North American Pediatric Renal Trials and Collaborative Studies

NAPRTCS

2010 Annual Transplant Report

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II. TRANSPLANTATION

SECTION 1: TRANSPLANT PATIENT CHARACTERISTICS

Patient and transplant characteristics are summarized in Exhibit 1.1 for the entire history of the cooperative study. Because of reporting lags, annual accrual totals are still likely to increase, particularly for the later years. As of July 24, 2010 (data base closure for this report), 11,603 renal transplants had been reported for 10,632 pediatric patients. This represents 841 new transplants and 778 patients with their first registry transplant since the 2008 Annual Report.

The percentage of males in the registry, 59%, has been relatively constant over time (from 55% - 62%). White patients comprise 59% of the cohort, black and Hispanic patients 17% each. The percentage of white patients in a given year has decreased from a high of 72% in 1987 to under 43% in 2007. There had been a fairly steady increase in the percent of living donors from 1987 (43%) through 2001 (64%). However, the percentage has been decreasing the last 5 years to 42% last year. Fifty-one percent of all allografts have come from a living donor. The percentage of young recipients (<6 years old) has remained constant over time at about 20%, while young deceased donors (<10 years old) has decreased from 35% in 1987, to 19% in 1991, to <10% since 2003.

Recipient history is further characterized in Exhibit 1.2. The most common primary diagnoses remain aplastic/hypoplastic/dysplastic kidneys (in 15.8% of the children) and obstructive uropathy (in 15.3%). Focal segmental glomerulosclerosis (FSGS) is the third most common (11.7%) and continues to be the most prevalent acquired renal disease. The five most frequent diagnoses, excluding unknown and “other” diagnoses, total over 50% of the cases, while the remaining diagnoses are each present in no more than 3% of patients. A diagnosis was established for 94% of patients, while biopsy or nephrectomy confirmation of diagnosis is known not to have occurred in 44% of patients. The distributions of the primary disease diagnoses vary between black and white patients. For blacks, FSGS is most prevalent (23.0%), followed by obstructive uropathy (14.8%), aplasia/hypoplasia/dysplasia (13.3%). Chronic glomerulonephritis (GN) (3.5%), SLE nephritis (3.4%) and prune belly (3.2%) are present in >3% of the black population. The prevalence of cystinosis (0.6%) reflux nephropathy (1.1)% and hemolytic uremic syndrome (1.5%) were present in under 2% of the black transplant patients. Among whites, however, the most prevalent diagnoses are aplasia/hypoplasia/dysplasia (16.8%), obstructive uropathy (16.7%), FSGS (9.0%) and reflux nephropathy (6.2%). With polycystic disease (3.7%), medullary cystic disease (3.6%),

hemolytic uremic disease (3.4%) and cyctinosis (3.1%) present in >3% of the population. The relative order of these prevalent primary diagnoses among Hispanics is similar to that for white patients, except chronic GN is present in 5.0% of the Hispanics (2.5% of the white patients) and medullary cystic disease is present in only 1.2% of Hispanics.

At the time of their index transplant (first NAPRTCS transplant), 13.5% (1,434/10,632) of patients were receiving their second (or greater) transplant. Twenty-four percent of primary transplants were preemptive, as these patients had never received maintenance dialysis (Exhibit 1.3). The rate of preemptive transplantation differs significantly ($p<0.001$) between recipients of living (34%) and deceased donor (13%) source organs; between males (28%) and females (20%); among age groups, with rates of 20%, 24%, 28%, 22%, and 21% for recipients 0-1, 2-5, 6-12, 13-17, and 18-20 years old; and across races with whites, blacks, Hispanics, and "other" races having preemptive transplantation rates of 31%, 13%, 16%, and 17%, respectively. Immediately prior to the primary transplant, the percentages of patients maintained exclusively on hemodialysis and peritoneal dialysis were 29% and 39%; 6% received both. At the time of primary transplant few spleens had been removed (<1%) and all native renal tissue had been removed in 22% of patients; transplanted grafts have been removed in 41% of the repeat transplants (Exhibit 1.3).

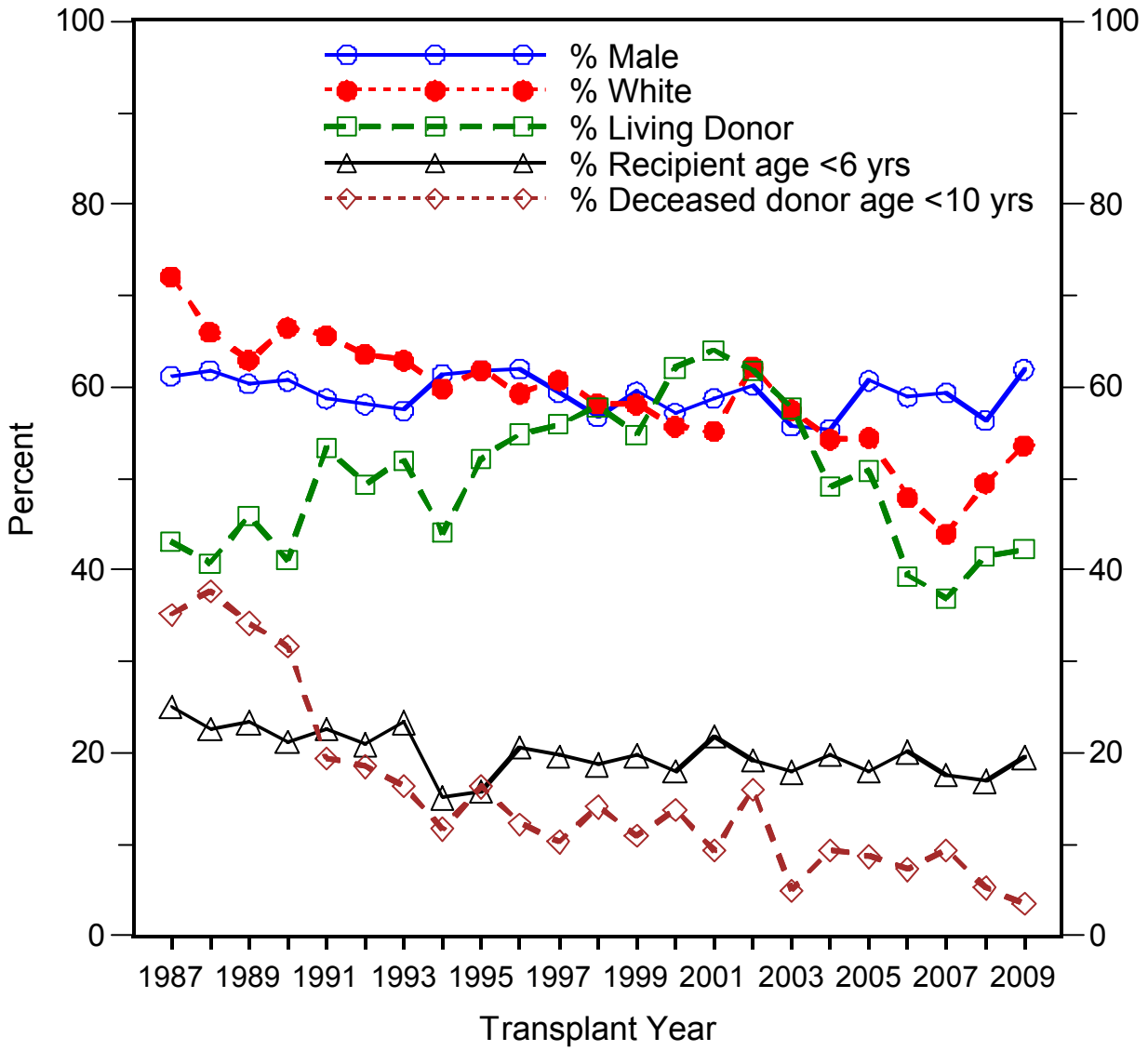
Exhibit 1.4 details recipient age at transplant. Of the 96 transplants occurring in children younger than 12 months old, there were 8, 22, and 65 transplants, respectively, within the 3-5, 6-8 and 9-11 months age categories, and only one was less than 3 months. Only 10 infant transplants have been performed since 2004, two in 2004, three in 2005, one in 2006, one in 2008 and three in 2009. In Exhibit 1.5, it is observed that the sex distribution is most unbalanced in the youngest age groups where 69% of 0-1 and 66% of 2-5 year old patients are male; the distribution is more even among adolescents (56% males). This is due to the fact that males comprise the majority of the aplasia/hypoplasia/dysplasia (62%) and obstructive uropathy (85%) diagnoses (see Exhibit 1.6) and these diagnoses decrease with age. Thirty-eight percent of male patients fall into these two diagnostic categories, compared to 21% of females. The contrast is particularly steep in the obstructive uropathy group, a diagnosis shared by 22% of the males, but only 6% of females.

Exhibit 1.6 provides for each primary diagnosis the percentages of patients who are male, white race, and known not to have had a biopsy or nephrectomy confirmation of diagnosis. Of transplant registrants with FSGS, 48% are white. Systemic lupus erythematosis is

predominantly a disease of females (83%) with a female-specific race distribution given by 23% white, 37% black, 29% Hispanic and 11% other. The percentages of patients *without* a histologically confirmed tissue diagnosis are 70%, 70%, and 65% in aplastic/hypoplastic/dysplastic, obstructive uropathy, and reflux nephropathy patients, respectively. The comparable rates for FSGS, hemolytic uremic syndrome, and lupus nephritis are 7%, 48%, and 4%.

Exhibit 1.7 categorizes primary diagnoses as either FSGS, GN, structural or other and demonstrates how these distributions differ according to age at transplant. GN is comprised of the following primary diagnoses: chronic glomerulonephritis, idiopathic crescentic glomerulonephritis, mebranoproliferative glomerulonephritis – Type I and Type II, SLE nephritis, Henoch-Schonlein nephritis, Berger's (IgA) nephritis, Wegener's granulomatosis, and membranous nephropathy. "Structural" diagnoses (prune belly, reflux nephropathy and aplasia/hypoplasia/displasias) account for the largest proportion of primary diagnoses among children ages 5 and under; whereas, GN and FSGS diagnoses are more prevalent with increasing age.

EXHIBIT 1.1
PATIENT REGISTRATIONS, TRANSPLANTS, AND SELECTED CHARACTERISTICS



Year of Transplant																									
# of	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	Total
Pts	531	502	463	498	500	546	573	551	628	553	562	499	525	433	487	453	409	411	376	341	295	284	190	22	10632
Txs	542	530	505	550	565	602	621	628	690	632	604	560	578	472	527	488	452	440	400	363	318	307	205	24	11603

EXHIBIT 1.2
INDEX TRANSPLANTS

Recipient and Transplant Characteristics	N	%
Total	10632	100.0
Sex		
Male	6298	59.2
Female	4334	40.8
Race		
White	6296	59.2
Black	1820	17.1
Hispanic	1806	17.0
Other	710	6.7
Primary Diagnosis		
Aplasia/hypoplasia/dysplasia kidney	1681	15.8
Obstructive uropathy	1630	15.3
Focal segmental glomerulosclerosis	1246	11.7
Reflux nephropathy	549	5.2
Chronic glomerulonephritis	340	3.2
Polycystic disease	323	3.0
Medullary cystic disease	287	2.7
Congenital nephrotic syndrome	277	2.6
Hemolytic uremic syndrome	273	2.6
Prune Belly	268	2.5
Familial nephritis	241	2.3
Cystinosis	221	2.1
Membranoproliferative glomerulonephritis - Type I	186	1.7
Pyelo/interstitial nephritis	184	1.7
Idiopathic crescentic glomerulonephritis	181	1.7
SLE nephritis	159	1.5
Renal infarct	140	1.3
Berger's (IgA) nephritis	135	1.3
Henoch-Schonlein nephritis	113	1.1
Membranoproliferative glomerulonephritis - Type II	85	0.8
Wegener's granulomatosis	66	0.6
Wilms tumor	56	0.5
Drash syndrome	55	0.5
Oxalosis	55	0.5
Membranous nephropathy	47	0.4
Other systemic immunologic disease	34	0.3
Sickle cell nephropathy	16	0.2
Diabetic glomerulonephritis	11	0.1
Other	1110	10.4
Unknown	663	6.2

EXHIBIT 1.3
TRANSPLANT CHARACTERISTICS

Transplant Type	N	%
Total Transplants	11603	100.0
Index Transplants	10632	91.6
Primary Transplants	9198	79.3
Index Non-primary Transplants	1434	12.4
Non-Index Transplants	971	8.4
Repeat Transplants	2405	20.7

Primary Transplants	N	%
Total Primary Transplants	9198	100.0
Preemptive	2241	24.4
Splenectomy	57	0.6
Native tissue removed	2007	21.8
Maintenance hemodialysis	2645	28.8
Maintenance peritoneal dialysis	3578	38.9
Both maintenance hemo & peritoneal dialysis	533	5.8

Repeat Transplants	N	%
Total Repeat Transplants	2405	100.0
Prior transplants removed	985	41.0

EXHIBIT 1.4
AGE AT TRANSPLANTATION

Age at Transplantation (years)	N	%
Total	11603	100%
<1	96	0.8
1	518	4.5
2	518	4.5
3	399	3.4
4	374	3.2
5	414	3.6
6	400	3.4
7	452	3.9
8	482	4.2
9	525	4.5
10	647	5.6
11	615	5.3
12	683	5.9
13	805	6.9
14	848	7.3
15	967	8.3
16	1000	8.6
17	927	8.0
≥ 18	933	8.0

Age Groupings (years)	N	%
0-1	614	5.3
2-5	1705	14.7
6-12	3804	32.8
13-17	4547	39.2
≥ 18	933	8.0

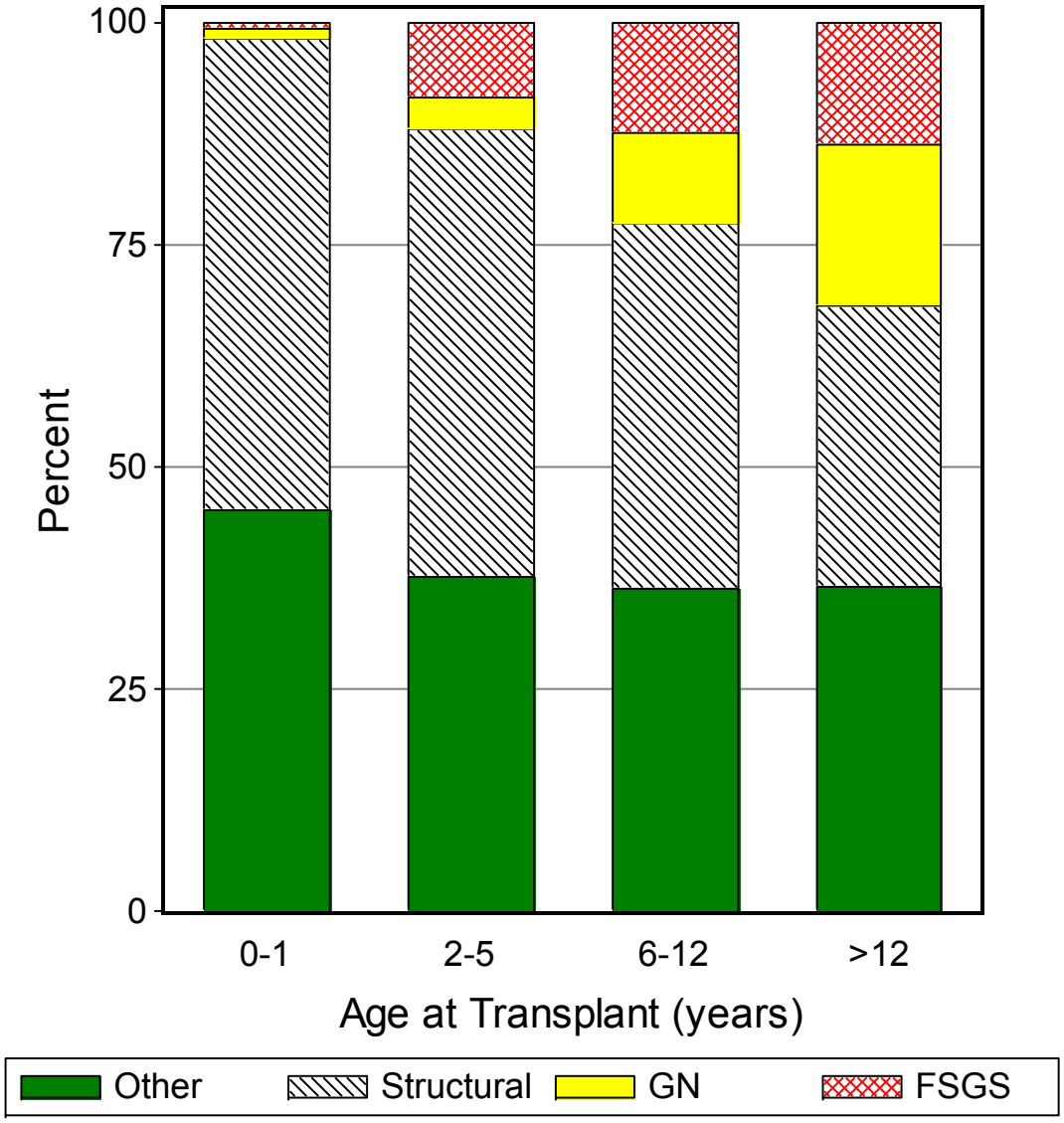
EXHIBIT 1.5
AGE AT INDEX TRANSPLANT
BY SEX, RACE, AND PRIMARY DIAGNOSIS

	Age at Transplantation				
	0-1 years (percent)	**2-5 years** (percent)	**6-12 years** (percent)	**13-17 years** (percent)	**≥18 years** (percent)
Gender					
Male	69.2	65.5	58.7	56.4	55.9
Female	30.8	34.5	41.3	43.6	44.1
Race					
White	73.6	63.0	60.3	56.1	51.7
Black	8.2	14.4	14.7	19.8	25.0
Hispanic	11.9	16.2	18.2	17.6	15.7
Other	6.3	6.4	6.9	6.5	7.6
Primary Diagnosis					
Renal plasias	29.0	23.5	16.6	11.3	9.6
Obstructive uropathy	18.6	20.6	16.0	13.2	10.1
Other	51.7	47.4	55.1	62.2	63.7
FSGS	0.7	8.4	12.3	13.2	16.6

EXHIBIT 1.6
SEX, RACE, AND BIOPSY DISTRIBUTIONS BY PRIMARY RENAL DIAGNOSIS

Primary Renal Diagnosis	N	% Male	% White	% Not Biopsied
Total	10632	59.2	63.5	44.0
Aplasia/hypoplasia/dysplasia	1681	61.5	67.0	69.8
Obstructive uropathy	1630	85.1	67.1	69.8
Focal segmental glomerulosclerosis	1246	57.7	48.0	6.5
Reflux nephropathy	549	43.7	78.2	64.7
Chronic glomerulonephritis	340	43.8	49.8	25.3
Polycystic disease	323	51.4	77.8	48.6
Medullary cystic disease	287	49.8	87.1	34.1
Congenital nephrotic syndrome	277	52.0	68.3	13.0
Hemolytic uremic syndrome	273	57.1	81.7	47.6
Prune Belly	268	97.8	62.9	61.9
Familial nephritis	241	80.9	59.9	28.2
Cystinosis	221	52.9	89.9	55.7
Membranoproliferative glomerulonephritis – Type 1	186	44.6	60.2	3.8
Pyelo/interstitial nephritis	184	47.3	74.7	22.8
Idiopathic crescentic glomerulonephritis	181	33.7	56.4	5.5
SLE nephritis	159	17.0	27.3	4.4
Renal infarct	140	47.9	81.5	64.3
Berger's (IgA) nephritis	135	54.1	71.7	5.9
Henoch-Schonlein nephritis	113	39.8	74.7	15.0
Membranoproliferative glomerulonephritis - Type II	85	49.4	77.5	4.7
Wegener's granulomatosis	66	43.9	68.3	9.1
Wilms tumor	56	55.4	75.0	7.1
Drash syndrome	55	56.4	70.0	9.1
Oxalosis	55	50.9	91.7	25.5
Membranous nephropathy	47	63.8	51.2	6.4
Other systemic immunologic disease	34	11.8	60.7	5.9
Sickle cell nephropathy	16	56.3	0.0	25.0
Diabetic glomerulonephritis	11	36.4	36.4	36.4
Other	1110	52.7	62.6	36.5
Unknown	663	52.9	33.6	65.5

EXHIBIT 1.7
PRIMARY DIAGNOSIS BY AGE



SECTION 2: DONOR HISTORY AND ANTIGEN MISMATCHES

As described in Exhibit 2.1, 49.2% of all transplants have involved a deceased donor source, 40.2% came from a parent, with the remaining 10.5% coming from other living donors. Parents comprise 79.2% of living donors: a cross-classification of parent and child sexes (n=4,309 pairs with complete data) reveals that mothers comprise the majority of parent-donors (55.7%), fathers donate to sons 63.1% of the time, while mothers make 59.0% of their donation to sons (p=0.006). There have been 407 transplants between siblings, and 188 (3.2%) live-donor grafts have been from donors under the age of 21. Sixteen living donors were under 18 years of age: 14 were transplants between siblings, 1 was a transplant from parent to child and one was unrelated. For these young sibling donors, the numbers of 3-, 4-, 5-, and 6-antigen matches were 1, 2, 3, and 7, respectively; one case had no antigen matches. The number of unrelated living donors has increased from an average of 3 per year in 1987-1995 to 16 per year since then.

Among deceased donor source transplants, 72 (1.4%) have come from donors less than 24 months old and 1106 (21.2%) from donors who were between 2 and 12 years of age; the use of deceased donors <10 years old has declined since the study's start (see Exhibit 1.1). Prior to 1992, infant donors comprised 2.9% (42/1,466) of deceased donor sources, compared to 0.8% (30/3,756) in transplants between 1992 and 2010. Of deceased donor source allografts, 13.1% were preserved by machine perfusion and 73.2% had cold ischemia times of 24 hours or less, with 18 (0.4%) exceeding 48 hours. The median cold time was 18.7 hours; the maximum was 64.5 hours.

Donor-specific transfusions with or without immunosuppression coverage were performed in 6.0% of living donor grafts but this procedure has been seldom used since 1995. The total number of random transfusions given to recipients differed by donor type: 51.8% of living donor graft recipients and 38.8% of deceased donor graft recipients had zero previous transfusions, while 12.1% and 24.7%, respectively, had more than five transfusions (p<0.001). The percent of patients without prior random transfusions has increased from 17.0% in 1987 (26.5% living and 9.6% deceased donor recipients) to an average of 66.2% since 2008 (74.9% living and 60.0% deceased donor recipients). Time trends in the utilization of donor-specific and random transfusions are provided in Exhibit 2.2.

To date, there have been 62 (0.6%) confirmed transplants across ABO blood group compatibility barriers out of 10,469 transplants with complete blood group data. Forty-four of these transplants have occurred since 2000. For O recipients, there have been 34 A donors, 9 B donors, and 3 AB donors; for A recipients, there have been 2 B donors and 3 AB donors; and for B recipients, there have been 8 A donors and 3 AB donors. A special analysis of an early cohort of these patients concluded that pediatric kidney transplantation across ABO compatibility barriers is an uncommon practice, but suggested — based on preliminary experience — that such transplants involving recipients whose anti-A titer history is low (1:4) are associated with satisfactory graft outcome and are deserving of further study. Current 3 year graft survival of these 62 transplants is 77%, similar to the compatible blood group transplants. Overall, 87.4% (9,154/10,469) of donor and recipient blood types were identical. Whereas blood group O is present in 56.5% of donors and 47.4% of recipients, blood group AB is present in 1.4% of donors and 3.9% of recipients.

Histocompatibility antigen data are shown in Exhibit 2.3. We count an allele as matching only if identical known alleles are reported for both donor and recipient. Among the living donor transplants, 70.9% had at least one match at each of the A, B, and DR loci, and there were mismatches at all 6 A, B, and DR loci for 15.9% of cases. No matches in either the B or DR loci occurred in 40.2% of the transplants from deceased donor sources; at least one locus match (of B and DR) occurred in 24.2%. Known matches of all 6 A, B and DR alleles occurred in 2.4% of deceased donor source transplants and in 3.4% of living donor source transplants.

Exhibit 2.4 compares donor sources with varying ages at transplant. Children under 5 years of age are more likely to receive a transplant from a living donor rather than a deceased donor, while children ≥ 13 years of age are more likely to receive a deceased donor transplant.

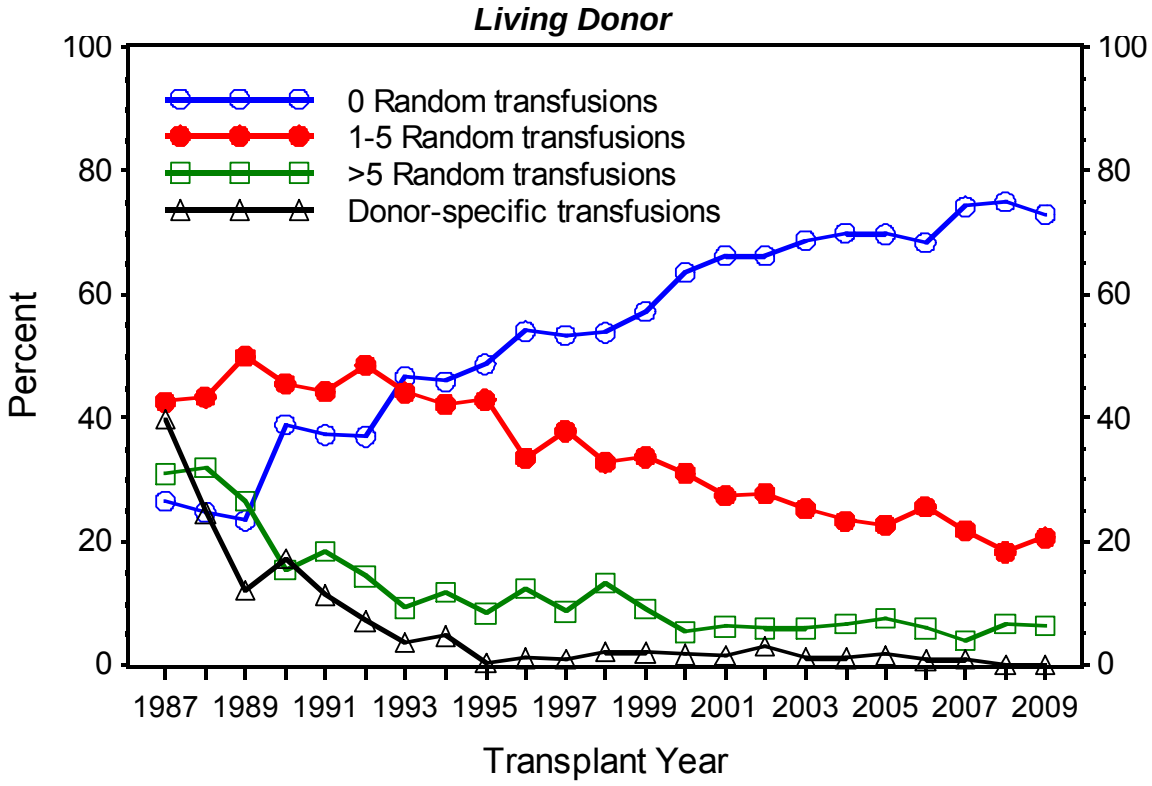
EXHIBIT 2.1
DONOR INFORMATION

Donor Source	N	%
Live donor/parent	4632	40.2
Live donor/sibling	407	3.5
Live donor/other related	535	4.6
Live donor/unrelated	272	2.4
Deceased Donor	5673	49.2
Missing Donor Type	(84)	

	Living Donor		Deceased Donor	
Donor Age	N	%	N	%
0-1	--	--	72	1.4
2-5	--	--	440	8.4
6-12	--	--	666	12.8
13-17	16	0.3	799	15.3
18-20	172	3.1	640	12.3
21-30	1189	21.5	1006	19.3
31-40	2487	45.0	755	14.5
41-50	1445	26.1	571	10.9
> 50	223	4.0	273	5.2
Missing Donor Age	(314)		(451)	

Deceased Donor Source Transplants	N	%
Machine Perfusion Used	624	13.1
Cold Ischemia Time $\leq$ 24 hours	3642	73.2
Cold Ischemia Time > 24 hours	1333	26.8

EXHIBIT 2.2
BLOOD TRANSFUSION USE BY YEAR OF TRANSPLANT



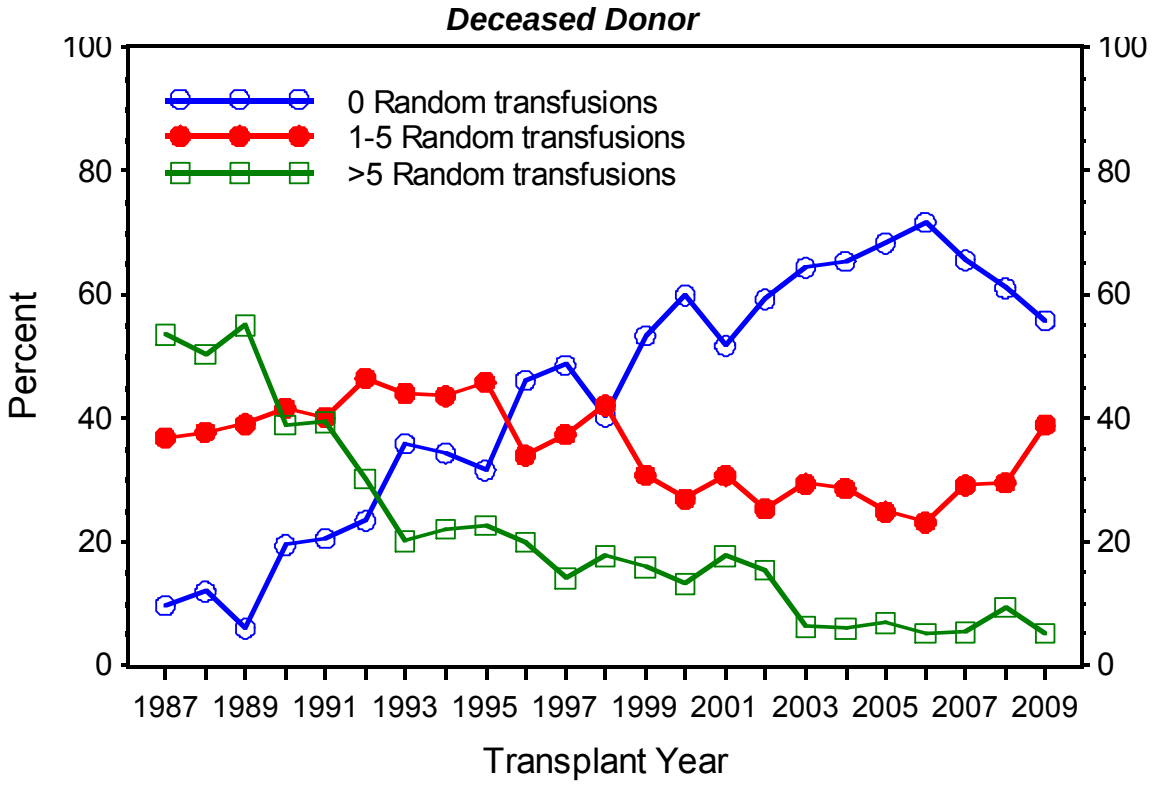


EXHIBIT 2.3
HLA MISMATCHES

	Donor Source			
	Living Donor		Deceased Donor	
	N	%	N	%
TOTAL	5846	100.0	5673	100.0
HLA-A				
0	827	14.1	442	7.8
1	3908	66.8	2048	36.1
2	1111	19.0	3183	56.1
HLA-B				
0	637	10.9	428	7.5
1	3979	68.1	1668	29.4
2	1230	21.0	3577	63.1
HLA-DR				
0	804	13.8	521	9.2
1	3616	61.9	2148	37.9
2	1426	24.4	3004	53.0
HLA-B and -DR				
0	303	5.2	194	3.4
1	776	13.3	311	5.5
2	3197	54.7	1116	19.7
3	543	9.3	1773	31.3
4	1027	17.6	2279	40.2
HLA-A, -B, and -DR				
0	200	3.4	134	2.4
1	275	4.7	131	2.3
2	978	16.7	260	4.6
3	2809	48.0	691	12.2
4	472	8.1	1309	23.1
5	181	3.1	1456	25.7
6	931	15.9	1692	29.8

EXHIBIT 2.4
DONOR SOURCE BY AGE AT TRANSPLANT

SECTION 3: THERAPY

The NAPRTCS collects information on post-transplant immunosuppressive medications and dosages at Day 30, Month 6, and every six months thereafter. In addition, a record of the initial day and dose of immunosuppressive medication used during the first post-transplant month is collected. Because of the changes in therapy over the years, this section is restricted to all transplants reported in more recent times starting in 1996. This encompasses 6370 transplants of which 92% are index transplants, 78% are primary transplants, 54% are from living donors and 46% are from deceased donors. Three percent (187) of the grafts failed by 30 days.

Detailed description of pre-operative immunosuppressive therapy is not collected, but it was employed in 43% of living donor transplants. The frequency of use of pre-operative immunotherapy among living donor transplant recipients over the last 5 years is about 40%. Among deceased donor transplants, the use of pre-operative immunotherapy has increased from 9% in 1996 to 24% in the past 5 years.

Immunosuppression during the First 30 Days

Exhibit 3.1 details immunosuppressive medication data for the first 30 days post-transplant. Polyclonal antibody ATG/ALG was used in 14% of living donor transplants, decreasing from 28% in 1996 to 5% in 2000, and increasing to 22% in 2009. ATG/ALG was used in 22% of deceased donor transplants, with a similar decrease from 36% in 1996, to 8% in 2001, with a 26% utilization rate in 2009. The median ATG/ALG course was 5 days. The use of monoclonal antibodies in living donors increased from 21% in 1996 to 55% in 2002. Currently (2008-2010) induction monoclonal antibodies are used in about 30% of the living donor transplants. Rates of induction monoclonal antibody use in deceased donors ranges from 30% in 1996 to 60% in 2002 to 35% currently (2008-2010). The type of monoclonal antibodies has also changed over the years from predominantly OKT3 in 1996 to balsiliximab or daclizumab from 2002 onward. The median length of an OKT3 course was 9 days; for basiliximab patients, it was 2 days; and for daclizumab recipients, the median course was 4 days. Alemtuzamab (campath) and rituximab have been added to the data collection, currently 16 cases have been documented using campath and 11 cases report using rituximab. Most therapy with monoclonal antibodies is initiated at transplant or Day 1 post transplant. These cases are considered to have induction antibody therapy. However, 183 cases have monoclonal antibody initiated after Day 1 (median day 4 range day 2-28). These cases are not considered induction and are not included in the

induction antibody exhibits. The rate of induction antibody use at transplant or one day post transplant, by transplantation year is shown graphically in Exhibit 3.2 and is as follows:

PERCENT INDUCTION ANTIBODY (Initiated at transplant or day 1 post transplant)														
	1996 n=632	1997 n=604	1998 n=560	1999 n=578	2000 n=472	2001 n=527	2002 n=488	2003 n=452	2004 n=440	2005 n=400	2006 n=363	2007 n=318	2008 n=307	2009 n=205
None	50.5	53.0	44.1	44.3	47.3	46.7	41.6	45.1	47.5	43.5	36.4	47.8	38.1	54.6
OKT3	21.7	14.4	9.6	4.7	0.4	1.0	0.8	0.4	0.0	0.0	0.8	0.0	0.0	0.0
Basiliximab	0.0	0.7	4.6	15.1	21.2	29.0	30.9	24.3	23.6	23.0	21.5	17.3	15.6	10.7
Daclizumab	0.0	4.8	17.91	24.7	19.5	15.0	15.2	12.8	12.5	13.5	16.3	6.0	10.4	8.8
Other	0.0	0.2	1.1	0.7	5.9	3.0	4.5	5.5	5.7	5.5	10.5	9.1	9.5	3.4
ATG/ALG	27.9	27.0	22.7	10.6	5.7	5.3	7.0	11.7	10.7	14.5	14.6	19.8	26.4	22.4

Sirolimus therapy first appeared in 1998 (<1% of the cases), peaked in 2002 with 25% of the cases receiving sirolimus and has tapered off to <3% currently. The median day of initiation is 0 day post-transplant with a median initial dose of 3.2 mg/m^2.

