with history of a single stone may be suitable for kidney donation if:

- No hypercalcaemia, hyperuricemia, metabolic acidosis, hypocitraturia, cystinuria or hyperoxaluria

- No urinary tract infection
- Multiple stones or nephrocalcinosis are not evident on computed tomography (CT) scan

Asymptomatic potential donor with *current single stone* may be suitable if [12]:

- The donor meets the criteria shown previously for single stone formers, and
- Current stone is <1.5 cm in size or potentially removable during transplant
- No evidence of nephrocalcinosis on imaging

Stone formers who should not donate are those with [12]:

- Nephrocalcinosis on X ray
- Multiple stone in one kidney or bilateral stone disease; and
- Stone types that have high recurrence rates and are difficult to prevent, such as:
 - Cystine stones that have a high rate of recurrence
 - Struvite stones or infection stones, which would be difficult to eradicate in an immunosuppressed host
 - Stones associated with inherited or other systemic disorders, such as primary or enteric hyperoxaluria, distal renal tubular acidosis, sarcoid and inflammatory bowel disease
 - Recurrence while on appropriate treatment

Spiral CT is the imaging technique of choice to detect stones or nephrocalcinosis. Age is an important clinical parameter that predicts recurrence since a stone detected in a person older than 50 years is unlikely to recur, whereas stone recurrence is higher in subjects aged 25-35 years [28].

3.1.5. Obesity

Obesity is defined by a BMI greater than 30kg/m². Obesity has been regarded as a risk factor for surgical complications, diabetes, glomerular disease (focal segmental glomerulosclerosis) with proteinuria, hypertension and ESRD in prospective living donors [29]. The relative risk for developing ESRD is threefold for a BMI between 30 and 35 kg/m² and nearly fivefold for a BMI of 35–40 kg/m² [30].

Obesity was shown to have a positive correlation with the development of proteinuria and renal insufficiency in patients who had previously undergone nephrectomy and who had normal renal function and no proteinuria at the time of the nephrectomy. Praga et al conducted a cross-sectional study in 73 patients who had undergone unilateral nephrectomy with normal kidney function at the time of nephrectomy. Indications for nephrectomy were stones, renal mass, pyelonephritis, hydronephrosis or tuberculosis. The group of patients who developed proteinuria and renal insufficiency at follow up had a mean BMI of 31 at the time of nephrectomy in comparison with a BMI of 24 in the group who did not have any proteinuria or renal insufficiency. The time elapsed between nephrectomy and onset of proteinuria was 10.1 +/- 6.1 years. The time elapsed between proteinuria appearance and the onset of renal insufficiency was 4.1 +/- 4.3 years [31].

On the other hand, a retrospective analysis of 553 kidneys donors showed that obese (BMI>35) vs. non obese (BMI<25) donors had a similar peri-operative complications except for more wound infections (9% vs. 94%) and longer operative time (mean increase 19 minutes) in the obese group. Both groups had similar GFR at 1 year and no blood pressure elevation or proteinuria at 1 year follow up [32].

About 50% of transplant centers in the USA exclude potential donors with BMI more than 35, and 10% exclude donors with BMI above 30kg/m² [26]. The Amsterdam Forum on the Care of the Live Kidney Donor [12] suggested that patients with a BMI > 35 kg/m² should be discouraged from donating, especially when other comorbid conditions are present and encouraged to adopt healthy lifestyle and to lose weight.

3.1.6. Diabetes

Diabetes Mellitus is defined as having fasting plasma glucose level of at least 126mg/dl or a plasma glucose level of at least 200mg/dl 2 hours after a 75 grams glucose challenge, confirmed by a repeat testing on a different day (see table 2).

	Prediabetes	Diabetes
Fasting plasma glucose (mg/dl)	100-125 (impaired fasting glucose: IFG)	≥ 126
2 hr plasma glucose after 75g glucose load (mg/dl)	140-199 (impaired glucose tolerance: IGT)	≥200
Hemoglobin A1c	5.7-6.4%	≥6.5%

Table 2. Diagnostic criteria for Diabetes and Prediabetes

All potential living donors should have a fasting plasma glucose testing. Those with fasting plasma glucose between 100 and 125 mg/dl and patients with risk factors for diabetes (BMI>30, parent or first degree relative with diabetes, history of gestational diabetes, delivery of large birth weight baby (>9lbs), BP>140/90, dyslipidemia, vascular disease, history of alcohol abuse, polycystic ovary syndrome, acanthosis nigricans), should have an oral glucose tolerance test (OGTT). Donors younger than 40 years old with a second-degree relative with type 2 diabetes should also undergo an OGTT [26].

