CHAPTER 31

National Kidney Registry: 213 Transplants in Three Years

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New options for end-stage renal disease patients who have a willing and medically suitable, but immunologically incompatible living kidney donor are among the most exciting advancements to the field of kidney transplantation. Kidney paired donation and particularly the increasing utilization of chains of transplants initiated by a non-directed donor (NDD) (1-4) have increased the number of living donor transplants performed each year. Since facilitating its first transplants in 2008, the National Kidney Registry (NKR) has organized more transplants than any other exchange program in the world. By the end of 2010, NKR had facilitated 213 transplants, including 130 in 2010 alone (Fig. 1). By working with many of the top 20 centers (by volume) and leveraging cutting edge computer technology, the National Kidney Registry has broken through many of the barriers that have frustrated preceding paired exchange efforts.

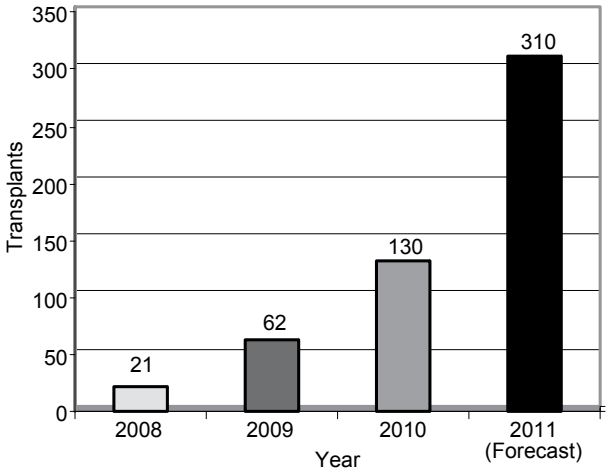

Figure 1. NKR Annual Transplants Facilitated.

THE NKR APPROACH

The National Kidney Registry was started and is personally managed by a complete transplant industry outsider – a dad who wanted to donate a kidney to his daughter, but could not because he was crossmatch incompatible. The frustrating search for a compatible donor for his daughter led him to recognize that there had to be a better way to find a compatible donor for the thousands of patients who need kidney transplants and have incompatible donors (www.kidneyregistry.org).

Rapid innovation and advanced computer technology

NKR has benefited from a lack of physician bias in the core development team. No member of the core team has a medical background – most have business and technology backgrounds, allowing for rapid innovation. The team has relied on the active support and oversight from an experienced Medical Board made up of transplant industry veterans. As a result, many bold and technically difficult innovations have been implemented, which have accelerated matching success, including:

- Utilization of a web portal for easy pair enrollment and fast center startup
- Elimination of all personal health information avoiding HIPAA issues
- Use of donor and recipient preferences to control the match process
- Use of real-time matching software allowing for up to 20-deep match offers
- Assessment of pair match probability for initiation of advanced match strategies

- Standardized identification and listing of all relevant HLA antigens and antibodies
- Inclusion of non-A1 donors to match acceptable O and B blood group patients
- Daily match runs supporting immediate match identification and chain repair
- Automated match offer tracking for organized and efficient operation
- Utilization of existing infrastructure to ship kidneys eliminating need for donor travel
- Implementation of real-time geotracking technology for shipped kidneys
- Effective incorporation of out of sequence chain transplants
- Creation of the children & high PRA program for ending chains
- Introduction of a standardized financial model for centers

Sophisticated match software

As the length of the matched clusters that make up the segments of each transplant chain is extended, the number of transplants that can be facilitated increases dramatically. For example, a pool of 100 incompatible donor/recipient pairs running a 3-deep chain will generate approximately 10 billion combinations. If the length of the matched cluster increases by just one, to 4-deep, the number of possible combinations increases to 100 trillion. Utilizing software that can find a cluster length of 20 deep, a staggering 10 to the 78th power of possibilities would be possible. Optimizing for ABO and HLA compatibility, age considerations, travel restrictions, additions of NDDs, additions of new pairs and other donor/recipient preferences requires extremely sophisticated software for finding and evaluating possible matches.

Over the past decade, different registries have developed a variety of computerized systems to support multi-center traditional paired exchanges and chain matching. Most of the early systems were based on integer programming algorithms which were the best tools to solve the complex mathematical problem presented by the traditional paired exchange reciprocity requirement. With the advent of chains, these original integer programming solutions had to be modified to accommodate the radically different mathematical challenge presented by chains. The NKR system was created solely based on the chain model utilizing technology components employed by modern capital market exchange systems (e.g. New York Stock Exchange) departing from integer programming algorithms historically used for paired exchange.

Innovations drive performance

The innovations pioneered by the National kidney Registry and its Medical Board have exceeded all prior paired exchange efforts. Key performance measurements include the average wait time and percent of pool transplanted and NKR centers have transplanted 64% of patients who were registered as average waiting times fell from 3.8 years in 2008 to 11 months for those transplanted in 2010 (Table 1).

