North American Pediatric Renal Trials and Collaborative Studies

NAPRTCS

2014 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 January 1, 2014 (data base closure for this report), 12,189 renal transplants had been reported for 11,186 pediatric patients. This represents 586 new transplants and 554 patients with their first registry transplant since the 2010 Annual Report.

The percentage of males in the registry, 59%, has been lower in the last 2 years of the registry: 53% in 2012 and 45% in 2013. These numbers may increase as accrual continues. 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 a low of 43% in 2007. Currently (2012/2013) 55% of the patients are of white race. There has been a fairly steady increase in the percent of living donors from 1987 (43%) through 2001 (64%). However, the percentage has been declining in recent years to 41% in 2012/2013. Fifty percent of all allografts have come from a living donor. The percentage of young recipients (<6 years old) has remained at about 20%, varying from 15% to 28% with no temporal trends noted. Young deceased donors (<10 years old) has decreased from 35% in 1987, to 19% in 1991, to <10% since 2011.

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 (22.6%), followed by obstructive uropathy (15.1%), aplasia/hypoplasia/dysplasia (13.3%). SLE nephritis (3.7%), Chronic glomerulonephritis (GN) (3.4%) and prune belly (3.1%) are present in >3% of the black population. The prevalence of cystinosis (0.6%) reflux nephropathy (1.1%) and hemolytic uremic syndrome (1.6%) 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 (16.5%), FSGS (9.0%) and reflux nephropathy (6.3%). Polycystic disease (3.8%), medullary cystic disease (3.6%), hemolytic uremic disease (3.4%) and cyctinosis (3.1%) are present in >3% of the population. The relative order of these prevalent primary diagnoses among Hispanics is similar to that for white patients with the most prevalent diagnoses of aplasia/hypoplasia/dysplasia (15.5%), obstructive uropathy (13.5%), FSGS (11.1%) and reflux nephropathy (4.8%). Chronic GN is present in 4.9% of the Hispanics (2.3% of the white patients), polycystic disease in 2.3% of Hispanics (3.8% of white patients) and medullary cystic disease is present in only 1.3% of Hispanics (while in 3.6% of white patients).

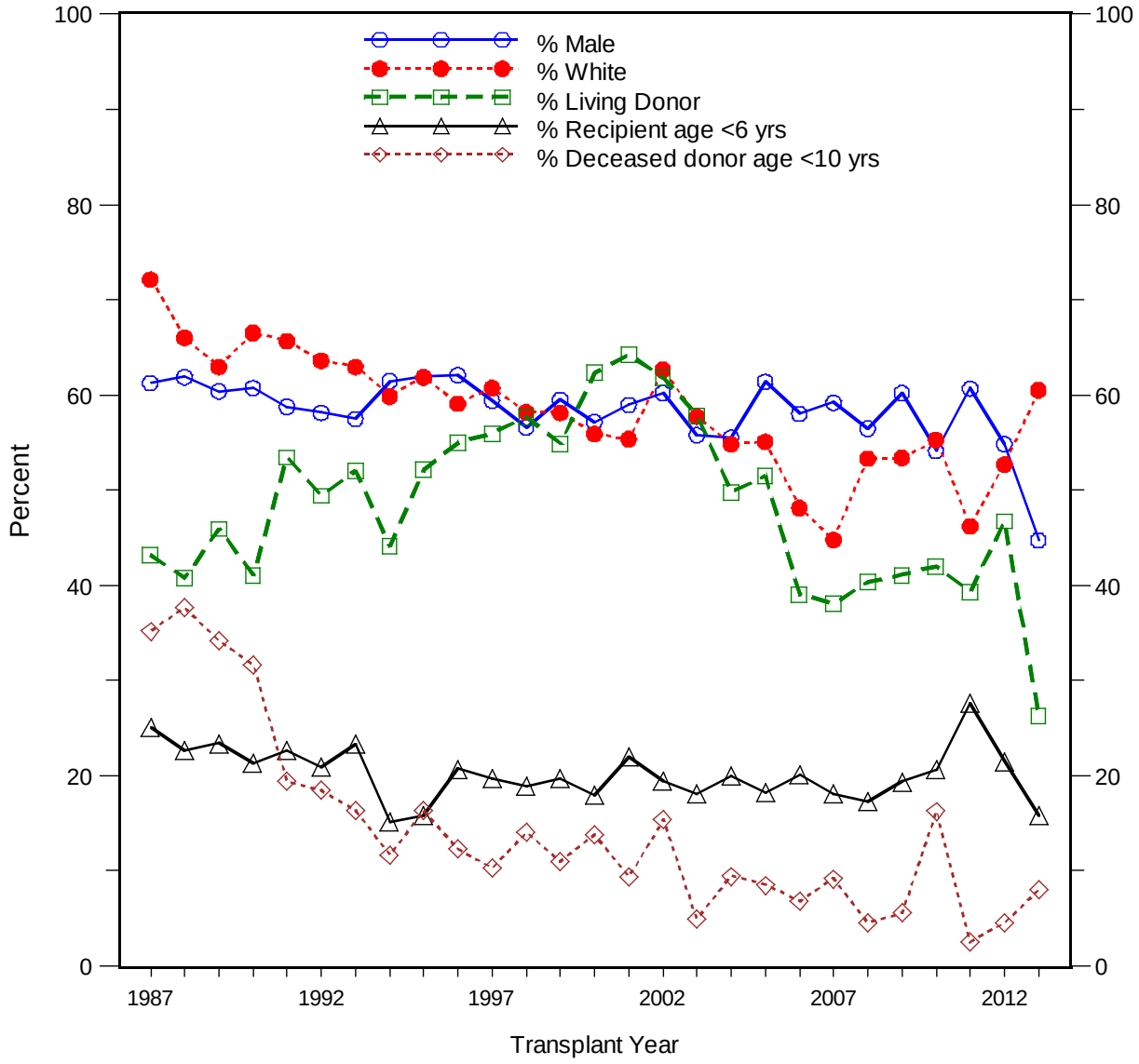
At the time of their index transplant (first NAPRTCS transplant), 14.1% (1,576/11,186) of patients were receiving their second (or greater) transplant. Twenty-five percent of primary transplants were preemptive, as these patients had never received maintenance dialysis (Exhibit 1.3). The rate of preemptive transplantation differs significantly ($p<0.001$) between recipients of living (34%) and deceased donor (14%) source organs; between males (28%) and females (20%); among age groups, with rates of 20%, 24%, 28%, 23%, 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%, 17%, and 18%, 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. There have been 2579 (21%) repeat transplants, with 1011 (39%) having the prior transplanted graft removed (Exhibit 1.3).