Single kidney diabetic patients have higher proportion of albuminuria and lower GFR than single kidney non diabetic patients and diabetic patients with 2 kidneys [33]. Most transplantation centers regard established diabetes mellitus as a contraindication to living donation. According to International Amsterdam forum on living donor care, individuals with a history of diabetes or fasting blood glucose of ≥126 mg/dl on at least two occasions (or 2-h glucose with OGTT ≥ 200mg/dl) should be precluded from donating [12].

Prediabetes is viewed as a relative contraindication to living donation. Prospective donors with prediabetes (IFG, IGT) should be assessed on an individual basis. A study by Okamoto of 44 donors with impaired glucose tolerance concluded that these patients had equal

survival compared to a non-diabetic cohort at 5, 10, and 20 years. None of these prediabetic donors had chronic kidney disease or required diabetic medications at mean follow-up point of 7 years [34]. Individuals with prediabetes should be counseled about lifestyle modifications, healthy diet, exercise, and smoking cessation. They should be counseled about the risk of progression to overt diabetes. Experts recommend against donation in patients who have impaired glucose tolerance and additional risk factors, as listed above. Patients with impaired fasting glucose in the high range have a high risk of progression to diabetes and are discouraged from donation.

3.1.7. Inheritable diseases

When evaluating related living donors, special attention should be given to evaluate for potential inherited renal diseases. An extensive family history of renal disease manifestations, as well as extrarenal manifestations, namely hearing and ocular abnormalities and biopsy documentation of recipient's renal disease provide critical information in the decision-making process of kidney donation [35].

APKD

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, occurring in 1 in 400–1,000 live births, and accounting for more than 5% of cases of ESRD in Europe and North America. 85 % of the cases are secondary to a mutation in PKD1 gene on chromosome 16, which encodes polycystin1 and progress to ESRD at a mean age of 54 years. The remaining 15% of the cases are caused by a mutation in PKD2 gene, located on chromosome 4, that encodes for polycystin 2 and manifest with ESRD at the age of 74 [36].

The diagnosis of ADPKD is made based on age-specific criteria. In families of unknown genotype, the presence of 3 or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis in individuals aged 15 to 39 years, two or more cysts in each kidney is sufficient for individuals aged 40 to 59 years, and four or more cysts in each kidney is required for individuals ≥ 60 years. Conversely, fewer than two renal cysts in at-risk individuals aged ≥ 40 years are sufficient to exclude the disease [37].

In at risk individuals aged more than 30 years, absence of cysts by ultrasound excludes diagnosis of ADPKD in 98% of cases. In at risk individuals less than 30 years, a negative ultrasound does not rule out the disease; more sensitive imaging is needed such as CT Scanning and T2 weighted MRI which are more sensitive in detecting small cysts (<2-3mm). In potential donors aged <30 years, a negative renal ultrasound scan does not exclude type 2 ADPKD; however, a negative renal ultrasound scan and a negative CT scan may be adequate to exclude type 1 ADPKD in such donors [35]. When results of imaging are equivocal, genetic testing is available. This includes linkage analysis and gene sequencing. Linkage analysis requires multiple affected and unaffected family members. However, in clinical practice, it is difficult to elucidate an extensive family history of ADPKD. In that case, direct PKD gene sequence analysis would be required and is the most commonly used genetic testing. Because of the high prevalence of polymorphisms,

the diagnosis is established unequivocally by gene sequencing in only about 40–60% of all cases [38].

The failure to confirm or exclude the diagnosis of ADPKD has broad implications for both the donor and recipient, especially when the prospective donor is a young family member, in whom ultrasonography is less likely to be helpful. Huang et al [39] attempted to provide a diagnostic strategy that is based on genetic testing of live kidney donors at 50% risk for ADPKD in whom renal imaging studies are inconclusive. First, if genetic linkage analysis is not feasible, then the prospective recipient undergoes PKD gene sequencing. If a PKD gene mutation is identified then directed genetic testing of the donor is done. A donor is ineligible if the genetic test is positive. If the mutation is not found in the donor, then the diagnosis of ADPKD is excluded and transplantation can proceed. If the recipient's genetic test is indeterminate, then genotyping of the donor is not performed and donation is deferred. This strategy is likely to increase the number of renal transplants from living related donors who would otherwise have been excluded by their indeterminate renal imaging. It can also uncover undiagnosed ADPKD. On the other hand, the diagnostic sensitivity of direct sequencing is relatively low, especially for the PKD1 gene, because it is highly polymorphic. The test is expensive and adds to the cost of pretransplant evaluation. In summary, living donation is contraindicated in potential donors aged <30 years old for whom imaging techniques do not show cysts but for whom genetic tests show positive results for mutated PKD genes, although no data exist on the risk of ESRD in such individuals [35]. It is considered safe to proceed with kidney donation if imaging studies and genetic studies exclude ADPKD.