Advanced matching strategies

Clinical experience in paired exchange demonstrates that the transplant center managing the donor/recipient pairs has a significant impact on the probability of the pair finding a match in an exchange. Centers that have implemented advanced matching strategies (Table 2) consistently are able to transplant 75% or more of their pairs, indicating that there is a material center effect at work in paired exchange. If this trend continues, we may see paired exchange centers of excellence emerge as patients become more aware of, and

Table 1. Program Statistics - including percent of pool transplanted.

		2008	2009	2010
A	Ending Candidate Pool	80	127	120
B	Transplants	21	62	130
C	Cumulative Transplants	21	83	213
D	Cumulative Candidate Pool	101	210	333
E	Percent Transplanted (C/D)	20%	40%	64%
F	Average Wait Time (A/B)	3.8 Years	2.0 Years	11 Months

Table 2. Advanced Matching Strategies.
Utilize non-A1 blood group donors for O and B patients with acceptable titers
Include compatible pairs (e.g. O donors with non-O patients)
Relax preference restrictions (e.g. accept shipped kidney, etc.) based on Match Power Report sensitivities
Raise MFI thresholds for unacceptable HLA antigens - combine with desensitization protocols for broadly sensitized patients
Utilize alternate potential donors – O donors are 20X more powerful
Start chains and take advantage of the NKR CHIP program to get patients without donors transplanted
Increase pool size by encouraging other centers to join and enrolling more pairs at your center
Outreach utilizing center-hosted seminars on paired exchange, call all patients on wait list and educate pairs up front.

seek out those centers that demonstrate superior performance in paired exchange.

To provide the information that allows participating centers to leverage advanced matching strategies, the NKR has automated the metrics for calculating adjusted PRA scores (A-PRA, which also reflects ABO incompatibility) as illustrated in Table 3. The A-PRA score is then inverted to determine the probability of a recipient finding a match in the pool at any given time. The recipient's paired donor is also evaluated to determine how many recipients in the pool they match to determine the power of the donor. The recipient score and donor score are then multiplied against each other to determine the pair's exchange power score (far right column). Based on

Table 3. Measuring Pool Liquidity & Pair Match Power.

			Raw Scores					Preference-Adjusted			
Recip	Antibody Count	Recip ABO	Recip Match Power	Donor	Donor ABO	Donor Match Power	Pair Match Power	Recip Erosion	Donor(s) Erosion	Pair Erosion	Pair Match Power
RKMT	0	O	30.7%	DMG	A	5.2%	159	11%	0%	11%	141
RKR	0	O	31.7%	DMT	A	2.3%	73	2%	0%	2%	72
RMD	2	B	18.6%	DMTB	O	15.5%	288	16%	4%	19%	232
RMV	35	AB	0.5%	DNV	O	14.9%	7	100%	4%	100%	0
ROI	0	O	31.7%	DEM	A	1.7%	54	22%	0%	22%	42
RPC	41	O	1.0%	DJEC	O	16.7%	17	0%	3%	3%	16
RRBR	13	A	0.5%	DMM	O	18.4%	9	0%	3%	3%	9
RRBUST	13	O	0.5%	DCH	O	17.8%	9	0%	3%	3%	9
GB	49	A	3.5%	SH	A	3.4%	12	0%	0%	0%	12
HL	0	O	31.7%	CP	A	2.3%	73	17%	0%	17%	60
R25UTMC	21	O	0.5%	D25UTMC DB25UTMC	A A	2.3% 2.3%	1 1	0%	0%	0%	1 1
R30UTMC	54	A	0.0%	D30UTMC	O	16.1%	0	0%	0%	0%	0
R33UTMC	63	A	0.5%	D33UTMC	A	4.0%	2	0%	0%	0%	2
R37UTMC	0	O	31.7%	D37UTMC	A	4.0%	127	90%	0%	90%	12
CLT9118	41	A	0.0%	ATT9548	AB	0.6%	0	0%	0%	0%	0
FBM7827	35	O	1.5%	DMH8749	A	1.7%	3	0%	0%	0%	3
JMB1124	53	O	0.0%	AHW4569	O	19.5%	0	0%	3%	3%	0
MNN9324	48	A	0.0%	MLN8213	A	1.7%	0	0%	0%	0%	0
SBMVT	50	O	0.0%	DRRVT	O	19.5%	0	0%	0%	0%	0
SPSVT	20	A	0.5%	LCPVT HMSVT	A O	2.9% 14.4%	1 7	100%	2%	100%	0 0
GE1956	0	B	37.2%	CRS1950	A	2.3%	86	1%	0%	1%	85
HH1978	0	O	31.7%	JPG1987	A	1.7%	54	13%	0%	13%	47
JH1949	61	A	0.0%	KAJ1951	A	2.9%	0	0%	0%	0%	0
JM1956	59	A	0.0%	ARP1967	A	2.9%	0	0%	0%	0%	0
TH1955	64	A	0.0%	END0051	AB	1.1%	0	0%	0%	0%	0
VZ1972	45	A	0.5%	END0055	AB	1.1%	1	0%	0%	0%	1
	30		2.5			12.0	3,722	14.36%	0.86%	14.97%	4,100

Table 4. Match Offer Email – Automated Process.