Exhibit 1.4 details recipient age at transplant. Of the 100 transplants occurring in children younger than 12 months old, there were 8, 23, and 68 transplants, respectively, within the 3-5, 6-8 and 9-11 months age categories, and only one was less than 3 months. Only 8 infant transplants have been performed since 2008, two in 2008, three in 2009, one each in 2010, 2011 and 2012. In Exhibit 1.5, it is observed that the sex distribution is most unbalanced in the youngest age groups where 70% 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 (61%) 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 22% white, 41% black, 28% Hispanic and 10% other. The percentages of patients *without* a histologically confirmed tissue diagnosis are 70%, 70%, and 66% in aplastic/hypoplastic/dysplastic, obstructive uropathy, and reflux nephropathy patients, respectively. The comparable rates for FSGS, hemolytic uremic syndrome, and lupus nephritis are 6%, 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	Pats	Txs	Year	Pats	Txs	Year	Pats	Txs
1987	531	542	1996	554	633	2005	388	412
1988	502	530	1996	562	604	2006	351	374
1989	463	505	1998	499	560	2007	302	326
1990	498	550	1999	525	578	2008	320	347
1991	500	565	2000	435	474	2009	261	279
1992	546	602	2001	489	529	2010	162	170
1993	573	621	2002	454	490	2011	135	145
1994	551	628	2003	416	459	2012	87	93
1995	628	690	2004	416	445	2013	38	38
Total 11,186 patients with 12,189 Transplants								

EXHIBIT 1.2
INDEX TRANSPLANTS

Recipient and Transplant Characteristics	N	%
Total	11186	100.0
Sex		
Male	6606	59.1
Female	4580	40.9
Race		
White	6605	59.0
Black	1911	17.1
Hispanic	1910	17.1
Other	760	6.8
Primary Diagnosis		
Aplasia/hypoplasia/dysplasia kidney	1769	15.8
Obstructive uropathy	1713	15.3
Focal segmental glomerulosclerosis	1308	11.7
Reflux nephropathy	576	5.1
Chronic glomerulonephritis	344	3.1
Polycystic disease	339	3.0
Medullary cystic disease	305	2.7
Congenital nephrotic syndrome	289	2.6
Hemolytic uremic syndrome	288	2.6
Prune Belly	279	2.5
Familial nephritis	247	2.2
Cystinosis	225	2.0
Idiopathic crescentic glomerulonephritis	195	1.7
Membranoproliferative glomerulonephritis - Type I	191	1.7
Pyelo/interstitial nephritis	189	1.7
SLE nephritis	172	1.5
Renal infarct	144	1.3
Berger's (IgA) nephritis	135	1.2
Henoch-Schonlein nephritis	115	1.0
Membranoproliferative glomerulonephritis - Type II	87	0.8
Wegener's granulomatosis	71	0.6
Wilms tumor	59	0.5
Oxalosis	58	0.5
Drash syndrome	57	0.5
Membranous nephropathy	51	0.5
Other systemic immunologic disease	34	0.3
Sickle cell nephropathy	16	0.1
Diabetic glomerulonephritis	11	0.1
Other	1223	10.9
Unknown	692	6.2

EXHIBIT 1.3
TRANSPLANT CHARACTERISTICS

Transplant Type	**N**	**%**
Total Transplants	12189	100.0
Index Transplants	11186	91.8
Primary Transplants	9610	78.8
Index Non-primary Transplants	1576	12.9
Non-Index Transplants	1003	8.2
Repeat Transplants	2579	21.2

Primary Transplants	**N**	**%**
Total Primary Transplants	9610	100.0
Preemptive	2358	24.5
Splenectomy	62	0.6
Native tissue removed	2135	22.2
Maintenance hemodialysis	2766	28.8
Maintenance peritoneal dialysis	3721	38.7
Both maintenance hemo & peritoneal dialysis	558	5.8

Repeat Transplants	**N**	**%**
Total Repeat Transplants	2579	100.0
Prior transplants removed	1011	39.2