Alport's syndrome

In approximately 85% of patients, Alport syndrome is inherited as an X linked disease and is caused by mutations in the COL4A5 gene, which encodes the $\alpha 5$ chain of type IV collagen. De novo mutations occur in 10% of cases of X linked Alport syndrome. In 15% of the cases, the transmission is autosomal recessive, and is caused by mutations affecting COL4A3 or COL4A4 located on chromosome 2. The autosomal dominant form of Alport syndrome is very rare and is caused by heterozygous mutations in COL4A3 or COL4A4 genes. Affected individuals can also have sensorineural hearing loss and ocular abnormalities. Sensorineural hearing loss is the most common extrarenal manifestation and the progression of hearing loss often parallels the progression of renal disease. Anterior lenticonus, a conical protrusion of the lens in the anterior chamber, develops progressively and mainly occurs in male patients. The most common renal manifestation is hematuria.

Prospective donors with a family history of Alport's should be assessed by a urinalysis, estimation of glomerular filtration rate, a vision test and a hearing test. Male siblings aged >20 years without hematuria are very unlikely to have the disease and are suitable donors. Sisters of affected male recipients with X linked disease have a 50% risk of being carriers, unless the disease in the brother is caused by a neomutation. Gross et al reported the long term outcomes of six heterozygous mothers with microhematuria who had donated a kidney to their affected children. Three of the women developed new onset hypertension

and two developed proteinuria over a mean follow up time of 6.7 years. Renal function declined significantly in four of the donors [40]. A female relative without hematuria, has a low risk for being a carrier and is a suitable donor. Female relatives with proteinuria should be excluded from donation. Female relatives with persistent microhematuria are most likely carriers. Up to 25% of female carriers of X-linked Alport mutations develop renal failure and they should not donate [41]. Genetic analysis of COL4A5 genotype is not useful for determining the suitability of women for kidney donation given the absence of correlation between the genotype and the phenotype in women [35].

Thin Basement Membrane Disease

Thin basement membrane disease (TBMD) affects around 1% of the general population. Approximately 50% of patients have a heterozygous mutation in COL4A3 or COL4A4 genes. Although the long term prognosis of the majority of patients with thin basement membrane nephropathy is excellent, some patients develop proteinuria and progressive renal failure, especially those with documented heterozygous mutations in COL4A3 or COL4A4 genes [35]. The clinical course of TBMD is generally benign. However, the duration of most longitudinal studies has been too short to reflect prognosis. One study reported that 7% of patients with biopsy-proven TBMD had renal dysfunction with a serum creatinine level greater than 1.2mg/dl. Risk factors for progression are proteinuria, hypertension and abnormal renal function [42]. Other coexistent glomerular lesions, found in about 5% of patients with TBMD, namely IgA nephropathy, amongst others, can explain the abnormal renal function in these patients [43].

Donation from patients with TBMD remains controversial, given the lack of long term studies that address the outcomes of kidney donation in these patients. Patients with hypertension, proteinuria, or abnormal kidney function should not donate. Careful assessment of the potential donor's family history and extrarenal manifestations of Alport syndrome should be done. Patients with isolated glomerular hematuria must be assessed thoroughly for atypical features and, when these are present, a renal biopsy is advised to detect possible Alport syndrome and any other disease such as IgA glomerulonephritis. A kidney biopsy, however, might not distinguish between TBMD and early Alport's syndrome [44]. Atypical features include episodic gross hematuria that is uncommon in TBMD, but common in IgA nephropathy and Alport's. A family history of renal failure is common in IgA nephropathy and Alport's but not in TBMD [45]. Prospective donors should be counseled that, although TBMD has a benign course in general, renal failure may occur and long term risks remain unknown.

Systemic lupus erythematosus (SLE)

SLE occurs in about 12% of first degree relatives of patients with SLE. Prospective donors should be screened for ANA (antinuclear antibody), complement levels and abnormal urinary findings. Antiphospholipid antibody testing is suggested if the medical history is positive for deep vein thrombosis, stroke, pulmonary embolism, fetal loss, thrombocytopenia, hemolytic anemia, or livedo reticularis. Family member of a patient with SLE who has a positive ANA has a 40 fold increased risk of SLE and should not donate [45].