Subject: NKR Alert - Match Offer - Chain 66/Cluster 1

Attach... Contacts20100629184750.xls (91 KB); FinancialAgreements20100629184751.rtf (727 KB); MedicalInformation20100629184747.xls (295 KB)

NKR Alert - Match Offer

Chain 66 **Cluster** 1

Match Acceptance Deadline

Friday, 7/9/2010, 9 PM EST (EST)

Participating Centers

CPMC
Stanford
Barnabas
UCLA
HUMC
Pinnacle
Our Lady
UTMC
Cornell

Match Participants *(Multiple Attachments – Please Use the Contacts Attachment to Communicate between Centers)*

Cluster Position	Donor Center	Donor Alias	Recip Center	R Alias (Right Click)	AntGen Pts	Donor ABO	Recip ABO	Donor Age	Recip Age	Age Δ (D Kilos) [D Kilos UnderWt]	Recip A-PRA	Considerations
[1]	NKR	PASQJ	Stanford	SUR2040	0	O	O	63	47	16 (58)		Ship
[2]	Stanford	SUD2041	Barnabas	MIGS	35	O	O	47	37	10 (83)		Ship
[3]	Barnabas	EVES	UCLA	RKARED	50	O	O	60	50	10 (18)		Ship
[4]	UCLA	DRH	HUMC	RFS02	10	O	O	44	2	42 (116)		Ship
[5]	HUMC	DFSSR	Pinnacle	DEPMAR	25	O	O	33	47	-14 (72)		Ship
[6]	Pinnacle	DEPBET	Our Lady	ALEFT	0	A	A	45	48	-3 (71)		Ship
[7]	Our Lady	OLEFT	CPMC	GASWE	25	O	O	52	73	-21 (90)		Ship
[8]	CPMC	ROHEI	UTMC	R22UTMC	40	A	O	64	63	1 (53)		Ship
[9]	UTMC	D22UTMC	UCLA	RLDB	10	A	A	35	51	-16 (102)		Ship
[10]	UCLA	DDDB	UCLA	RJF	35	B	B	45	67	-22 (60)		Same Cntr
[11]	UCLA	DMF	UCLA	RJW	0	A	A	40	47	-7 (75)		Same Cntr
[12]	UCLA	DSWW	CPMC	JEMED	25	B	B	44	37	7 (58)		Ship

BD No.	Center	Alias	Trvls?	ABO	Age
1	CPMC	MIMED	No	A	35

Match Acceptance Commitments

these metrics, participating centers can implement advanced matching strategies that have proven to increase the odds of a pair finding a match and getting transplanted.

Automated match offers and tracking

One of the non-trivial challenges in making a large number of match offers across multiple centers is the organization of the match offer and tracking process. Since its inception, NKR has continued to automate and streamline this process so that match offers (Table 4) can be identified, evaluated, emailed and closed out in under 48 hours. This ability to initiate match offers at any time and complete the offer cycle in less than 48 hours, allows for rapid transplantation of participants, as well as immediate repair of broken chains.

Standardized identification and listing of all relevant HLA antigens and antibodies

When the NKR program was in the start-up phase, unexpected cross match failures were disrupting more than half of the match offers being made. In May of 2009, the virtual cross match accuracy rate was 43%. At that time, a national lab director group was formed by the leading NKR centers to improve virtual cross match accuracy. By the end of 2010, the virtual cross match accuracy rate had increased to 91% with many of the failures no longer attributed to histocompatibility issues but to simple clerical errors. This dramatic improvement (Fig. 2) has greatly accelerated the rate of paired exchange transplantation and is the direct result of the collaboration of many experienced and skilled lab directors from leading NKR centers. Key innovations that have improved the process include:

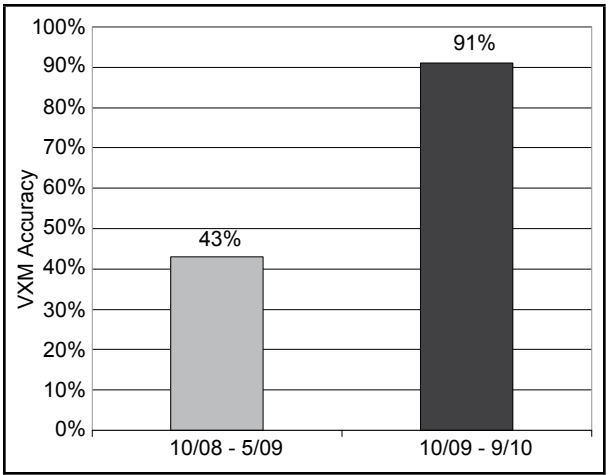

Figure 2. Improved Virtual Cross Match Accuracy.