Cyclosporine was used for 42% of transplants but has decreased from 81% in 1996 to <2% in 2009/2010. Cyclosporine began on the day of transplant for 23%, on day 1 for 27%, days 2-6 for 39% and after day 6 for 10% of the transplants. The median dose of cyclosporine increased during the first month by 1.4 mg/kg and the most common formulation used was Neoral (83%). Tacrolimus was used in 47% of the transplants increasing from 6% in 1996 to 74% in 2009. Tacrolimus was started the day before transplant (2%) or the day of transplant in 19%, on day 1 for 38%, day 2-6 for 33% and after day 6 for 8% of the transplants. The median dose of tacrolimus increased by 0.05 mg/kg during the first month. Prednisone was used (at day 30) in 95% of the cases in 1996. From about the year 2001 prednisone utilization has been decreasing and in 2009, 49% of the cases are treated with prednisone at day 30. Although early graft failures decrease the number of patients still available for immunosuppressive therapy by day 30, the percentages being treated with prednisone is relatively stable during the first month (81% initially and 80% at day 30 in patients with functioning graft). Over the month, the median dose of prednisone decreased to approximately 1/3 of the initial amount.

Exhibit 3.4 shows the marked changes in day 30 post transplant dosing strategies (in patients with functioning grafts) that have been observed in the past years. These are substantially

caused by the introduction of new drugs such as mycophenolate mofetil and tacrolimus. Use at Day 30 of combination cyclosporine, prednisone, and azathioprine has declined since 1996-1998, from 33% of living donor and 31% of deceased donor organ recipients, to <1% in each group since 2005. The regimen of prednisone, tacrolimus, and mycophenolate mofetil has become more popular. It is used in 55% of living donor and 63% of deceased donor organ transplant since 2005, compared to about 7% of all transplants in 1996-1998.

PERCENT DRUG UTILIZATION – DAY 30 POST TRANSPLANT
(Patients with functioning grafts)

	1996 n=598	1997 n=581	1998 n=534	1999 n=555	2000 n=454	2001 n=511	2002 n=478	2003 n=443	2004 n=434	2005 n=391	2006 n=356	2007 n=315	2008 n=306	2009 n=203
Prednisone	94.8	95.7	94.8	92.6	91.2	86.5	85.2	73.4	68.4	65.7	61.5	56.5	57.2	48.8
Cyclosporine	82.1	78.8	71.7	68.1	57.1	45.4	26.2	15.8	9.2	10.2	4.8	7.6	3.9	1.0
Tacrolimus	3.7	14.8	22.3	24.5	34.4	41.7	58.2	60.1	71.4	68.8	71.9	70.8	73.5	62.1
MMF	9.0	44.8	66.7	66.9	63.9	54.2	57.7	58.5	65.2	71.6	69.4	70.5	69.9	59.6
Azathioprine	49.3	34.4	19.7	16.0	13.7	12.9	2.7	3.8	3.2	1.0	2.0	3.2	3.6	2.5
Sirolimus	0.0	0.0	0.2	0.4	7.5	21.7	25.5	18.3	12.2	6.1	6.7	2.2	2.3	0.5

This table above mirrors the data in Exhibit 3.4, showing substantial increases in tacrolimus and mycophenolate mofetil, along with a significant decrease in cyclosporine and azathioprine usage. Azathioprine usage has decreased sharply from 49% in 1996 to 3% by 2002, where it remains. Cyclosporine was used in 82% of the 1996 transplants at day 30, and it continues to show a decline in utilization to 1% in 2009. Prednisone use has slowly been decreasing in recent years from 95% in 1996 to 49% in 2009.

Immunosupppression during Follow-up

Exhibit 3.5 presents immunosuppressive therapy dosages for patients with functioning grafts for selected drug combinations during follow-up. Median daily prednisone doses decrease over the first 2 years after transplantation, while the percentage of transplanted patients receiving alternate day therapy increases from 7% at Month 6 to 17%, 27%, and 34% at years 1, 2 and 4, respectively. Living and deceased donor recipients show similar rates of alternate day prednisone therapy. Tacrolimus combination drug recipients generally receive lower steroid and MMF doses than those on cyclosporine.

Combination therapy at 30 days post transplant and during follow-up for patients with

functioning grafts is as follows:

PERCENT DRUG UTILIZATION - POST TRANSPLANT (Patients with functioning grafts)								
	Transplant Era 1996-2002				Transplant Era 2003-2010			
	30 days	1 year	3 years	5 years	30 days	1 year	3 years	5 years
Prednisone/CsA/MMF	33.6	35.3	28.4	21.8	6.6	6.9	7.1	6.2
Prednisone/CsA/Aza	20.5	15.8	12.7	8.1	0.7	0.4	0.4	0.4
Prednisone/Csa	11.2	5.1	4.4	4.9	1.7	1.1	0.7	2.1
Prednisone /TAC/MMF	17.8	22.5	26.6	31.3	56.2	52.1	45.6	40.9
Prednisone /TAC/Aza	2.2	4.5	6.1	6.6	2.1	2.4	2.6	3.7
Prednisone /TAC	7.7	9.2	10.9	11.6	6.2	10.1	11.2	9.9
TAC/MMF	0.6	1.5	2.3	3.5	14.8	12.2	12.8	14.9
Other combination	6.4	6.2	8.6	12.3	11.9	14.8	19.7	21.9

Type of therapy during follow-up remains relatively stable, with decreases in cyclosporine based regimens and increases in tacrolimus based regimens between the eras, reflecting the change in immunosuppressive therapies over time.

Exhibit 3.6 displays the percentage of patients at selected follow-up time points who were receiving the eight most common maintenance regiments, by graft donor source. Through 3 years, about 24% of the patients received combination immunosuppressives with prednisone, cyclosporine, and MMF, compared to approximately 11% of patients with prednisone, cyclosporine and azathioprine. About 33% received therapy with prednisone, tacrolimus and MMF and about 10% received prednisone and tacrolimus. Note that therapy strategies appear similar for deceased donor recipients and live donor recipients and dosing strategies change little over the post transplant years.

Because of the differential graft survival in black and non-black patients, calcineurin inhibitor blood levels have been examined. At 1 year post transplant, median cyclosporine level was 177 ng/mL in black and non-black patients; and median tacrolimus level was 5.9 ng/mL in black patients (versus 6.0 ng/mL for non-blacks). Blood levels by measurement methods are presented below.

IMMUNOSUPPRESSION DOSE AND BLOOD LEVELS (ng/mL) AT 12 MONTHS								
	BLACK				NON-BLACK			
	N	Median	Mean	SE	N	Median	Mean	SE
Cyclosporine Dose (mg/kg/D)	263	6.0	6.6	0.2	1599	6.0	6.7	0.1
CsA Blood Level Method - HPLC	39	162	172.5	14.2	333	135	147.9	3.8
CsA Blood Level Method - TDx	145	194	229.9	15.2	782	205	240.4	6.3
CsA Blood Level Monoclonal RIA-specific	40	146	174.7	16.6	262	167.5	188.4	5.7
Tacrolimus Dose (mg/kg/D)	517	0.17	0.20	0.01	2104	0.12	0.14	0.00
TAC Blood Level Method - HPLC	32	5.8	6.2	0.4	228	6.2	7.9	0.8
TAC Blood Level Method - IMx	183	5.9	6.4	0.2	545	5.8	6.3	0.1

Concomitant Medications

The percentage of patients receiving concomitant anti-hypertensive, prophylactic antibiotic, and anticonvulsant medications, by donor source, are displayed in Exhibit 3.7. A substantial percentage of transplanted children receive antihypertensive medications and antibiotics throughout the follow-up period. The use of antihypertensive medication is 83% for deceased donor and 78% for live donor recipients at transplant. This rate decreases similarly in both groups to 71% in deceased donor and 64% in live donor recipients at 2 years. At 5 years post transplant, the rates are 70% vs. 58% for deceased and live donor recipients. The use of antihypertensive medications at transplant has decreased over the years from 81% in 1996 to 74% in 2009 for living donors and 89% in 1996 to 76% in 2009 for deceased donors.

The use of prophylactic antibiotics is similar for deceased and live donors: 81% at transplant falling to 48% at 18 months, where it remains constant to 5 years (45%). At one year, prophylactic antibiotics are used in 48% of those with focal segmental glomerulosclerosis, 55% of those with renal dyplasia, 65% of patients diagnosed with reflux nephropathy and 68% with obstructive uropathy. The use pf prophylactic antibiotics at transplant has remained constant over the years for both living and deceased donors.

An anticonvulsant medication was given initially to 5% of the transplant recipients, with no

difference observed among recipients of deceased donor organs versus living donor organ recipients. This rate remains constant over the follow-up period. The percent receiving anticonvulsant medications at transplant also remains constant over the years for both living and deceased donors.

EXHIBIT 3.1

MEDICATION DATA – FIRST 30 DAYS

Therapy	Percent treated Initially	Median Day of Initiation	Median Initial Dose (mg/kg/D)	Percent treated Day 30*	Median Day 30* Dose (mg/kg/D)
Prednisone	81.1	3	1.48	80.3	0.51
Methylprednisolone	73.4	0	9.52	--	--
Cyclosporine	42.4	1	8.38	40.9	9.80
Tacrolimus	47.0	1	0.15	43.7	0.20
Azathioprine	22.4	0	2.07	14.5	2.02
Mycophenolate Mofetil	63.3	1	27.17	57.0	28.17
ATG/ALG	17.6	0	2.17	--	--
Monoclonal Antibody	40.8	0	--	--	--
OKT3	5.9	0	0.11	--	--
Basiliximab	17.6	0	0.41	--	--
Daclizumab	13.3	0	1.02	--	--
Other	4.0	0	1.04		
Sirolimus	7.4	0	0.11	--	--

For Mycophenolate Mofetil: Median initial dose in mg per body surface area is 838.91 and day 30 daily dose is 879.40 mg/m^2/day.

For Sirolomus: Median initial dose in mg per body surface area was 3.16 mg/m^2/day.

For ATG/ALG: Median dose has decreased from 15.00 mg/kg/D in 1996 to 1.65 mg/kg/D in 2000. In 2010 the median dose is 1.48 mg/kg/D.

* Day 30 results includes only patients with functioning grafts.

EXHIBIT 3.2
INDUCTION ANTIBODY USE BY YEAR OF TRANSPLANT

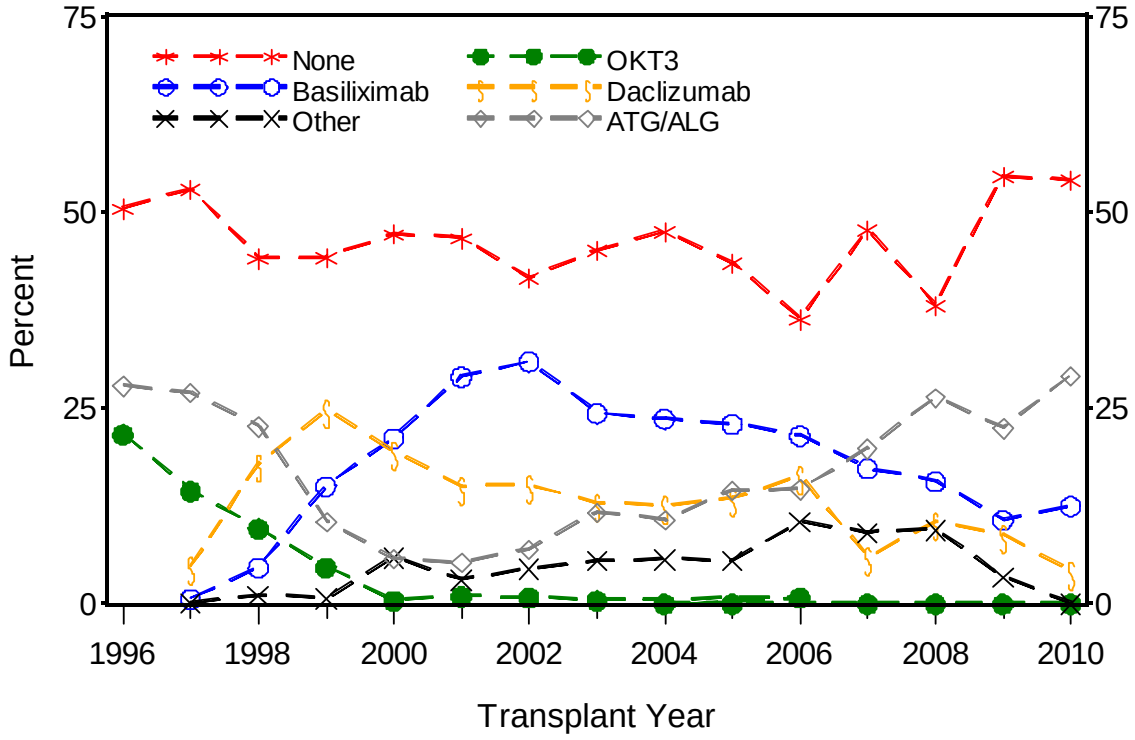


EXHIBIT 3.3
INDUCTION ANTIBODY USE BY WEEK 1 CALCINEURIN INHIBITOR

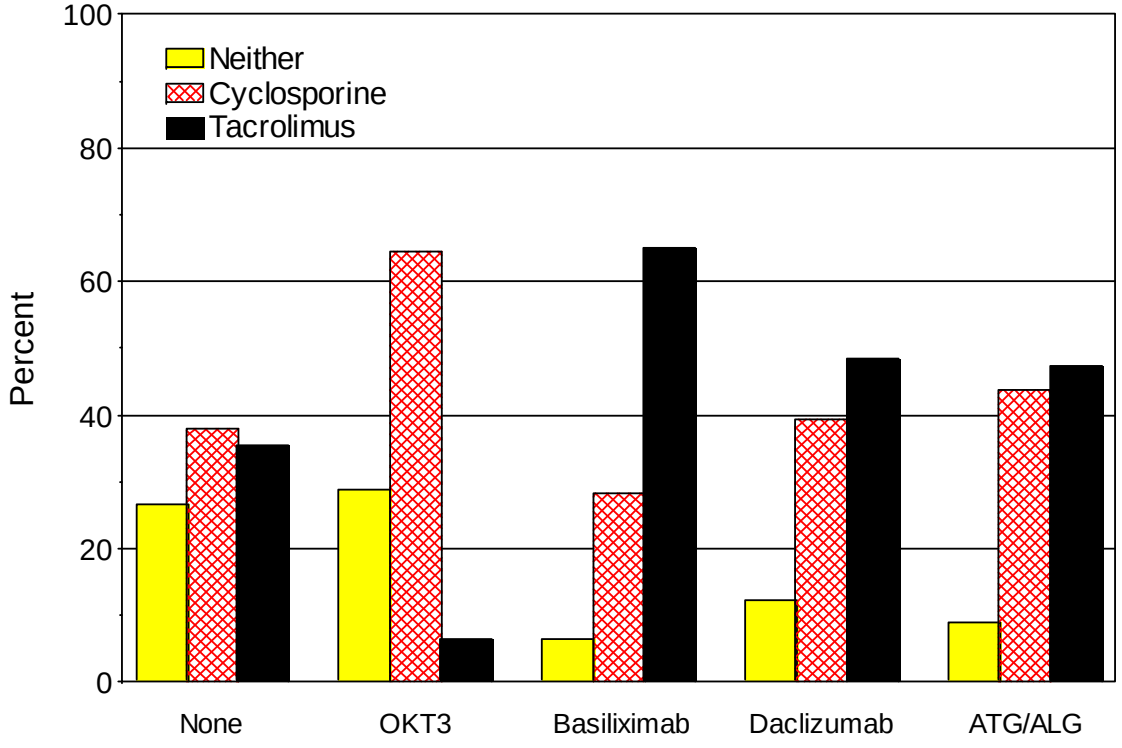
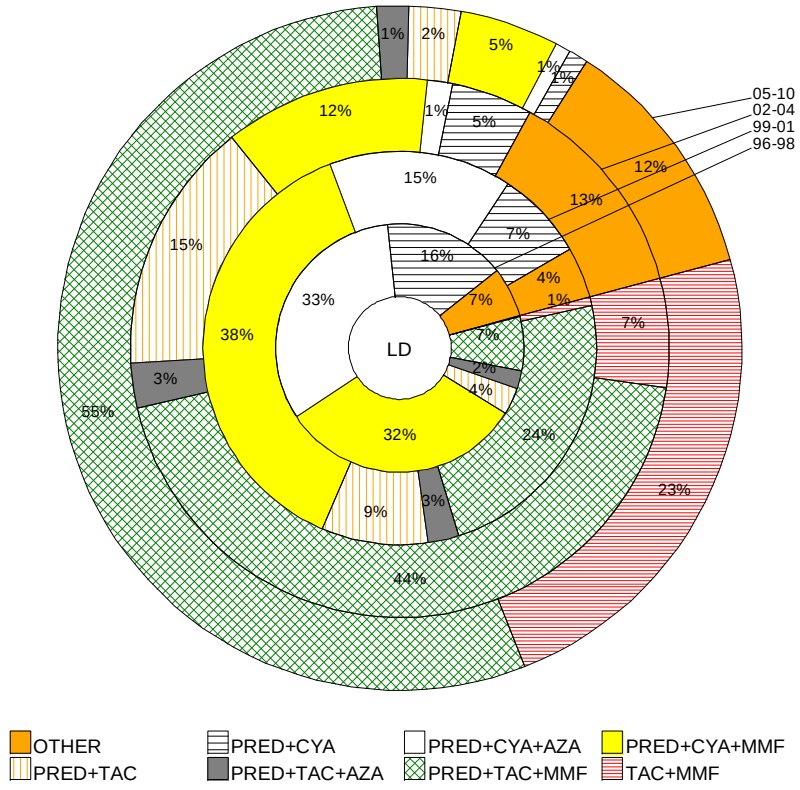


EXHIBIT 3.4
IMMUNOSUPPRESSIVE MEDICATION 30 DAYS POST TRANSPLANT
(patients with a functioning graft)



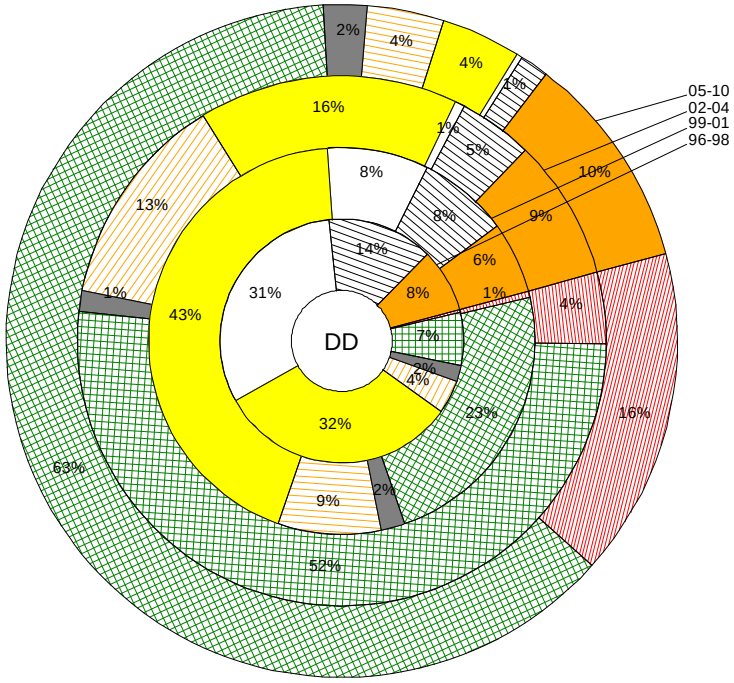
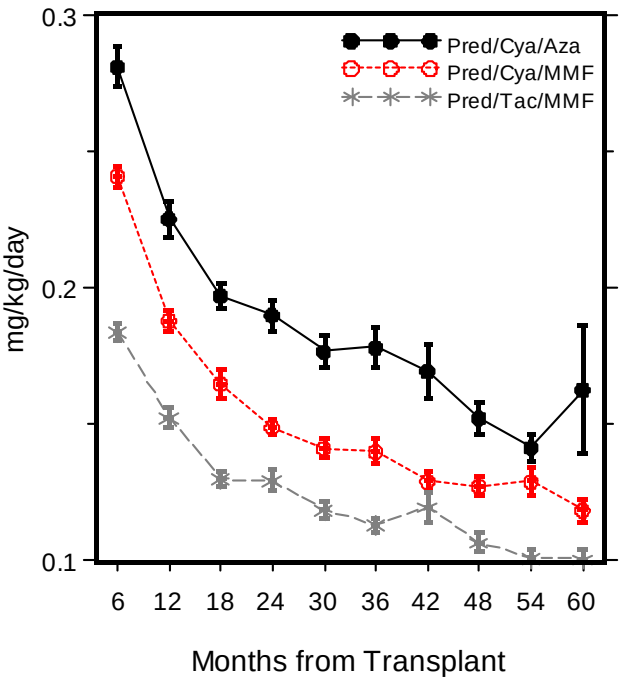
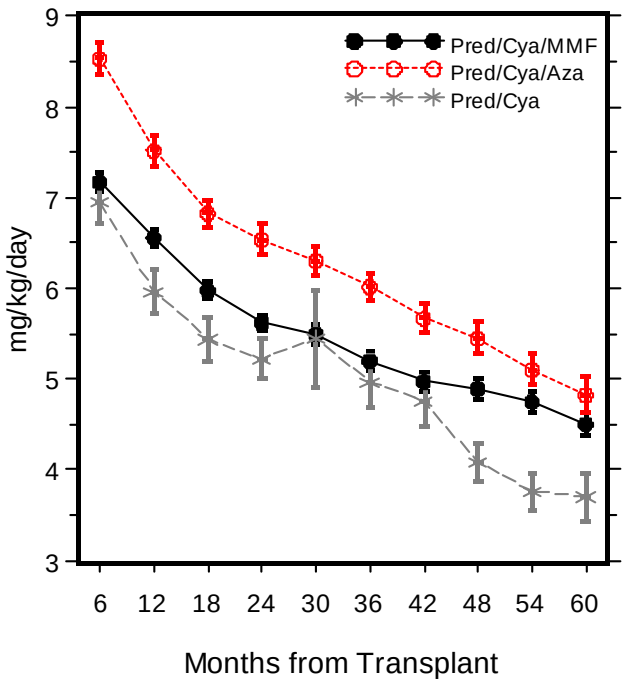


EXHIBIT 3.5
MEAN (±SE) DAILY DRUG DOSAGES BY FOLLOW-UP TIME

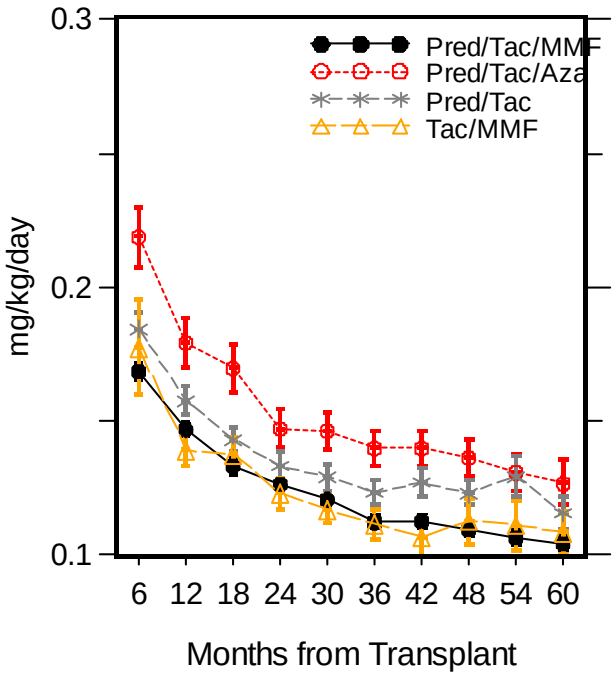
Prednisone



Cyclosporine



Tacrolimus



Mycophenolate Mofetil

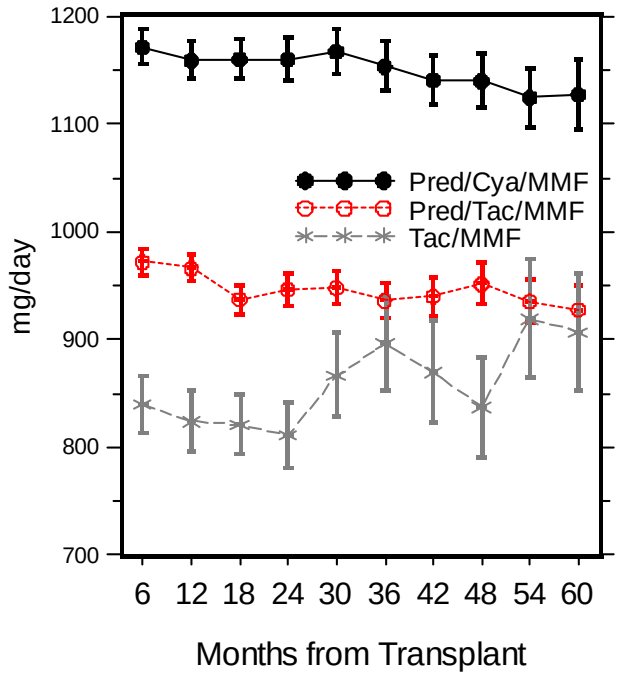


EXHIBIT 3.6
MAINTENANCE IMMUNOSUPPRESSION MEDICATION BY FOLLOW-UP TIME
(patients with a functioning graft)

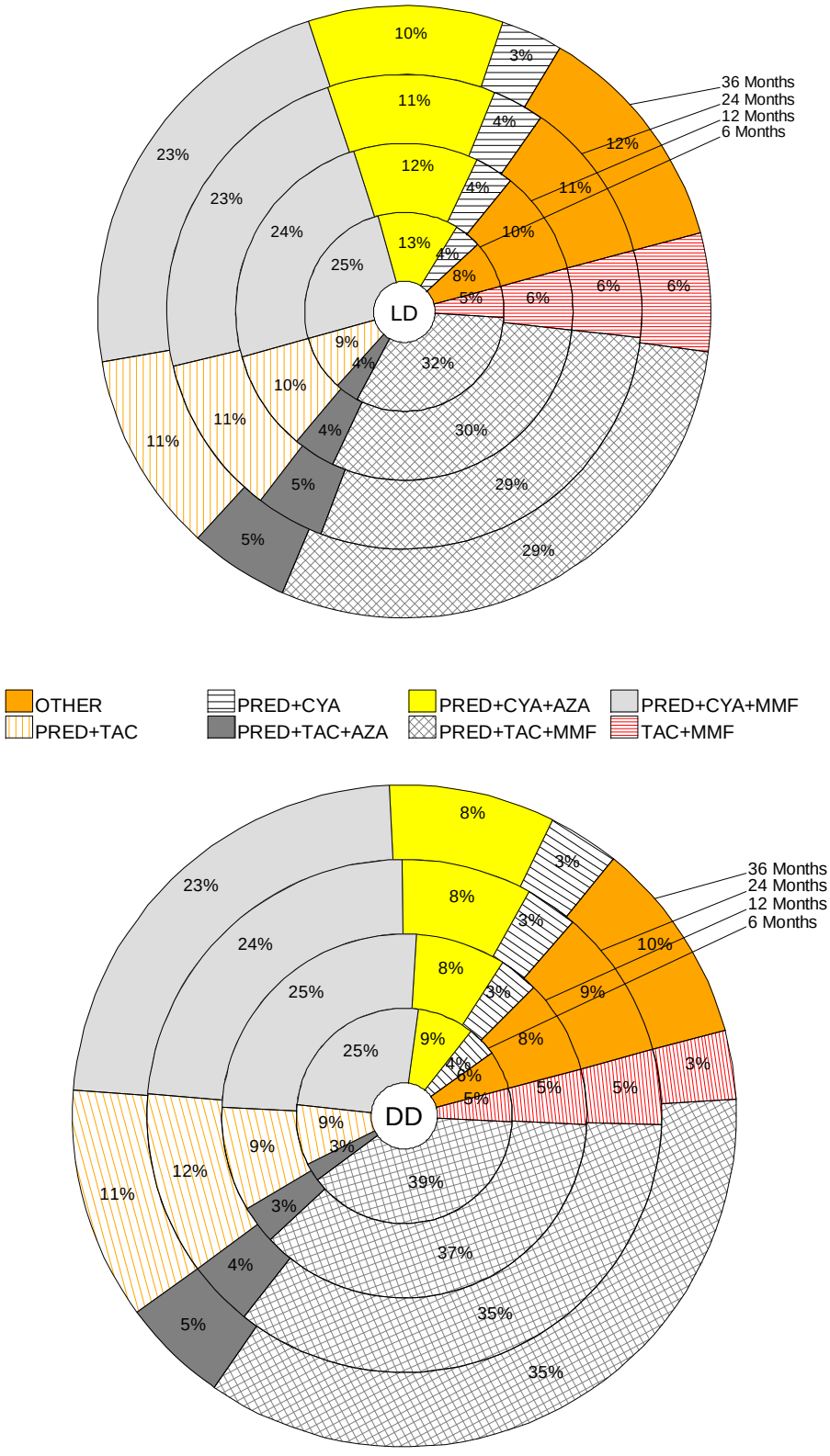
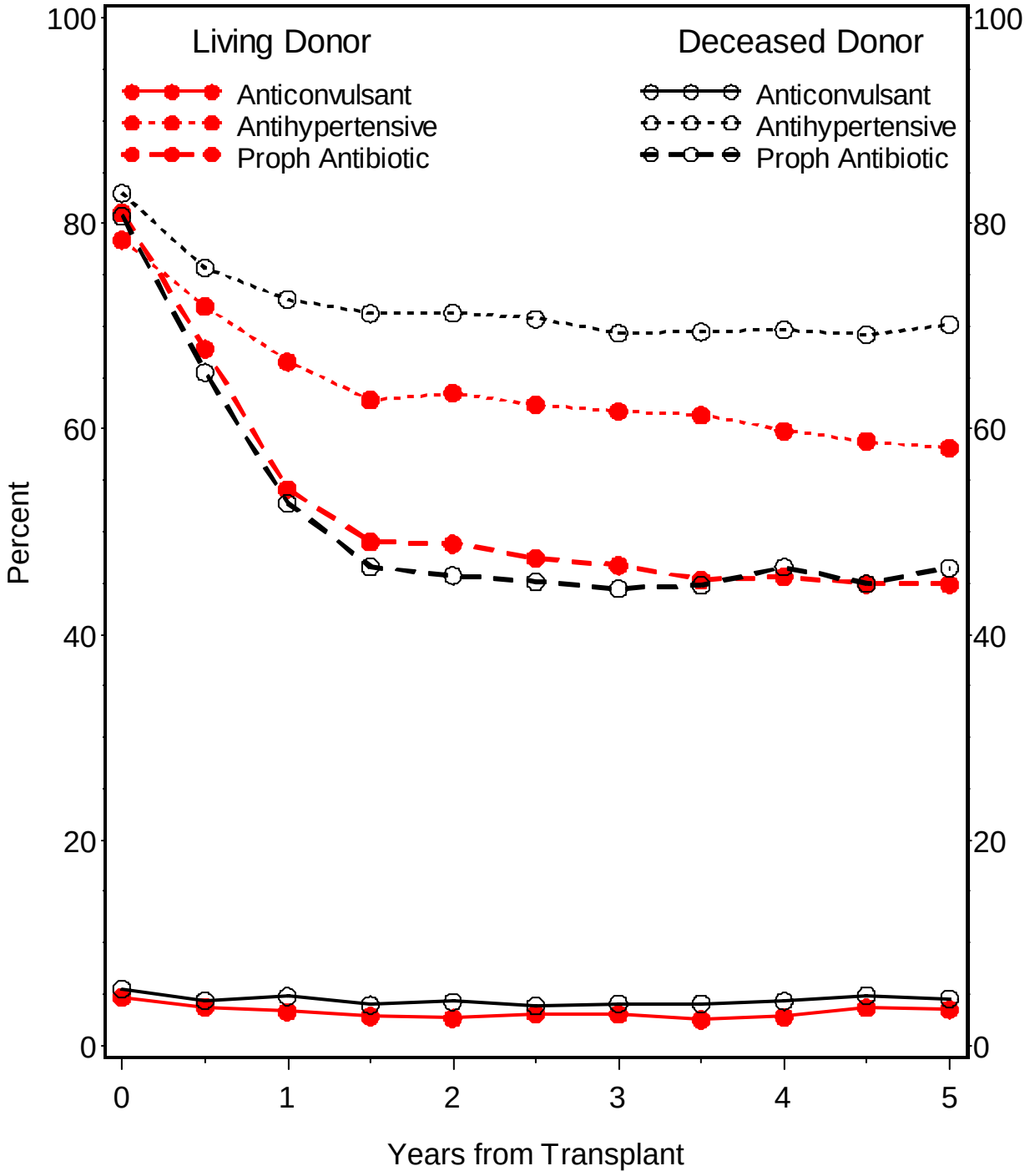


EXHIBIT 3.7
CONCOMITANT MEDICATIONS



SECTION 4: REJECTION

In NAPRTCS, a rejection episode is defined by the physician's decision to initiate specific anti-rejection therapy. For time to event analyses, a rejection episode is also considered to have occurred if rejection is the reported cause of graft failure even in the absence of an acute rejection report and 79 episodes were included as such. As a result, a total of 10,420 episodes of rejection in the 11,603 transplants were available for analysis, as described below.

There were 10,406 acute rejection reports submitted for 11,519 transplants with known donor source. Acute rejection reversal outcome had not been established for 91 of the 10,406 acute rejection reports at the time of database closure.

The frequency of reported acute rejections is presented in Exhibit 4.1A, indicating that of the 11,519 transplants, no acute rejections were reported for 6,263, exactly one rejection was reported for 2,715, two rejections for 1,253, three rejections for 653, and four or more rejections were reported for 635 transplants. 45.6% of the transplants had at least one rejection episode (41% in live donors and 51% in deceased donors). The number of rejections per transplant ranged from 0 to 12. Rejection rates were over 70% in 1987-1990 and decreased steadily over the years to 13% since 2007. Acute rejection ratios (number of rejections/number of transplants) are shown in Exhibit 4.1B for transplant era 1987 – 1995 and Exhibit 4.1C for 1996 – 2010. On average, 0.77 acute rejections were reported for each living donor transplant, a ratio of 1.19 for 1987 – 1995 and 0.45 for 1996 – 2010 transplants. On average there were 1.04 rejections for each deceased donor transplant, 1.50 in the early years and 0.61 in recent years. Age-specific ratios vary with the lowest rates in the 0-1 year olds in all groups and the highest rates in the 6-12 year olds in 1987 – 1995 group and >12 years in the 1996 – 2010 group for both living and deceased donor recipients. The biopsy rates of reported acute rejections over time are shown in Exhibit 4.1D. Rates of biopsy have increased from 45% in 1987 and continue to rise being 93% since 2008.