EXHIBIT 1.4
AGE AT TRANSPLANTATION

Age at Transplantation (years)	N	%
Total	12189	100%
<1	100	0.8
1	560	4.6
2	550	4.5
3	420	3.4
4	391	3.2
5	435	3.6
6	420	3.4
7	469	3.8
8	503	4.1
9	556	4.6
10	670	5.5
11	643	5.3
12	711	5.8
13	844	6.9
14	898	7.4
15	1005	8.2
16	1047	8.6
17	990	8.1
≥ 18	977	8.0

Age Groupings (years)	N	%
0-1	660	5.4
2-5	1796	14.7
6-12	3972	32.6
13-17	4784	39.2
≥ 18	977	8.0

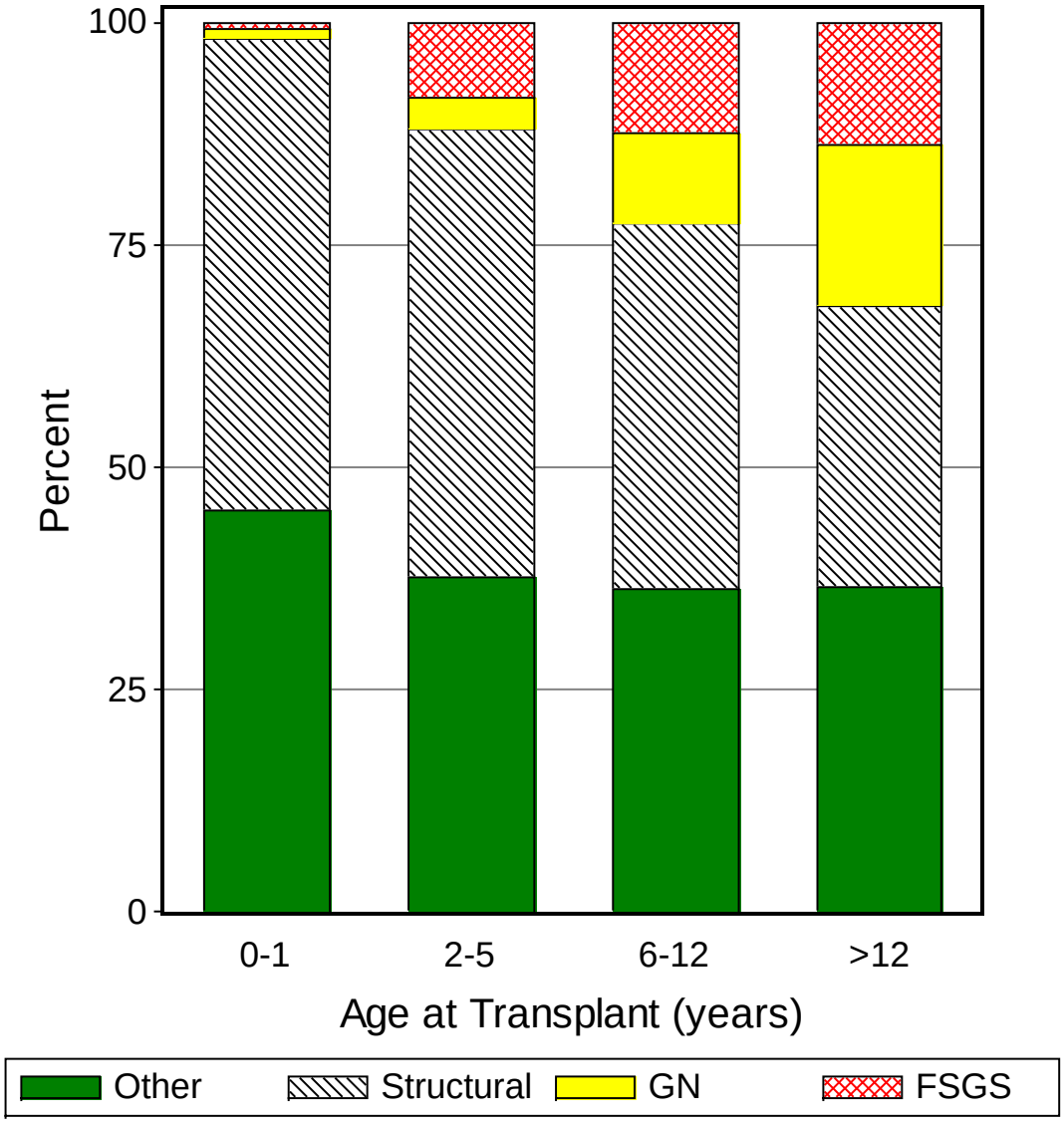
EXHIBIT 1.5
AGE AT INDEX TRANSPLANT
BY SEX, RACE, AND PRIMARY DIAGNOSIS

	Age at Transplantation				
	0-1 years (percent)	**2-5 years** (percent)	**6-12 years** (percent)	**13-17 years** (percent)	**≥18 years** (percent)
Gender					
Male	69.7	65.6	58.6	56.1	55.2
Female	30.3	34.4	41.4	43.9	44.8
Race					
White	73.3	63.0	60.2	55.9	51.1
Black	8.1	14.3	14.7	19.9	25.8
Hispanic	12.3	15.8	18.0	17.7	15.8
Other	6.3	6.9	7.0	6.5	7.3
Primary Diagnosis					
Renal plasias	28.9	23.7	16.5	11.4	9.7
Obstructive uropathy	18.9	20.4	15.8	13.3	10.1
FSGS	0.6	8.2	12.4	13.2	16.7
Other	51.6	47.7	55.3	62.1	63.5