3.2. Evaluation of renal function

3.2.1. Glomerular Filtration Rate (GFR)

The most common approach to estimating GFR is with a 24-hour urine for creatinine clearance. This is the method used by approximately 90% of transplant centers in US, with the remaining programs using a radioactive isotope or iodinated tracer [16]. Creatinine based estimation equations are not reliable in the donor population, who have normal kidney function and should not be used. However, inadequate collection, low protein diet, low muscle mass and other factors may lead to low creatinine clearances in those with actually normal kidney function. Radionuclide methods, including iodine 124-iothalamate or technetium 99m-diethylenetriamine are used if the 24-hour creatinine clearance is borderline. The general cutoff for most centers is GFR of 80 mL/min/1.73 m², although as many as 20% of U.S. transplant centers would accept a creatinine clearance as low as 60 ml/min/1.73m² [12]. Some centers take into account the normal decline in GFR with aging at a rate of 4-5ml/min/1.73m² per decade of life starting the age of 20, allowing for kidney donation at lower limits of GFR.

3.2.2. Proteinuria

Proteinuria should be assessed with a 24-hour urine collection. Spot urine protein to creatinine ratio may underestimate the level of proteinuria. Most programs use protein >300 mg/day in a 24-hour urine collection as the cutoff to exclude donation [12,16]. Special attention should be made to transient causes of proteinuria, such as fever, urinary tract infections and exercise. When abnormal, the collection should be repeated to confirm the persistence of proteinuria.

3.2.3. Hematuria

Urinalysis is indicated in all prospective donors. Microscopic hematuria, defined as more than 3-5 RBC/HPF, needs further evaluation. Menstruation in premenopausal women should be ruled out as well as urinary tract infection. Persistent hematuria, confirmed on more than one urinalysis, deserves more investigation. Medical history should look carefully for a family history of TBMD, Alport's, ADPKD. The concomitant presence of proteinuria or RBC casts or dysmorphic RBCs is suggestive of underlying glomerular disease. Patients with persistent isolated hematuria should have urine cytology and urological workup including cystoscopy. They should also be screened for nephrolithiasis by a CT urogram (routinely performed as part of CT angiogram; discussed next). African American patients should be screened for sickle cell disease. In the absence of any specific abnormalities, a kidney biopsy may be indicated looking for Alport's, IgA nephropathy, among other pathologies [12,46]. If a full evaluation for persistent isolated hematuria is negative, most centers proceed with donation, since the risk for progressive renal disease is small. However, a survey of US transplant centers showed that 21% of programs automatically exclude potential donors with greater than 10 RBC/HPF, regardless of work-up [16].

3.2.4. Pyuria

In the presence of pyuria, urinary tract infections and prostatitis in men should be ruled out. If pyuria is persistent, renal tuberculosis should be ruled out with 3 morning urine acid-fast bacilli cultures. If these tests are negative, a renal biopsy should be considered to rule out interstitial nephritis or chronic pyelonephritis. Donation is contraindicated if there is evidence of renal tuberculosis, or interstitial nephritis or pyelonephritis [45].

3.3. Radiologic Evaluation of potential allografts

CT-based imaging is routinely used to evaluate the potential donor's anatomy. The 64 slice multidetector CT (MDCT) urogram and angiogram has become the gold standard imaging technique and has replaced the traditional arteriography and intravenous urography.

MDCT can provide assessment of the renal vein and artery, ureteral structure, renal parenchymal lesions, renal cystic diseases, stones, and surrounding anatomic variant. In addition, MDCT can measure kidney volume, a more sensitive index of size than length as available from sonography [47].

The left kidney is preferred for laparoscopic living donor nephrectomy because of its relative technical ease of removal and flexibility afforded by the longer left venous pedicle. MDCT permits detection of vascular abnormalities and variants. A right donor nephrectomy may be performed if complex vascular anatomy (e.g., multiple arteries or veins) is present in the left kidney. Preoperative imaging also helps identify the lower quality kidney (i.e., with incidental findings such as a small stone or hemorrhagic cyst), which is usually chosen in living donor transplantation [48].

MDCT detects asymmetry in the size of the kidneys, in which case a renal scan (MAG3) may be needed and the lower functioning kidney would be chosen for donation. The urogram phase of MDCT can delineate the presence of stones and abnormalities in the collecting system, such as ureteral diverticulum, calyceal diverticulum, hydronephrosis and ureteropelvic junction obstruction, ureteral duplication that may alter the surgical approach. Up to 30% of kidneys evaluated by MDCT have incidental renal finding such as renal cysts or calyceal calcifications. Patients with multiple stones, large single stone (>1.5cm), nephrocalcinosis or medullary sponge kidney are excluded from donation. [26,45] MDCT can also detect the amount of perirenal fat. This information is useful to determine if donors with higher BMI are amenable to a laparoscopic nephrectomy [26].

Donation is usually contraindicated if the following are present [45]:

- parenchymal abnormalities, including significant unilateral atrophy, or horseshoe kidney, presence of 2 or 3 cysts in each kidneys or complex or septated cyts, or angiomyolipoma
- vascular abnormalities: significant atherosclerotic disease, fibromuscular dysplasia

Compared to MRI/MRA, MDCT has greater accuracy, is faster, and more cost effective. MRA has inferior resolution in evaluating the renal vein anatomy. It is useful in patients with iodinated contrast allergy [49].