Exhibit 4.2 displays the cumulative distribution of times to first rejection by allograft source and transplant year for index transplants. Improvements in rejection experience have occurred over the life of the registry. These changes have been substantial throughout the life of the project. The table below presents 12-month probabilities of acute rejection by transplant year for all transplants. While historically over half of deceased organ recipients experienced a rejection in

the first post transplant weeks, the majority of patients now experience an acute rejection free year. Interestingly, in the most recent cohort, improvements in deceased donor 1 year rejection percentages have slowed down and the absolute difference between living and deceased donors is as large as in any cohort since 1991-1994.

PROBABILITY OF FIRST REJECTION AT 12 MONTHS				
	Living Donor		Deceased Donor	
Transplant Year	%	SE	%	SE
1987-1990	54.2	1.7	68.9	1.5
1991-1994	44.9	1.5	60.3	1.6
1995-1998	33.0	1.4	40.5	1.7
1999-2002	21.9	1.3	26.6	1.8
2003-2006	12.8	1.3	17.1	1.5
2007-2010	8.6	1.8	16.6	2.1

Donor source-specific analyses were performed to assess the influence of selected patient and transplant characteristics on the occurrence of first rejection episodes. These analyses were restricted to index transplants. Relative hazards (RH) of first rejection episode by cohort era are presented in Exhibits 4.3A and 4.3B. For living donor transplantation in the early cohort, the incidence of first rejection was increased for black patients, for children over 24 months, for patients with one or two HLA-DR mismatches, and for patients who did not receive antibody prophylaxis on post transplant days 0 or 1. Because of its importance the analysis was adjusted with a linear term for transplant year. No significant effects were observed for transfusion history, donor-specific transfusions or the use of pre-operative immunotherapy. There was an approximate 6% reduction in the hazard of rejection with each increasing transplantation year ($p<0.001$).

For living donor transplants in the later cohort, the relative hazard was significantly lower (RH=0.51) for children under 24 months. There was an approximate 9% reduction in the hazard of rejection with each increasing transplantation year ($p<0.001$). In addition, in the later cohort of living donor transplant recipients, the previously identified race effect was not observed. The hazard rate was increased for children with 1 HLA-DR mismatch but not for children with 2 HLA-DR mismatches. The importance of acute tubular necrosis (ATN) on subsequent acute rejection was evaluated by restricting the analysis to cases with more than 7 days of graft function. Patients with first week dialysis, the operational definition of ATN, were at a

significantly increased risk of subsequent acute rejection in both the early and late cohort eras (RH=1.88, p<0.001 and RH=1.93, p<0.001, respectively).

For deceased donor transplantation in the early cohort, black patients had 27% higher hazard of first acute rejection (RH=1.27, p<0.001) than non-black patients. Additional risk factors include two HLA-DR mismatches compared to no mismatches (RH=1.32, p=0.002) and no induction therapy (RH=1.20, p<0.001). The effect of transfusion history and cold storage time are not significant when adjusted for the other predictors in the model. The effect of transplant year for the deceased donor model is similar to that for living donor transplantation. For deceased donor recipients in the later cohort era, black race was associated with a higher relative hazard of first rejection (RH=1.43, p<0.001) and there was a 7% reduction in the relative hazard of rejection with each increasing transplantation year (p<0.001).

Cumulative rejection distribution estimates are shown in Exhibit 4.4 for selected patient transplant characteristics. For living donors, significant differences are seen for age, HLA-DR mismatches and ATN (log-rank p<0.001 for each); race is also significant with the Log-rank p=0.024. For deceased donor recipients, significant differences in time to first rejection are seen in age (p<0.001), race (p<0.001) ATN (p<0.001) and use of induction antibody (p=0.001).

Exhibit 4.5A presents the complete (i.e., return to baseline serum creatinine) and partial (i.e., graft function without return to baseline creatinine) reversal rates for each of the treated rejections, by donor source. Among living donor (LD) graft recipients, 52% had a complete reversal of rejection, 44% had a partial reversal, and 5% ended in graft failure or patient death. A poorer prognosis is observed for deceased donor (DD) graft recipients, where 45% of rejection episodes were completely reversed, 48% partially reversed, and 7% ended with graft failure or patient death. The percentage of complete recoveries from acute rejection decreases substantially with increasing number of episodes, averaging 60% and 54%, respectively, for LD and DD sources following the first acute rejection, but only about 43% and 33%, respectively, following the third episode. When stratified by age, the young (infant) transplant recipients of both LD and DD sources are observed to have more severe outcomes from acute rejection, particularly among deceased donor transplants: 12% of acute rejections of DD sources result in graft failure or death and 7% of infants from LD sources. In addition, among living donor transplant recipients, infants have high rates of complete reversal (64%). When restricted to the *first* episode of acute rejection (Exhibit 4.5B), the outcome for infants was particularly poor:

10% of LD and 17% of DD rejections resulted in graft failure or death. Non-biopsied rejections had slightly higher reversal rates than biopsied rejections, suggesting an association between the severity of the rejection episode and the decision to biopsy. Treatment with induction antibody at the time of transplant did not by itself appear to negatively influence the probability of completely reversing later rejections.

Exhibit 4.6 provides additional information on rejection reversal rates, by transplant year. Despite the decreasing rejection frequency, reversal rates appear to be unchanging. In living-donors, complete reversal rates are 52% in 1987 and 53% since 2007. Graft failure/death rates as a rejection outcome in living donors were 4% in 1987 and have remained fairly constant over the years. However there have been only 2 graft failures/deaths from rejection cases transplanted since 2007. Deceased donors fluctuate more, with 46% complete reversal rate in 1987, a drop to around 38% from 1998 – 2005 (with a corresponding rise in partial reversals). More recent years are still accruing data.

Rejection history was examined for patients who were rejection-free for a minimum of 365 days post-transplantation and for whom 12-month follow-up data were available. Of the 5711 patients satisfying these criteria, 1128 (20%) subsequently experienced an acute rejection episode (defined here as a ***late*** first rejection). Exhibit 4.7 presents rejection rates by selected characteristics for this group. There were 430 (38%) complete reversals, 606 (54%) partial reversals, and 68 (6%) graft failures/ deaths as a result of the rejection episodes.

EXHIBIT 4.1A
FREQUENCY OF ACUTE REJECTIONS
1987-2010

	Total*		Living Donor		Deceased Donor	
	N	**%**	**N**	**%**	**N**	**%**
All Transplants	11519	100.0	5846	100.0	5673	100.0
Transplants with at Least 1 Rejection	5256	45.6	2388	40.9	2868	50.6
Number of Acute Rejections						
0	6263	54.4	3458	59.2	2805	49.4
1	2715	23.6	1289	22.1	1426	25.1
2	1253	10.9	597	10.2	656	11.6
3	653	5.7	263	4.5	390	6.9
≥4	635	5.5	239	4.1	396	7.0
Transplants with at Least 1 Rejection by Transplant Era						
1987-1990	1509/2127	70.9	593/908	65.3	916/1219	75.1
1991-1994	1463/2413	60.6	668/1198	55.8	795/1215	65.4
1995-1998	1126/2473	45.5	571/1362	41.9	555/1111	50.0
1999-2002	653/2046	31.9	359/1239	29.0	294/807	36.4
2003-2006	394/1621	24.3	163/808	20.2	231/813	28.4
2007-2010	111/839	13.2	34/331	10.3	77/508	15.2

*Total with known donor source (84 additional transplants have unknown donor source).

EXHIBIT 4.1B
ACUTE REJECTION RATIOS
1987-1995

	Living Donor			Deceased Donor		
	No. of Transplants	**No. of Rejections**	**Rejection Ratio**	**No. of Transplants**	**No. of Rejections**	**Rejection Ratio**
Total	2465	2941	1.19	2763	4151	1.50
Recipient age						
0-1 years	193	142	0.74	87	87	1.00
2-5 years	413	456	1.10	398	602	1.51
6-12 years	869	1183	1.36	963	1522	1.58
> 12 years	990	1160	1.17	1315	1940	1.48

EXHIBIT 4.1C
ACUTE REJECTION RATIOS
1996-2010

	Living Donor			Deceased Donor		
	No. of Transplants	**No. of Rejections**	**Rejection Ratio**	**No. of Transplants**	**No. of Rejections**	**Rejection Ratio**
Total	3381	1537	0.45	2910	1777	0.61
Recipient age						
0-1 years	252	52	0.21	75	26	0.35
2-5 years	519	206	0.40	361	175	0.48
6-12 years	1048	497	0.47	899	559	0.62
> 12 years	1562	782	0.50	1575	1017	0.65

EXHIBIT 4.1D
BIOPSY RATE OF REPORTED ACUTE REJECTIONS

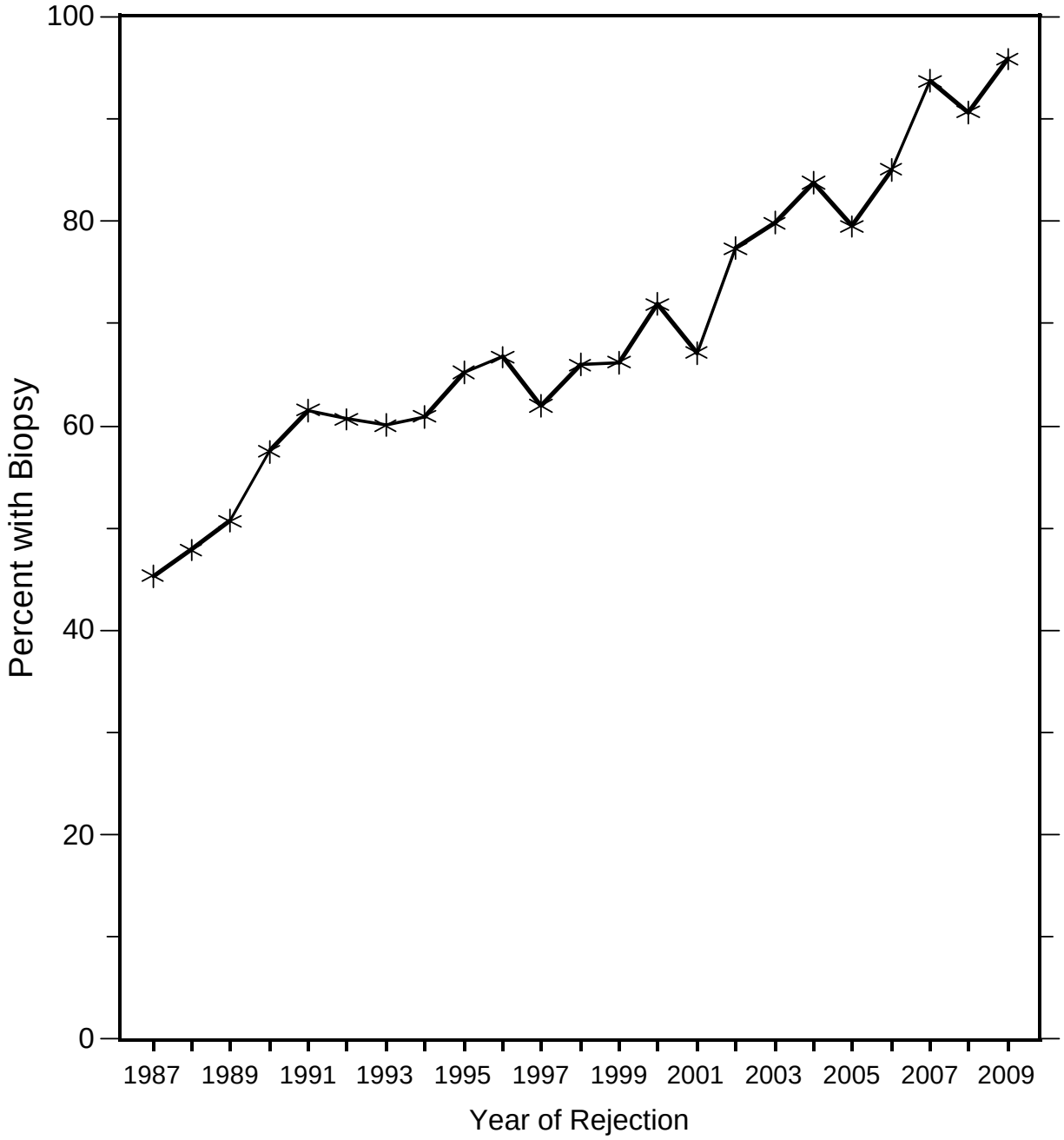
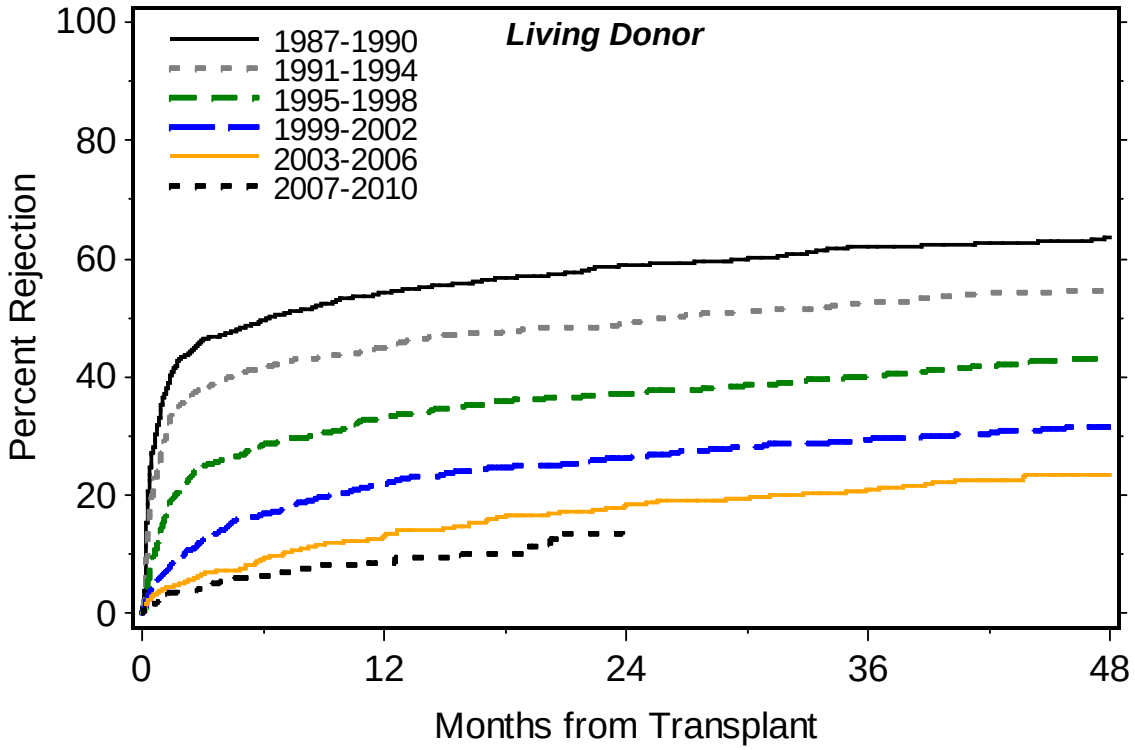


EXHIBIT 4.2
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS



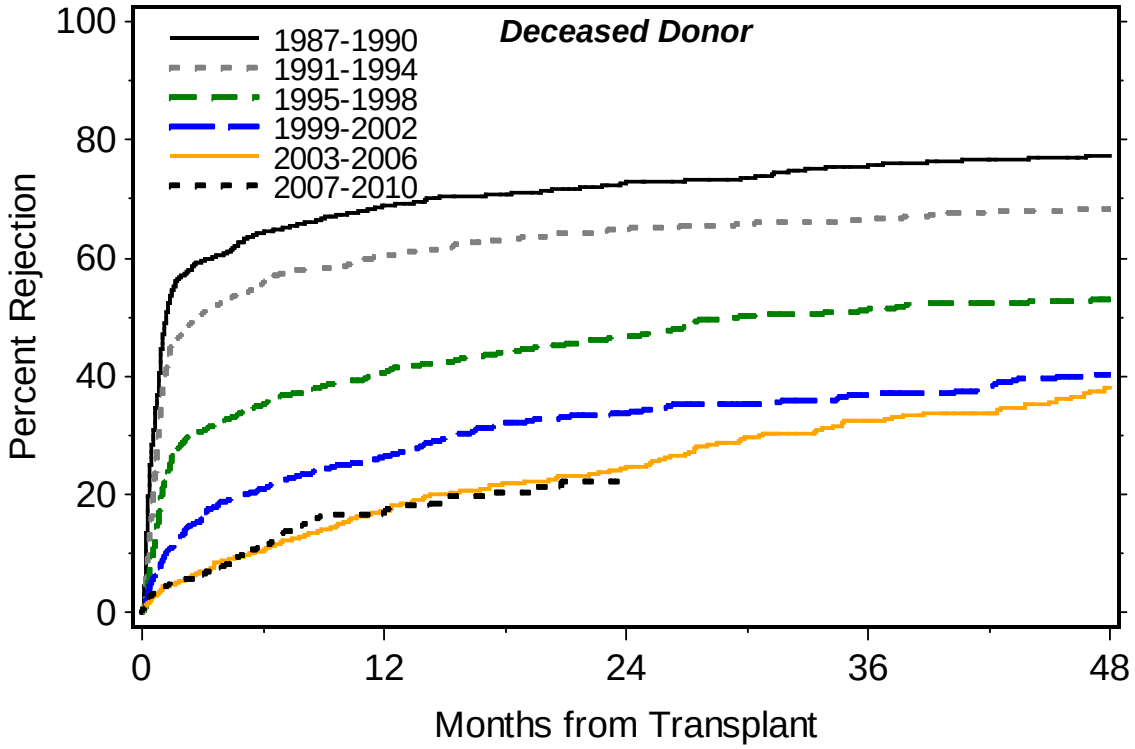


EXHIBIT 4.3A
RELATIVE HAZARD (HR) OF FIRST REJECTION EPISODE
INDEX TRANSPLANTS 1987-1995

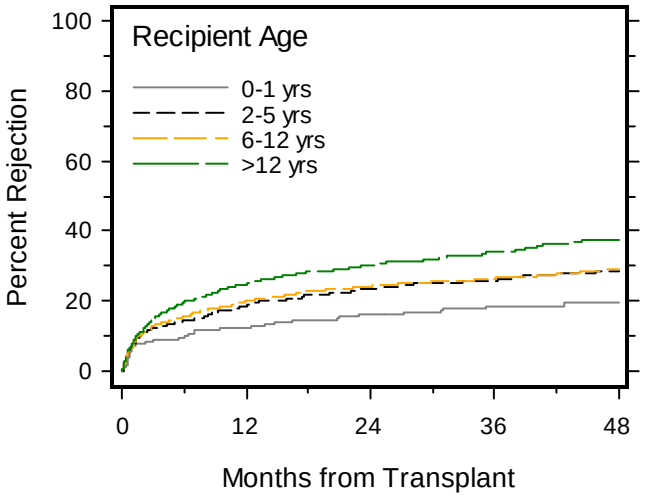
Characteristic	Comparison Group	Reference Group	Living Donor		Deceased Donor	
			RH	p-value	RH	p-value
Recipient Race	Black	Non-black	1.33	<0.001	1.27	<0.001
Recipient Age	<24 months	≥24 months	0.74	0.009	1.13	0.438
HLA-DR Mismatch	1 mismatch 2 mismatches	None	1.63 1.46	<0.001 <0.001	1.13 1.32	0.188 0.002
Induction therapy	No	Yes	1.24	<0.001	1.20	<0.001
Prior random transfusions	1-5 >5	None	0.93 1.08	0.223 0.368	0.93 0.98	0.273 0.805
Donor specific transfusions	Yes	No	0.89	0.204	--	--
Pre-op Immunotherapy	Yes	No	0.96	0.521	--	--
Cold storage time	>24 hours	≤24 hours	--	--	0.99	0.883
Transplant year	1987-1995		0.94	<0.001	0.93	<0.001

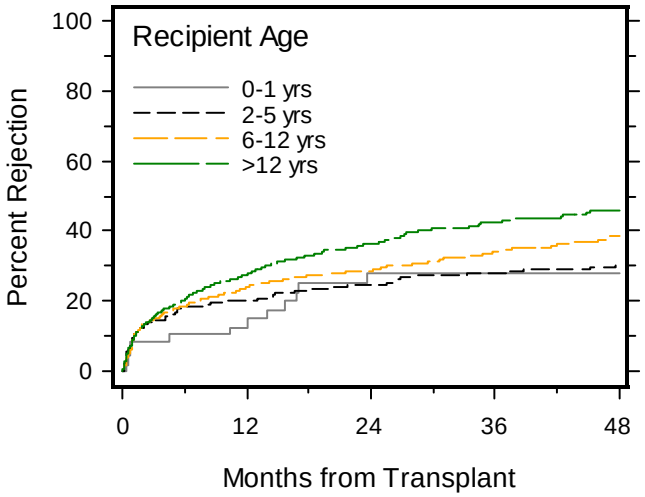
EXHIBIT 4.3B
RELATIVE HAZARD (HR) OF FIRST REJECTION EPISODE
INDEX TRANSPLANTS 1996-2010

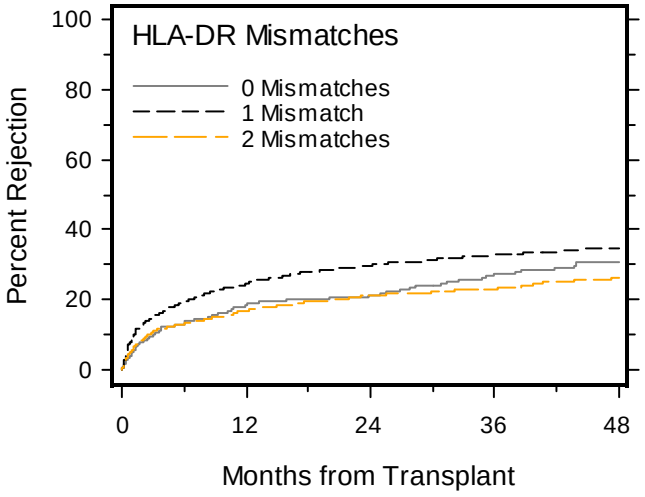
Characteristic	Comparison Group	Reference Group	Living Donor		Deceased Donor	
			RH	p-value	RH	p-value
Recipient Race	Black	Non-black	1.05	0.628	1.43	<0.001
Recipient Age	<24 months	≥24 months	0.51	<0.001	0.89	0.700
HLA-DR Mismatch	1 mismatch 2 mismatches	None	1.31 1.01	0.020 0.929	1.27 1.20	0.137 0.253
Induction therapy	No	Yes	1.15	0.060	0.89	0.191
Prior random transfusions	1-5 >5	None	1.02 1.00	0.811 0.985	1.00 0.92	0.995 0.543
Donor specific transfusions	Yes	No	0.52	0.070	--	--
Pre-op Immunotherapy	Yes	No	1.05	0.538	--	--
Cold storage time	>24 hours	≤24 hours	--	--	1.11	0.366
Transplant year	1996-2010		0.91	<0.001	0.93	<0.001

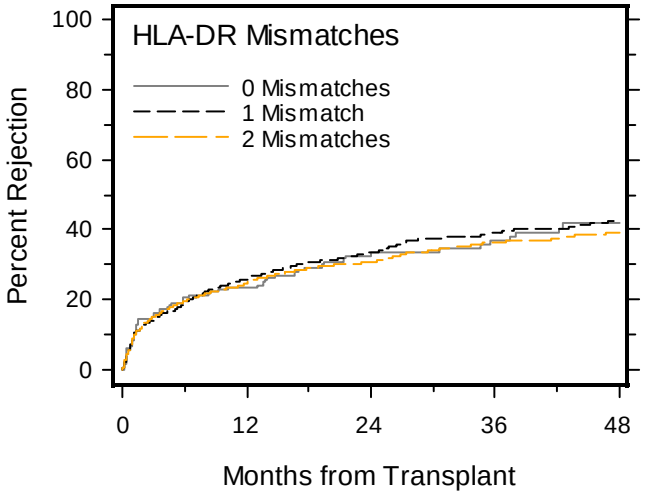
EXHIBIT 4.4
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS 1996-2010

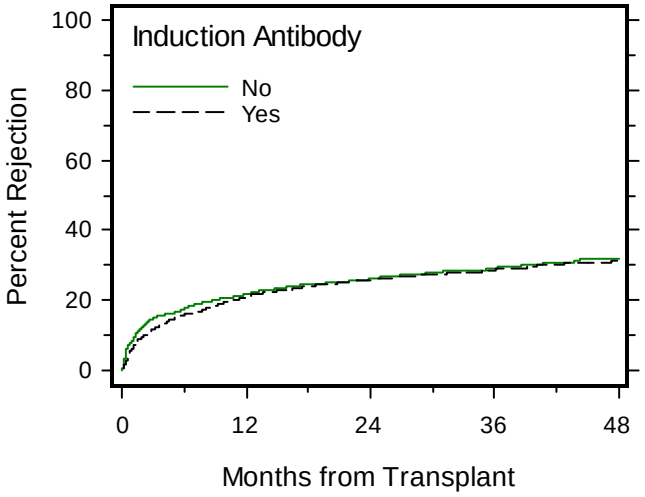
Living Donor ***Deceased Donor***











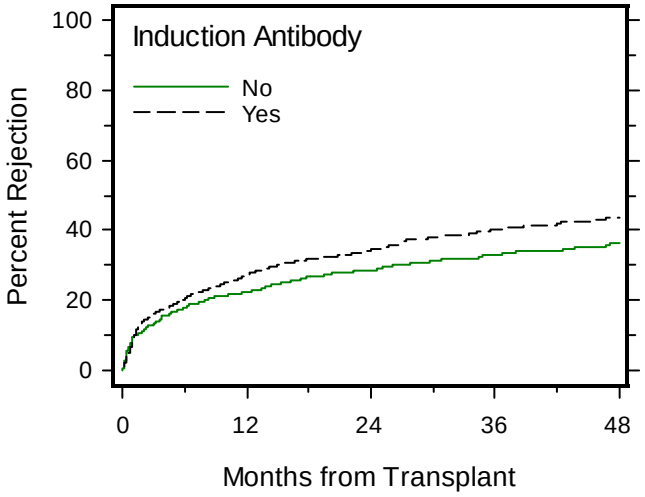
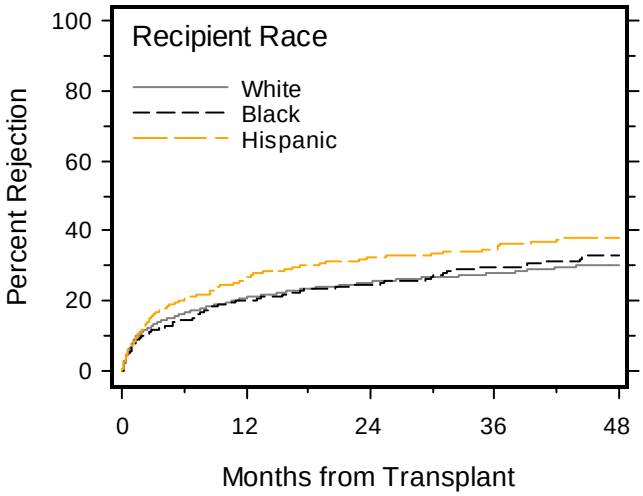
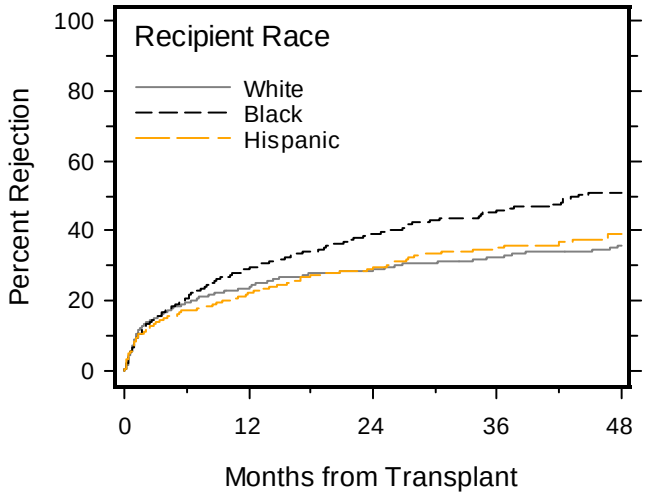
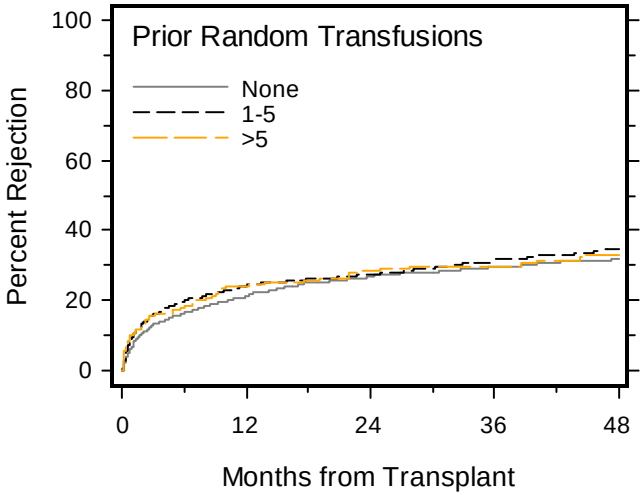


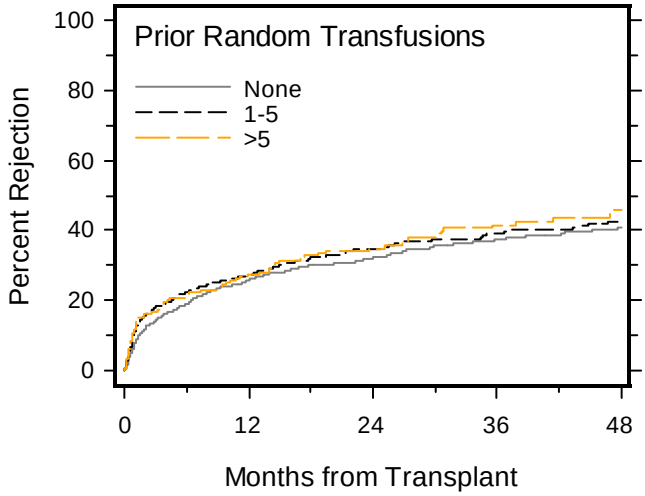
EXHIBIT 4.4 (continued)
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS 1996-2010

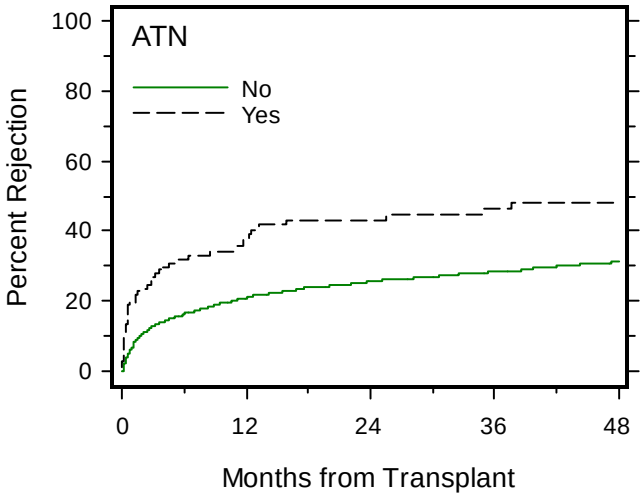
Living Donor | ***Deceased Donor***

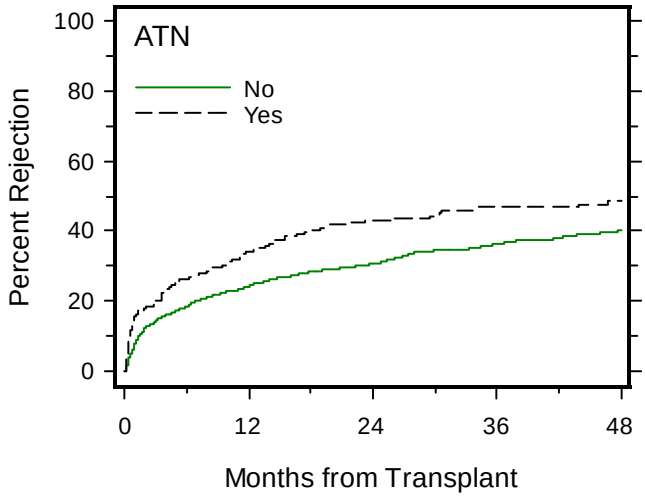












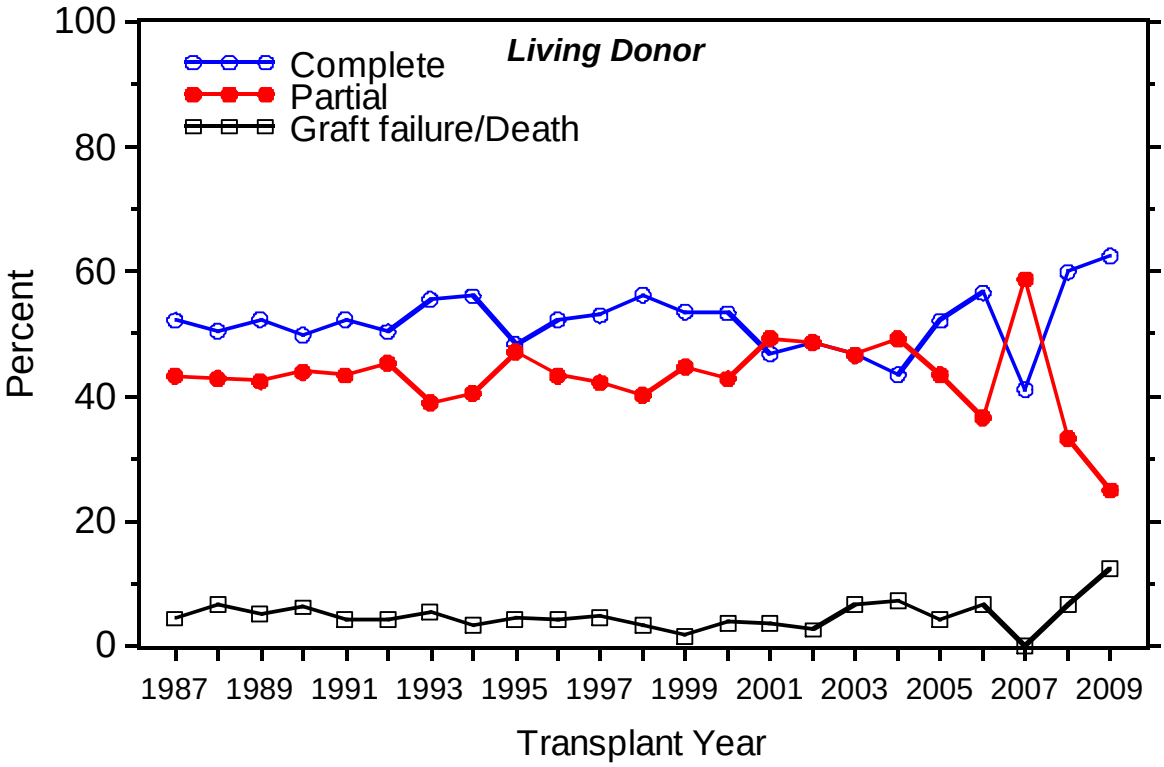
EXIHIBIT 4.5A
REJECTION REVERSAL OUTCOME BY PATIENT CHARACTERISTICS

	Living Donor				Deceased Donor			
	N of Rejections	% Complete Reversal	% Partial Reversal	% Graft Failure /Death	N of Rejections	% Complete Reversal	% Partial Reversal	% Graft Failure /Death
Total Rejection Episodes	4444	51.8	43.6	4.6	5871	45.3	48.0	6.7
Rejection Number								
1	2373	59.5	35.7	4.8	2847	54.1	37.6	8.3
2	1091	45.5	49.7	4.9	1429	44.8	50.1	5.1
3	496	42.7	54.0	3.2	777	33.1	61.6	5.3
≥4	484	38.0	57.9	4.1	818	27.1	67.7	5.1
Recipient Age								
0-1 years	190	64.2	28.9	6.8	113	54.0	33.6	12.4
2-5 years	659	57.8	37.8	4.4	771	55.4	38.1	6.5
6-12 years	1667	51.5	44.6	4.0	2061	45.9	47.3	6.8
> 12 years	1928	48.9	46.1	5.0	2926	41.9	51.7	6.4
Biopsy								
No	1498	58.5	38.1	3.4	2171	48.2	47.0	4.8
Yes-needle	1403	48.5	47.8	3.7	1560	40.7	53.1	6.2
Yes-tissue	1508	49.3	45.8	4.9	2073	47.0	46.5	6.5
D-R Antigen								
0 mismatch	532	52.3	43.4	4.3	605	47.1	47.1	5.8
1 mismatch	3125	52.8	42.8	4.4	2428	44.2	49.7	6.1
2 mismatch	787	47.6	46.9	5.5	2838	45.9	46.8	7.3
Induction Antibodies								
No	2546	52.1	42.7	5.2	2336	45.7	47.4	6.9
Yes	1898	51.5	44.7	3.7	3535	45.1	48.4	6.5
Transplant Era								
1987-1995	2937	52.0	43.2	4.9	4143	46.8	46.1	7.1
1996-2000	957	53.6	42.7	3.7	1050	42.9	51.5	5.6
2001-2010	550	48.2	47.1	4.7	678	40.1	54.1	5.8