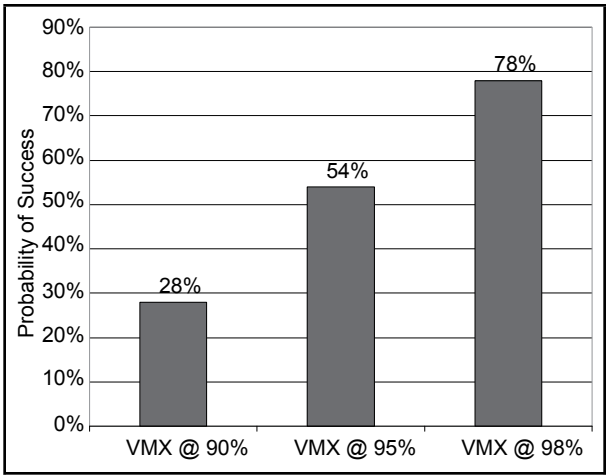

Figure 3. Probability of Success by VXM Accuracy.

- Standardization of all antigen and antibody codes
- Review of all cross match failures by laboratory directors
- Corrective action plan for centers failing live cross matches
- Required entry of HLA-DP antibodies and HLA-DP donor antigens

As the virtual cross match accuracy increased, driven by the innovations adopted by the national lab director team, it became feasible to make larger match offers. So in early 2010 NKR's matching system was upgraded to find clusters up to 12 deep so that large match offers could be made. Figure 3 and Table 5 demonstrate the importance that virtual cross match accuracy has on the probability of a 12-deep match offer actually working. Since the implementation of 12-deep matching capabilities, several 12-deep chains have actually gone from offer to completion. As a result of this success, the NKR matching system was further enhanced to go 20-deep at the end of 2010. In December 2010, the longest match offer, an 18-deep cluster, was accepted and is undergoing cross match testing.

Shipping living donor kidneys

Shipping living donor kidneys was an unsettling prospect to many transplant professionals. The perceived association between prolonged cold ischemic time and poorer graft function, which has incorrectly been considered the defining difference between living and deceased donor kidneys (5), caused some physicians to move cautiously. Lacking a strong bias and with the flexibility in the start times of chain transplants, shipping living donor kidneys was the model that the donors and recipients preferred and expressed via the NKR preferences. The willingness to ship living donor kidneys expanded the options for pairs as it broadened the geographic area from which compatible donors and recipients could participate. In 2010 NKR centers shipped nearly 100 living donor kidneys, sometimes from coast to coast. Many had cold ischemia times of more than 14 hours (6). A recent compilation of

Table 5. Probability of Success with 12-Deep Match Offer.

Position	VMX at 90%	Cumm VMX	VMX at 95%	Cumm VMX	VMX at 98%	Cumm VMX
1	90%	90%	95%	95%	98%	98%
2	90%	81%	95%	90%	98%	96%
3	90%	73%	95%	86%	98%	94%
4	90%	66%	95%	81%	98%	92%
5	90%	59%	95%	77%	98%	90%
6	90%	53%	95%	74%	98%	89%
7	90%	48%	95%	70%	98%	87%
8	90%	43%	95%	66%	98%	85%
9	90%	39%	95%	63%	98%	83%
10	90%	35%	95%	60%	98%	82%
11	90%	31%	95%	57%	98%	80%
12	90%	28%	95%	54%	98%	78%

the outcomes for 56 shipped living donor kidneys from 30 centers, including many shipped by NKR centers, showed good early function despite longer cold ischemia, and attests to the safety and feasibility of the practice (7).

Currently, when chain participants express preferences requiring the shipment of kidneys, the kidney travels instead of the donor. This allows the donor to recover with their intended recipient (spouse, family member or friend), rather than traveling and recovering in an unfamiliar city and surroundings. These living donor organs have been typically shipped unaccompanied on commercial airlines, although there is now an increasing trend to utilize charter flight options as transplant centers strive to minimize the unreliability of commercial flights. Transport is arranged by local organ procurement organizations (OPOs) or national courier firms, who utilize the same policies and procedures that are well established for the transportation of deceased donor organs. This existing organ shipping capability is being enhanced with geo-tracking devices to provide real-time tracking of the organ to prevent lost or misrouted kidneys.

The United States has already established international exchanges for deceased donor organs, so it would not be much of a stretch to apply this to living donor organs. In fact, in the same time it takes for a kidney to travel across the United States a kidney could also travel across the Atlantic, between New York and London. This would greatly expand the donor pool. More practically, living donor kidneys could easily be shipped between the major centers of Canada and the United States, where health care standards are similar and flight times are often less than 3 hours.