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

Primary Renal Diagnosis	N	% Male	% White	% Not Biopsied
Total	11186	59.1	63.4	44.3
Aplasia/hypoplasia/dysplasia	1769	61.3	66.9	70.2
Obstructive uropathy	1713	85.0	66.6	70.0
Focal segmental glomerulosclerosis	1308	57.4	48.0	6.4
Reflux nephropathy	576	43.4	79.0	65.5
Chronic glomerulonephritis	344	43.9	49.2	25.0
Polycystic disease	339	50.1	78.2	49.0
Medullary cystic disease	305	50.2	86.3	35.4
Congenital nephrotic syndrome	289	51.2	68.8	13.8
Hemolytic uremic syndrome	288	54.5	81.6	48.3
Prune Belly	279	97.8	63.5	62.0
Familial nephritis	247	81.0	60.1	27.9
Cystinosis	225	53.3	90.0	55.6
Idiopathic crescentic glomerulonephritis	195	34.4	56.8	5.1
Membranoproliferative glomerulonephritis – Type 1	191	44.0	59.7	3.7
Pyelo/interstitial nephritis	189	48.1	73.7	22.8
SLE nephritis	172	16.9	25.6	4.1
Renal infarct	144	47.2	81.3	65.3
Berger's (IgA) nephritis	139	53.2	71.8	5.8
Henoch-Schonlein nephritis	115	40.9	75.0	14.8
Membranoproliferative glomerulonephritis - Type II	87	50.6	76.8	4.6
Wegener's granulomatosis	71	42.3	69.2	8.5
Wilms tumor	59	54.2	74.6	6.8
Oxalosis	58	50.0	92.2	24.1
Drash syndrome	57	56.1	70.6	8.8
Membranous nephropathy	51	62.7	48.9	5.9
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	1223	53.2	62.6	37.4
Unknown	692	52.9	33.9	65.9

EXHIBIT 1.7
PRIMARY DIAGNOSIS BY AGE



SECTION 2: DONOR HISTORY AND ANTIGEN MISMATCHES

As described in Exhibit 2.1, 49.7% of all transplants have involved a deceased donor source, 39.5% came from a parent, with the remaining 10.8% coming from other living donors. Parents comprise 78.5% of living donors: a cross-classification of parent and child sexes (n=4,465 pairs with complete data) reveals that mothers comprise the majority of parent-donors (55.5%), fathers donate to sons 63.4% of the time, while mothers make 58.9% of their donation to sons (p=0.002). There have been 421 transplants between siblings, and 195 (3.2%) live-donor grafts have been from donors under the age of 21. Eighteen living donors were under 18 years of age: 14 were transplants between siblings, 2 were transplants from parent to child, one was other related and one was unrelated. For these young sibling donors, the numbers of 4-, 5-, and 6-antigen matches were 3, 1, and 9, respectively; one case was missing antigen values. The number of unrelated living donors has increased from 1.3 per 100 living donor transplants in 1987-1995 to 6.0 per 100 transplants in 1996-2004. In recent years (2005-2013) the rate is 13.3 unrelated living donors per 100 living donor transplants.

Among deceased donor source transplants, 74 (1.3%) have come from donors less than 24 months old and 1137 (20.6%) 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% (32/4,062) in transplants between 1992 and 2013. Of deceased donor source allografts, 13.3% were preserved by machine perfusion and 74.4% had cold ischemia times of 24 hours or less, with 18 (0.3%) exceeding 48 hours. The median cold time was 18.2 hours; the maximum was 64.5 hours.

Donor-specific transfusions with or without immunosuppression coverage were performed in 5.8% 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: 52.6% of living donor graft recipients and 40.3% of deceased donor graft recipients had zero previous transfusions, while 12.1% and 23.9%, 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 70.9% in the past 5 years (76.8% living and 66.6% 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 64 (0.6%) confirmed transplants across ABO blood group compatibility barriers out of 11,006 transplants with complete blood group data. Forty-six of these transplants have occurred since 2000. For O recipients, there have been 36 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 transplants is 78.2±6.7%, is not statistically different from the compatible blood group transplants of. 82.9±0.4% using first NAPRTCS transplants. Overall, 87.5% (9,627/11,006) of donor and recipient blood types were identical. Whereas blood group O is present in 56.5% of donors and 47.5% 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 alleles are reported for both donor and recipient. If one allele is reported as '99' (undetermined allele) and the other is known, the undetermined allele is set to the value of the known allele. If an allele is missing, it is counted as missing. Among the living donor transplants with known alleles, 83.9% 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 2.7% of cases. No matches in both the B or DR loci occurred in 29.7% of the transplants from deceased donor sources; at least one locus match (of B and DR) occurred in 28.2%. Known matches of all 6 A, B and DR alleles occurred in 3.4% of deceased donor source transplants and in 5.5% of living donor source transplants with known alleles.