EXHIBIT 4.5B
REJECTION REVERSAL OUTCOME BY PATIENT CHARACTERISTICS
FIRST ACUTE REJECTION EPISODE

	Living Donor				Deceased Donor			
	N of Rejections	% Complete Reversal	% Partial Reversal	% Graft Failure /Death	N of Rejections	% Complete Reversal	% Partial Reversal	% Graft Failure /Death
Total Rejection Episodes	2373	59.5	35.7	4.8	2847	54.1	37.6	8.3
Rejection Number								
1	2373	59.5	35.7	4.8	2847	54.1	37.6	8.3
Recipient Age								
0-1 years	126	65.9	24.6	9.5	71	60.6	22.5	16.9
2-5 years	362	66.0	28.5	5.5	361	62.9	27.1	10.0
6-12 years	847	59.5	35.4	5.1	999	53.9	37.1	9.0
> 12 years	1038	56.5	39.7	3.9	1416	51.8	41.3	6.9
Biopsy								
No	781	69.7	27.7	2.7	963	60.5	33.6	5.8
Yes-needle	772	55.8	40.5	3.6	793	48.0	45.6	6.3
Yes-tissue	791	55.0	40.1	4.9	1030	55.8	37.0	7.2
D-R Antigen								
0 mismatch	289	58.5	37.4	4.2	274	58.4	33.9	7.7
1 mismatch	1644	60.9	34.4	4.6	1148	54.2	39.0	6.8
2 mismatch	440	54.8	39.1	6.1	1425	53.3	37.1	9.6
Induction Antibodies								
No	1337	60.1	34.1	5.8	1138	56.2	35.1	8.7
Yes	1036	58.8	37.6	3.6	1709	52.7	39.3	8.0
Transplant Era								
1987-1995	1443	60.4	34.0	5.7	1894	56.1	34.7	9.2
1996-2000	573	59.7	37.0	3.3	538	51.5	42.0	6.5
2001-2010	357	55.7	40.3	3.9	415	48.7	45.1	6.3

EXHIBIT 4.6
REJECTION REVERSAL OUTCOME



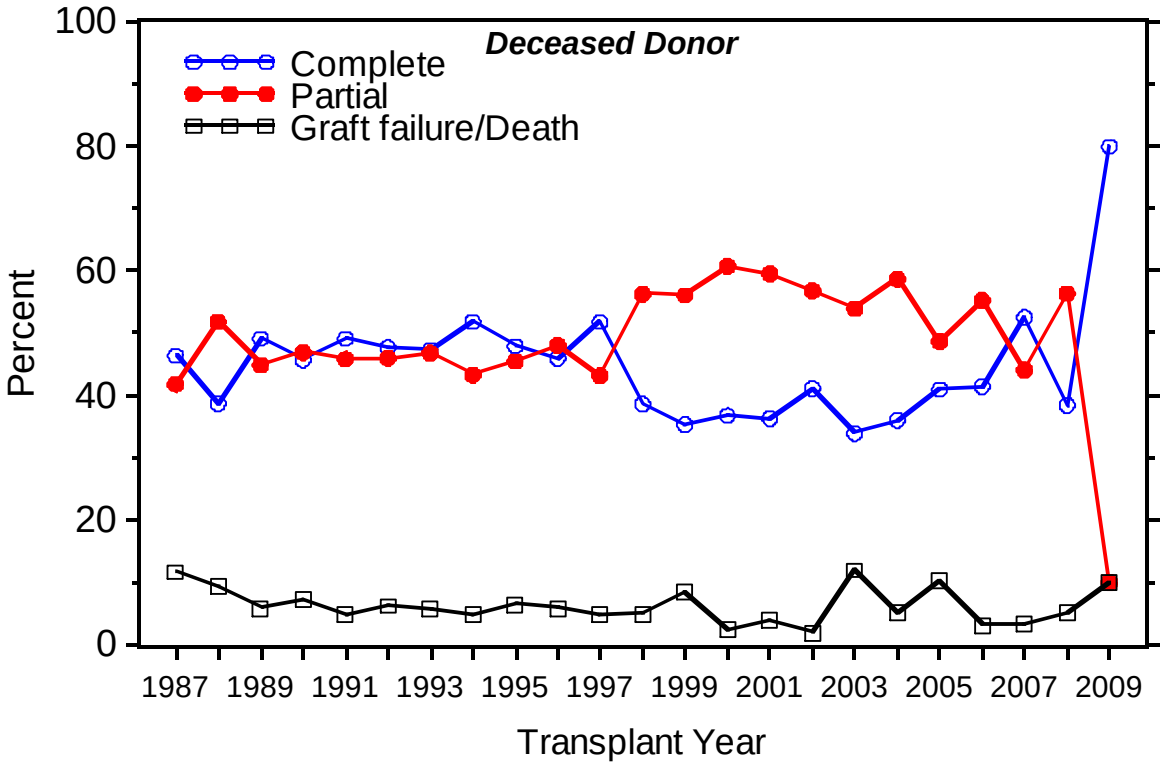


EXHIBIT 4.7
LATE FIRST REJECTIONS BY SELECTED CHARACTERISTICS

Patient Characteristics	No. of Transplants	No. of Rejections	Percent Rejection
Total	5711	1128	19.8
Donor source			
Living Donor	3233	574	17.8
Deceased Donor	2430	550	22.6
Age			
0-1 years	342	41	12.0
2-5 years	880	160	18.2
6-12 years	1948	443	22.7
> 12 years	2541	484	19.0
Sex			
Male	3367	656	19.5
Female	2344	472	20.1
Race			
White	3478	630	18.1
Nonwhite	2233	498	22.3

Late Rejection Outcome	No. of Rejections	Percent
Total	1128	100.0
Rejection outcome		
Unknown	24	2.1
Complete	430	38.1
Partial	606	53.7
Graft failure/Death	68	6.0

SECTION 5: GRAFT FUNCTION

A total of 2,920 graft failures among 11,603 (25.2%) transplants have occurred. This includes 300 patients who have lost 2 or more grafts since the study's start, of which 29 subjects had 3 graft failures and 3 had 4 graft failures. Of index transplants, 2,580 of 10,632 (24.6%) transplants have failed, while 335 of 971 (34.5%) subsequent transplants have failed. Of these 2,920 failures, 263 (9.0%) were deaths with functioning graft. In the remaining failures (with known determination), graft failure was determined by a return to dialysis in 91.9% and a retransplant in 7.6%. Exhibit 5.1 provides the distribution of graft failure causes. Note that tissue confirmation of cause was obtained in 1,611 (60.6%) failures. Of the index graft failures occurring since January 1, 2000, chronic rejection accounted for 40.5% (364/899) while 94 (10.5%) were acute rejection graft failures, (plus 2 hyper acute and 3 accelerated acute rejection), 53 (5.9%) cases discontinued medication, 62 (6.9%) failed from graft thrombosis, 70 (7.8%) had disease recurrences, and 74 (8.2%) were deaths with a functioning graft. With increased length of follow-up of the study cohort, chronic rejection continues to be the most common cause of graft failure. Overall, 50.9% of all graft failures are caused by rejection, with chronic rejection accounting for 35.6% and acute rejection accounting for 13.2% of the failures. Recurrence of original disease as a cause of graft failure has been observed 202 times as follows: focal segmental glomerulosclerosis (93), membranoproliferative glomerulonephritis Type II (18), hemolytic uremic syndrome (18), oxalosis (10), chronic glomerulonephritis (7), others (56). Vascular thrombosis remains a major cause of failure; 378 graft failures are attributed to primary non-function, vascular thrombosis, or miscellaneous technical causes, suggesting that such problems will occur in 3.3% of pediatric transplants. Renal artery stenosis as a cause of graft failure is observed in 1 living donor versus 14 deceased source transplants. Chronic rejection causes graft failure in 7.3% of living donor versus 10.7% of deceased source transplants and respective failure rates due to primary non-function are 0.3% versus 0.7% while those for thrombosis are 1.9% versus 3.1%.

Because of the clinical and statistical significance of donor source, graft failure distributions are presented separately for living and deceased donor transplants. Survival distribution estimates for the index transplants are presented in Exhibit 5.2 by donor source and transplant era. Overall, the mean and median follow-up for subjects with functioning grafts is 4.5 and 3.8 years. Estimated graft survival probabilities are 93.6%, 88.2%, 82.6% and 75.4% at Years 1, 3, 5 and 7 post-transplant, respectively, for recipients of living donor organs. Corresponding estimates for

recipients of deceased donor source organs are 87.3%, 77.3%, 69.7% and 62.1%. Notice from Exhibit 5.2, that more recent deceased donor source transplants have a graft survival experience very similar to that of living donor transplant from the earlier (1987-1995) era. The graft survival in 1996-2010 is significantly better than in prior years for both deceased donor source ($p<0.001$) and living donor grafts ($p<0.001$). Exhibit 5.3 displays graft failure information by transplant source and selected transplant characteristics (the percentage of grafts in the subgroup, the percentage of failures, the product limit estimate of 5-year graft survival probability and associated standard error are provided). Exhibits 5.4-5.8 provide graft survival distributions for selected donor and recipient characteristics.

The table below shows the relative hazard (RH) of individual prognostic factors in the presence of other factors in multivariate proportional hazards models.

MULTIVARIATE PROPORTIONAL HAZARDS REGRESSION MODEL						
	Comparison	Reference	Living Donor		Deceased Donor	
Characteristic	Group	Group	RH	p-value	RH	p-value
Recipient Age	≥ 24 months	<24 months	1.23	0.0698	0.67	0.0036
Transplant History	Prior transplants	No prior tx's	1.50	<0.0001	1.45	<0.0001
Induction Therapy	Induction	No induction	0.84	0.0051	0.92	0.1405
Transfusion History	>5	≤ 5	1.22	0.0164	1.25	0.0006
HLA-B Mismatch	0 mismatches	1-2 mismatches	1.32	0.0183	1.15	0.0170
HLA-DR Mismatch	0 mismatches	1-2 mismatches	0.82	0.0532	1.13	0.0333
Recipient Race	Black	Non-black	1.94	<0.0001	1.58	<0.0001
Dialysis History	Prior dialysis	No prior dialysis	1.16	0.0375	1.23	0.0326
Cold Storage Time	>24 hours	≤ 24 hours	--	--	1.15	0.0201
Native Nephrectomy	Not removed	Tissue removed	0.86	0.0264	0.92	0.2335
Gender	Male	Female	0.88	0.0382	0.85	0.0039
Transplant Year	Per year 1987-2010		0.95	<0.0001	0.94	<0.0001

For recipients of living donor grafts, the most influential prognostic variables (of index transplant graft survival) are race (black vs. non-black; RH=1.94, $p<0.001$), prior transplant (RH=1.50, $p<0.001$), induction antibody therapy (RH=0.84, $p=0.005$), HLA-B mismatches (RH=1.32, $p=0.018$) and transfusion history (RH=1.22, $P=0.016$. A linear trend in improvement in graft retention with later year of entry is also observed (RH=0.95 per year $p<0.001$).

For recipients of deceased donor source organs, review of Exhibit 5.3 indicates multiple variables that are important prognostic factors of graft survival. Exhibit 5.5 shows the graft survival distribution estimates for some of these variables. These include race (black versus non-black; RH=1.58, p<0.001), prior transplant (RH=1.45, p<0.001), transfusion history (RH=1.25, p<0.001) age ≥ 24 months (RH=0.67, p=0.004), and male gender (RH=0.85, p=0.004). The model includes a linear term for year of transplant, whose estimated relative risk increase implies a decreasing hazard (RH=0.94 per year p<0.001). Note that interpretation of the use of induction antibody therapy is hampered by selection factors that motivate its usage; the size and direction of these biases cannot be quantified and the evaluation of this factor cannot be considered definitive.

Plots of graft survival distributions for temporal cohort groups are included in Exhibit 5.6. Marked improvement in deceased donor source graft survival is observed over time. The following table displays graft survival percentages for the various cohorts. (Standard errors range from 0.6% to 1.0% at 1 year and 1.1% to 2.0% at 5 years for living donor, and from 0.7% to 1.3% at 1 year and 1.6 to 2.3% at 5 years for deceased donor source grafts.) These results may be related to temporal trends in such factors as immunosuppressive drugs and dosages, decreased transfusion requirements, and decreased use of young deceased donors.

	GRAFT SURVIVAL RATES					
	LIVING DONOR			DECEASED DONOR		
Cohort Group	1yr	3yr	5yr	1yr	3yr	5yr
1987-1990	89.4	81.1	74.6	75.1	63.4	54.8
1991-1994	91.7	85.3	80.3	85.2	76.4	69.5
1995-1998	94.0	90.7	85.2	90.7	81.9	74.2
1999-2002	96.0	91.6	86.8	92.8	83.9	79.2
2003-2010	96.5	91.5	84.3	95.1	84.1	78.0

Exhibit 5.7 shows graft survival for HLA-A, HLA-B and HLA-DR mismatches for living and deceased donors. Living donors show a slight graft survival advantage for patients with no HLA-DR mismatches and deceased donors show an advantage for patients with no HLA-B mismatches.

Graft survival for the eight most common categories of primary diagnosis is shown in Exhibit 5.8 for living and deceased donors. In living donors, patients with FSGS have a 5 year graft

survival rate of 72% and patients with GN have a 5 year rate of 78%. All other shown categories of primary diagnoses for living donors have a 5 year graft survival rate above 83%. In the deceased donor group, 5 year graft survival rates are between 62% and 65% for GN, FSGS, CNS and HUS and are above 70% for congenital structural, renal infarct, and cystinosis. Familiai nephritis diagnoses has 5-year graft survival rates around 68%.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is defined by the cooperative study as the use of dialysis in the first transplant week. This delay in graft function is reported for 5.1% of index living donor transplants which is significantly less than the ATN rate reported for deceased donor source transplants (15.6%).

Among the living donor transplants, increased rates of ATN are noted with >5 prior transfusions (11.1%), infants <24 months (8.0%), prior transplants (7.9%), black race (7.9%), children with a native nephrectomy (7.3%) and children receiving prior dialysis (6.9%). These factors continue to be significant in a multivariate logistic regression model with prior dialysis (OR=4.2) and >5 transfusions (OR=2.0) highly significant at $p<0.0001$. Black race is also a risk factor with an OR=1.7, p=0.003.

For transplants with deceased donor source organs, the ATN rate increases significantly with several factors: >5 transfusions (27.6%), cold ischemia times >24 hours (24.0%), prior transplant (23.3%), native nephrectomy (21.9%), and black recipients (21.4%). Donor (Age <2 years, 23.9%), donor age ($\geq$50 years, 28.4%) and prior dialysis (17.7%) also had higher rates of ATN. The ATN rate differs for Collins iced electrolyte solution (21.3%) versus Wisconsin solution (15.5%), but not with use of machine perfusion (14.9%). In a multivariate logistic regression analysis, the following variables were significantly predictive of ATN risk in deceased donor graft recipients: prior dialysis (OR=15.3, $p<0.001$), older donor age (OR=2.1, $p<0.001$), cold time ≥ 24 hours (OR=1.9, $p<0.001$), number of prior transfusions (OR=1.9, $p<0.001$), black race (OR=1.8, $p<0.001$), prior transplant (OR=1.6, $p<0.001$) and native nephrectomy (OR=1.3, p=0.014).

Graft survival after the first week is displayed in Exhibit 5.9, and is significantly worse in the presence of acute tubular necrosis in both donor source groups. In the living donor group, 5 year graft survival rates are 85.1% for grafts without ATN and 65.1% for grafts with ATN (log-

rank p<0.001). ATN is significant in the multivariate analysis (RH=2.25, p<0.001) along with race, recipient age, transplant history, and transplant year. Induction therapy and nephrectomy are of borderline significance. Among functioning deceased donor grafts at 1 week, 74.5% of subjects without first week dialysis are estimated to be functioning at 5 years as opposed to 55.9% of those with ATN (log-rank p<0.001). For deceased donor grafts, after one week, the variates that maintain predictive capability of graft failure include the following: ATN (RH=1.67, p<0.001), race, transplant history, recipient age, HLA-B matches, gender, and transplant year. Transfusion history is a borderline significance (p=0.042) and cold storage time is not predictive (p=0.604) after adjustment for first week results.

Serum Creatinine and Creatinine Clearance

Exhibits 5.10 and 5.11 display the means and standard errors of serial serum creatinine and creatinine clearance measurements. At each time point only individuals with functioning grafts are included.

Creatinine clearance (mL/min/1.73 m^2) values were calculated using the Schwartz formula and available morphologic data, with length replacing height in younger recipients, as follows:

SCHWARTZ FORMULA FOR CREATININE CLEARANCE	
Patient's weight (kg)	Creatinine clearance (mL/min/1.73m2)
<10 kg	$\frac{0.45 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$
10kg to 70 kg	$\frac{0.55 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$
>70 kg	$\frac{1.55 \times \text{age(years)} + 0.5 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$

From Exhibit 5.10, decreases in creatinine clearance are observed in living donor recipients over the first 4 years post transplantation. Younger recipients begin with higher calculated clearances that are subject to greater absolute declines, while the oldest subjects behave similarly to adult populations. Likewise, baseline creatinine clearance appears lower in deceased donor organ recipients, but clearance values for both organ source groups approach equivalence in the later years. Serum creatinine rises throughout the course of the study with

older patients and black race patients maintaining a higher mean value over time. (See Exhibit 5.11.)

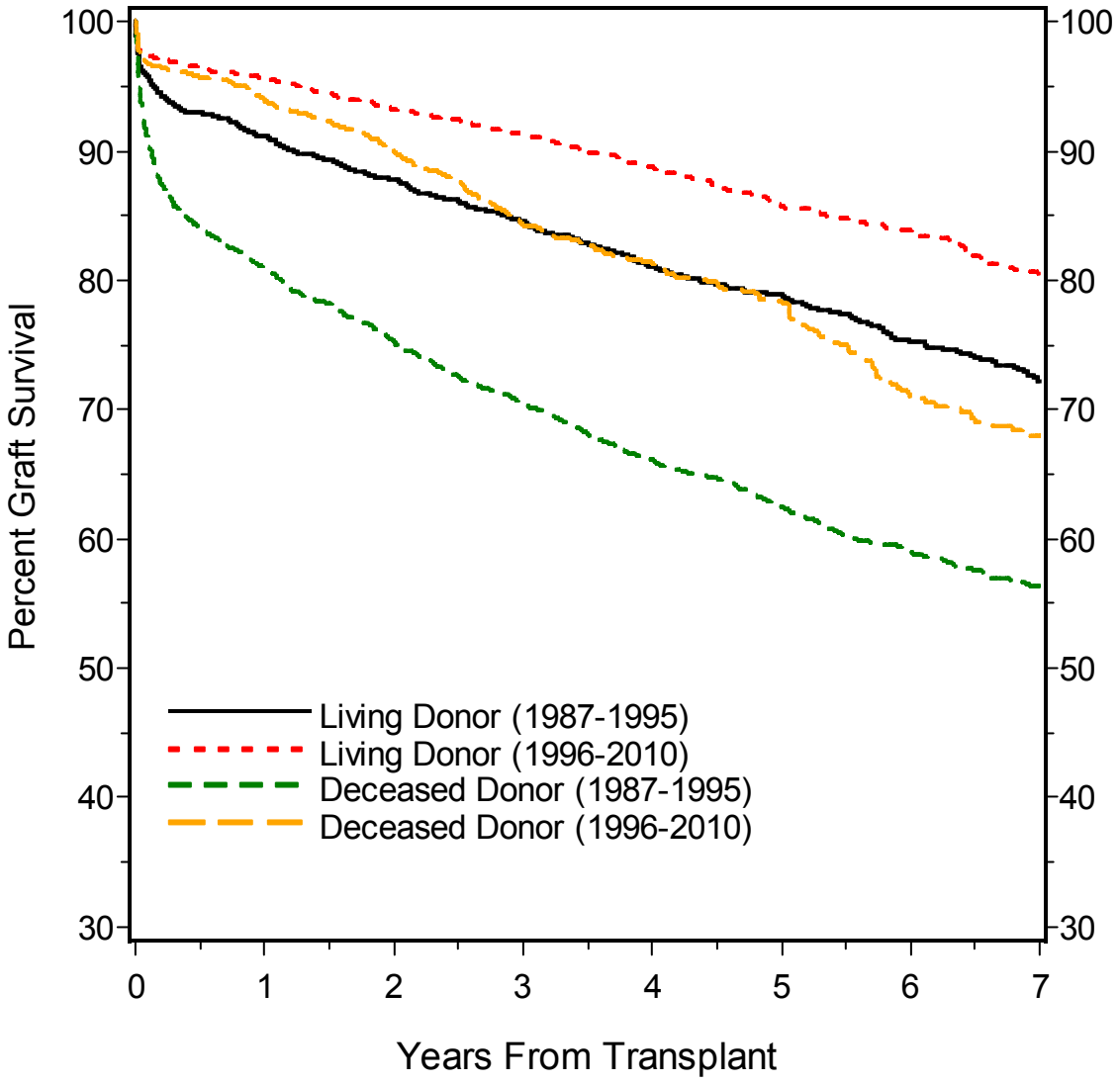
In Exhibits 5.12 - 5.14, graft survival percentage and mean calculated clearance values for subjects with functional grafts are plotted at each annual follow-up visit for various groups, including donor source, transplant year, race and induction antibody therapy use. Continued decreases in both graft survival and graft function are seen through the first five post-transplant years. Relative to the first decade of the registry, temporal improvements in median creatinine clearance accompanies the improvements in graft survival.

The impact of race on calculated clearance and graft survival is observed in Exhibit 5.14. Despite the relatively greater number of graft failures in black recipients, there is no trend towards convergence in serum creatinine values and black recipients have both lower graft survival and clearance values throughout.

EXHIBIT 5.1
CAUSES OF GRAFT FAILURE

	Index Graft Failures		Subsequent Graft Failures		All Graft Failures	
	N	%	N	%	N	%
Total transplants with graft failure	2585	100.0	335	100.0	2920	100.0
Cause of Graft Failure						
Death with functioning graft	238	9.2	25	7.5	263	9.0
Primary non-function	58	2.2	2	0.6	60	2.6
Vascular thrombosis	247	9.6	38	11.3	285	9.8
Other technical	29	1.1	4	1.2	33	1.1
Hyper-acute rejection	15	0.6	4	1.2	19	0.7
Accelerated acute rejection	33	1.3	8	2.4	41	1.4
Acute rejection	342	13.2	44	13.1	386	13.2
Chronic rejection	913	35.3	126	37.6	1039	35.6
Recurrence of original kidney disease	170	6.6	32	9.6	202	6.9
Renal artery stenosis	15	0.6	0	0.0	15	0.5
Bacterial/viral infection	47	1.8	5	1.5	52	1.8
Cyclosporine toxicity	13	0.5	0	0.0	13	0.5
De novo kidney disease	8	0.3	2	0.6	10	0.3
Patient discontinued medication	120	4.6	8	2.4	128	4.48
Malignancy	34	1.3	2	0.6	36	1.2
Other/Unknown	303	11.7	35	10.5	338	11.6

EXHIBIT 5.2
GRAFT SURVIVAL BY ALLOGRAFT SOURCE AND TRANSPLANT YEAR



	Years Post Transplant							
	Year 1		Year 3		Year 5		Year7	
	%	SE	%	SE	%	SE	%	SE
Living Donor 1987 - 1995	91.2	0.59	84.6	0.76	78.9	0.89	72.3	1.05
Living Donor 1996 - 2010	95.5	0.37	91.3	0.56	85.7	0.81	80.5	1.13
Deceased Donor 1987 - 1995	80.7	0.81	70.5	0.96	62.4	1.06	56.3	1.15
Deceased Donor 1996 - 2010	93.9	0.50	84.3	0.88	78.4	1.15	67.9	1.71

EXHIBIT 5.3
GRAFT FAILURE SUMMARY BY SELECTED TRANSPLANT CHARACTERISTICS

	Living Donor (N=5581)				**Deceased Donor** (N=4971)			
	% of Total	% Failing	5 year Graft Survival	5 year rate SE	% of Total	% Failing	5 year Graft Survival	5 year rate SE
Total	100.0	19.9	82.6	0.6	100.0	29.5	69.7	0.8
Sex								
Male	60.4	19.3	83.6	0.7	57.9	28.5	71.5	1.0
Female	39.6	21.0	81.0	1.0	42.1	30.9	67.2	1.3
Race								
White	68.5	19.5	84.0	0.7	49.0	29.0	73.3	1.0
Black	11.2	31.1	71.6	2.1	23.5	35.3	58.9	1.8
Hispanic	16.0	15.3	83.7	1.5	18.2	26.5	69.0	2.0
Other	4.3	14.6	84.7	3.0	9.4	23.6	75.9	2.4
Transplant History								
No prior tx	89.3	19.0	82.9	0.6	83.6	27.5	71.5	0.8
Prior tx	10.7	27.6	80.0	1.9	16.4	39.0	60.9	2.0
Dialysis History								
No prior dialysis	32.7	16.4	86.3	1.0	12.8	23.2	78.4	1.9
Prior dialysis	67.3	21.7	80.7	0.8	87.2	30.4	68.4	0.9
Recipient Age								
0-1 years	8.0	20.5	83.8	1.9	3.1	40.4	60.7	4.6
2-5 years	16.2	23.7	85.4	1.3	13.7	34.2	74.1	1.9
6-12 years	33.0	21.9	84.5	0.9	33.1	32.9	72.1	1.2
>12 years	42.8	16.9	78.6	1.1	50.0	25.3	66.1	1.3
Donor Age								
<2 years	--	--	--	--	1.5	56.7	50.2	6.5
2-17 years	--	--	--	--	37.0	33.9	67.4	1.3
18-49					55.7	26.7	71.8	1.1
≥50 years	--	--	--	--	5.9	41.0	57.7	3.7
Cold Ischemia Time								
≤24 hours	--	--	--	--	73.9	27.8	70.6	1.0
>24 hours	--	--	--	--	26.1	40.8	62.2	1.6

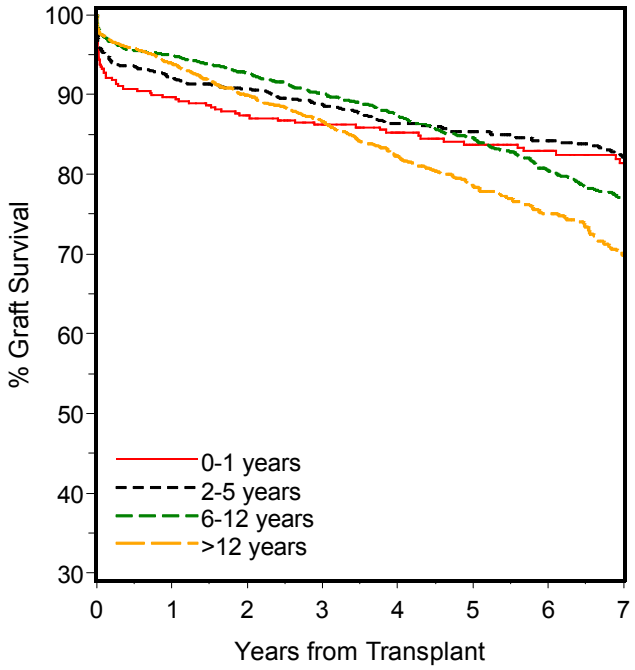
EXHIBIT 5.3 (continued)
GRAFT FAILURE SUMMARY BY SELECTED TRANSPLANT CHARACTERISTICS

	Living Donor (N=5581)				Deceased Donor (N=4971)			
	% of Total	% Failing	5 year Graft Survival	5 year rate SE	% of Total	% Failing	5 year Graft Survival	5 year rate SE
Machine Perfusion								
No	--	--	--	--	75.9	30.8	69.5	0.9
Yes	--	--	--	--	11.8	37.7	60.2	2.5
Unknown	--	--	--	--	12.3	20.2	77.6	2.2
HLA-A Mismatches								
0	14.2	20.1	82.3	1.6	7.3	30.2	71.0	2.8
1	66.9	21.8	81.9	0.7	35.0	32.4	68.5	1.3
2/missing	18.9	13.4	85.5	1.4	57.8	27.7	70.2	1.1
HLA-B Mismatches								
0	10.9	17.5	85.3	1.7	6.9	25.6	76.1	2.6
1	68.4	21.8	81.8	0.7	28.3	32.9	69.0	1.4
2/missing	20.8	15.0	83.6	1.4	64.7	28.4	69.3	1.0
HLA-DR Mismatches								
0	14.0	18.2	86.7	1.4	9.1	29.4	70.6	2.6
1	62.2	22.0	80.9	0.8	37.6	31.6	68.8	1.3
2/missing	23.8	15.5	84.8	1.2	53.3	28.1	70.4	1.1
Pre-operative immunosuppression								
No	51.0	18.1	83.7	0.8	--	--	--	--
Yes	49.1	22.5	81.1	0.9	--	--	--	--
Native Nephrectomy								
No	73.8	18.4	83.1	0.7	80.1	28.3	70.5	0.9
Yes	26.2	24.8	80.8	1.2	19.9	36.8	65.1	1.8
Lifetime Transfusion								
0	53.1	16.4	84.0	0.9	41.8	22.3	74.9	1.3
1-5	35.7	22.2	83.5	1.0	37.2	30.2	71.3	1.3
>5	11.2	33.2	72.4	2.0	21.0	47.3	56.7	1.8
Induction Antibody								
No	53.1	21.6	80.7	0.9	42.2	30.2	67.7	1.2
Yes	46.9	18.3	84.7	0.8	57.8	29.0	71.1	1.0

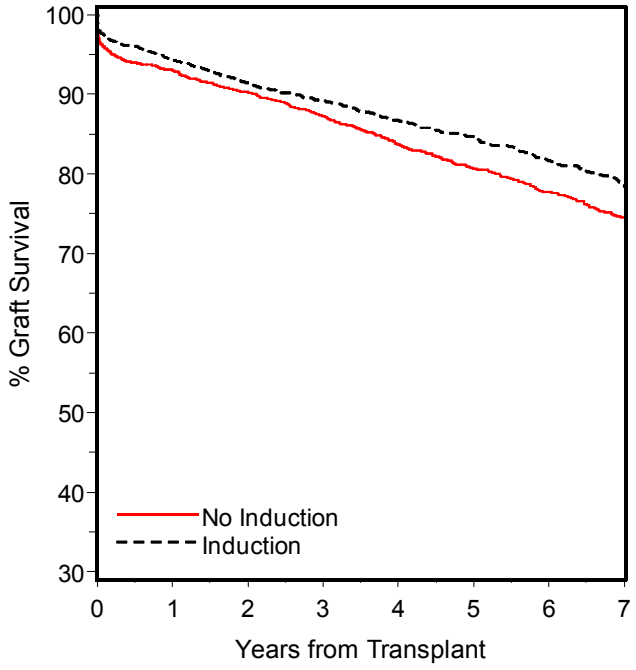
EXHIBIT 5.4
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Living Donor

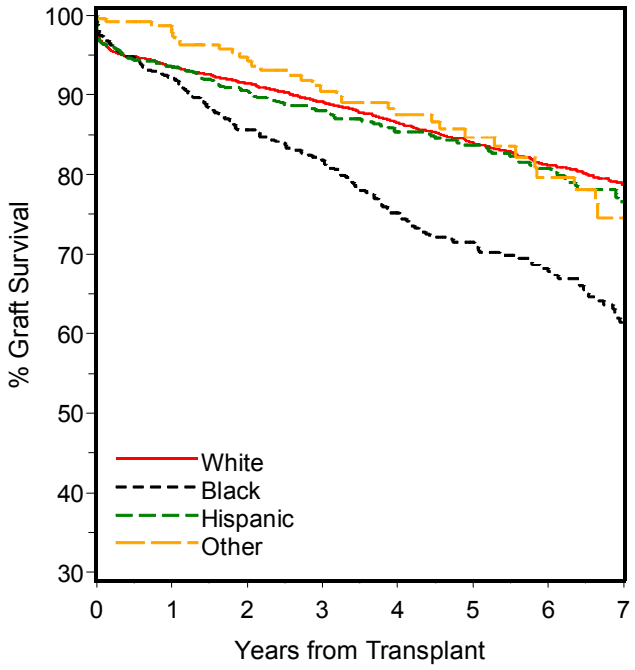
Recipient Age



Induction Antibody



Recipient Race



Transfusion History

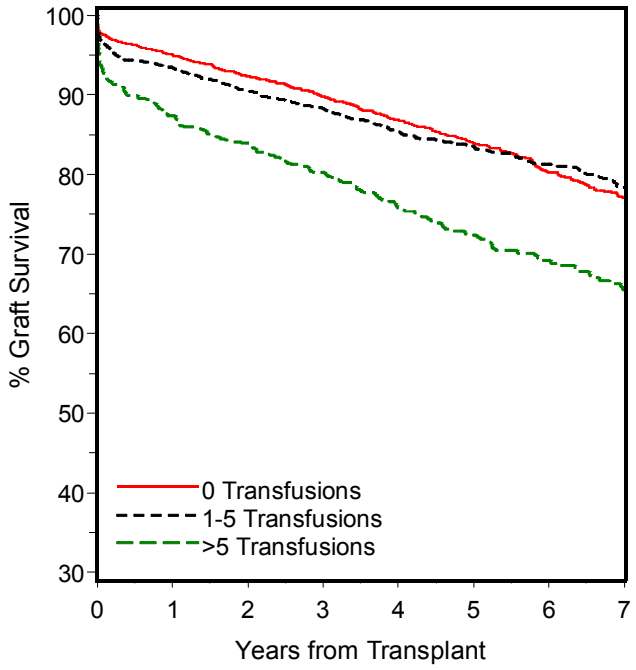
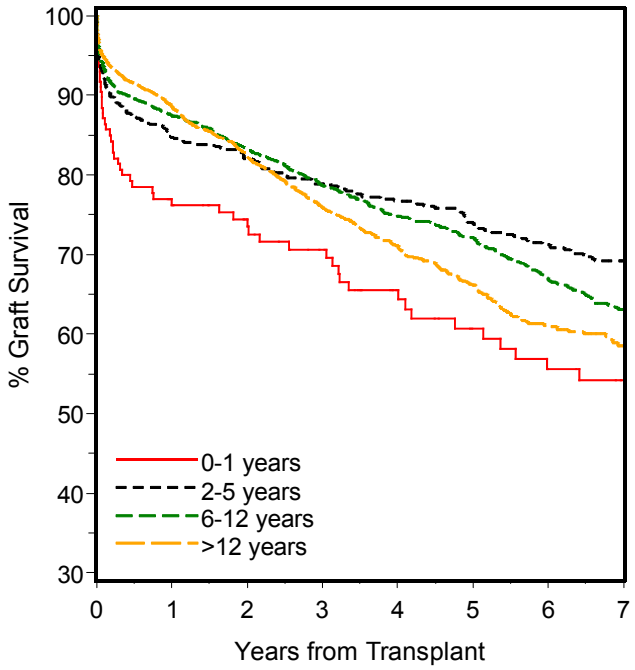