Creation of the children and high PRA program (CHIP)

Several members of the NKR Medical Board pointed out in early 2010 that the NKR matching system could be utilized to get patients transplanted who have a low probability to receive a deceased donor transplant because they are very highly sensitized. By sharing bridge donors and hard to match non-directed donors across the NKR member centers, the process would improve the odds for hard-to-match patients enrolled in the program. Later in the testing of the program, the NKR Medical Board voted to include pediatric candidates in the program. The program was subsequently named the CHIP (Children and High PRA) program. Table 6 outlines the CHIP program parameters.

Table 6. Children & High PRA Program (CHIP). The CHIP program helps patients without donors who are either children or are disadvantaged because they have high PRA.

NKR member centers that have net chains started >0 may enroll up to 30 candidates in the CHIP program
Net chains started is the total number of chains that a center starts less the total number of chains a center ends
CHIP candidates must be children (18 or younger) or adults that have a PRA score >50%
The most likely blood types to find a CHIP match are AB and A blood types. Sometimes B candidates can be matched, but it is rare

Standard financial model between centers

One of the underappreciated barriers to paired exchange transplantation was the payment process between transplant centers. This is necessary so that the donor centers can recover their costs of providing the donor surgery services. This barrier became a crisis in late 2009 when an NKR facilitated triple exchange was cancelled a day prior to surgery because the transplant centers involved could not agree on how much to pay each other. Not only were 3 patients left on dialysis, but this last minute cancellation was the catalyst for a broken chain as the bridge donor for this cluster eventually withdrew. In the wake of this devastating situation, the leading NKR member centers came together and developed a standard financial model (Table 7) that has eliminated nearly all of the problems related to payments between centers involved with NKR facilitated exchanges.

Table 7. Match Offer Financial Agreement.

National Kidney Registry

Match Acceptance & Financial Agreement

Chain 92, Cluster 1, Position 2

Donor Hospital and Recipient Hospital hereby accept this match offer and agree to the following financial arrangement.

Billing Information	Donor Hospital	Recipient Hospital
Hospital bill to name	Hackensack University Medical Center	Saint Barnabas
Billing contact name	Joyce *****	Andrea ******
Billing contact phone	(201) 996-****	(973) 322-****
Street	Organ Transplantation Sanzari, 401, 30 Prospect Av	94 Old Short Hills Rd. 3rd Fl. EW
City, State & Zip	Hackensack NJ 7601	Livingston NJ 7039

	Donor Hospital		Recipient Hospital	
Financial Contacts	**Primary Contact**	**Backup Contact**	**Primary Contact**	**Backup Contact**
Name	Joyce ******	Joan ******	Andrea ******	Vickie ******
Phone	(201) 996-****	(201) 996-****	(973) 322-****	(973) 322-****
Email	*****@humed.com	*****@humed.com	*****@sbhcs.com	*****@sbhcs.com
Fax	(201) 498-****		(973) 322-2634	

Patient Information	Donor	Recipient
Hospital	HUMC	Barnabas
Patient Alias	MICHLEO	JAMB
Year of Birth	1962	1954
Name		
SSN		

Recipient Information

Insurance		Subscriber if not patient		Global case rate	
Ins Last Updated		Precert phone		Professional case rate	
Benefit phone		Case manager name		Case manager phone	

1) General: In all cases the donor shall not be billed for transplant related medical services including donation evaluation, in-patient stay for donation and post donation complications per Medicare standards. Out of state Medicaid/Medi-Cal patients are not covered by this agreement. All claims must be submitted to the Recipient Hospital within 120 days from the last day of service. Acknowledgement is due upon receipt of claims. Claims payment is due as soon as possible and no later than 90 days from the receipt of an accurate claim.

2) Pre-Transplant Donor Evaluation Services: The Donor Hospital shall provide pre-transplant donor evaluation services. The Donor Hospital shall allocate all costs for the donor evaluation to their Medicare cost report. Physicians participating in the donor evaluation shall bill the Donor Hospital.

3) Organ Transportation: Transportation of the donor organ to the recipient hospital shall be coordinated by the Donor Hospital's Organ Procurement Organization who will bill the Recipient Hospital for the costs associated with transporting the organ.

4) Recipient Inpatient Services: The Recipient Hospital shall bill for services as customary with claims submitted to the recipient's insurance. The physicians shall bill the recipient's insurance for services rendered.

5) Donor Complications: If Medicare is primary, physician services shall be billed to Medicare. If Medicare is not primary then physician services shall be billed to the recipient's insurance unless there is a global arrangement. Technical services are billed to the Donor Hospital.

6) Hospital Donor Nephrectomy: The Donor Hospital shall bill the Recipient Hospital for the donor organ recovery by billing the Recipient Hospital with a copy of their most currently filed Medicare Cost Report, Worksheet D-6, Part I, which will document the cost per day and the appropriate cost to charge ratios along with a worksheet that reduces the Donor Hospital bill from charges to cost. This will document the cost of the case which is the amount to be paid by the Recipient Hospital.