3.4. Surgical evaluation

3.4.1. Workup and evaluation

Potential donors should have a careful assessment of their perioperative risk for cardiovascular and pulmonary complications as well as thrombotic complications.

Unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease are contraindications to live kidney donation. Most of the intermediate predictors (mild angina, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus) are also contraindications to donation. Other, minor predictors warrant further testing [12]. Cardiovascular testing includes a transthoracic echocardiography if the history is positive for chest pain, palpitations, dizziness, syncope or SOB and/or the physical exam reveal a murmur.

A holter monitoring is indicated if history of arrhythmia, syncope, dizziness, or palpitations. Some transplant centers perform cardiac stress testing in prospective donors if they have one or more risk factors for coronary artery disease (age > 45 years old in men, and more than 55 in women, family history of premature coronary artery disease, hypertension, smoking).[26,45] However, the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines published in 2007, recommended stress testing only in high risk patients with poor functional capacity, who are scheduled for vascular surgery and only when such testing would change the management [50]. In most instances, when evaluating prospective donors, cardiac stress testing does not appear to be indicated.

Pulmonary function testing (PFT)

Pulmonary function testing (PFT) is not routinely indicated unless the history and physical examination suggest lung disease, in which case further testing, including PFT is indicated. Moderate to severe pulmonary disease is a contraindication to living donation (Forced expiratory volume (FEV1) or forced vital capacity (FVC) less than 70% of predicted or FEV1:FVC ratio less than 65% on PFTs). Patients with asthma who are well controlled, and with a peak flow measurement less than 80% predicted, can be considered on an individual basis for live kidney donation [51].

Smoking cessation

Smokers have a higher risk of pulmonary and wound infections after surgery than nonsmokers. Observational evidence suggests a benefit to smoking cessation before surgery [52]. Abstinence of smoking for only 12 hours can greatly reduce carboxyhemoglobin concentrations, improve oxygen content and reverse negative inotropic and arrhythmic effects. Polycythemia and increased blood viscosity take a few days to reverse. Sputum

production declines 6 weeks after smoking cessation. Amsterdam forum guidelines recommend smoking cessation at least 4 weeks prior to donation.

Alcohol abstinence

An increase in postoperative morbidity is reported for alcohol abusers who drink at least five drinks (more than 60 g ethanol) a day. Observational evidence in other clinical suggest that alcohol withdrawal is recommended for at least 1 month before surgery [53].

Hypercoagulability

Persons with personal history of one or more venous thrombosis or recurrent miscarriage or with a family history of thrombotic disease should be screened for hypercoagulable disorders. These include activated protein C resistance associated with factor V Leiden mutation, lupus anticoagulant, anticardiolipin antibody, prothrombin gene mutation (FII-20210), hyperhomocystenemia. Factor V-Leiden is the most common hereditary blood coagulation disorder, present in 3–8% of the healthy white population [54]. The odds ratio of a venous thrombotic event is 11 times greater in women taking oral contraceptives who have the Factor V Leiden mutation than for those who do not [55]. Some experts suggest that oral contraceptives and hormone replacement therapy should be withheld for 3 months prior to an elective surgery, given the high incidence of factor V Leiden in the population. A history of thrombotic disorders and presence of risk factors for future events (such as lupus anticoagulant, anticardiolipin antibody, abnormal activated protein C resistance ratio) as well as disorders requiring chronic anticoagulation are contraindications for kidney donation. However, a person with heterozygous factor V Leiden mutation and without previous thrombotic episodes is not necessarily excluded from donation [12,26,45].

3.5. Psychosocial evaluation

Every prospective donor should undergo a psychosocial evaluation. This evaluation is especially important for unrelated donation. The psychiatric evaluation should be performed by a psychiatrist or mental health professional who has no personal and clinical relationship with the recipient. The evaluation should address the protection of donor's confidentiality and should be performed in the absence of the recipient or recipient's advocates. If translation is needed, translators should be unknown to recipient and donor.

The evaluation would start by obtaining standard background information, such as donor's educational level, living situation, religious beliefs, cultural background, and employment history.

- The main elements of the psychosocial evaluation include the following:
- The donor's ability to make a decision should be assessed carefully, by evaluating for any underlying psychiatric disorders and any history of substance abuse. The donor should demonstrate a full capacity to give informed consent.
- The evaluation should assess the donor's accurate knowledge of recipient's health benefits, and the accurate understanding of the donation process, and its physical and

mental consequences, including short term surgical complications and long term effects of donation on health outcomes.