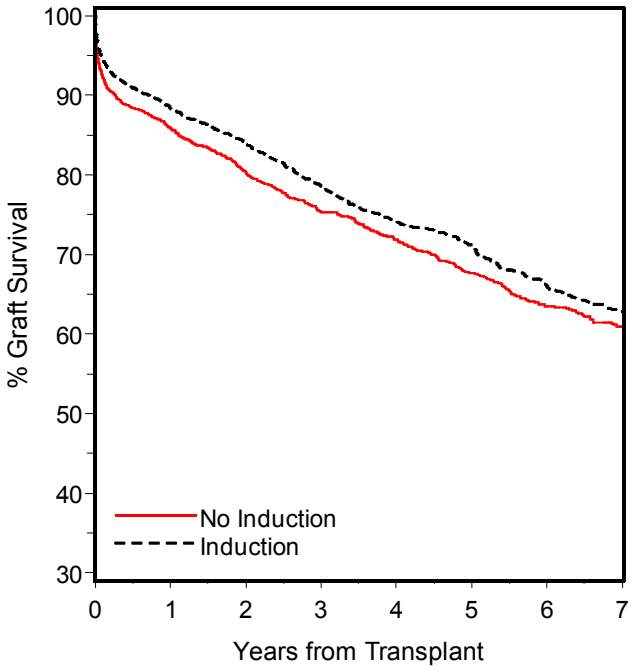
EXHIBIT 5.5
GRAFT SURVIVAL BE SELECTED CHARACTERISTICS

Deceased Donor

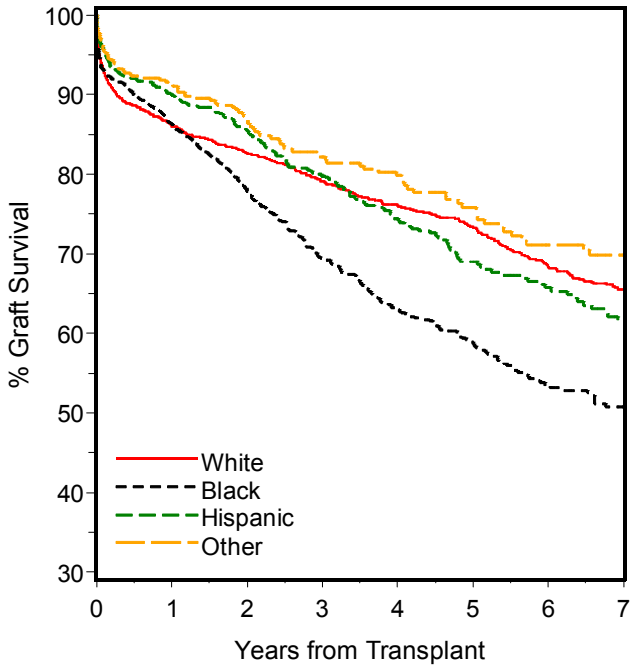
Recipient Age



Induction Antibody



Recipient Race



Transfusion History

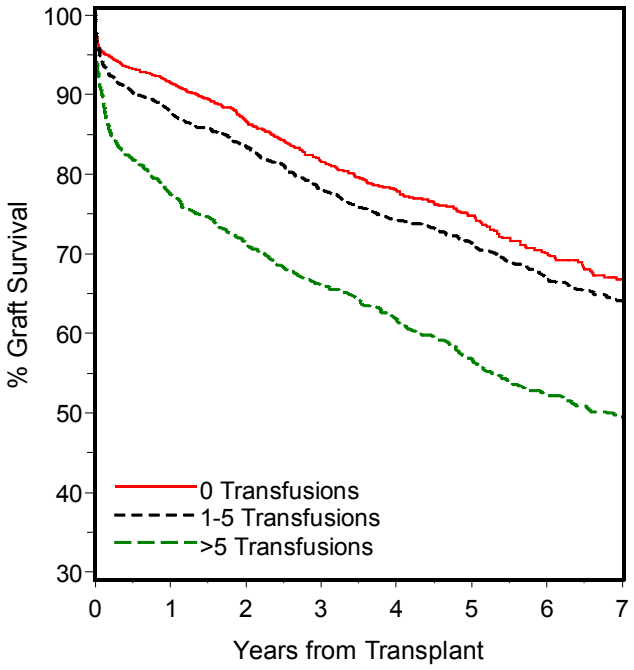
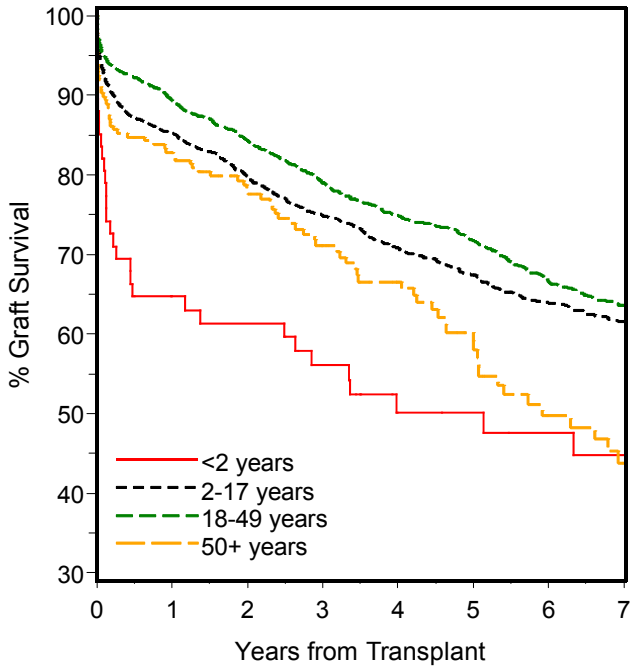


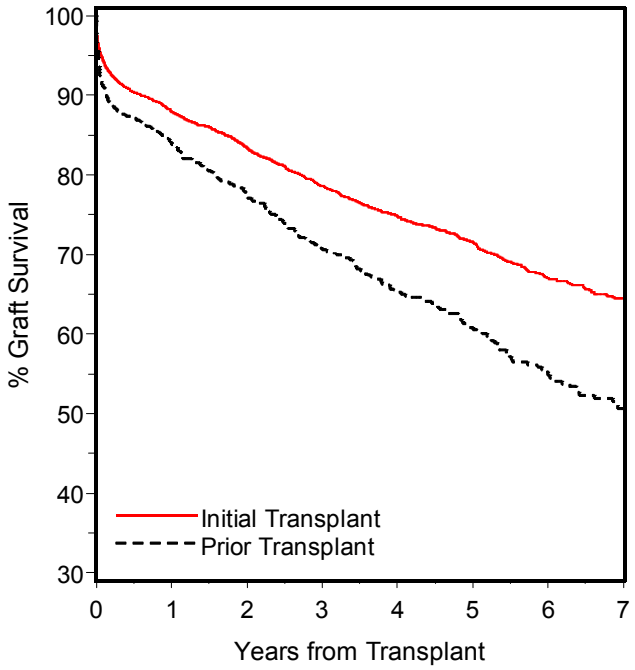
EXHIBIT 5.5 (continued)
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Deceased Donor

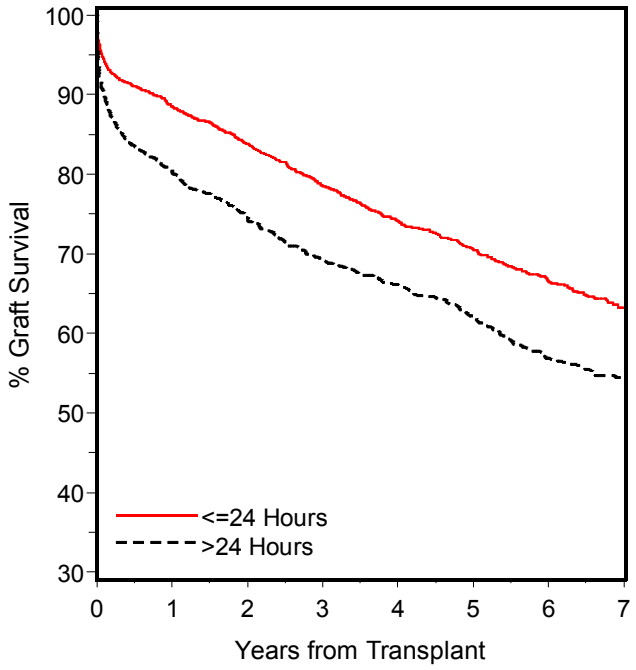
Donor Age



Transplant History



Cold Ischemia Time



Dialysis History

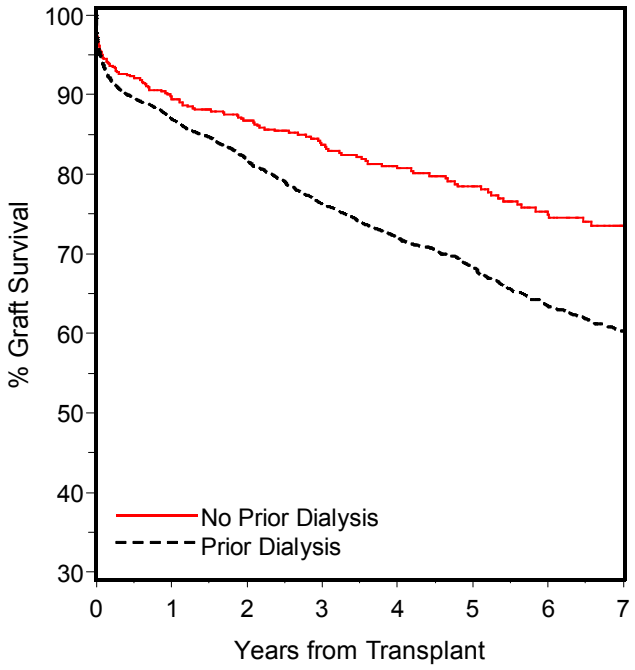
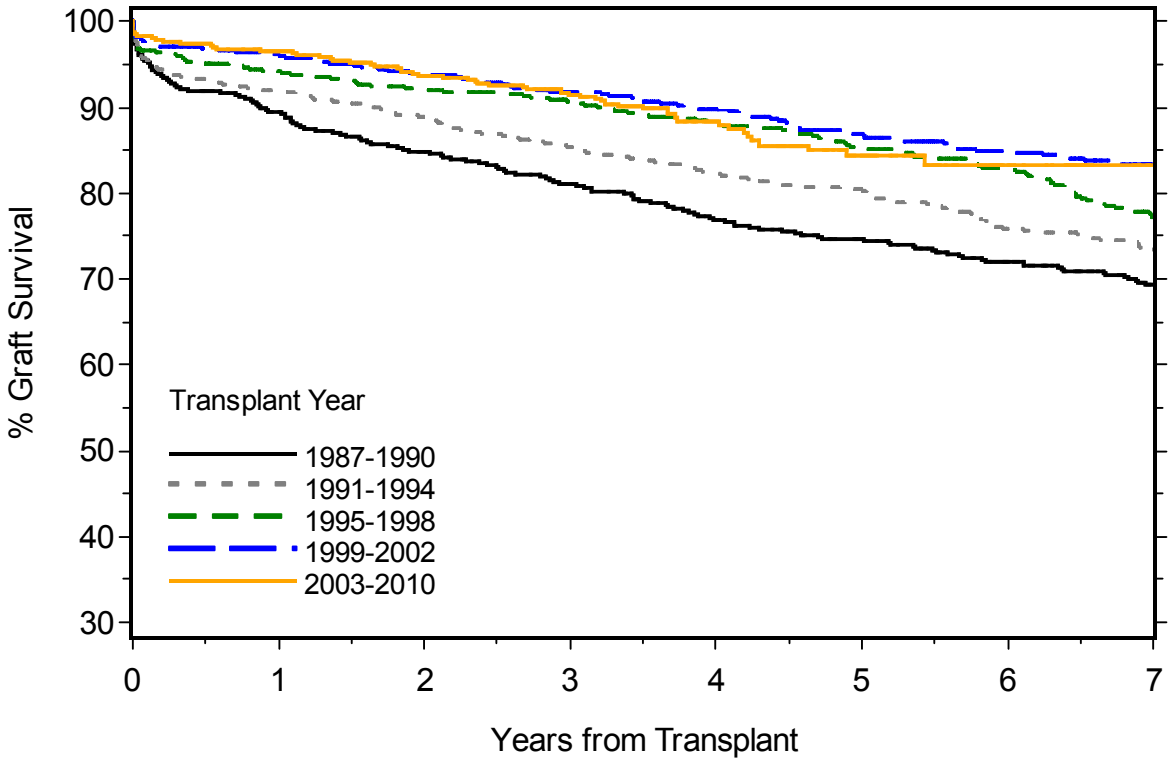


EXHIBIT 5-6
GRAFT SURVIVAL BY TRANSPLANT YEAR

Living Donor



Deceased Donor

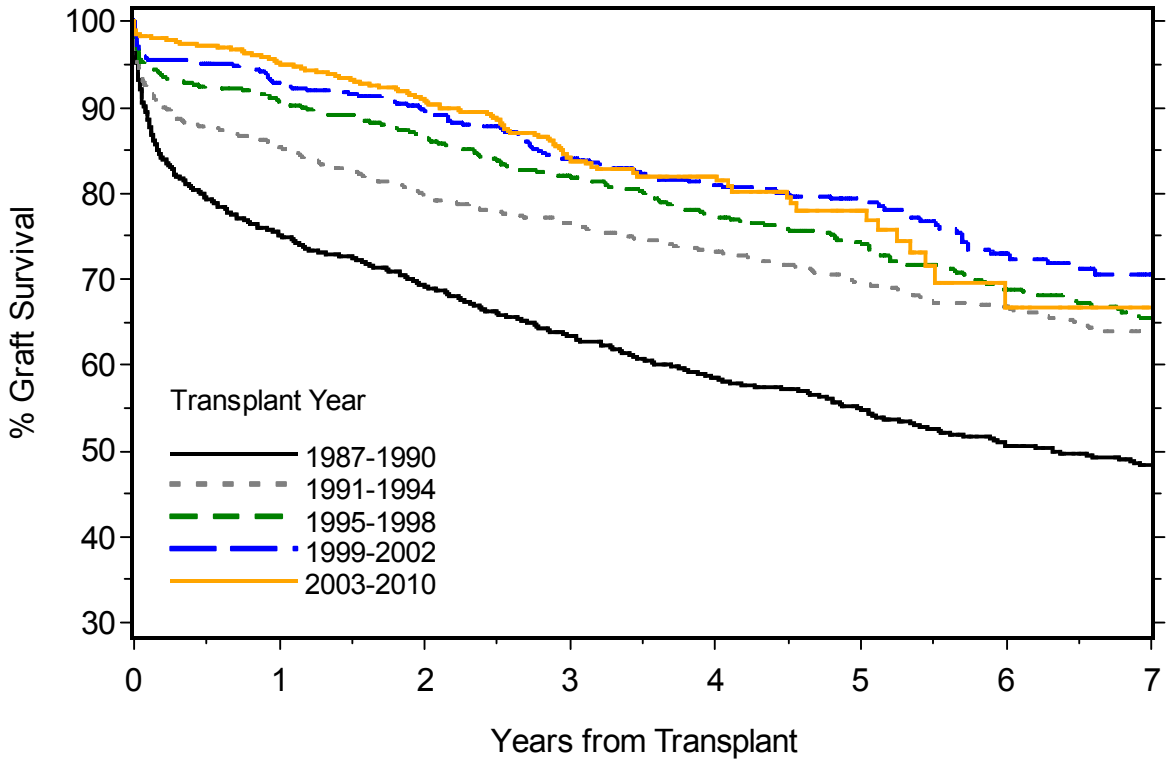
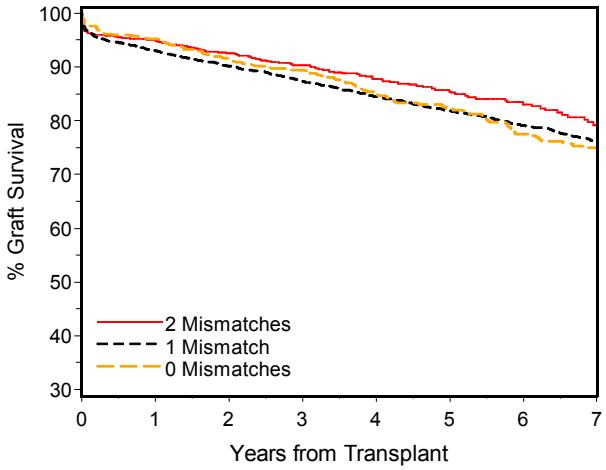


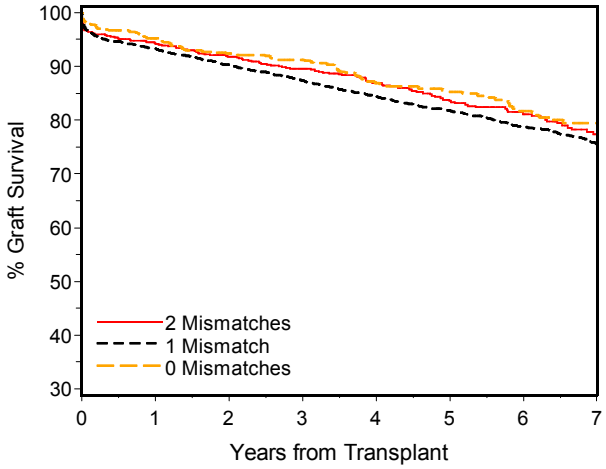
EXHIBIT 5.7
HISTOCOMPATIBILITY DATA

Living Donor

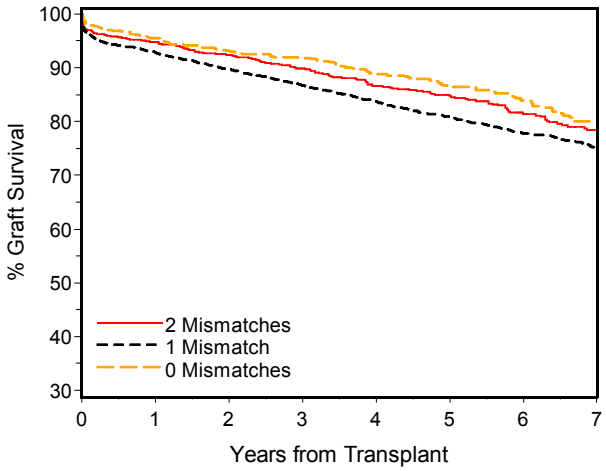
HLA-A



HLA-B

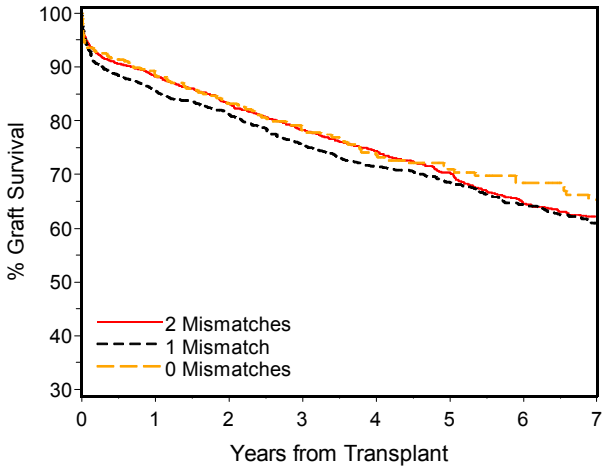


HLA-DR

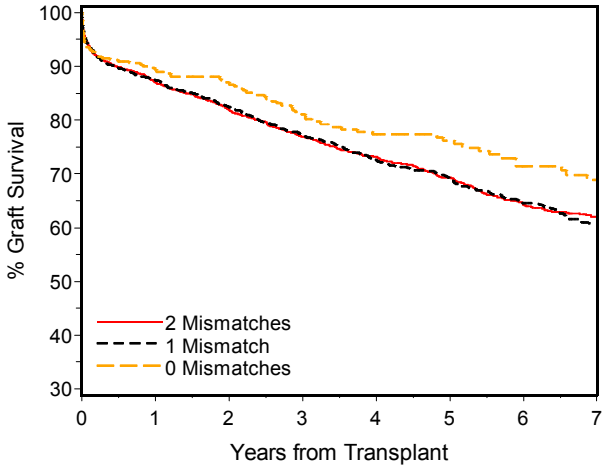


Deceased Donor

HLA-A



HLA-B



HLA-DR

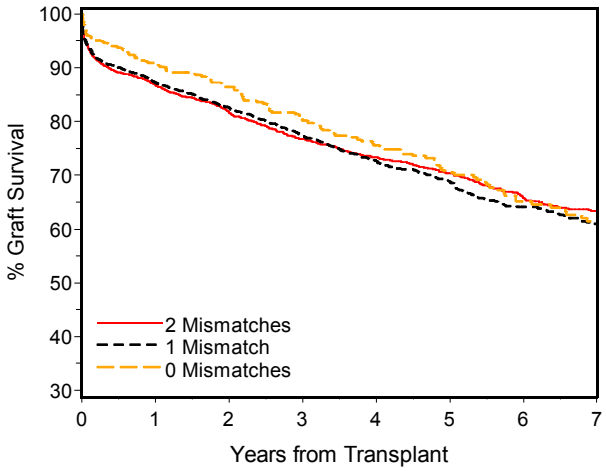
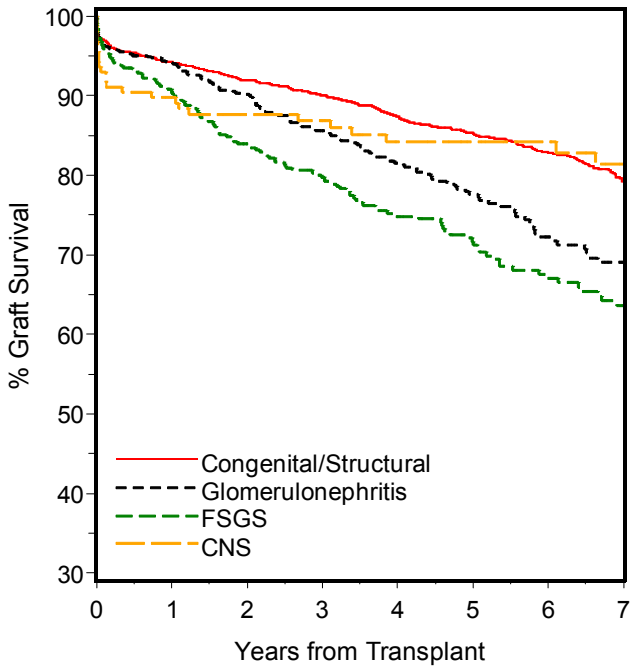
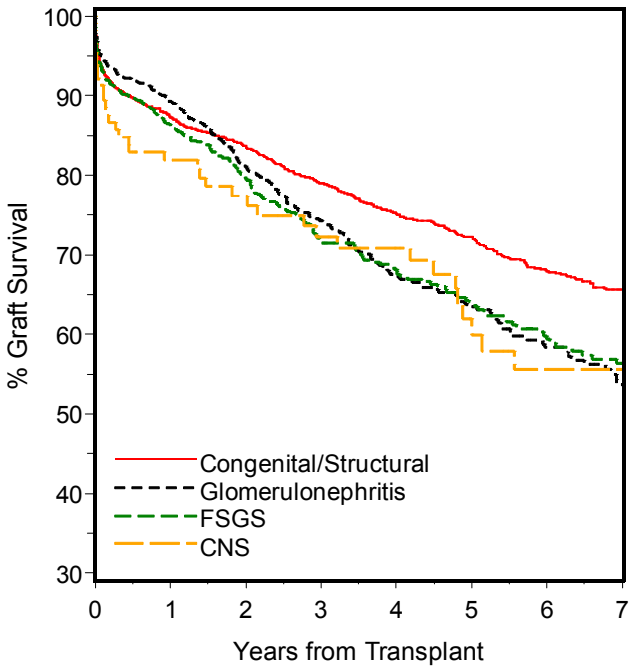
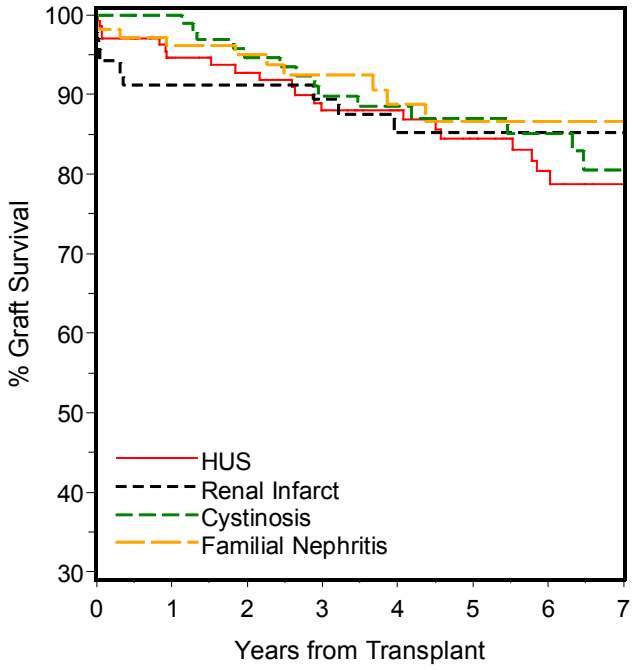


EXHIBIT 5.8
GRAFT SURVIVAL BY PRIMARY DIAGNOSIS

Living Donor ***Deceased Donor***







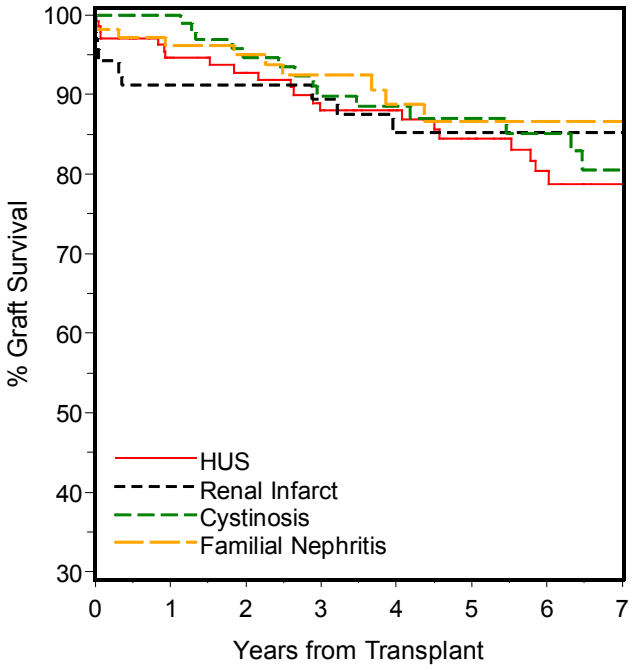
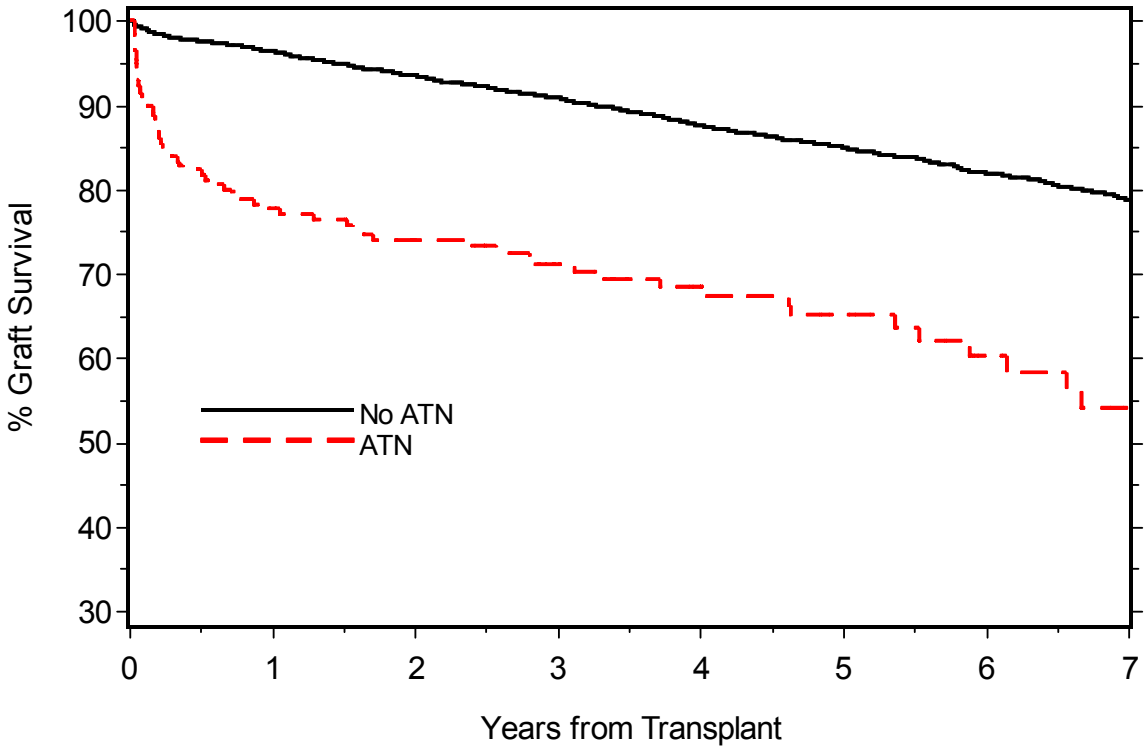


EXHIBIT 5.9
GRAFT SURVIVAL BY ACUTE TUBULAR NECROSIS STATUS
Grafts Surviving beyond 7 days

Living Donor



Deceased Donor

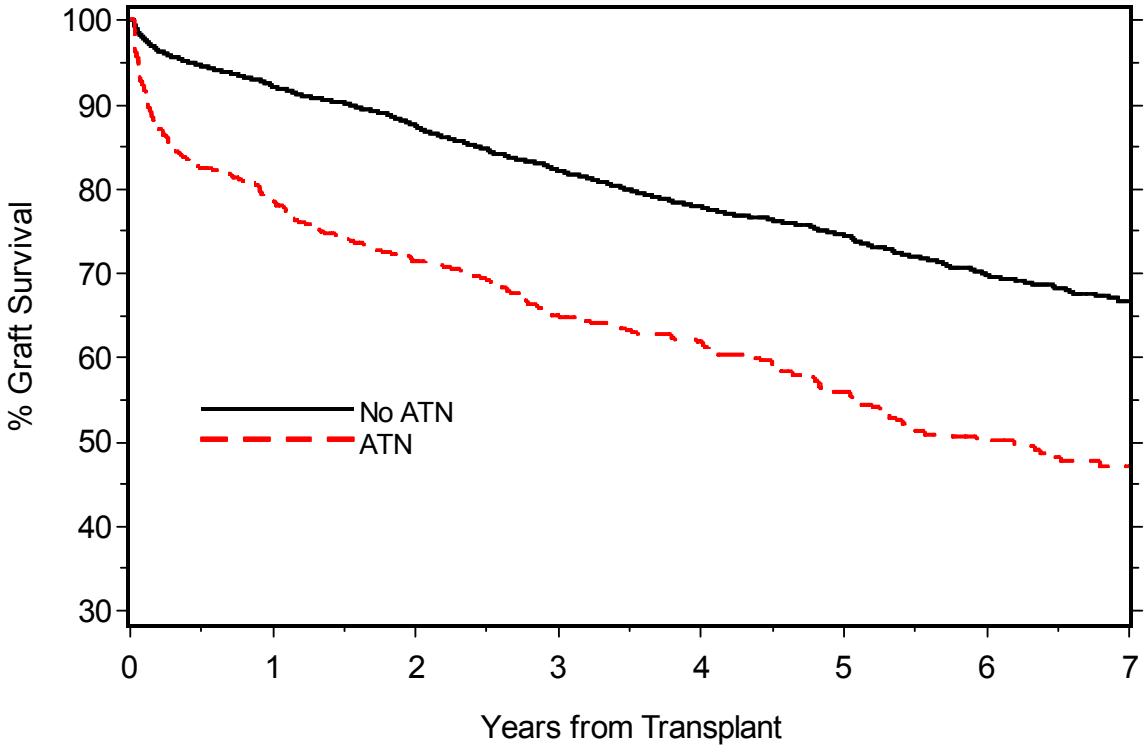
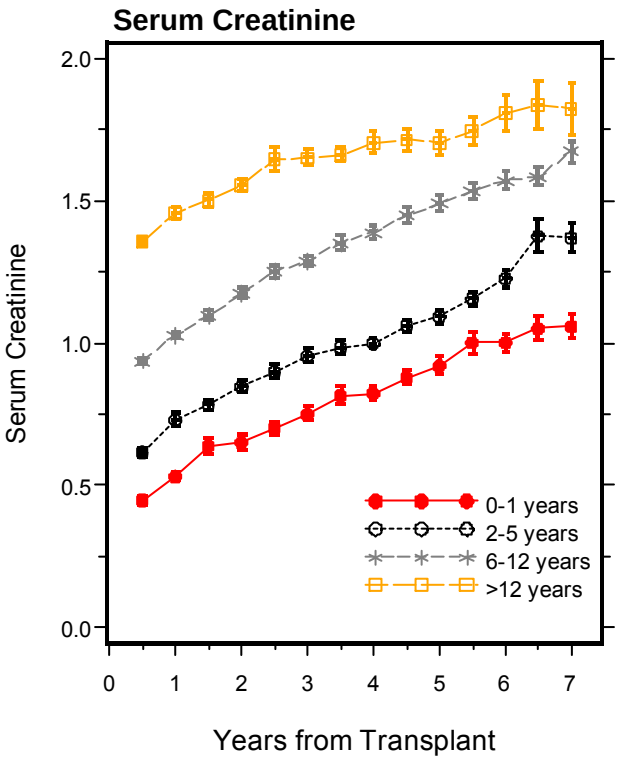
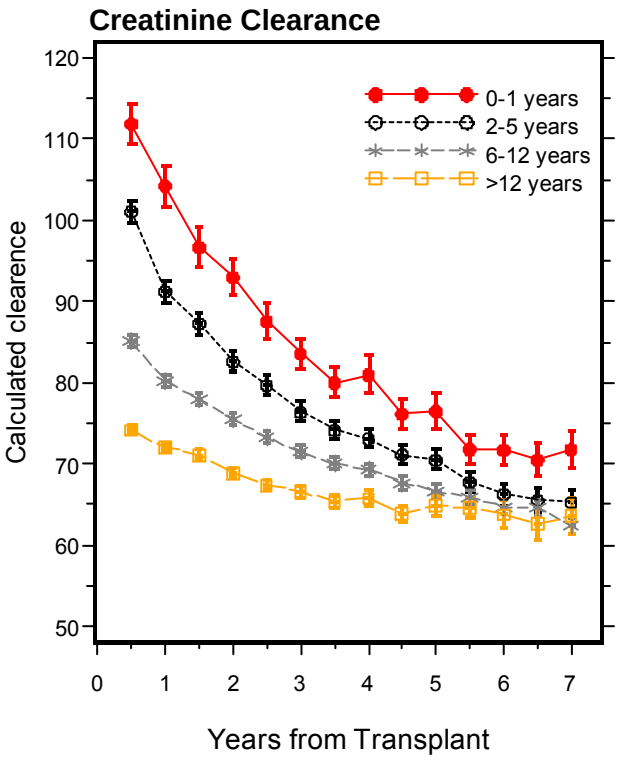