7) Physician Donor Nephrectomy: Physicians shall bill the Recipient Hospital or recipient's insurance for services rendered according to the following:

- If Medicare is Primary, physicians shall bill Medicare utilizing the recipients Medicare number.
- If the Recipient Center has a "global" or "case rate" arrangement, the donor physicians shall bill and receive payment from the Recipient Center at 150% of Medicare Participating. Anesthesiology shall bill and be reimbursed at $65.29/ASA unit.
- If the recipient center does not have a "global" or "case rate" arrangement, the recipient center will work with the donor center to ensure the donor physicians get paid appropriately.

FUTURE DIRECTIONS

Government sponsored kidney paired exchange programs

While Korean and Dutch government sponsored national kidney registries have enjoyed success (8,9), other government sponsored programs have lagged. In the United States, UNOS has been working on a national paired exchange program since 2004 with a total of 2 transplants facilitated by the end of 2010. Meanwhile, non-government efforts including the NKR have filled the void by facilitated numerous transplantations and engendering cooperation between transplant centers from coast to coast. The practical aspects of exchanges may be evolving too rapidly for a bureaucratic organization such as UNOS to keep up with the rapid pace of innovation. Additionally, the paired exchange program being piloted by UNOS includes limitations such as infrequent monthly match runs, the requirement for simultaneous surgeries, lack of web based portal for data entry and use of software considered obsolete by many in the transplant community. The process of monthly match runs has been shown to slow the process and reduce transplant opportunities. The simultaneous surgery requirement, although mitigating some risk, requires capacity that only exists in the largest centers, and will exclude smaller transplant centers from participating. The matching software employed by UNOS may be the most significant limitation as it only finds matches for 2- and 3-deep traditional paired exchanges. Actual experience demonstrates that 20-deep chain matching will find more matches including the hardest to match patients and will maximize transplant opportunities for ESRD patients.

Economic benefits of chain transplantation

The economic benefits of paired exchange to the US health care system over the next decade may be in excess of $100 billion dollars based on our research (http://www.kidneyregistry.org/docs/NKR%20White%20Paper.pdf). When ESRD patients are removed from dialysis through paired exchange transplantation, an enormous economic savings is generated. There are 3 primary financial beneficiaries of a paired exchange transplant 1) transplant centers 2) insurance companies and their self-insured customers and 3) Medicare and the US government. When a paired exchange transplant takes place, the transplant center/hospital realizes approximately $80,000 - $200,000 in incremental revenue. If the patient is covered by private insurance, the insurance company saves about $300,000 (Table 8) based on figures provided by the largest health insurance companies in the United States. Finally Medicare and the US government save approximately $1,100,000, mostly by avoiding ongoing dialysis costs (Table 9). To date, neither the insurance industry nor Medicare has provided any material financial support to the paired exchange efforts with most of the funding coming from charitable contributions and transplant centers. If Medicare and the insurance industry provided financial contributions to support paired exchange, commensurate with their financial interest, many more paired exchange transplants could be facilitated.

Table 8. Insurance Company Savings.

Annual Dialysis Costs *	$150,000
Years on Dialysis	X 3
Dialysis Savings	$450,000
Cost of Transplant	($100,000)
Post-Transplant Costs	($50,000)
Net Savings	$300,000

* Pittsburg Inquirer 9/28/09 – does not include other dialysis related costs.

Table 9. Medicare Savings.

Dialysis Less Transplant Maintenance (GAO study)	$42,388
Disability & Lost Tax Revenue (NKR White Paper)	$18,500
Total Annual Savings	$60,888
Average Kidney Life Years *	X 20
	$1,217,760
Approximate Cost of Transplant	($100,000)
Present Value of Savings (assumes inflation is roughly equal to the U.S. government cost of capital)	$1,117,760

* Does not include additional kidney life years from compatible pairs who achieve better compatibility through paired exchange.