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

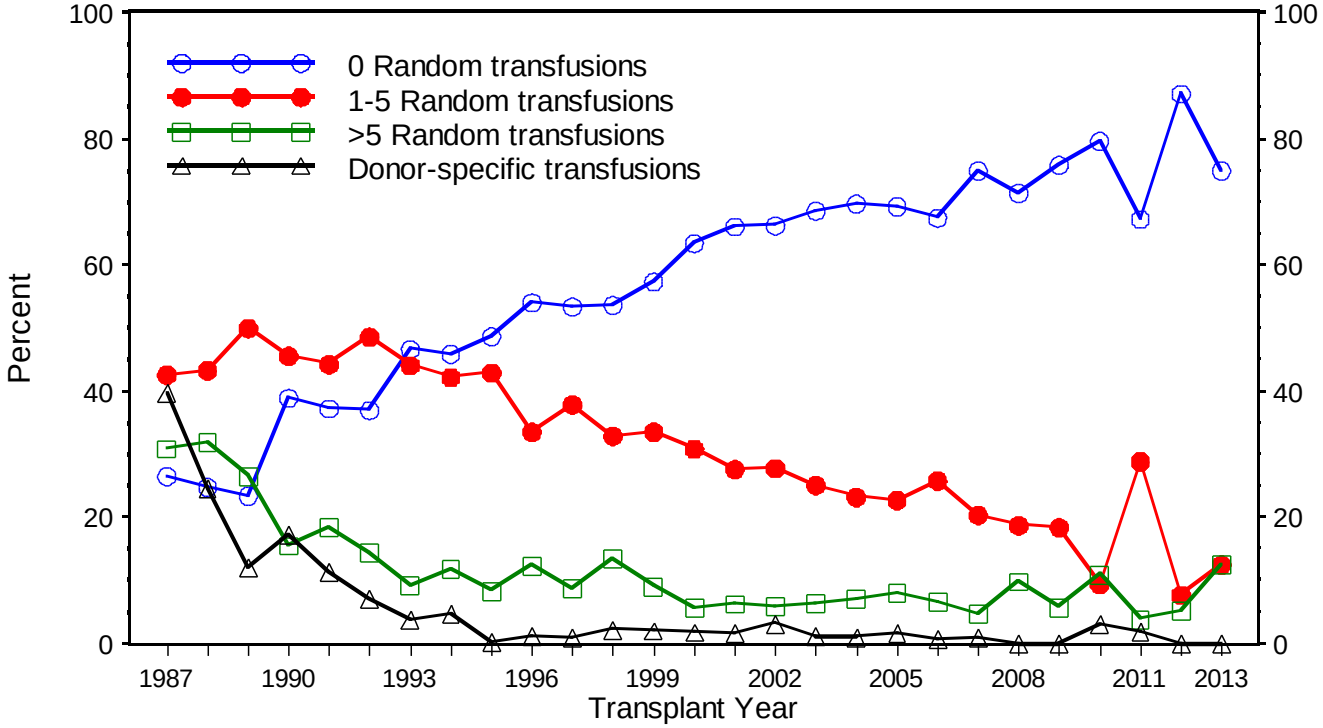
Donor Source	N	%
Live donor/parent	4789	39.5
Live donor/sibling	421	3.5
Live donor/other related	574	4.7
Live donor/unrelated	316	2.6
Deceased Donor	6016	49.7
Missing Donor Type	(73)	

	Living Donor		Deceased Donor	
Donor Age	N	%	N	%
0-1	--	--	74	1.3
2-5	--	--	447	8.1
6-12	--	--	690	12.5
13-17	18	0.3	858	15.5
18-20	177	3.1	697	12.6
21-30	1235	21.5	1135	20.5
31-40	2576	44.8	780	14.1
41-50	1510	26.2	572	10.3
> 50	239	4.2	275	5.0
Missing Donor Age	(345)		(488)	

Deceased Donor Source Transplants	N	%
Machine Perfusion Used	662	13.3
Cold Ischemia Time $\leq$ 24 hours	3899	74.4
Cold Ischemia Time > 24 hours	1342	25.6