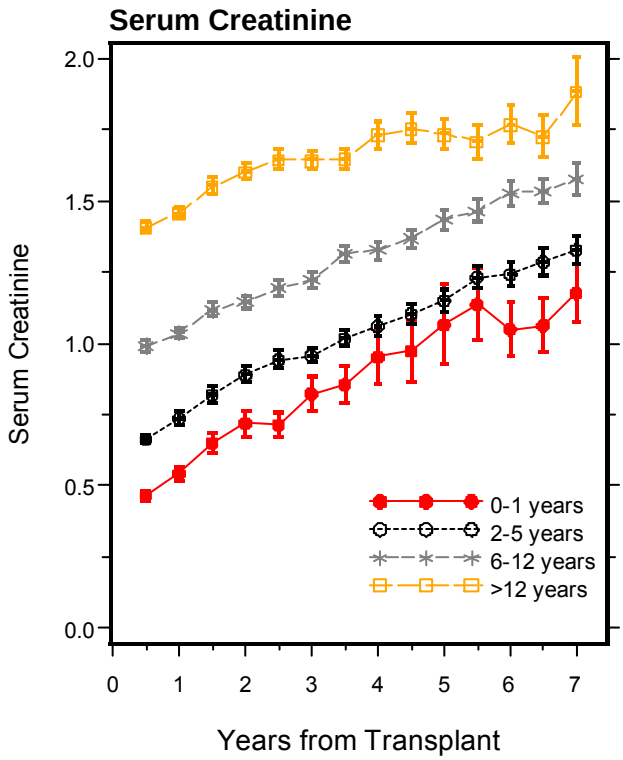
EXHIBIT 5.10
SERUM CREATININE AND CREATININE CLEARANCE (MEAN ± SE) BY AGE
(Index Transplants with Functioning Grafts)

Living Donor





Deceased Donor



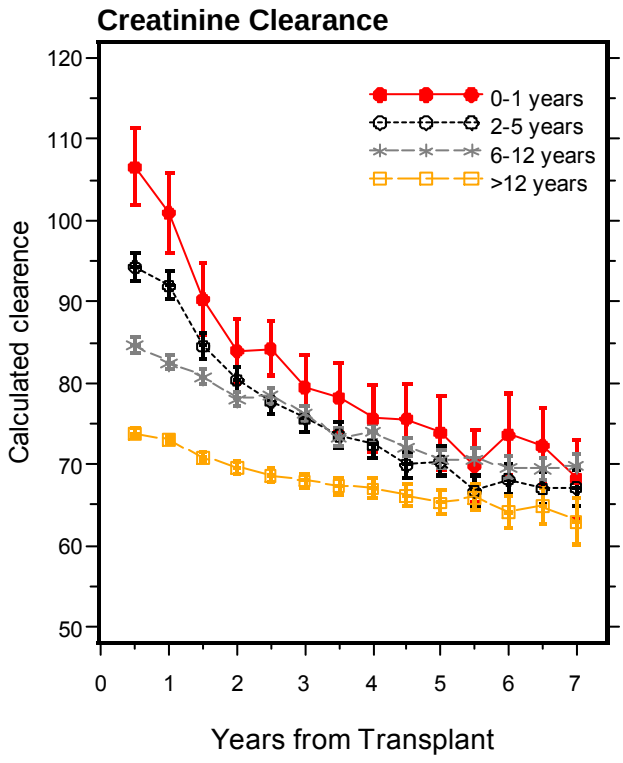


EXHIBIT 5.11
SERUM CREATININE (MEAN ± SE) BY RACE AND INDUCTION ANTIBODY
(Index Transplants with Functioning Grafts)

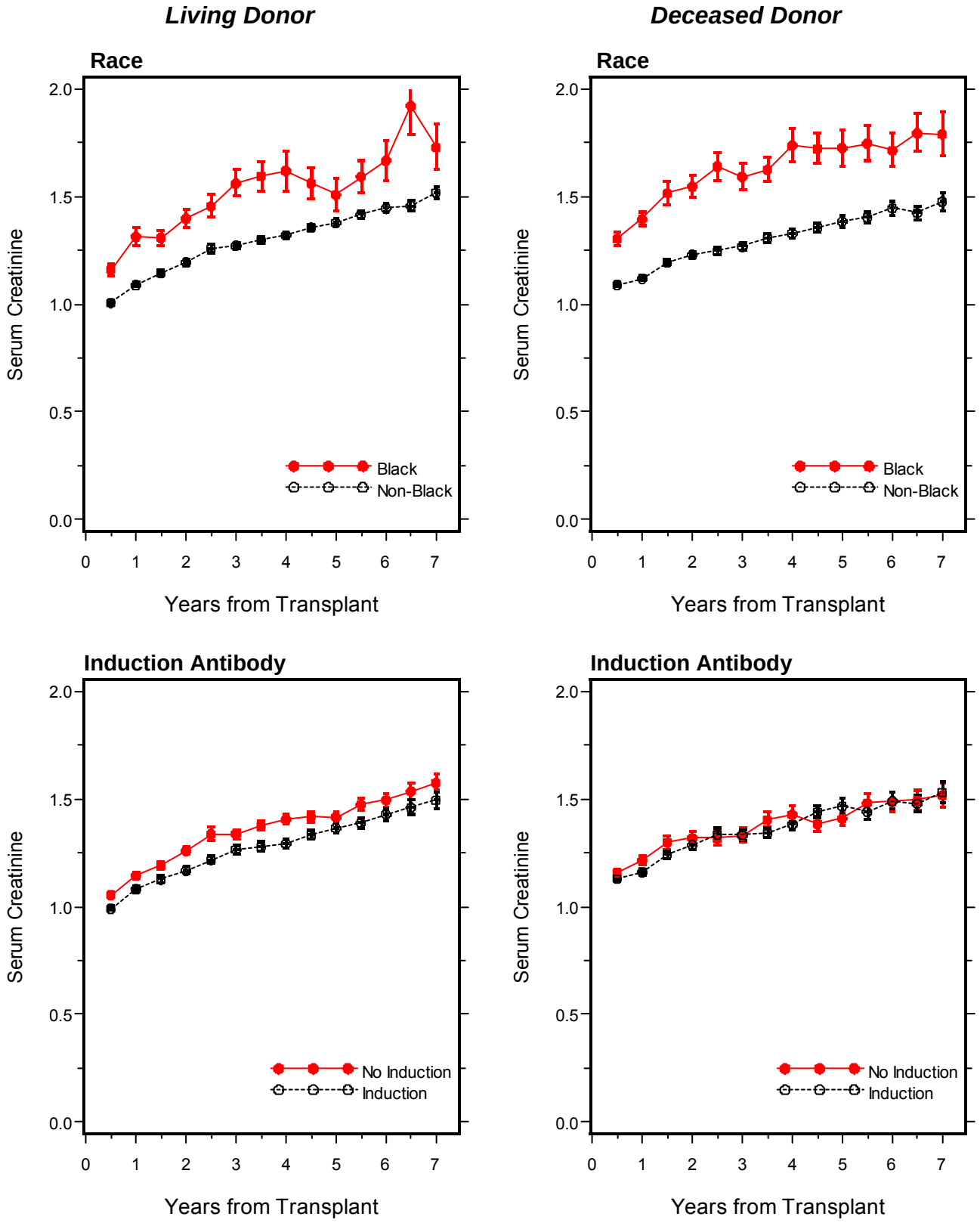
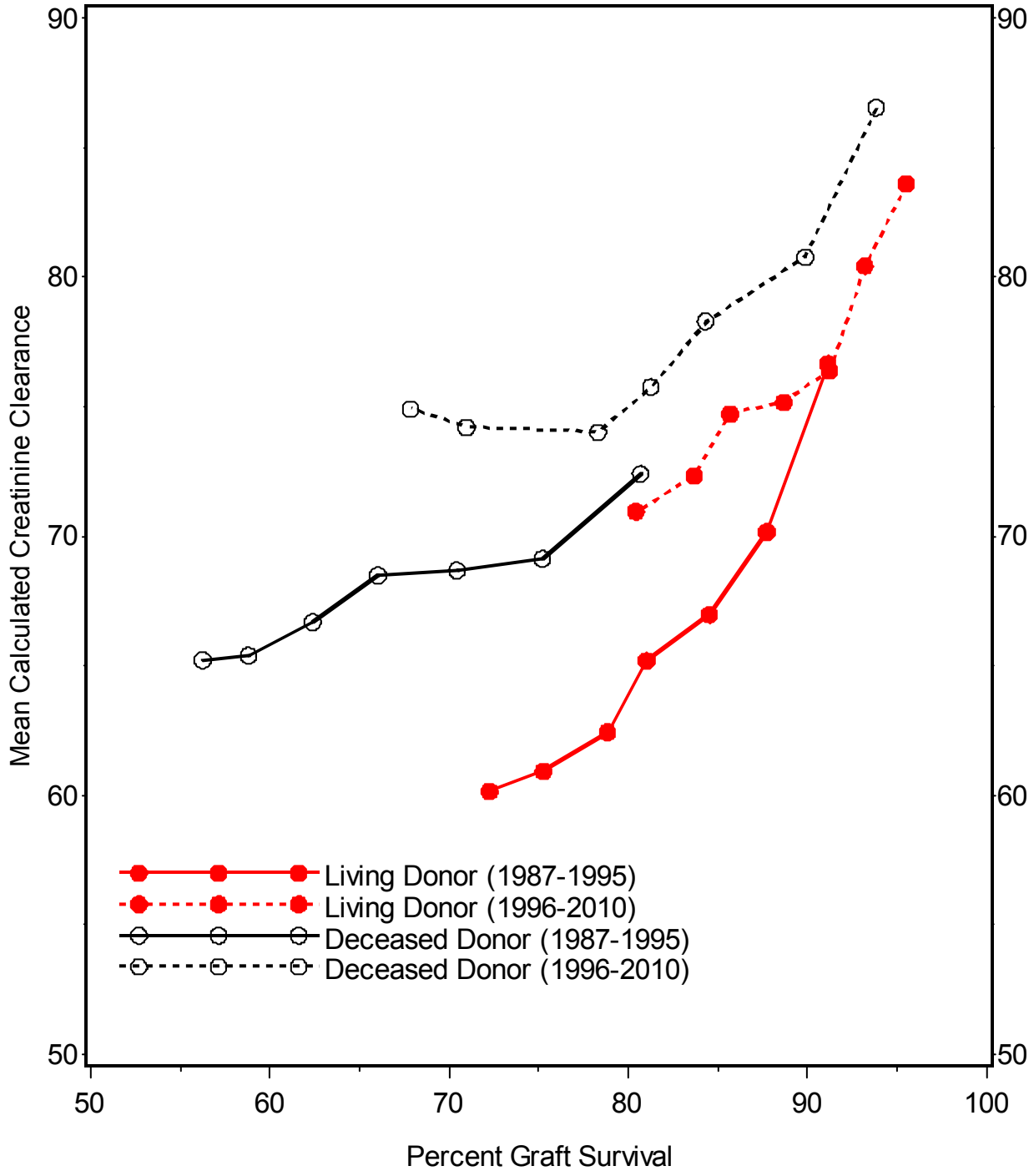


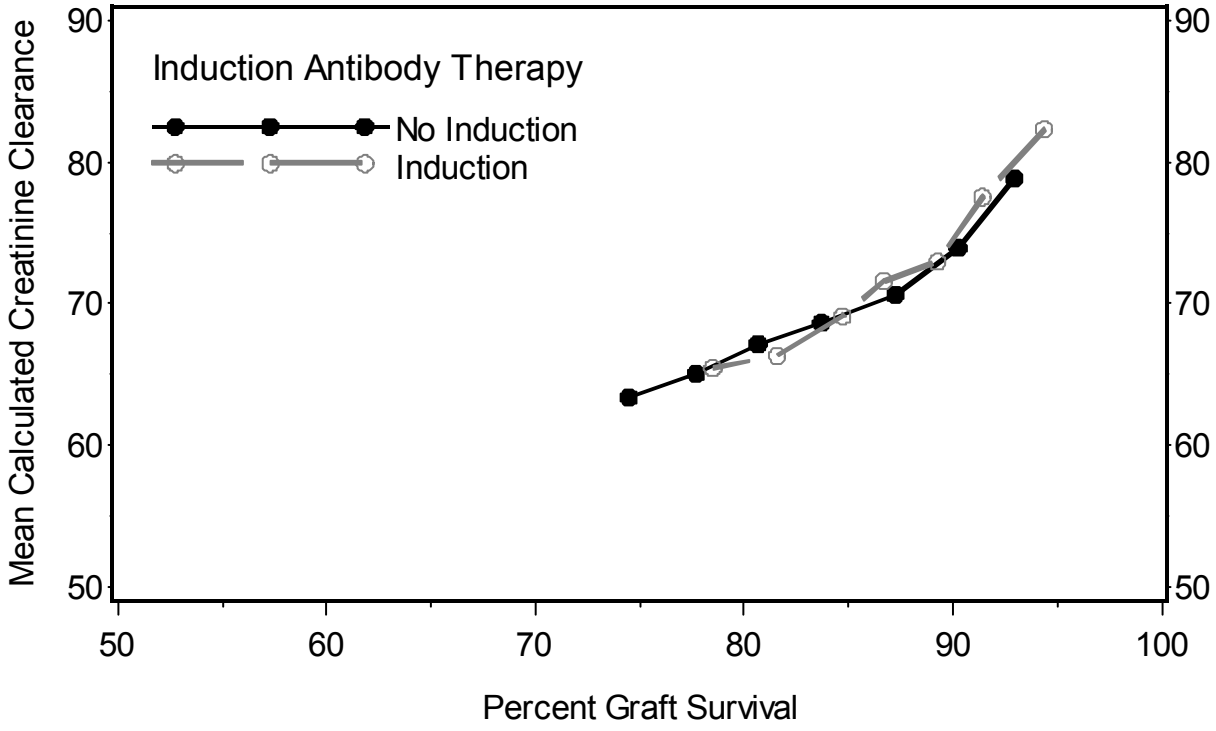
EXHIBIT 5.12
GRAFT FUNCTION
Graft Survival and Mean Calculated Clearance at Annual Follow-up



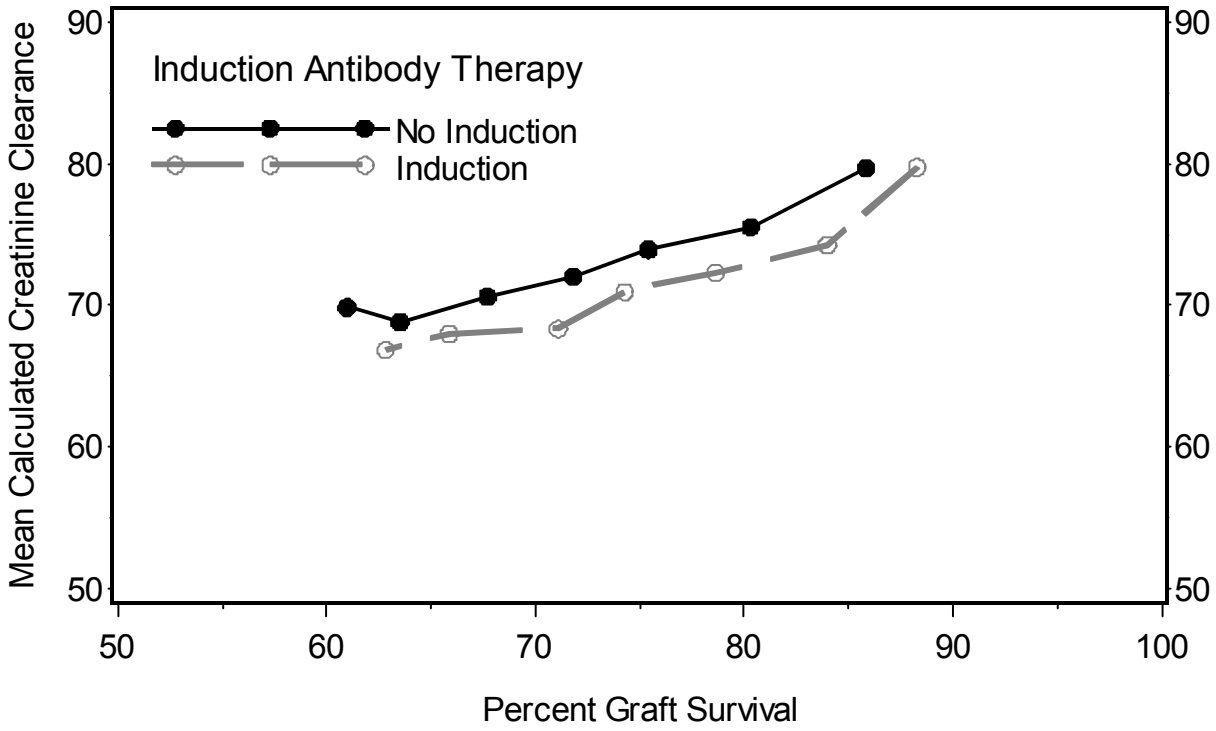
Note: Symbols represent annual follow-up. Year 1 is farthest right and year 7 is farthest left.

EXHIBIT 5.13
GRAFT FUNCTION
Graft Survival and Mean Calculated Clearance at Annual Follow-up

Living Donor



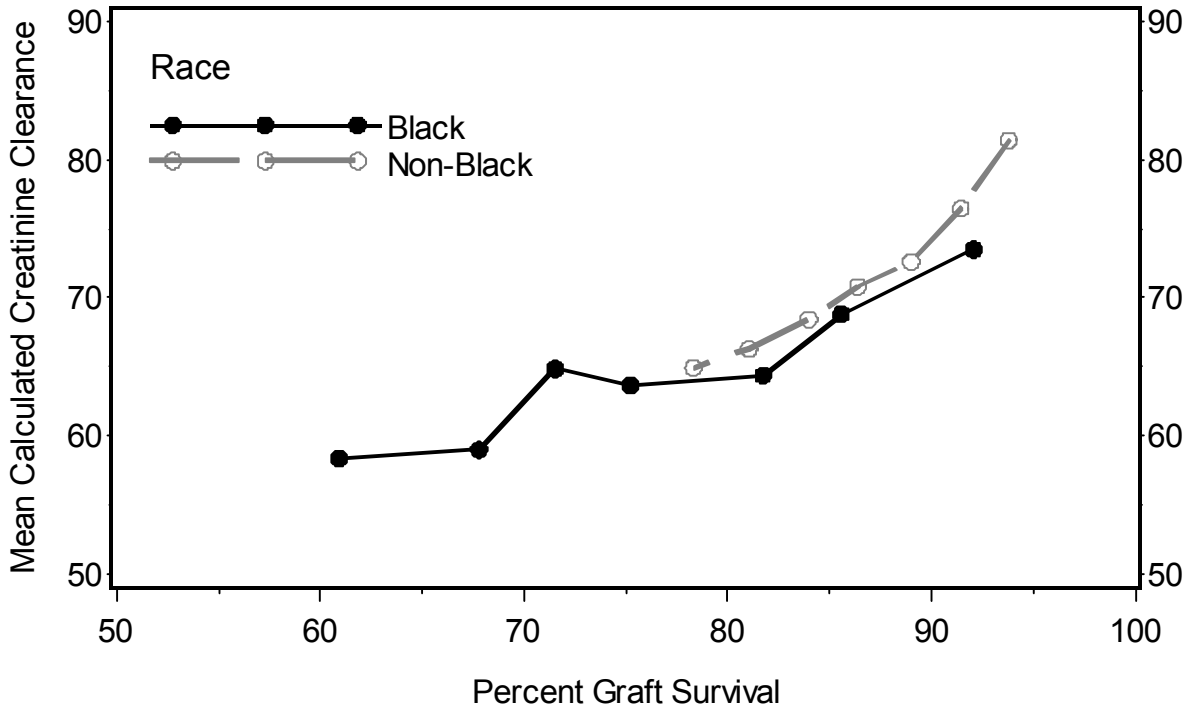
Deceased Donor



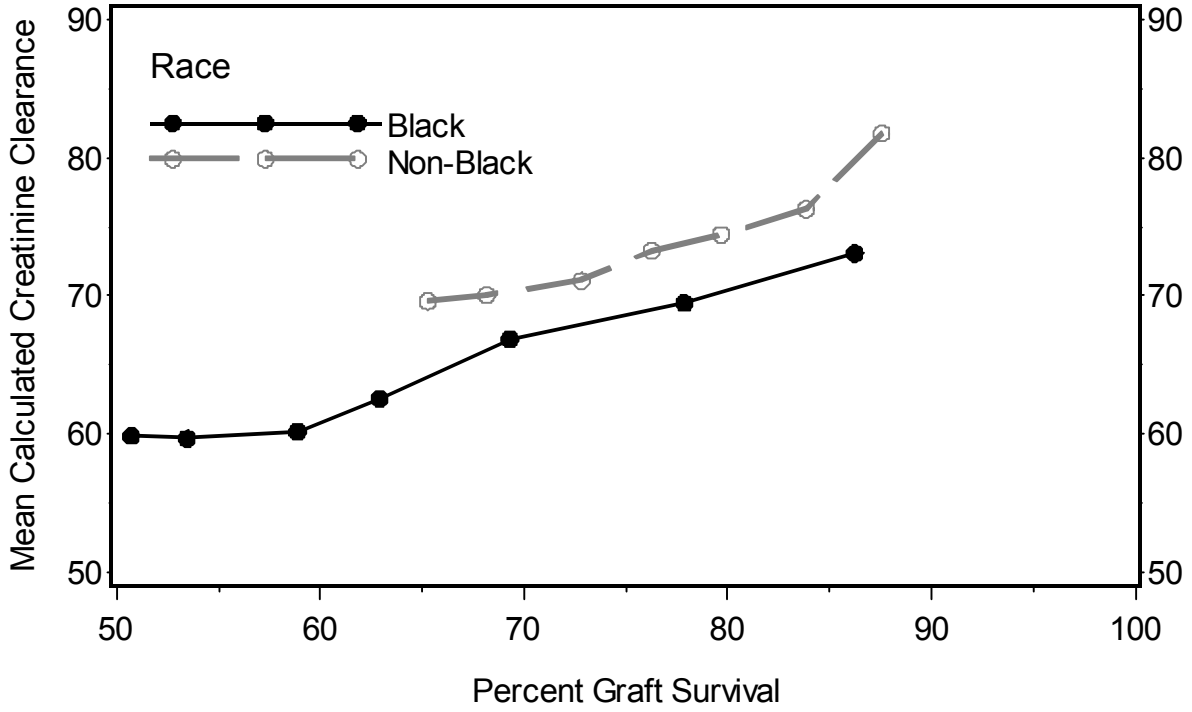
Note: Symbols represent annual follow-up. Year 1 is farthest right and year 7 is farthest left.

EXHIBIT 5.14
GRAFT FUNCTION
Graft Survival and Mean Calculated Clearance at Annual Follow-up

Living Donor



Deceased Donor



Note: Symbols represent annual follow-up. Year 1 is farthest right and year 7 is farthest left.

SECTION 6: GROWTH

At each six-month follow-up, the cooperative study requests the submission of height and weight information on all transplanted patients. Standardized Z-scores are computed following an age- and sex-specific formula based on the NHANES III 2000 growth chart data set. NHANES III is a study sponsored by the National Center for Health Statistics/CDC which provides values at monthly intervals for each sex until the age of 21 years. This is a change in the standardized height and weight calculation from early reports, thus direct comparisons to reports prior to the 2004 annual report should not be made. This section reports on index transplants with functioning grafts.

Exhibit 6.1 presents standardized height and weight Z-scores for patients at entry and at 2, 4 and 6 year follow-up visits for selected characteristics. At transplantation, the mean height deficits for all patients is -1.75; that is, the average patient is nearly 1.8 standard deviations below the appropriate age- and sex-adjusted height level or is shorter than the fourth percentile of their peers. This deficit is greater for males (-1.78) than females (-1.70). Younger subjects (between 2 and 5) and those with prior transplants have greater height deficits at the time of transplantation. Overall, mean height scores remain relatively constant over the available follow-up period. However, growth patterns differ by age at transplant, with younger subjects (less than 6 years of age) experiencing improvement in mean growth deficit. This is further characterized in Exhibit 6.2, where mean Z-scores and Exhibit 6.3 where mean changes from baseline Z-scores are presented graphically. For the youngest age group, an immediate increase in height of 0.29 standard deviations is observed in the first six months post-transplant, which increases to 0.51 by 12 months and 0.68 by 2 years post transplant. Subjects with functioning grafts who were age 2-5 at transplant appear to achieve similar acceleration in linear growth for a couple of years and have a mean increase in Z-score of 0.54 at 2 years. For subjects aged 6-12, linear growth appears to be stable, at about 2 standard deviation below the normal population, and the older subjects have no mean increase in Z-scores.

With respect to weight scores, a rapid increase in standardized weight scores is observed for all age groups in the first 6 months after transplant. Patients gain an average of 0.81 standard deviations in weight in the first year following transplantation, with relative stability in average standardized weight scores over the next 5 years.

Note that as the study has matured, some transplant patients have reached their adult height. The mean Z-score of these subjects, at least 19 years of age (N=2,867), is -1.40. Twenty-five percent of these patients have a Z-score of -2.20 or worse, and 10% are over 3.24 standard deviations below the population average. Significant improvement in terminal height has been observed with the 1987 - 1991 cohort having an average terminal height of -1.93, -1.51 for 1992-1996 cohort; -1.05 for the 1997-2001 cohort and -0.94 for the most recent cohort.

Exhibit 6.4 demonstrates the improvement in height and weight deficit at the time of initial transplant that has occurred over time. In 1987, patients receiving their initial transplant were an average of 2.43 standard deviations below average in height and 1.91 standard deviations below average in weight. This has improved over the years to -1.23 for height and -0.70 for weight in the 2009 cohort. This increase is shown for age groups in Exhibit 6.5.

Besides age and donor source, use of antihypertensive medication is predictive of 2-year standardized height changes. Recipients of living donor organs had an average increase of 0.24 standard deviations and deceased donors increased by 0.12 standard deviations at 2 years. Subjects not receiving anti-hypertensive therapy during the first post-transplant month have better growth in the first two post-transplant years, an increase of 0.38 standard deviations versus 0.14 for those using antihypertensive medication ($p<0.001$), a difference which is maintained at 3 years.

EXHIBIT 6.1
STANDARDIZED SCORES (MEAN ± SE)
BY SELECTED CHARACTERISTICS AND FOLLOW-UP TIMES

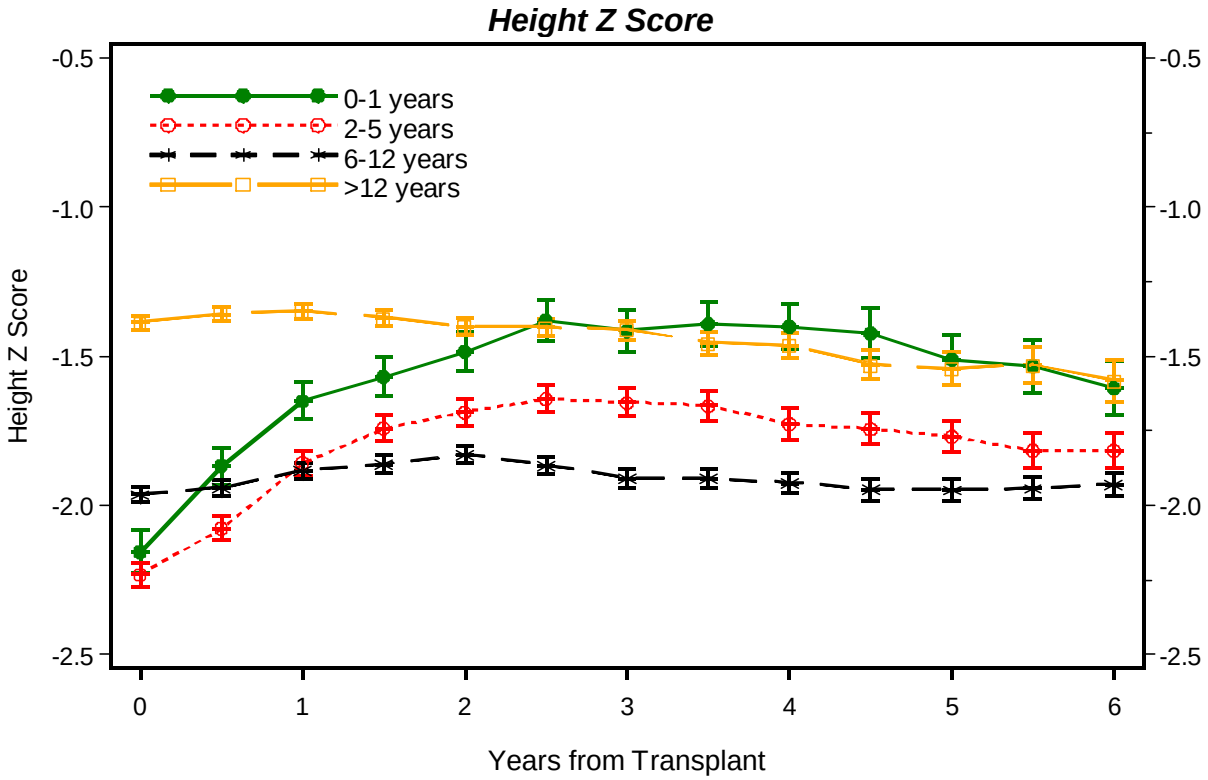
Height Z Score

	Baseline (N=10112)		**2 years** (N=6266)		**4 years** (N=3996)		**6 years** (N=2371)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Total	-1.75	0.02	-1.61	0.02	-1.71	0.02	-1.82	0.03
Sex								
Male	-1.78	0.02	-1.63	0.02	-1.75	0.03	-1.85	0.03
Female	-1.70	0.03	-1.59	0.03	-1.65	0.04	-1.75	0.05
Age								
0-1 years	-2.16	0.07	-1.48	0.07	-1.40	0.08	-1.61	0.09
2-5 years	-2.23	0.04	-1.69	0.04	-1.73	0.05	-1.82	0.06
6-12 years	-1.97	0.03	-1.83	0.03	-1.93	0.03	-1.93	0.04
>12 years	-1.39	0.02	-1.40	0.03	-1.47	0.04	-1.58	0.07
Prior Transplant								
No	-1.69	0.02	-1.56	0.02	-1.66	0.02	-1.77	0.03
Yes	-2.15	0.05	-1.95	0.05	-2.06	0.07	-2.15	0.09

Weight Z Score

	Baseline (N=10224)		**2 years** (N=6312)		**4 years** (N=3776)		**6 years** (N=2182)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Total	-1.10	0.02	-0.26	0.02	-0.30	0.03	-0.36	0.03
Sex								
Male	-1.09	0.02	-0.29	0.03	-0.34	0.03	-0.40	0.04
Female	-1.12	0.03	-0.22	0.03	-0.25	0.04	-0.29	0.06
Age								
0-1 years	-1.48	0.07	-0.45	0.07	-0.43	0.08	-0.41	0.08
2-5 years	-1.20	0.04	-0.31	0.04	-0.13	0.05	-0.16	0.06
6-12 years	-1.24	0.03	-0.18	0.03	-0.29	0.04	-0.43	0.05
>12 years	-0.92	0.03	-0.28	0.03	-0.44	0.06	-0.46	0.14
Prior Transplant								
No	-1.08	0.02	-0.24	0.02	-0.27	0.03	-0.32	0.04
Yes	-1.28	0.05	-0.40	0.06	-0.50	0.08	-0.61	0.10

EXHIBIT 6.2
STANDARDIZED SCORE (MEAN ± SE) BY AGE AT TRANSPLANT
(Index transplants with functioning graft)