- The evaluation process should explore the nature of the relationship of the donor with the recipient, if any, and whether the donation was imposed by some expectations or perceived obligations on the part of either the donor or the recipient.
- The evaluation should assess the donor's motivation and inform the donor about the available option of not donating and the other treatment options available for the recipient. The prospective donor's rationale and reasoning for donating should be explored. The evaluation should exclude coercion, secondary gain (monetary or other personal gain, such as stabilizing self-image or dealing with a psychological conflict).
- The interview should inquire about the employment status of the donor and the availability of family support resources during the operative recovery period. The donor should have adequate financial and social support.
- The outcomes of transplantation should be explored, these include increased self-esteem after a successful transplantation and resentment and depression after an unsuccessful transplantation. In case of altruistic donation, the donor may experience depression because s/he may not witness and enjoy the positive outcome of the donation [45,56,57].

The major psychosocial contraindications for live donation include [57]:

- active psychiatric illness or substance use
- the presence of major financial stressors that could either have a coercive effect on the donor's decision to donate, or interfere with the need for medical care after donation
- evidence that the prospective donor has experienced pressure or coercion from others to donate
- a limited understanding or capacity to understand the donor's or the recipient's risks and benefits from kidney donation
- ambivalence about proceeding with the donation

3.5.1. Financial aspects

The economic impact of donation should be discussed with the prospective donor. The medical expenses are usually covered by the recipient's insurance, or, in certain circumstances, by the Transplant Centers Organ Acquisition Fund. The expenses include:

- the donor evaluation
- the actual donation surgery
- the post operative care

Other non medical expenses such as travel and lodging expenses are not covered by the recipient's insurance.

The act of donation should not preclude the donor from obtaining medical insurance or increase the cost of insurance [45]. In the USA, the organ donor leave act was created in 1999 and entitles the donor for 30 days of paid leave (Organ Donor Leave Act of 1999). However,

it is recommended that the prospective donor obtain health and life insurance prior to donation.

The donor should be financially stable and free of financial hardship. The evaluation should explore the ability of the donor to cover financial obligations for expected and unexpected donation-related expenses. The donor should be able to afford time away from work mainly for unplanned extended recovery time [56].

Paid donation

Despite the legal constraints, paid donation and commercialism are common in many parts of the world. In the USA, the Uniform Anatomical Gift Act was created in 1968 in order to establish an ethical system that regulated the availability of organs for transplantation. Further advances were made in 1984 by the National Organ Transplant Act, which established the nationwide computer registry operated by the United Network for Organ Sharing. The same act prohibits buying or selling of organs in the United States. Similar laws have been enacted in other countries around the world. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism strictly condemns all forms of organ trade [58]. It should be mentioned that other experts argue that the donors should be allowed to have monetary compensation and that the donors are entitled to use their bodies as they see fit. To address this issue and the concern of the short supply of kidneys available for donation, a regulated system of living unrelated paid donor kidney transplantation was legally adopted in Iran in 1988 [59]. However, most of the donors are poor and uneducated and follow up studies have shown that their lives have not improved after compensation for donation. Several types of regulated models offering indirect incentives or compensation for organ donations, such as health insurance, life insurance, disability coverage, or social benefits, have been proposed to encourage organ donations in developed countries [60]. Paid donation carries significant risks of exploitation of the poor. It poses significant health risks both for the donor and the recipient, including infectious complications, as well as other surgical and medical complications that, in part, are due to poor donor screening and evaluation [61].

4. Risks to donor

4.1. Surgical complications

Open nephrectomy is now largely replaced by laparoscopic surgical techniques that account for more than 50% of donor nephrectomy procedures in the USA [62]. Compared to open nephrectomy, laparoscopic procedure provides shorter hospital stays (2 to 4 days compared with 3 to 7 days), less incisional discomfort, minimal surgical scar and better cosmetic appearance and an earlier return to work (12 to 21 days compared with 30 to 60 days) [63].

Traditionally, laparoscopic nephrectomy (LN) is performed through 3 to 5 small incisions and has become the standard of care in most academic centers. Newer techniques are available; these include single port technique that has been shown to improve cosmetic results and lead to faster recovery [64-66].

Other new techniques include robotic assisted laparoscopic nephrectomy that allows the surgeon to dissect more meticulously and prevent bleeding more easily, along with shorter hospital stays [67].

Conversion to open nephrectomy occurs in approximately 2% of procedures [63]. The perioperative mortality reported for living kidney donors including both open and laparoscopic methods is 0.03% [13,62], although in a recent survey, all reported deaths were after laparoscopic nephrectomy [68].

The risk of perioperative and postoperative complications from unilateral laparoscopic nephrectomy is 10-15% [69]. These include, but are not limited to, bleeding, infection, bowel injury, hernia, and postanaesthesia depression.