EXHIBIT 2.2
BLOOD TRANSFUSION USE BY YEAR OF TRANSPLANT

Living Donor



Deceased Donor

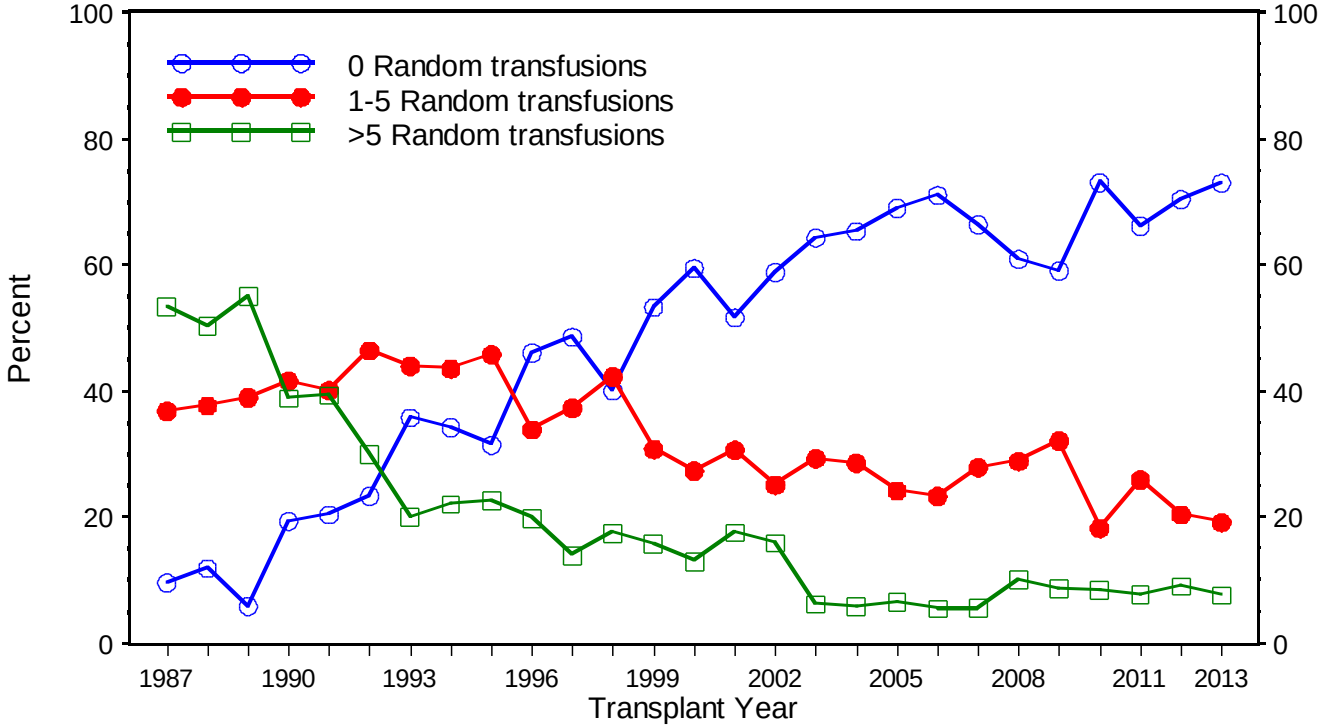
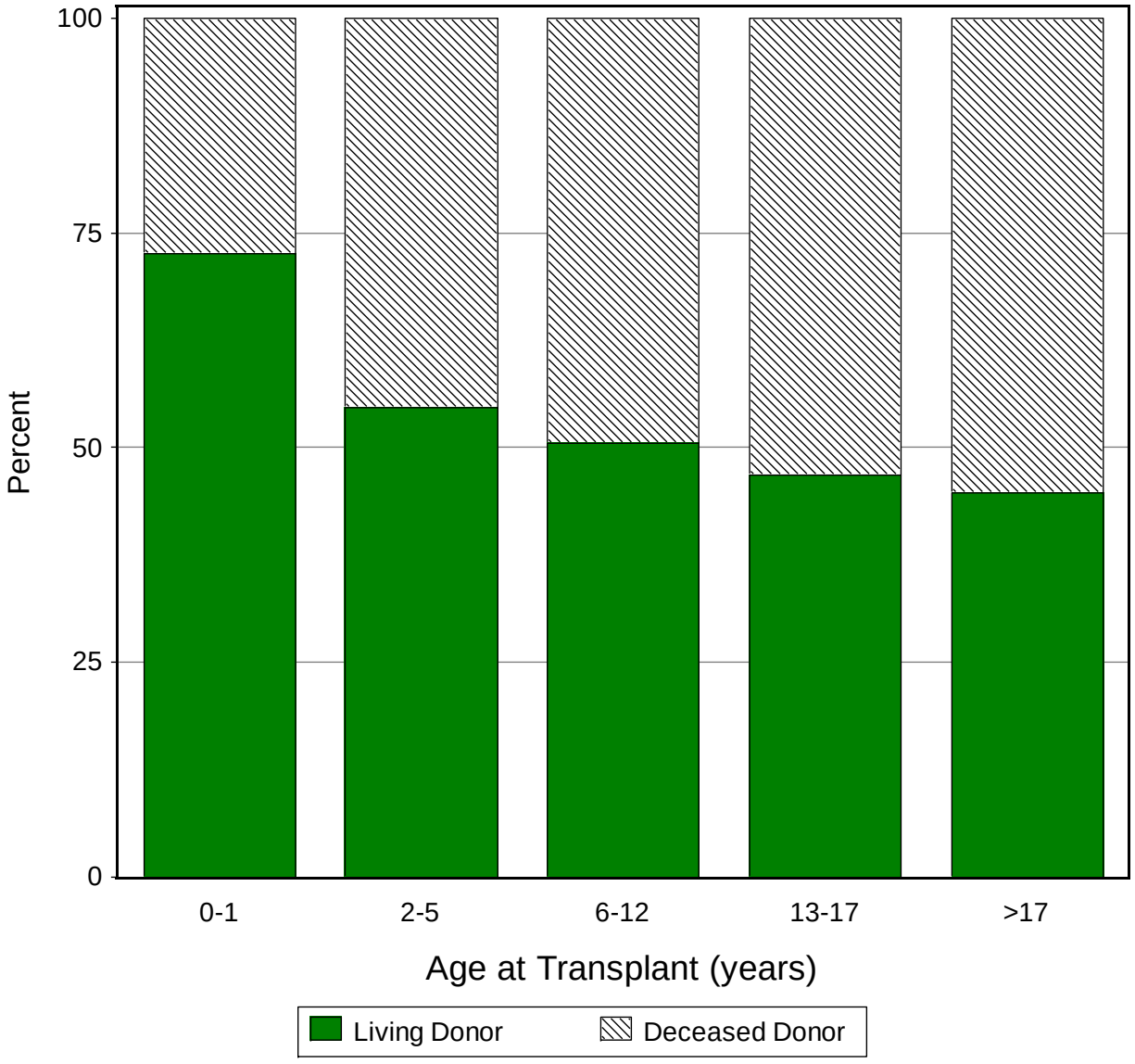