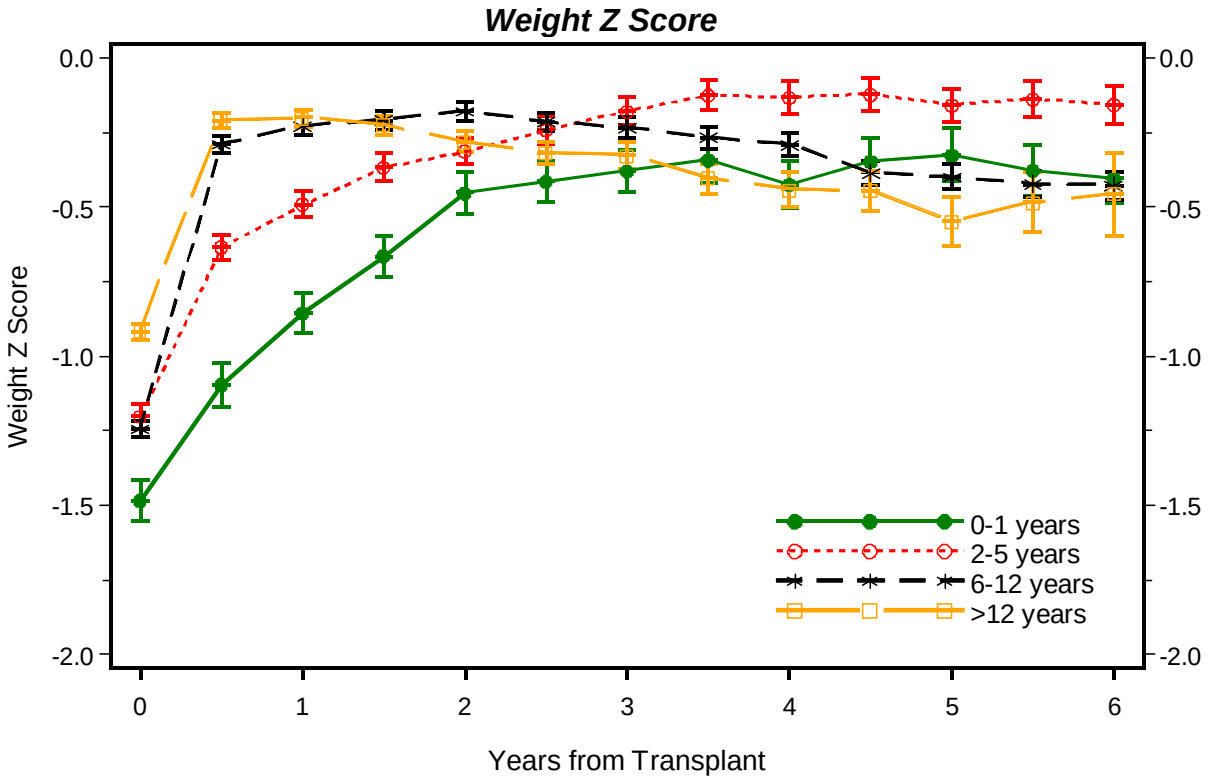
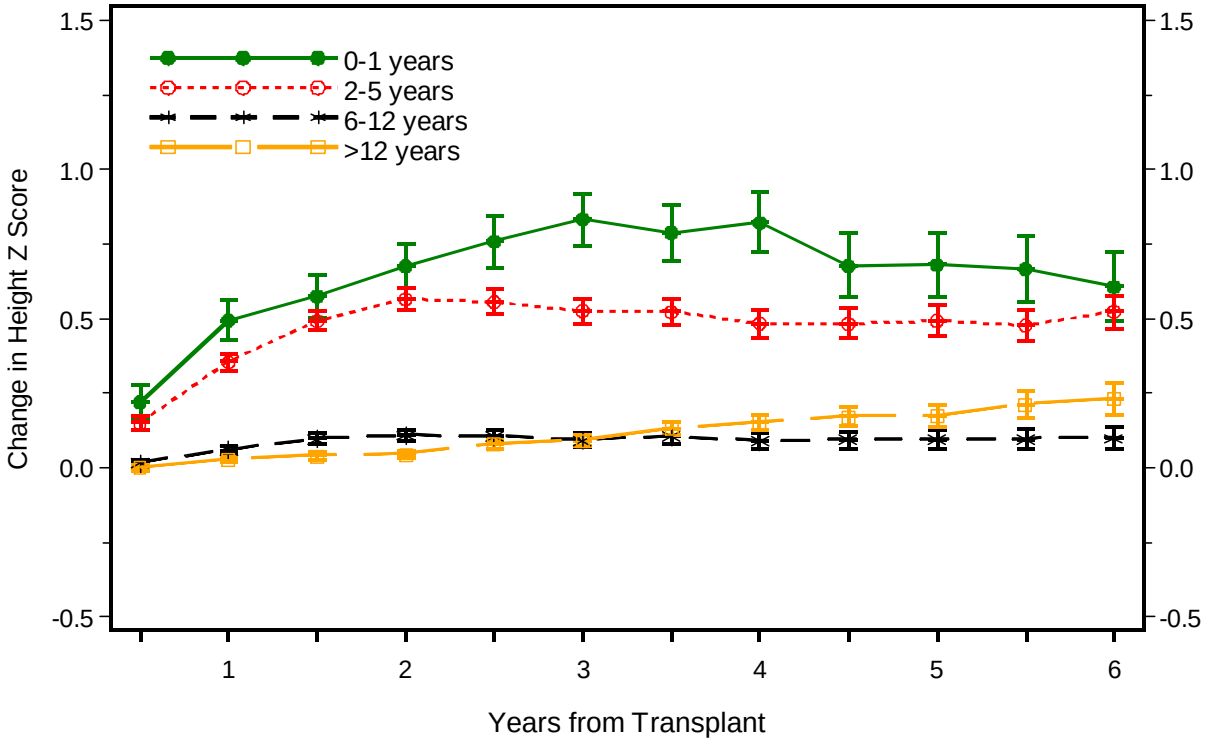


EXHIBIT 6.3
CHANGE FROM BASELINE IN STANDARDIZED SCORE (MEAN ± SE)
BY AGE AT TRANSPLANT
(Index transplants with functioning graft)

Change in Height Z Score



Change in Weight Z Score

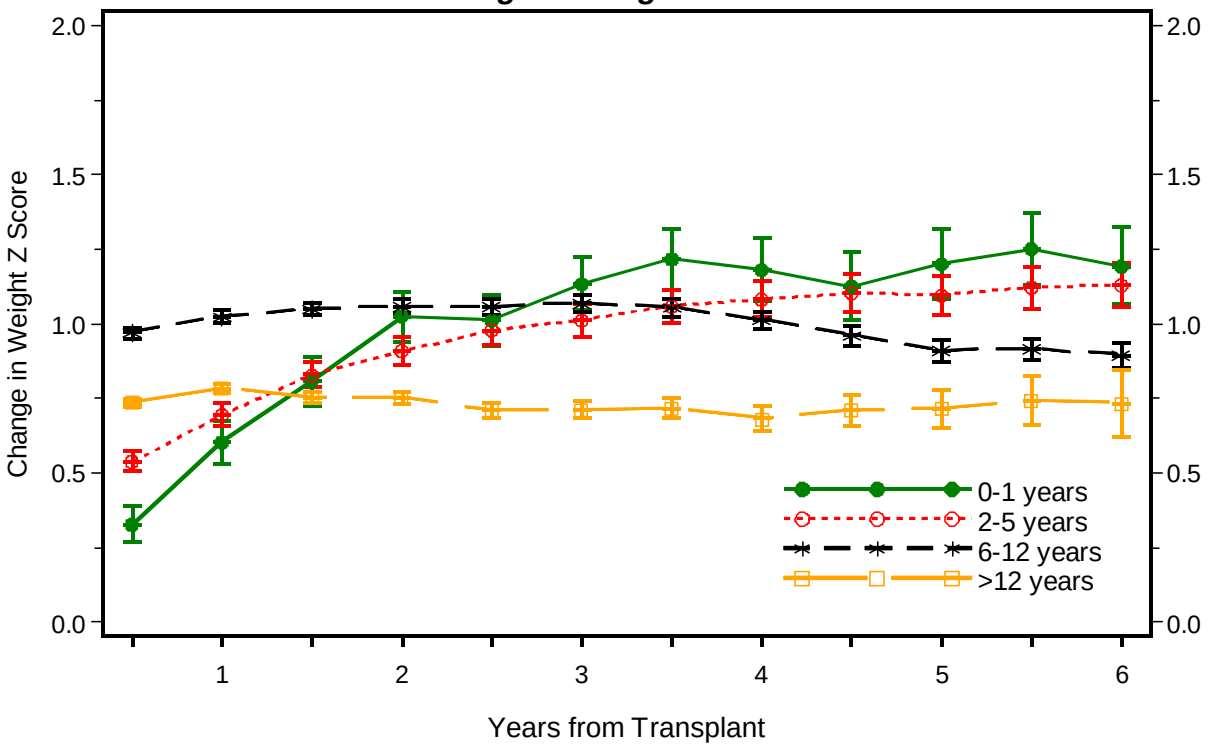


EXHIBIT 6.4
STANDARDIZED SCORES (MEAN ± SE) AT TRANSPLANT
BY YEAR OF TRANSPLANT
(Index transplants)

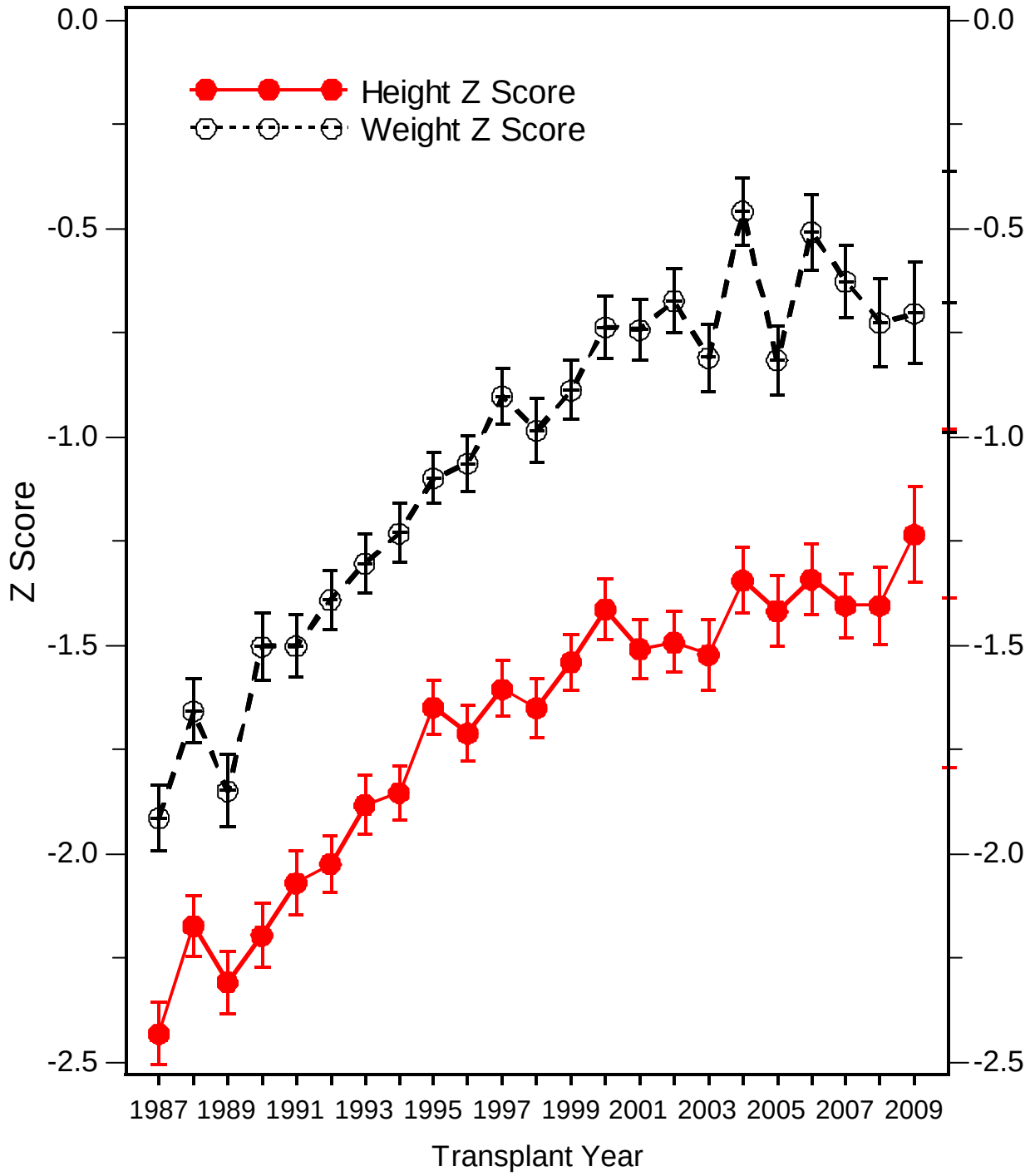
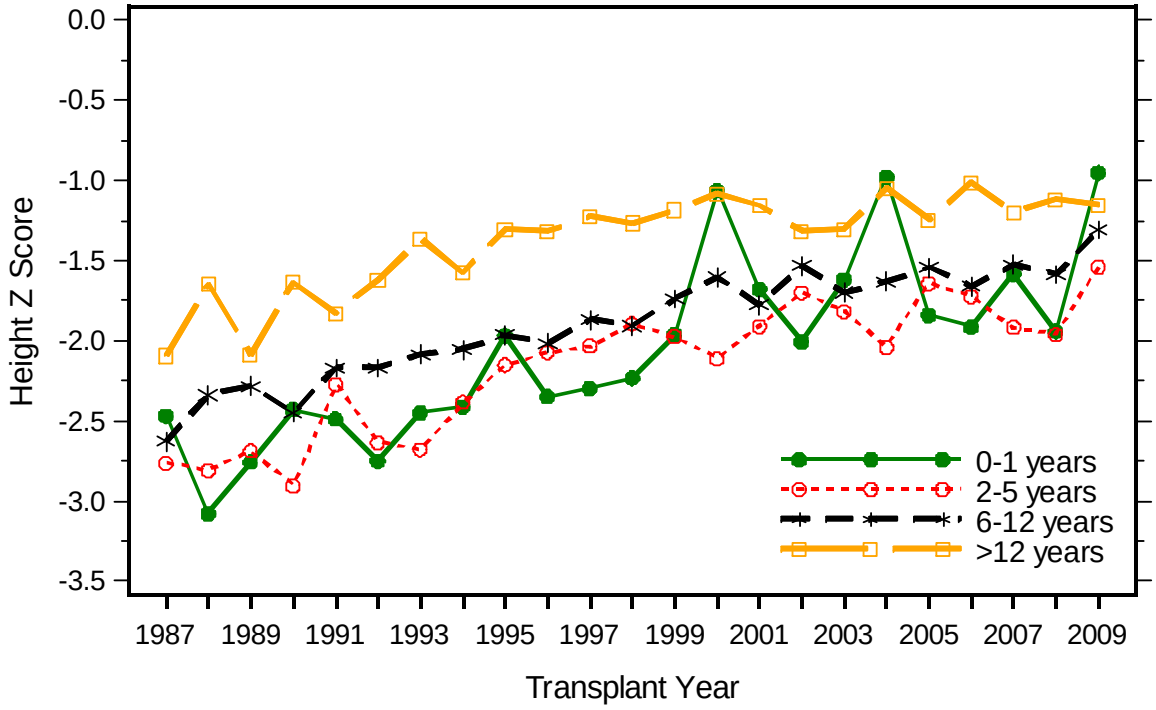
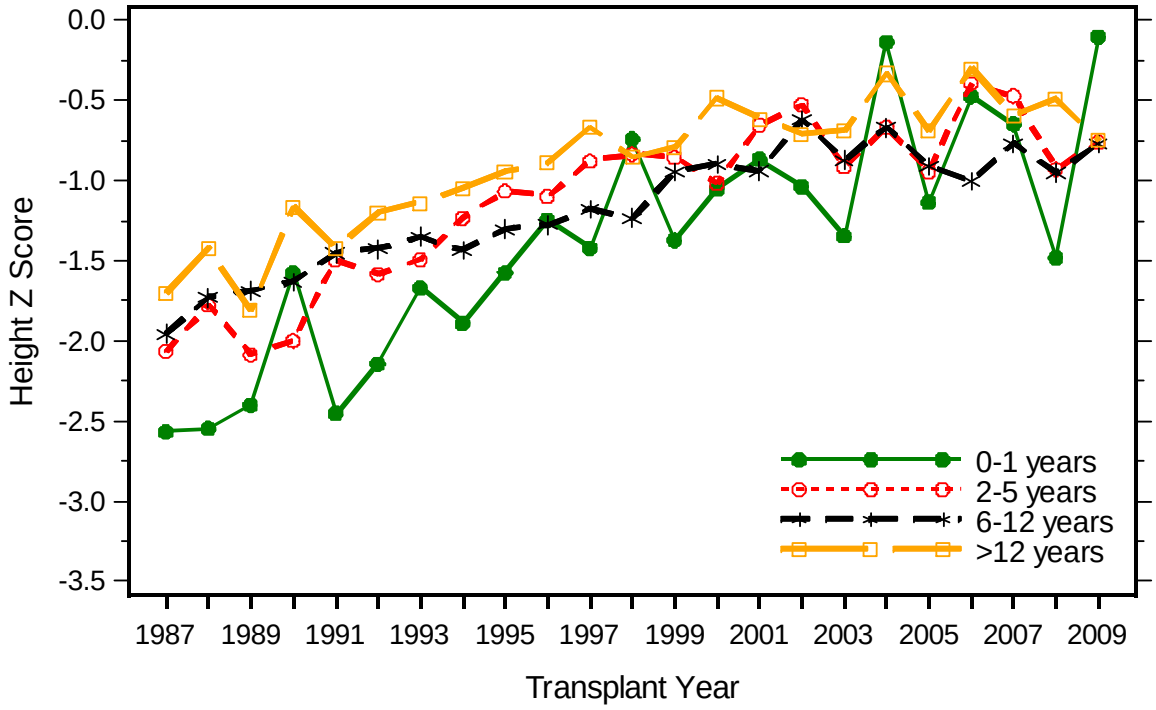


EXHIBIT 6.5
STANDARDIZED SCORES (MEAN) AT TRANSPLANT
BY AGE AT TRANSPLANT AND YEAR OF TRANSPLANT

Height Z Score



Weight Z Score



SECTION 7: MORBIDITY, MALIGNANCY, AND MORTALITY

Morbidity

In this report, we measure morbidity by the number of hospitalization days. The median duration (to initial discharge) of hospitalization at the time of transplant is 12 days, with lower and upper quartiles of 8 and 18 days. Due to re-hospitalization, patients were hospitalized for a median duration of 13 days during the transplant month with lower and upper quantities of 8 and 20 days. Transplant month hospitalization times are negatively correlated with patient age such that the median hospital stays are 18, 16, 13 and 11 days for patients aged 0-1, 2-5, 6-12, and >12 years, respectively during the transplant month. The median number of hospitalization days in the transplant month for recipients of deceased donor source allografts (14 days) is 2 days longer than for those who received grafts from a living donor. Donor-specific mean (± SE) hospitalization during for the first post transplant month are presented in Exhibit 7.1. In 1987, living donor (LD) transplant recipients, on average, were hospitalized for 18.1 days during the first post transplant month, compared to 21.6 days for deceased donor (DD) transplant recipients. In 1996, mean hospital stays during this initial post transplant period were 12.3 days for LD recipients and 14.7 days for DD transplant recipients. By 2009, mean hospital stays decreased to 8.7 days for LD recipients and 10.5 days for DD recipients.

Exhibit 7.2A, 7.2B, and 7.2C present transplant month hospitalization data for selected patient and transplant characteristics (of all, LD, and DD transplants). In regression analyses that consider transplant era (1987-1995 vs. 1996-2010) and the characteristics shown in Exhibit 7.2A, each characteristic, with the exception of prior transplant, was statistically significant at less than the 0.001 level of significance — in the overall and living donor recipient groups. However, among deceased donor recipients, all characteristics were statistically significant at less than 0.001 level with the exception of prior transplant and prior dialysis. Overall, the transplant month mean hospitalization stays have been over six days shorter in the recent era (1996-2010) compared to the earlier era (1987-1995).

Exhibit 7.3 details length of hospital stays during follow-up and reasons for hospitalization for those patients surviving the interval with a functioning graft. Results are provided separately for living and deceased donor sources. During months 1-5, 45.6% of living donor graft recipients were re-hospitalized compared to 52.4% of deceased donor graft recipients. The most common

reason for hospitalization in this interval was treatment of rejection, which occurred in 23.8% and 16.9% of DD and LD patients, respectively. Viral (14.2% versus 12.3%) and bacterial (13.0% versus 11.7%) infections and treatment of hypertension (5.2% versus 3.3%) were other major causes of hospitalization. Hospital stays decrease in both frequency and length by month 6 and beyond. In recent years (2000 - 2010), both the frequency and length of hospitalization in first five months after transplant has decreased. In patients with living donor transplants, 49% of the patients were hospitalized for a median of 8 days (prior to 2000) versus 39% of the patients hospitalized for a median of 6 days since 2000. Deceased donor recipients showed similar results with decreases in hospitalization rates from 57% to 42% and decrease in median days from 10 to 6 days. Hospitalization for rejection has also decreased from 21.3% prior to 2000 to 8.2% since 2000 in live donor recipients and 30.6% to 10.1% in deceased donor recipients in the first five months of follow-up.

Malignancy

To date, 274 malignancies have been reported of which 268 have confirmed diagnoses — 225 lymphoproliferative (LPD) and 43 non-lymphoproliferative (non-LPD). These malignancies have been repeated in 270 patients. Three patients had multiple malignancies at the same transplant. One case reported 3 malignancies: 2 PTLD's 2 years apart and a smooth muscle lung-tumor 18 months after the first PTLD. The other two cases had two LPD's – one case had 2 PTLD's 21 months apart and one case had Hodgkins disease 1-year after PTLD. Exhibit 7.4 shows selected transplant characteristics for the cohort with malignancy. 2.4% of transplants are associated with development of malignancy during the follow-up period. The median time from transplant to malignancy for those with a confirmed diagnosis of LPD was 12.7 months (range 0.9-161.8) and 17.0 months (range 0.9 – 161.8) for all malignancies. One- and three-year product limit estimates of the malignancy rates by era of entry are as follows:

POST TRANSPLANT MALIGNANCY RATE By Transplant Era				
	1 Year		3 Year	
	%	SE	%	SE
1987 – 1990	0.68	0.20	1.05	0.25
1991 – 1994	1.03	0.22	1.41	0.26
1995 – 1998	1.73	0.28	2.88	0.37
1999 – 2002	1.85	0.32	2.96	0.43
2003 - 2010	0.74	0.20	1.13	0.28

While substantial temporal improvements have been observed in graft failure, rejection and other endpoints, similar trends for malignancy rates were not observed, although the most recent cohort suggests that there has been some improvement.

Mortality

To assess post transplant patient survival, we considered 10,552 index transplants (5,581 LD and 4,971 DD). We have not adjusted the analysis for patient deaths that occurred subsequent to graft failure while the patient was receiving maintenance dialysis. Percent patient survival estimates (with standard errors) for all patients at 1, 2, 5 7, and 10 years post transplant are 97.9±0.1, 97.1±0.2, 94.9±0.3, 92.8±0.3, and 89.9±0.5 respectively. Exhibit 7.5A depicts patient survival by allograft source. Percent patient survival estimates for recipients of index living donor kidneys are 98.4±0.2, 97.7±0.2, 96.1±0.3, 94.2±0.4 and 92.4±0.6 percent, at 1, 2, 5, 7 and 10 years post transplant, respectively. Comparable values for recipients of deceased donor allografts are 97.4±0.2, 96.5±0.3, 93.3±0.4 and 91.1±0.6 and 86.6±1.0 percent (log-rank $p<0.001$). Exhibit 7.5B compares patient survival for transplants in 1987-1995 (early era) versus 1996 – 2007 (recent era), by primary allograft source. Patient survival has significantly improved for DD patients in the recent era ($p<0.001$). Their 5-year post transplant survival in the early era was 90.9±0.7, compared to 96.3±0.6 for the recent era. LD patients have also shown some improvement in survival rates with 5-year survival rate of 95.1±0.5 in the early era and 97.0±0.4 in the recent era (Log Rank $p<0.001$).

Patient survival for transplants in 1996-2010, by recipient age at transplant, is shown below and in Exhibits 7.6A and 7.6B for living and deceased donor source transplants. Post transplant survival is markedly lower for infants (<24 months old at transplant) receiving a deceased donor graft, however this group is small, 6 deaths in 73 patients. The following table shows percent survival at 36 months post transplant, by age at transplantation for patients transplanted between 1996 and 2010. Although infants' post transplant survival is lower compared to the other age groups, the situation has been significantly improved in the later cohort. The 3-year patient survival of infants receiving deceased donor source grafts has increased from 78.6% (SE=4.6%) between 1987 and 1995 to 93.4% (SE=3.2%) in 1996 and later. For infants receiving living donor grafts, their 3-year survival also improved from 89.8% (SE=2.2%) in 1987-1995 to 95.9% (SE=1.3%) in 1996 and beyond.

PATIENT SURVIVAL BY AGE AT 3 YEARS POST TRANSPLANT Transplant Era 1996 – 2010				
	Living Donor		Deceased Donor	
	%	SE	%	SE
All Patients	97.9	0.3	97.8	0.4
Age 0-1 years	95.9	1.3	93.4	3.2
Age 2-5 years	97.4	0.8	96.3	1.2
Age 6-12 years	98.3	0.5	98.9	0.4
Age >12 years	98.1	0.4	97.6	0.6

In total, death reports have been received for 573 of the 10,552 patients (5.4%). Crude donor source-specific mortality rates are 4.5% (251/5,581) for recipients of living donor index transplants and 6.5% (322/4,971) for recipient of deceased donor index transplants. Reasons for patient death are shown in Exhibit 7.7. Infection was the cause of death in 163 patients (28.5% of deaths). Other reported causes include cancer/malignancy (n=65, 11.3%), cardiopulmonary (n=84, 14.7%), and dialysis-related complications (n=18, 3.1%). Of the expired patients, 272 (47.5%) died with a functioning graft.

EXHIBIT 7.1
HOSPITALIZATION DAYS (MEAN ± SE)
DURING THE FIRST POST-TRANSPLANT MONTH

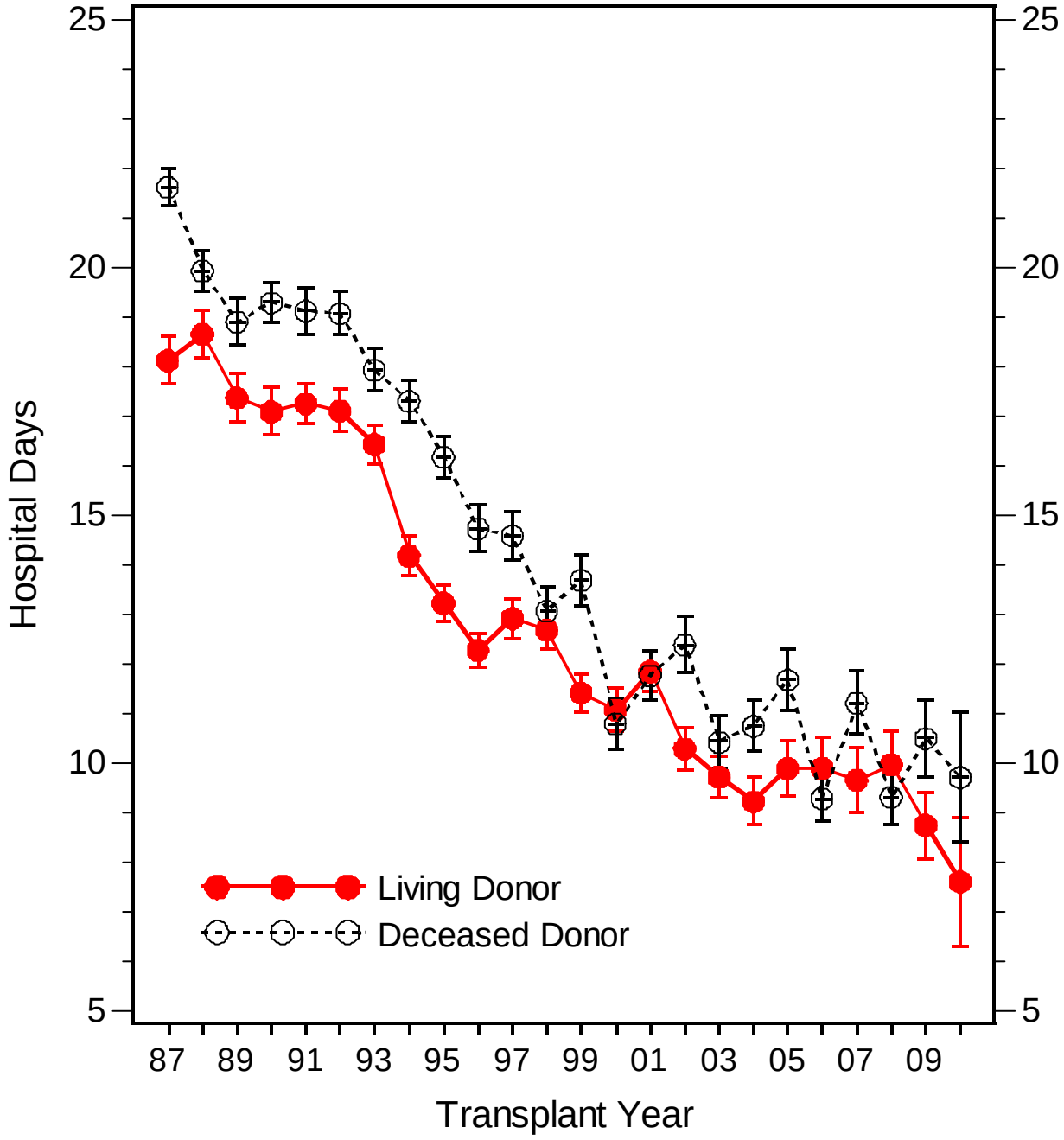


EXHIBIT 7.2A
HOSPITALIZATION DAYS DURING THE FIRST POST- TRANSPLANT MONTH

	Total (N=11183)			**Living Donor** (N=5668)			**Deceased Donor** (N=5515)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	SECTIOI EDIAN
All transplants	14.4	0.08	13.0	13.4	0.10	12.0	15.4	0.11	14.0
Age at transplant									
0-1	18.8	0.36	18.0	18.4	0.39	18.0	19.9	0.83	23.0
2-5	17.0	0.21	16.0	16.2	0.27	15.0	18.0	0.32	17.0
6-12	14.7	0.13	13.0	13.5	0.17	12.0	15.9	0.19	15.0
>12	12.9	0.10	11.0	11.4	0.13	10.0	14.1	0.15	13.0
Transplant History									
No prior transplant	14.2	0.08	13.0	13.4	0.11	12.0	15.2	0.13	14.0
Prior transplant	14.9	0.18	14.0	13.1	0.29	11.0	15.8	0.23	14.0
ATN									
No	13.7	0.08	12.0	13.1	0.10	11.0	14.6	0.12	13.0
Yes	19.5	0.24	19.0	19.6	0.50	20.0	19.5	0.27	19.0
Rejection (during 1st month)									
No	12.7	0.08	11.0	12.0	0.10	10.0	13.4	0.12	12.0
Yes	20.6	0.15	21.0	19.7	0.24	19.0	21.4	0.20	22.0
Native Nephrectomy									
Tissue removed	13.8	0.09	12.0	12.6	0.12	11.0	14.9	0.13	14.0
No tissue removed	16.4	0.15	15.0	15.7	0.20	15.0	17.2	0.24	16.0
Dialysis History									
No prior dialysis	12.7	0.15	11.0	12.1	0.17	10.0	14.4	0.33	13.0
Prior dialysis	14.8	0.09	13.0	14.0	0.13	12.0	15.5	0.12	14.0

EXHIBIT 7.2B
HOSPITALIZATION DAYS DURING THE FIRST POST- TRANSPLANT MONTH
TRANSPLANT YEARS 1987 - 1995

	Total (N=5191)			**Living Donor** (N=2447)			**Deceased Donor** (N=2744)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	Median
All transplants	17.7	0.10	17.0	16.4	0.15	15.0	18.8	0.14	18.0
Age at transplant									
0-1	22.2	0.44	23.5	21.1	0.52	21.0	24.7	0.79	28.0
2-5	20.2	0.27	20.0	19.5	0.36	19.5	21.0	0.40	21.0
6-12	18.0	0.17	17.0	16.5	0.24	15.0	19.3	0.23	18.0
>12	16.0	0.15	15.0	14.1	0.21	13.0	17.4	0.20	16.0
Transplant History									
No prior transplant	17.2	0.11	16.0	16.2	0.15	15.0	18.4	0.17	17.5
Prior transplant	19.4	0.24	19.0	18.4	0.46	17.0	19.8	0.28	19.0
ATN									
No	17.2	0.11	16.0	16.2	0.15	15.0	18.3	0.16	17.0
Yes	21.1	0.31	22.0	21.1	0.70	22.5	21.1	0.34	21.0
Rejection (during 1st month)									
No	15.6	0.12	14.0	14.5	0.16	14.0	16.7	0.17	16.0
Yes	21.5	0.16	22.0	20.7	0.26	20.0	22.1	0.21	23.0
Native Nephrectomy									
Tissue removed	17.2	0.12	16.0	15.8	0.17	14.0	18.4	0.16	18.0
No tissue removed	19.0	0.20	18.0	18.0	0.27	17.0	20.2	0.29	19.5
Dialysis History									
No prior dialysis	16.5	0.22	15.0	15.4	0.25	14.0	19.1	0.43	18.0
Prior dialysis	18.0	0.12	17.0	16.8	0.18	16.0	18.7	0.15	18.0

EXHIBIT 7.2C
HOSPITALIZATION DAYS DURING THE FIRST POST- TRANSPLANT MONTH
TRANSPLANT YEARS 1996 – 2010

	Total (N=5992)			**Living Donor** (N=3221)			**Deceased Donor** (N=2771)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	SECTIOI EDIAN
All transplants	11.5	0.09	10.0	11.1	0.12	9.0	12.0	0.15	10.0
Age at transplant									
0-1	15.7	0.51	15.0	16.2	0.54	16.0	13.7	1.26	14.0
2-5	13.9	0.28	13.0	13.4	0.35	12.0	14.5	0.46	13.0
6-12	11.4	0.17	10.0	10.9	0.21	9.0	12.0	0.26	11.0
>12	10.5	0.12	9.0	9.6	0.16	8.0	11.4	0.19	10.0
Transplant History									
No prior transplant	11.6	0.11	10.0	11.2	0.13	9.0	12.1	0.17	10.0
Prior transplant	11.3	0.21	10.0	10.6	0.31	9.0	11.8	0.29	10.0
ATN									
No	10.9	0.09	9.0	10.7	0.12	9.0	11.1	0.15	10.0
Yes	17.7	0.36	17.0	18.5	0.69	18.0	17.4	0.42	16.0
Rejection (during 1st month)									
No	10.9	0.09	9.0	10.6	0.12	9.0	11.3	0.15	10.0
Yes	17.7	0.34	17.0	17.0	0.49	16.0	18.4	0.48	18.0
Native Nephrectomy									
Tissue removed	10.9	0.11	9.0	10.3	0.14	8.0	11.5	0.16	10.0
No tissue removed	13.7	0.21	12.0	13.5	0.27	12.0	13.9	0.34	12.0
Dialysis History									
No prior dialysis	9.7	0.17	8.0	9.6	0.18	8.0	10.1	0.38	9.0
Prior dialysis	12.1	0.11	10.0	11.8	0.16	10.0	12.3	0.16	11.0

EXHIBIT 7.3
HOSPITALIZATION RESULTS DURING FOLLOW-UP
(Transplants with Functioning Graft)

Living Donor

	Months 1-5	Months 6-11	Months 12-17	Months 18-23	Months 30-35	Months 42-47	Months 54-59
Total Transplants	5011	4664	4266	3941	3307	2699	2129
Median days hospitalized	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean days hospitalized	5.5	2.5	2.0	1.4	1.2	1.0	1.0
Hopitalized Transplants							
Median days hospitalized	7.0	5.0	5.0	4.0	4.0	4.0	4.0
Mean days hospitalized	11.9	8.8	8.6	6.8	6.7	5.9	6.5
% Hospitalized	45.6	28.4	22.9	19.9	17.6	16.0	15.4
% Hospitalized for:							
Bacterial infection	11.7	7.5	6.7	5.8	4.4	4.5	5.2
Fungal infection	0.7	0.2	0.3	0.2	0.2	0.3	0.2
Viral infection	12.3	8.0	5.6	5.2	3.9	3.5	3.7
Rejection	16.9	7.8	5.6	4.7	4.0	3.1	3.0
Hypertension	3.3	1.6	1.3	0.9	0.7	0.7	0.7

Deceased Donor

	Months 1-5	Months 6-11	Months 12-17	Months 18-23	Months 30-35	Months 42-47	Months 54-59
Total Transplants	4582	4150	3724	3285	2558	1971	1522
Median days hospitalized	1.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean days hospitalized	7.5	3.3	2.5	1.9	1.6	1.5	1.3
Hopitalized Transplants							
Median days hospitalized	9.0	6.0	6.0	5.0	4.0	4.5	4.0
Mean days hospitalized	14.2	10.4	9.7	7.9	7.3	7.7	7.0
% Hospitalized	52.4	31.4	25.9	24.0	21.3	18.6	18.2
% Hospitalized for:							
Bacterial infection	13.0	9.2	6.6	5.2	5.2	5.0	4.2
Fungal infection	1.0	0.5	0.3	0.1	0.2	0.2	0.1
Viral infection	14.2	7.6	5.8	5.8	4.7	3.8	4.0
Rejection	23.8	10.8	8.3	7.7	6.0	4.9	4.1
Hypertension	5.2	2.7	2.0	2.1	1.9	2.0	1.1

EXHIBIT 7.4
MALIGNANCY RATES BY SELECTED CHARACTERISTICS

	Malignancies*	
	N	**%**
All Transplants	270	2.33
Donor Source		
Living Donor	137	2.34
Deceased Donor	132	2.33
Age at Transplant		
0-1 years	15	2.44
2-5 years	70	4.11
6-12 years	89	2.34
>12 years	96	1.75
Sex		
Male	163	2.36
Female	107	2.27
Race		
White	197	2.84
Black	30	1.53
Hispanic	31	1.60
Other	12	1.59
Transplant Year		
1987-1990	44	2.07
1991-1994	64	2.65
1995-1998	82	3.30
1999-2002	62	3.00
2003-2010	18	0.72

*Transplants with multiple malignancies are only counted once.