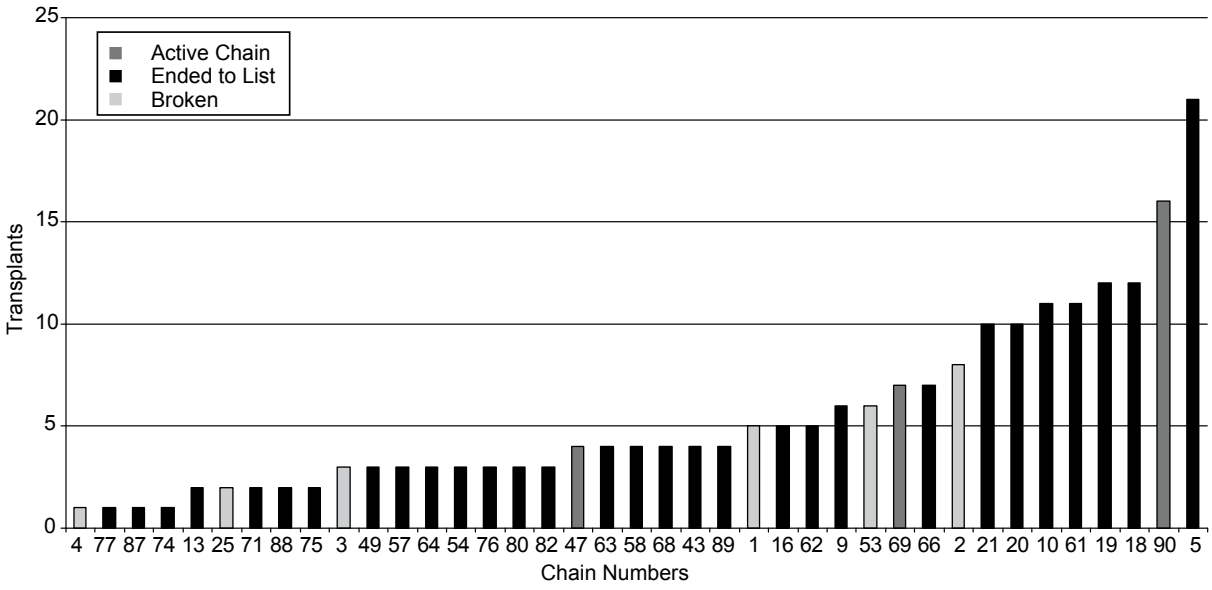

Figure 4. Review of NKR Chain Lengths.

Table 10. Summary of Broken Chains by Year.			
Year	# Bridge Donors	# Broken Chains	% Broken Per Year
2008	9	3	33%
2009	29	2	7%
2010	61	1	2%
Total	99	6	

Table 11. Strategies to Reduce Broken Chains.
Utilize larger clusters/ longer chains
Transplant clusters simultaneously
Evaluate bridge donor candidates
Only hold blood group O bridge donors
End blood group A, B and AB donors to the list
Don't allow bridge donors to wait too long
Complete bridge donors' medical evaluations
Avoid canceling exchanges at the last minute

Donor withdrawal and broken chains

There has been much debate about whether bridge donors can be trusted to pass on the generosity and donate to the next recipient in the chain after their intended recipient has already received a kidney transplant. Based on NKR observations of over 200 chain transplantations, the frequency of broken chains has decreased significantly as centers have become more astute in selecting bridge donors and as more chains have been ended to the wait list (Table 10, Fig. 4). By 2010 the bridge donor withdrawal rate was down to 2% reflecting the successful implementation of strategies employed to reduce broken chains (Table 11).

Actual clinical experience indicates that most bridge donors are so grateful of their intended recipient's improved health that they look forward to "paying the gift forward" to the next recipient in the chain. Even if bridge donors have to wait months before donating, are required to lose weight or need to modify their lifestyle (i.e. reduce alcohol intake) they remain motivated and follow through with donation to the next complete stranger in the chain. In fact, one bridge donor donated after waiting more than a year and several other donors have donated their kidney to the next recipient in the chain 1-21 days BEFORE their intended recipient received a kidney (6). In these situations, the recipient lost their "bargaining chip" as their intended donor had already donated, but had faith that the upstream donor would honor their promise to donate.

Compatible pairs

Many medical professionals and their patients are beginning to realize that compatible pairs can improve their donor recipient match by participating in a chain (10,11). These benefits are most pronounced for compatible pairs comprising an O donor and unsensitized non-O patient, since there

are shortages of these blood types in all exchange programs. Improved matches are usually evaluated on 3 dimensions; donor age, HLA match and donor size. Although the improvements in patient outcomes are well documented related to donor age and HLA match, there is limited research to demonstrate donor size improves graft survival or half-life. In addition to finding a better matched donor and potentially achieving a better outcome, the compatible pair will typically facilitate many more transplantations by filling a missing gap in the chain and increasing the liquidity of the pool. This is a strong yet underappreciated factor for patients and their prospective donors.

In some cases a compatible pair will have a low probability of improving their match by participating in a chain. For example, when the recipient of the compatible pair is highly sensitized and does not have an O donor, or when an HLA-matched sibling is donating to another sibling, there would be no advantage to exchanging. The match quality for these types of compatible pairs may be difficult to improve upon but given that half of all living donors in the US are now unrelated biologically, the odds are favorable that paired exchange can improve the match and allow the transplanted kidney to last longer for other compatible pairs.