EXHIBIT 2.3
HLA MISMATCHES

	Donor Source			
	Living Donor		Deceased Donor	
	N	%	N	%
HLA-A				
0	1008	19.3	536	10.6
1	3875	74.3	2047	40.9
2	334	6.4	2467	48.6
Missing	(n=883)		(n=939)	
HLA-B				
0	719	13.8	480	9.5
1	4034	77.3	1685	33.2
2	465	8.9	2906	57.3
Missing	(n=882)		(n=945)	
HLA-DR				
0	942	18.5	605	12.1
1	3618	71.2	2179	43.5
2	524	10.3	2225	44.4
Missing	(n=1016)		(n=1007)	
HLA-B and -DR				
0	380	7.5	232	4.6
1	828	16.3	339	6.8
2	3190	62.8	1117	22.3
3	446	8.8	1825	36.5
4	236	4.6	1485	29.7
Missing	(n=1020)		(n=1018)	
HLA-A, -B, and -DR				
0	277	5.5	171	3.4
1	274	5.4	144	2.9
2	1107	21.8	283	5.7
3	2730	53.8	685	13.7
4	366	7.2	1332	26.7
5	186	3.7	1509	30.2
6	138	2.7	870	17.4
Missing	(n=1022)		(n=1022)	

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 from 1996 to the present. This encompasses 6956 transplants of which 92% are index transplants, 78% are primary transplants, 53% are from living donors and 47% are from deceased donors. Three percent (197) 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 44%. Among deceased donor transplants, the use of pre-operative immunotherapy has increased from 9% in 1996 to 26% 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 15% of living donor transplants, decreasing from 28% in 1996 to 4% in 2001, and increasing to 23% by 2010. ATG/ALG was used in 22% of deceased donor transplants, with a similar decrease from 36% in 1996, to 8% in 2001, with a 29% utilization rate in 2010. The median ATG/ALG course was 5 days. The use of monoclonal antibodies in living donors increased from 21% in 1996 to 50% in 2001. Currently (2009-2013) induction monoclonal antibodies are used in about 32% of the living donor transplants. Rates of induction monoclonal antibody use in deceased donors ranges from 30% in 1996 to 62% in 2001 to 28% currently (2009-2013). The type of monoclonal antibodies has also changed over the years from predominantly OKT3 in 1996 to basiliximab or daclizumab from 2001 to mainly basiliximab since 2010. 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 (rituxan) have been added to the data collection, currently 36 cases have been documented using campath. Most therapy with monoclonal antibodies is initiated at transplant or Day 1 post transplant. These cases are considered to have induction antibody therapy. However, 189 cases have monoclonal antibody initiated after Day 1 (median start is 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=633	1997 n=604	1998 n=560	1999 n=578	2000 n=474	2001 n=529	2002 n=490	2003 n=459	2004 n=445	2005 n=412	2006 n=374	2007 n=326	2008 n=347	2009 n=279	2010 n=170	2011 n=145	2012 n=93	2013 n=38
None	50.6	53.0	44.1	44.3	47.3	46.7	41.8	45.1	47.4	44.4	36.6	45.1	36.3	50.9	47.1	37.2	38.7	60.5
OKT3	21.6	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	0.0	0.0	0.0	0.0
Basiliximab	0.0	0.7	4.6	15.1	21.1	28.9	30.8	24.4	24.0	22.6	21.1	18.4	16.7	12.2	12.9	26.2	24.7	7.9
Daclizumab	0.0	4.8	17.7	24.7	19.4	14.9	15.1	12.6	12.4	13.6	16.8	7.1	11.0	10.4	5.9	0.0	1.1	0.0
Other	0.0	0.2	1.1	0.7	5.9	3.0	4.5	5.5	5.6	5.3	10.4	9.8	8.9	3.6	3.5	9.0	9.7	5.3
ATG/ALG	27.8	27.0	22.9	10.6	5.9	5.5	6.9	12.0	10.6	14.1	14.2	19.6	27.1	22.9	30.6	27.6	25.8	26.3

Sirolimus therapy first appeared in 1998 (<1% of the cases), peaked in 2002 with 26% of the cases receiving sirolimus and has tapered off to <1% currently. The median day of initiation is 1 day post-transplant with a median initial dose of 3.2 mg/m^2.

Cyclosporine was used for 39% of transplants but has decreased from 81% in 1996 to <3% over the past 5 years. 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 daily 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 50% of the transplants increasing from 6% in 1996 to 83% over the past 5 years. Tacrolimus was started the day before transplant in 2%, the day of transplant in 18%, on day 1 for 38%, day 2-6 for 34% and after day 6 for 8% of the transplants. The median daily dose of tacrolimus increased by 0.06 mg/kg during the first post-transplant 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 2010, 50% 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 (80% initially and 78% 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 1996-2001, from 24% of living donor and 22% of deceased donor organ recipients, to <1% in each group in 2008-2013. The regimen of prednisone, tacrolimus, and mycophenolate mofetil has become more popular. It is used in 50% of living donor and 54% of deceased donor organ transplant in 2008-2013, compared to about 14% of all transplants in 1996-2001.