EXHIBIT 7.5A
PATIENT SURVIVAL BY ALLOGRAFT SOURCE

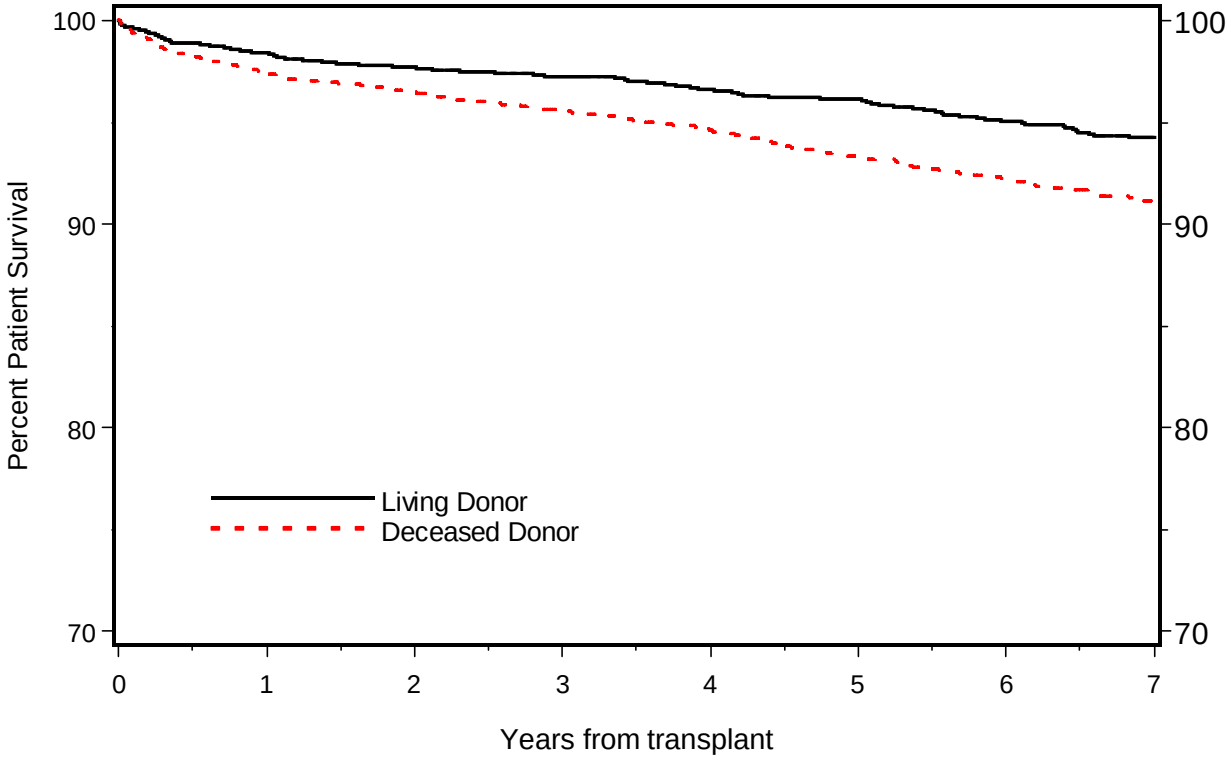


EXHIBIT 7.5B
PATIENT SURVIVAL BY TRANSPLANT ERA AND ALLOGRAFT SOURCE

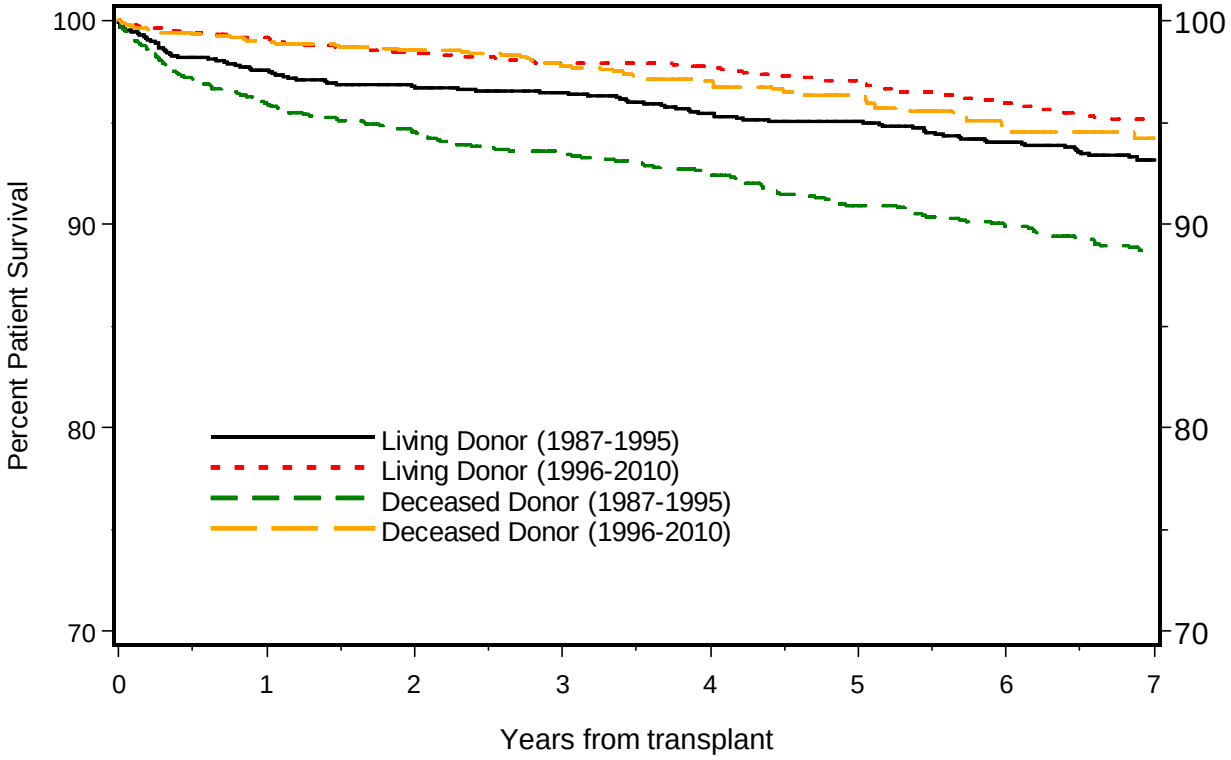


EXHIBIT 7.6
PATIENT SURVIVAL BY AGE AT TRANSPLANT
TRANSPLANT ERA 1996-2006

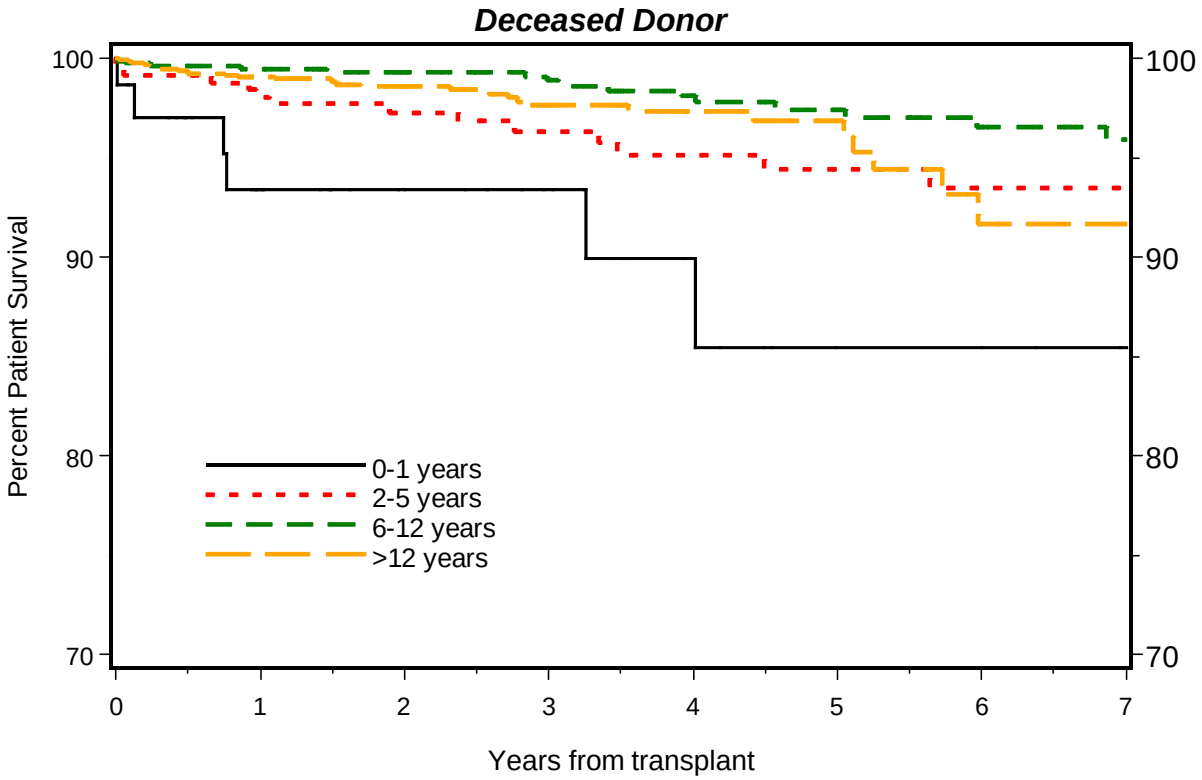


EXHIBIT 7.7
CAUSES OF DEATH FOLLOWING INDEX RENAL TRANSPLANTATION

	Total			Living Donor			Deceased Donor		
	N	%	Func graft	N	%	Func graft	N	%	Func graft
All deceased patients	573	100.0	272	251	100.0	125	322	100.0	147
Cause of Death									
Infection,Viral	44	7.7	23	24	9.6	13	20	6.2	10
Infection,Bacterial	73	12.7	36	34	13.5	15	39	12.1	21
Infection, Not Specified	46	8.0	15	23	9.2	8	23	7.1	7
Cancer/malignancy	65	11.3	46	36	14.3	26	29	9.0	20
Cardiopulmonary	84	14.7	39	30	12.0	15	54	16.8	24
Hemorrhage	33	5.8	12	9	3.6	2	24	7.5	10
Recurrence	10	1.7	1	4	1.6	1	6	1.9	0
Dialysis-related Complications	18	3.1	0	8	3.2	0	10	3.1	0
Other	145	25.3	73	63	25.1	34	82	25.5	39
Unknown	55	9.6	27	20	8.0	11	35	10.9	16

SECTION 8: SUPPLEMENTAL ANALYSES

Machine Perfusion and Cold Storage Time

Of the 4971 deceased donor index transplants, 557 have used machine perfusion for the preservation of the donor kidney, 3594 have not. There are 820 transplants were machine use has not been documented. While the use of machine perfusion has ranged from 16% in 1987 to a low of 4% in 2000 to 20% in 2009 (Exhibit 8.1), the rate of unknown/missing data shown a marked increase in more recent years from 3% in 1987 to 19% in 1996 to 35% in 2009 (data not shown). The cold storage time of the deceased donor kidneys has been decreasing over the life of the registry with 45% >24 hours in 1987 (mean±SE, 24.3±0.6 hours), 19% >24 hours in 1996 (18.7±0.5 hours) and 5% in 2009 (13.5±0.7 hours). Graft survival during the first year post-transplant in this cohort is categorized by both machine perfusion and cold storage time. Exhibit 8.2 shows graft failure rates during the first 12 months post-transplant for the following groups: No machine perfusion and cold time ≤ 24 hours; Machine perfusion and cold time ≤ 24 hours; No machine perfusion and cold time >24 hours; and Machine perfusion and cold time > 24 hours. Additional details and graft survival are provided in Exhibit 8-3. For the most recent era, graft survival rates are similar (91%-94%) at 12 months post-transplant for no machine perfusion (regardless of cold time) and machine perfusion with cold time > 24 hours; for machine perfusion and cold time > 24 hours 12 months graft survival is 83% (log-rank p=0.027). ATN rates are similar (13%-17%) for no machine perfusion (regardless of cold time) and machine perfusion with cold time ≤ 24 hours; for machine perfusion and cold time > 24 hours ATN rate is 26% (chi-square p<0.001)

Primary Disease Sub-analyses

The NAPRTCS registry now spans more than 22 years and has collected information on the transplants of over 10,500 children. There is a special opportunity to evaluate patient and graft survival in some of the more rare primary renal diseases.

Membranoproliferative glomerulonephritis (MPGN) type I has occurred in 186 patients and type II has occurred in 85 patients. While there is no statistical difference in patients survival (92% vs. 93% at 5 years for type I and type II respectively), graft survival is significantly higher in type I (75% at 5 years) than type II (50% at 5 years), log-rank p=0.002. Causes of graft failure for

the 51 type I cases that failed included 5 vascular thrombosis, 7 acute rejection and 17 chronic rejection. Disease recurrence was quite common in type II disease, occurring in 15 (18%) of the cases.

Sickle cell nephropathy has been diagnosed in 16 patients over the course of the registry. There have been 7 with living donor transplants and 9 with deceased donor transplants. Eight of the 16 grafts have failed: 4 from chronic rejection, 1 each from acute rejection, disease recurrence, infection and other. Two cases have died from septicemia and unknown causes.

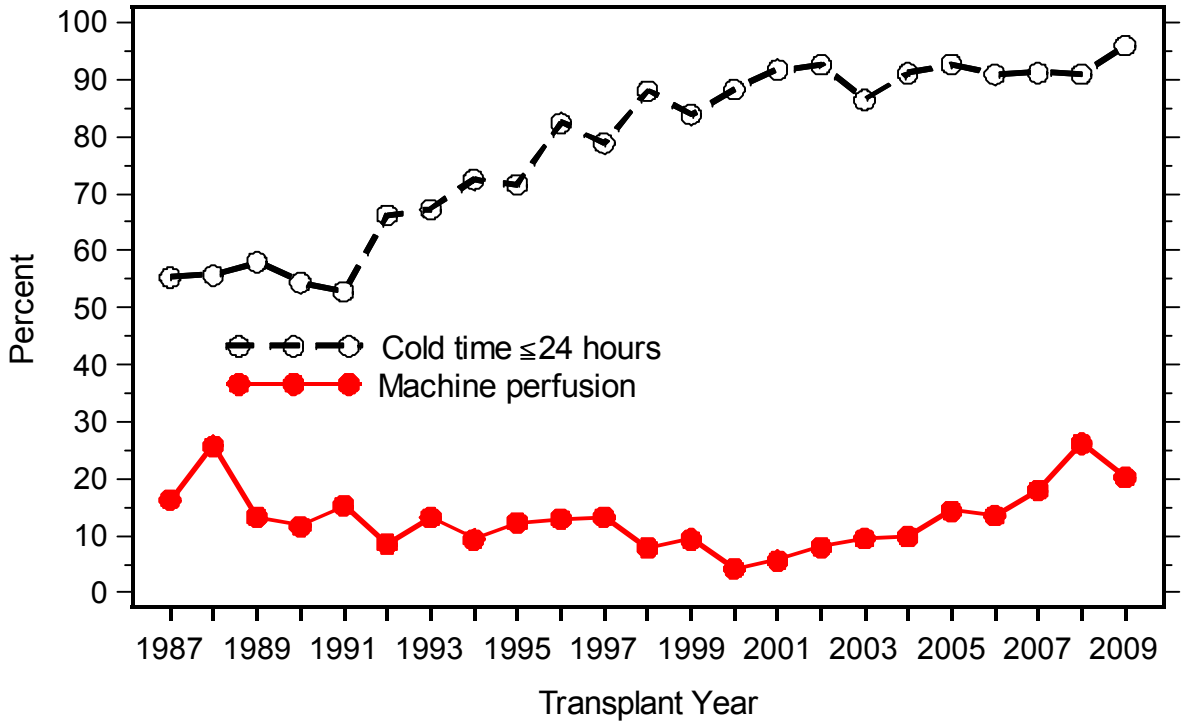
Glomerular disease includes 864 cases with specific diseases of: Congenital nephrotic syndrome (n=277), MPGN type I (n=186), Idiopathic cresentic glomerulonephritis (n=181), Berger's nephritis (IgA) (n=135) and MPGN type II (n=85). Patient survival at 5 years is 94% and graft survival at 5 years is 73%.

There are currently 1246 cases with Focal segmental glomerulosclerosis as the primary cause of kidney failure. 538 of these patients received living donor grafts, with patient survival of 96% and graft survival of 72% at 5 years. Patients receiving deceased donor grafts had patient survival rates of 93% and graft survival rates of 64% at 5 years. The most common causes of graft failure are chronic rejection (9.1%) and recurrence of original kidney disease (7.0%).

Metabolic diseases include 221 cases with cystinosis and 55 cases with oxalosis. There are significant differences between cystinosis and oxalosis, with 5 year rates of graft survival of 81% and 52% respectively (log-rank p=<0.001). The most frequent causes of graft failure are chronic and acute rejection in the cases with cystinosis and recurrence of kidney disease and death with functioning graft in the cases with oxalosis. Patient survival also differs between the two groups with 5 year rates of 95% for patients with cystinosis and 76% for patients with oxalosis.

Genetic disease comprises 111 patients, 56 Wilm's tumor and 55 Drash syndrome. There was no difference in patient (93% at 5 years) or graft (82% at 5 years) survival between the 2 groups. The most common causes of graft failures included death with a functioning graft, chronic rejection and acute rejection.

EXHIBIT 8.1
DECEASED DONOR INDEX TRANSPLANTS
MACHINE PERFUSION USE AND COLD ISCHEMIA TIME BY TRANPLANT YEAR



DECEASED DONOR INDEX TRANSPLANTS
COLD ISCHEMIA TIME (MEAN ± SE) BY TRANSPLANT YEAR

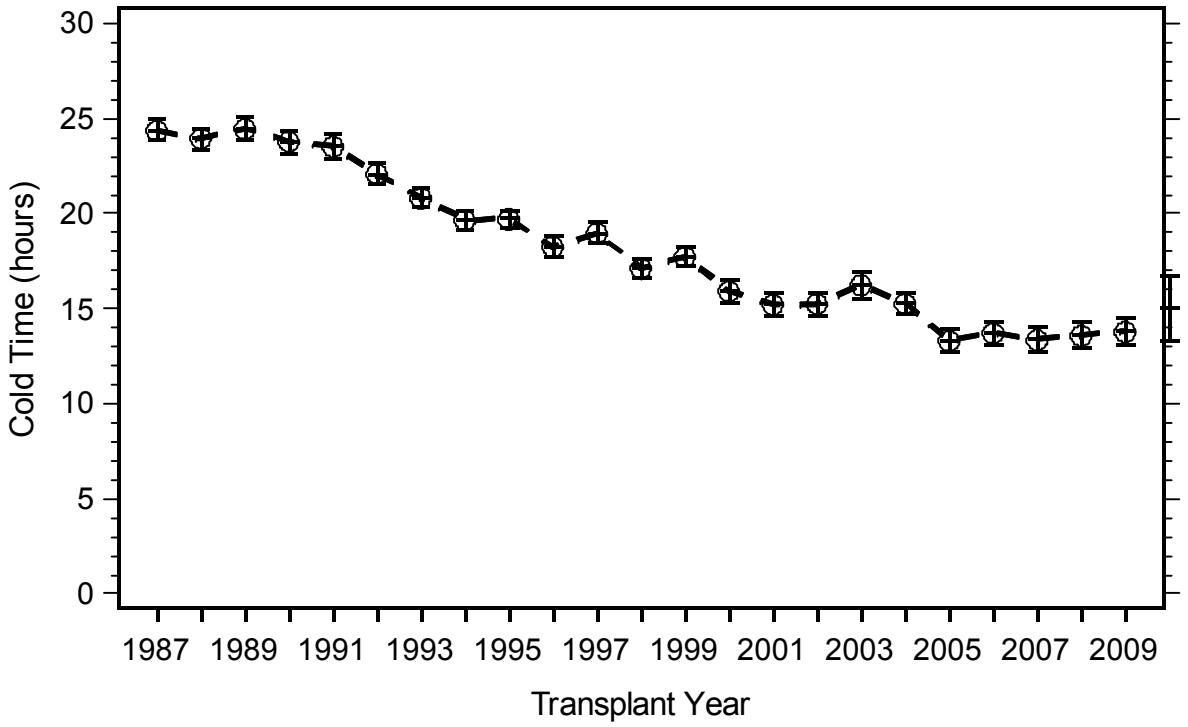


EXHIBIT 8.2
DECEASED DONOR INDEX TRANSPLANTS
GRAFT SURVIVAL BY MACHINE PERFUSION USE AND COLD ISCHEMIA TIME

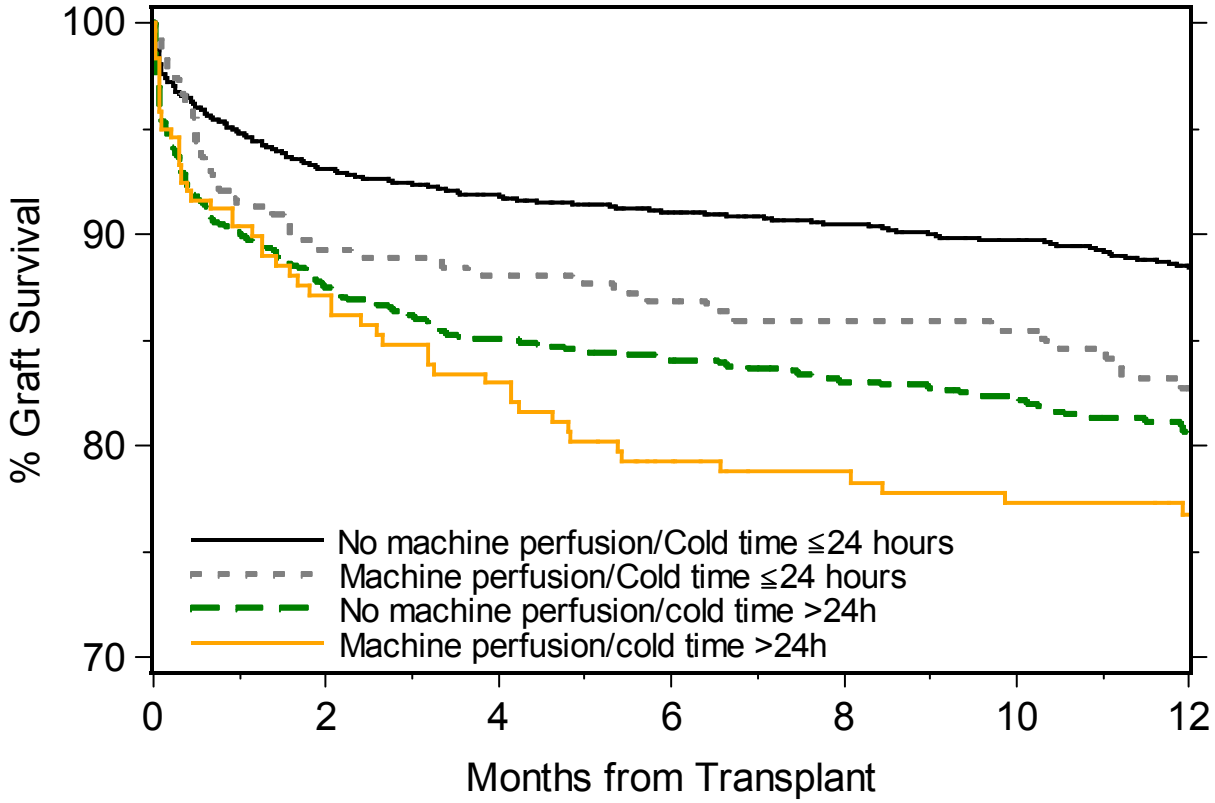


EXHIBIT 8.3
DECEASED DONOR INDEX TRANSPLANTS
GRAFT SURVIVAL AND ATN BY TRANSPLANT ERA AND MACHINE PERFUSION USE AND COLD ISCHEMIA TIME

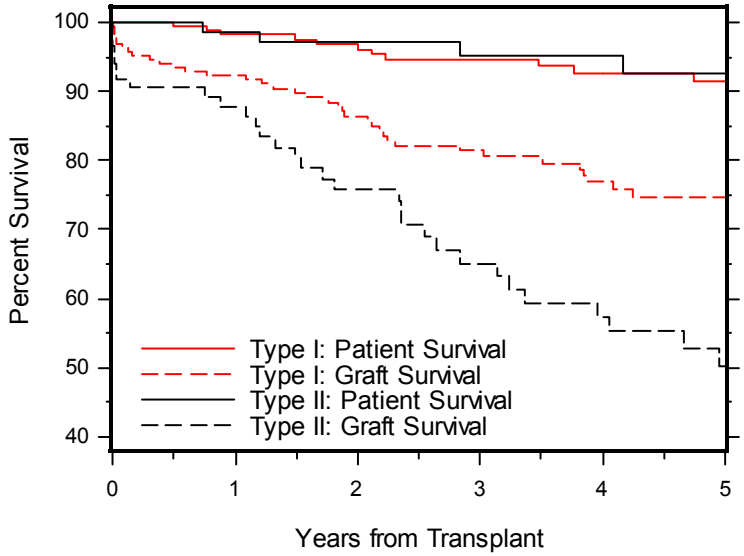
	Total				1987-1995				1996-2010			
		1 year Graft survival		%		1 year Graft survival		%		1 year Graft survival		%
	N	Rate	SE	ATN	N	Rate	SE	ATN	N	Rate	SE	ATN
No machine perfusion/ Cold time ≤ 24 hours	2595	88.5	0.6	14.1	1267	83.1	1.1	14.9	1328	93.8	0.7	13.4
Machine perfusion/ Cold time ≤ 24 hours	266	82.8	2.4	13.0	132	74.6	3.8	10.6	134	91.2	2.7	15.4
No machine perfusion/ Cold time >24 hours	820	80.5	1.4	25.9	674	77.8	1.6	25.8	146	93.0	2.1	26.4
Machine perfusion/ Cold time >24 hours	238	76.8	2.8	18.1	191	75.5	3.2	18.4	47	83.2	6.0	17.0

EXHIBIT 8-4
RARE PRIMARY DISEASES

MPGN Type I and Type II

Type I						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	62	88.1±4.3	45	65.3±7.3	107	78.2±4.1
1997-2010	47	88.7±5.4	30	78.9±9.7	79*	85.5±4.8
Total	109	88.5±3.3	75	70.6±5.8	186*	81.4±3.1
Type II						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	22	78.6±9.6	25	43.1±10.7	47	59.5±7.7
1997-2010	20	76.2±12.8	16	68.9±13.4	38*	73.5±9.1
Total	42	78.3±7.4	41	52.3±8.6	85*	65.1±5.9

*2 type I cases and 2 type II cases from 1997-2010 are missing donor source.



Sickle Cell Nephropathy

Era	LD (n)	DD (n)	Total (n)
1987-1996	3	6	9
1997-2010	4	3	7
Total	7	9	16

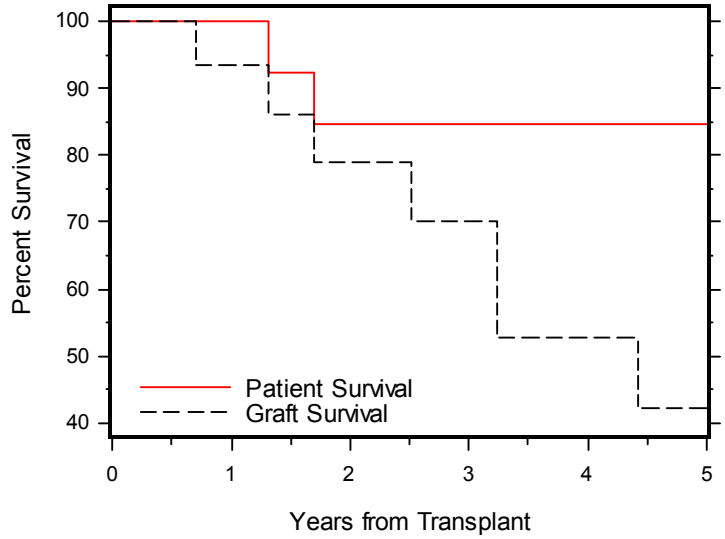
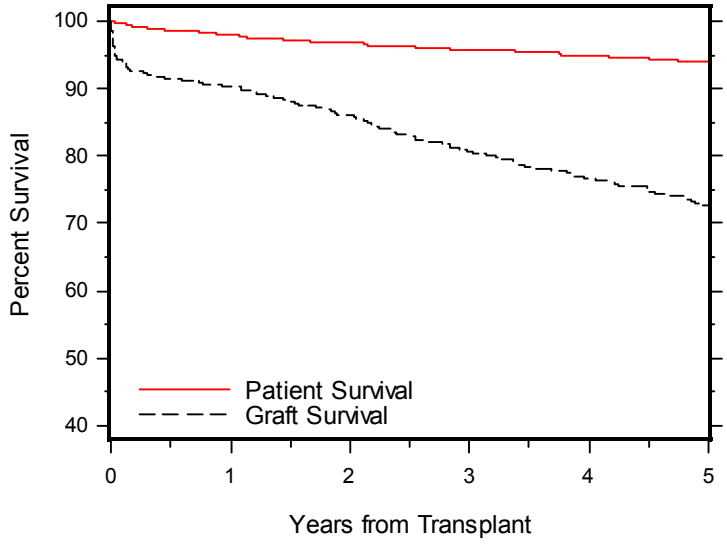


EXHIBIT 8-4 (continued)
RARE PRIMARY DISEASES

Glomerular Disease

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	232	83.3±2.5	195	62.8±3.6	428	74.0±2.2
1997-2010	256	90.1±2.2	173	83.4±3.5	436*	87.6±1.9
Total	488	86.8±1.7	368	72.2±2.6	864*	80.6±1.5

*1 case from 1987-1996 is missing donor source.
7 cases from 1997-2010 are missing donor source.



Focal Segmental Glomerulosclerosis

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	246	73.7±2.9	329	65.5±2.7	575	69.1±2.0
1997-2010	292	85.8±2.4	373	77.8±2.7	671*	81.2±1.8
Total	538	79.8±1.9	702	71.7±1.9	1246*	75.2±1.4

*6 cases from 1997-2010 are missing donor source

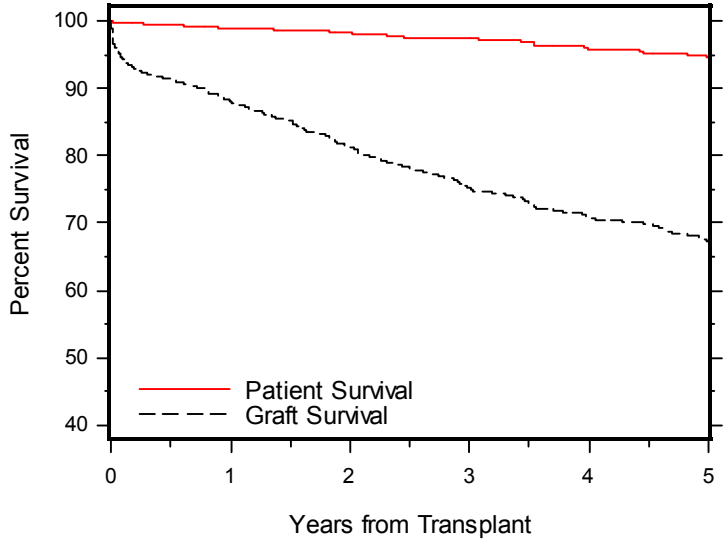
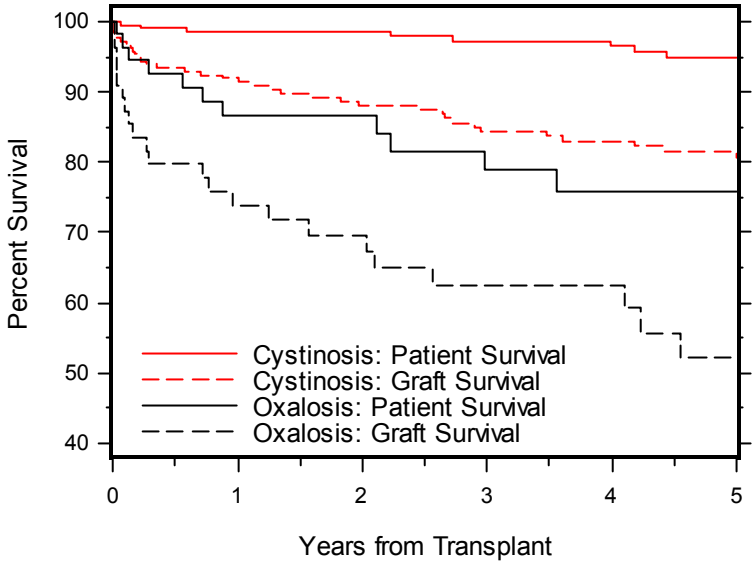


EXHIBIT 8-4 (continued)
RARE PRIMARY DISEASES

Metabolic Disease

Cystinosis						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	43	89.3±5.1	66	70.6±5.7	109	77.9±4.1
1997-2010	70	90.3±4.1	42	92.6±5.2	112*	91.1±3.3
Total	113	89.8±3.2	108	78.6±4.2	221*	84.4±2.7
Oxalosis						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	14	35.7±12.8	22	58.0±10.7	36	49.05±8.4
1997-2010	5	--	13	91.7±8.0	19*	94.4±5.4
Total	19	48.6±12.1	35	69.7±8.1	55*	62.5±6.9

1 oxalosis case from 1997-2010 is missing donor source.



Genetic Disease

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	30	76.4±7.8	25	79.8±8.1	55	78.0±5.6
1997-2010	38	96.4±3.5	18	86.2±9.1	56	92.8±4.0
Total	68	87.4±4.2	43	82.4±6.1	111	85.4±3.5

*6 cases from 1997-2010 are missing donor source