Matas et al [68] surveyed 234 kidney transplant programs to determine living donor morbidity and mortality for open nephrectomy, hand-assisted LN, and non-hand-assisted LN between 1999 and 2001:

- 52% of nephrectomies were done by open procedure, 21 % by hand-assisted Laparoscopic nephrectomy, and 27% via non-hand-assisted LN
- 2 donors (0.02%) died from surgical complications, both after laparoscopic nephrectomy
- Reoperation was necessary in 0.4% of the open cases, 1.0% of the hand-assisted LN cases, and 0.9% of the non-hand-assisted LN cases
- Complications not requiring reoperation were reported in 0.3% -1% of the cases without statistical difference between the groups
- Readmission rate was higher for LN (1.6%) vs. open (0.6%) donors, mainly secondary to gastrointestinal symptoms, (nausea, vomiting, ileus, constipation)

With more experience, the reported complications of laparoscopic nephrectomy have decreased, after an initial steep learning curve. The morbidity of the laparoscopic procedure has decreased with more experience, and the mortality rate remains low.

A 2008 meta-analysis evaluated 73 studies that included 3751 and 2843 patients who had undergone laparoscopic surgery and open nephrectomy, respectively. Compared with open nephrectomy, the laparoscopic surgery group had a significantly shorter hospital stay and a quicker recovery. Both groups had similar rates of delayed allograft function and allograft loss [70].

While operative time is longer in laparoscopic nephrectomy (3-4 hours versus 2-3 hours in open nephrectomy), both procedures have similar recipient outcomes, graft function, rejection rate and graft survival [70,71].

4.2. Life expectancy

The survival of donors appears to be similar to that of the controls in the general population [8]. A Swedish study analyzed survival of 430 living donors. After 20 years of follow-up, 85% of donors were alive, whereas the expected survival rate was 66%. The better survival among donors is likely due to the selection process involved in donor work-up. Patients

with health issues are ruled out. Mortality pattern was similar to that in the general population, the most common causes of death being cardiovascular diseases and cancer [72].

4.3. Likelihood of renal disease in donor

4.3.1. Renal function and proteinuria

Unilateral nephrectomy is followed by a compensatory increase in the GFR in the remaining kidney to achieve about 70%-80% of pre-nephrectomy GFR within days to weeks after nephrectomy. Some proposed that the degree of compensation may be better in younger patients [73]. The detrimental effect of kidney hyperfiltration and hypertrophy are more pronounced when nephron number is reduced in infancy than when nephron number is reduced later in life [74]. This has been shown in many studies, including the study of 56 world war II soldiers, who had a unilateral nephrectomy at an average age of 25 years old, and who were reassessed 45 years following nephrectomy and compared to veterans with 2 kidneys. Mortality, prevalence of HTN and proteinuria were equal in both groups. 10 subjects had autopsy examinations and glomerular sclerosis was not increased [75].

Studies examining renal outcome in donors are heterogeneous and frequently lack a control group. However, long term follow up studies, more than 30 years after nephrectomy, did not show an accelerated decline of renal function. The decline in renal function seemed to parallel the age related decline of healthy individuals with 2 kidneys.

A study of 3,698 kidney donors from 1963 through 2007 showed that mortality of kidney donors was comparable to the general population. From 2003 till 2007, kidney function of 255 donors was assessed by iohexol clearance and urinary albumin to creatinine ratio. The mortality was comparable to the general population. 85.5% of the donors had an iohexol GFR >60 mL/min/1.73 m². Hypertension was noted in 32% of the donors, albuminuria (defined as urine albumin/creat ratio above 0.02) in 12.7%, and none of the donors with albuminuria had an iohexol GFR lower than 45 ml per minute per 1.73 m². Importantly, the prevalence of hypertension and albuminuria in kidney donors were similar to those in controls who were matched for age, sex, race or ethnic group, and body-mass index. There was no excess risk of ESRD in donors. Factors linked to a reduced GFR in donors are the same as those that have been observed in the general population, namely, age and obesity [8].

In this study, a longer time since donation, however, was independently associated with albuminuria. This may be attributable to single nephron hyperfiltration, secondary to reduced renal mass but does not seem to be associated with higher risk of renal dysfunction.

In a review that summarizes 48 studies that included a total of 5000 donors on average, kidney donation resulted in small increases in urinary albumin, which increased with the time after donation (three studies totaling 59 controls and 129 donors; controls 83mg/day, donors 147mg/day, weighted mean difference 66mg/day, 95% confidence interval (CI) 24–108) [76]. Whether the hyperfiltration injury that is reflected by the albuminuria leads to a progressive deterioration in kidney function has been the subject of many debates.