Combining desensitization with chains

Transplant teams specializing in desensitization often see the rapid growth of chain transplantations as a threat to their clinical workload. Likewise, proponents of exchanges often point out the added expense ($30,000/transplant) and immune-mediated injury associated with desensitization (12). However, these 2 approaches are not mutually exclusive and are actuality quite complementary. With access to desensitization and chain matching, a center can essentially stack the deck in favor of the patient. For example, a potential recipient who has multiple HLA antibodies, some of which are stronger and others that are weaker. When this pair is placed into a registry, the weaker antibodies that are removed through desensitization can be ignored in the matching process. In this case, the center would not list these weak antibodies for this patient and the patient could receive a transplant through a chain in combination with desensitization (e.g. single-dose IVIG). The combination for paired exchange and desensitization is often the best modality of highly sensitized patents. The NKR is adding a “toolbox” to the website that will allow centers to see the effects of removing one or more unacceptable HLA antigens (as well as certain patient preferences) on the matchability of their registered pairs.

Speed to match

As more recipients learn of chain transplantation, the pool of pairs will increase in size allowing for more match combinations. As the pool increases in size and the transplant centers learn the new process of multi-center chain transplantation, the time from initial listing in a registry to finding a match will shorten. This is critically important in light of the fact that the longer a patient is on dialysis, the lower their graft survival rates.

Ethical considerations

Living donor transplants have not been actively overseen by government agencies and are not subject to universal regulations regarding their allocation. With the growth of living donor transplants and particularly chains where donors are allocated to patients they may not know, there is a need for the transplant community to establish some guidelines. At a minimum, centers starting chains should fully disclose to non-directed donors all of the potential donation options and exchange programs should periodically report their average wait time and percent of pool transplanted so patients and regulatory authorities can understand paired exchange performance between transplant centers and the various exchange programs.

NDD allocation and coercion

Social concerns for NDDs include their motivation, possible hidden compensation and psychiatric history to name a few. Our experience indicates that only 2% of inquiring NDD candidates make it all the way through the evaluation process to

actual donation. In addition to appropriate medical and psychological screening, other ethical issues exist. Should the kidney be allocated to the center's deceased donor list, 6-antigen match national list, a child, or to start a chain? These questions can only be answered by the donor, so it is important that donors know all the options before they decide.

Utility vs. Justice

Taken at face value, the concept of never ending chains described by Michael Rees sounds tremendous (3). A single nondirected donation can be theoretically expanded to facilitate hundreds of transplantations (utility). However, over time, this concept has been challenged. First, computer simulations and clinical experience indicate that chains do not go on indefinitely. The average length of NKR chains is approximately 6 transplants, but varies widely with changes in pool liquidity. Second, since the non-directed living donor organ allocated to trigger a chain is an organ not allocated to the deceased donor list, critics argue that such an arrangement disadvantages the candidates on the deceased donor wait list. One solution to this criticism is for the last donor in a chain to donate to the next candidate on the deceased donor waiting list (justice). In fact, chain segments that have the greatest propagation power (those that end with a blood group O bridge donor) might be encouraged to continue while weaker chain segments (those ending with an AB bridge donor or any chain where there is difficulty placing a bridge donor) would be ended by donation to the deceased donor list.

It is important to realize that candidates on the deceased donor waiting list collectively benefit when non-directed living donor organs are allocated to initiate chains. Living donors are liberated throughout a chain, removing patients from the wait list. Without chains these living donors would never have been utilized due to incompatibility. This net gain of living donors reduces the competition for deceased donors for those candidates on the waiting list allowing other patients to move up the wait list and take the place of the recipients on the wait list that received a kidney from a living donor in a chain. The resulting multiplier effect is powerful. For example, if one donor starts a chain that is closed after 6 transplants, 5 recipients are removed from the wait list when they receive a living donor transplant and one recipient on the wait list receives a kidney directly from the last living donor in the chain.

CONCLUSION

We believe that competition between transplant centers is giving way to cooperation and the sharing of paired exchange best practices between centers, is allowing more patients to get transplanted. By the end of the decade, the current practice of living donors giving their kidney to a friend or family member may be a relic of the past (except for well-matched siblings/relatives) with most donors giving their kidney to a stranger in a chain so that all recipients get better matched donors, allowing the transplanted kidneys to last longer. The increased volume and liquidity in paired exchange will set the stage to match and transplant over 99% of all recipients with incompatible donors and greatly expand the donor pool, facilitating transplants for thousands of additional patients, saving the US health care system billions in dialysis-related costs.

SUMMARY

Since its establishment in 2008, the National Kidney Registry has facilitated 213 kidney transplants between unrelated living donors and recipients at 28 transplant centers. Rapid innovations in matching strategies, advanced computer technologies, good communication and an evolving understanding of the processes at participating transplant centers and histocompatibility laboratories are among the factors driving the success of the NKR. Virtual cross match accuracy has improved from 43% to 91% as a result of changes to the HLA typing requirements for potential donors and improved mechanisms to list unacceptable HLA antigens for sensitized patients. A uniform financial agreement among participating centers eliminated a major roadblock to facilitate unbalanced donor kidney exchanges among centers. The NKR transplanted 64% of the patients registered since 2008 and the average waiting time for those transplanted in 2010 was 11 months.

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