In this same review, after an average of 7 years after donation, the average 24 h urine protein was 154 mg/day and the average GFR was 86 ml/min. Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls. In addition approximately 12% of donors developed a GFR less than 60 ml/min during follow-up. However, after the initial decrement in GFR from the nephrectomy, there was no evidence of an accelerated loss in GFR over that anticipated with normal aging [76].

4.3.2. Hypertension

Although some studies show that the prevalence of HTN among donors is identical to that observed in the general population [77], other studies did reveal that the incidence of hypertension increases after kidney donation [78,79].

However, in most of these studies, this increase in arterial pressure is statistically significant but clinically irrelevant and most of the donors do not reach values to be considered as hypertensive [80]. In a meta-analysis done by Boudville et al [79] in 2006, the authors described an increase of 5 mmHg in the 5–10 years following the kidney donation.

However, racial disparities should be taken into account as it has been suggested recently that non-Caucasian donors could have a higher risk of HTN. This has been shown in a retrospective analysis of the prevalence of Diabetes, HTN and CKD among 4650 donors compared to the prevalence patterns in the 2005-2006 National Health and Nutrition Examination Survey (NHANES) for the general population. Compared to white donors, AA and hispanic donors were found to have increased risk of HTN, diabetes and CKD. The absolute prevalence of diabetes among all donors did not exceed that in the general population, but the prevalence of hypertension exceeded NHANES estimates in some subgroups. End-stage renal disease was identified in less than 1% of donors but was more common among black donors than among white donors [81]. These findings emphasize the importance of increased attention to health outcomes among demographically different donors and the need for close medical follow up.

4.4. The need for transplantation of previous living kidney donors

The UNOS database has recorded since 1987 an incidence of about 0.04% of living donors who have been listed for kidney transplantation, similar to the 0.03% incidence in the general US population. In the follow up study by Ibrahim et al of 3698 donors, 11 donors developed ESRD, at a rate of 180 cases per million per year, compared to the rate of 268 per million persons per year in the white population in USA. Three of the 11 donors had the same cause of ESRD as their sibling recipients, suggesting unrecognized familial renal disease or risk factors.

Upon review of the OPTN (Organ Procurement and Transplantation Network) database, as of February 2002, a total of 56 previous living donors have been identified as having been listed for deceased donor kidney transplant. The majority of these patients originally donated a kidney to a sibling (86%); five patients donated to a parent, and three patients donated to a child, highlighting again the possible role of unrecognized familial risk factors for kidney disease [82].

According to the UNOS/OPTN database between 1993 and 2005, African-Americans constitute 40% of the donors on the waiting list for transplant, although they represent only 14% of the whole living kidney donor population, emphasizing the fact that AA might be at greater risk for ESRD after kidney donation [15].

The Amsterdam forum proposed the current UNOS policy for live kidney donors that assigns an allocation priority for a deceased donor kidney if the previous live kidney donor subsequently become a candidate for a kidney transplant later in life. However, there was no consensus to develop such a policy internationally [12].

5. Non directed donation

As of January 2009, biologically unrelated donors constituted about 40% of the living donors in the USA. Most of these donors were emotionally related and have an apparent, strong and deep relationship with the recipient (spouse, close friend, significant other, adopted sibling). Prospective donors with a much more casual relationship with the recipient (coworkers, members of faith community) or with little or no relationship to donors (solicited through internet, media...) are becoming increasingly common and about half of unrelated donors fall into this category.

Non directed donors, also called altruistic donors, or 'Good Samaritan Donors' donate their kidney to a completely unknown recipient, whom the donor might never meet. They represent about 1.5% of all living donors in the USA as of January 2009. This practice is not allowed in some countries in Europe and South America because of the fear that the donor might be selling his/her kidney.

Generally, the recipient is a patient on the deceased donor list, with a compatible blood group, the most waiting time and a negative crossmatching. The nondirected donors play an important role in kidney paired donation and living donor exchange programs. The evaluation process of nondirected donors has a strong emphasis on the psychosocial aspects of the donation, exploring any false perceptions or covert depression. Nondirected donors might be at a greater risk for depression or regret since they might not be able to enjoy the positive psychological gain that comes from seeing the recipient benefit from their altruism [26,57].

6. Paired kidney donation

Patients with potential donors who are incompatible due to ABO differences or positive crossmatch can still reap the benefits of living donation through kidney paired donation (KPD). A simple "two-way" exchange, or swap, can be arranged between two incompatible pairs or a more complicated combination can be achieved using many pairs in many different hospitals. Such a large exchange is often initiated by a non-directed donor. This concept of KPD was first suggested by Felix Rapaport in 1986 and in 1991, the first kidney exchange was performed in South Korea. The next year, the first KPD transplants were performed in the USA in 2000. As of the third quarter of 2010, over 1000 KPD transplants have been performed in the USA [57,83].

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