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

	1996 n=599	1997 n=581	1998 n=534	1999 n=555	2000 n=456	2001 n=513	2002 n=480	2003 n=450	2004 n=439	2005 n=403	2006 n=367	2007 n=323	2008 n=344	2009 n=277	2010 n=166	2011 n=141	2012 n=93	2013 n=38
Prednisone	94.7	95.7	94.8	92.6	91.2	86.4	84.8	73.3	68.6	64.3	61.3	57.3	54.4	48.7	50.0	55.3	51.6	34.2
Cyclosporine	82.0	78.8	71.9	68.1	57.0	45.2	25.8	15.6	9.1	10.4	5.2	8.1	4.1	1.4	3.6	2.8	2.2	0.0
Tacrolimus	3.7	14.8	22.1	24.5	34.4	41.7	58.1	60.2	71.5	68.2	71.4	71.2	72.4	68.6	73.5	77.3	77.4	52.6
MMF	9.0	44.8	66.7	66.9	63.8	54.2	57.5	58.2	64.5	70.7	69.2	71.8	68.6	64.2	65.7	74.5	78.5	47.4
Azathioprine	49.3	34.4	19.7	16.0	13.8	12.9	2.7	3.8	3.2	1.0	1.9	3.4	4.1	2.5	4.8	2.8	3.2	5.3
Sirolimus	0.0	0.0	0.2	0.4	7.5	21.6	25.6	18.4	12.5	6.2	6.5	2.2	2.3	0.4	1.8	0.7	0.0	0.0

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 also to about 3% currently. Prednisone use has slowly been decreasing in recent years from 95% in 1996 to about 50% currently.

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 8% at Month 6 to 17%, 27%, and 35% 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 1996-2001				Transplant Era 2002-2007				Transplant Era 2008-2013			
	30 days	1 year	3 years	5 years	30 days	1 year	3 years	5 years	30 days	1 year	3 years	5 years
Prednisone/CsA/MMF	35.6	38.2	30.7	22.5	10.0	8.8	8.0	7.9	1.7	2.4	0.9	--
Prednisone/CsA/Aza	23.1	17.7	14.2	8.9	0.8	0.8	0.6	0.7	0.2	0.1	0.4	--
Prednisone/Csa	11.5	5.4	4.8	5.4	3.4	1.6	1.0	1.4	0.8	0.3	0.0	--
Prednisone /TAC/MMF	14.6	19.7	24.5	30.2	52.0	50.3	44.6	42.7	52.0	46.8	42.3	--
Prednisone /TAC/Aza	2.3	4.9	6.5	6.9	1.8	2.4	2.6	4.0	2.2	2.1	4.0	--
Prednisone /TAC	6.1	7.7	10.5	11.8	9.6	11.4	11.5	8.4	4.0	10.9	13.2	--
TAC/MMF	0.4	1.1	1.7	2.7	10.7	9.7	11.8	13.5	28.7	22.3	22.5	--
Other combination	6.3	5.3	7.2	11.6	11.6	15.1	20.0	21.5	10.4	15.1	16.7	--

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 22% of the patients received combination immunosuppressives with prednisone, cyclosporine, and MMF, compared to approximately 10% of patients with prednisone, cyclosporine and azathioprine. About 34% 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 175 ng/mL in black and 177 ng/mL in 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 Post-Transplant								
	BLACK				NON-BLACK			
	N	Median	Mean	SE	N	Median	Mean	SE
Cyclosporine Dose (mg/kg/D)	265	6.0	6.6	0.2	1618	6.0	6.7	0.1
CsA Blood Level Method - HPLC	39	162	172.5	14.2	338	135	147.9	3.8
CsA Blood Level Method - TDx	146	193	229.1	15.1	787	205	241.2	6.3
CsA Blood Level Monoclonal RIA-specific	40	146	174.7	16.6	263	168	188.3	5.7
Tacrolimus Dose (mg/kg/D)	621	0.16	0.19	0.01	2466	0.11	0.14	0.00
TAC Blood Level Method - HPLC	47	5.9	6.7	0.5	309	6.1	7.5	0.6
TAC Blood Level Method - IMx	195	5.9	6.4	0.2	605	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 63% in live donor recipients at 2 years. At 5 years post transplant, the rates are 71% 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 66% since 2010 for living donors and 89% in 1996 to 79% since 2010 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 (46%). At one year, prophylactic antibiotics are used in 49% of those with focal segmental glomerulosclerosis, 55% of those with renal dyplasia, 64% of patients diagnosed with reflux nephropathy and 69% 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	79.6	3	1.46	77.7	0.50
Methylprednisolone	72.9	0	9.52	--	--
Cyclosporine	39.2	1	8.37	37.8	9.80
Tacrolimus	50.2	1	0.14	46.3	0.20
Azathioprine	20.8	0	2.07	13.6	2.02
Mycophenolate Mofetil	65.2	1	26.88	58.0	27.78
ATG/ALG	18.2	0	1.72	--	--
Monoclonal Antibody	40.3	0	--	--	--
OKT3	5.4	0	0.11	--	--
Basiliximab	17.9	0	0.41	--	--
Daclizumab	12.7	0	1.02	--	--
Other	4.2	0	1.00		
Sirolimus	7.0	1	0.11	--	--

For Mycophenolate Mofetil: Median initial dose in mg per body surface area is 828.42 and day 30 daily dose is 866.62 mg/m^2/day.

For Sirolomus: Median initial dose in mg per body surface area was 3.15 mg/m^2/day.

For ATG/ALG: Median dose has decreased from 15.00 mg/kg/D in 1996 to 1.63 mg/kg/D in 2000. In 2012 the median dose is 1.46 mg/kg/D.

Other monoclonal antibody includes 0.5% alemtuzamab.

* Day 30 results includes only patients with functioning grafts.

EXHIBIT 3.2
INDUCTION ANTIBODY USE BY YEAR OF TRANSPLANT

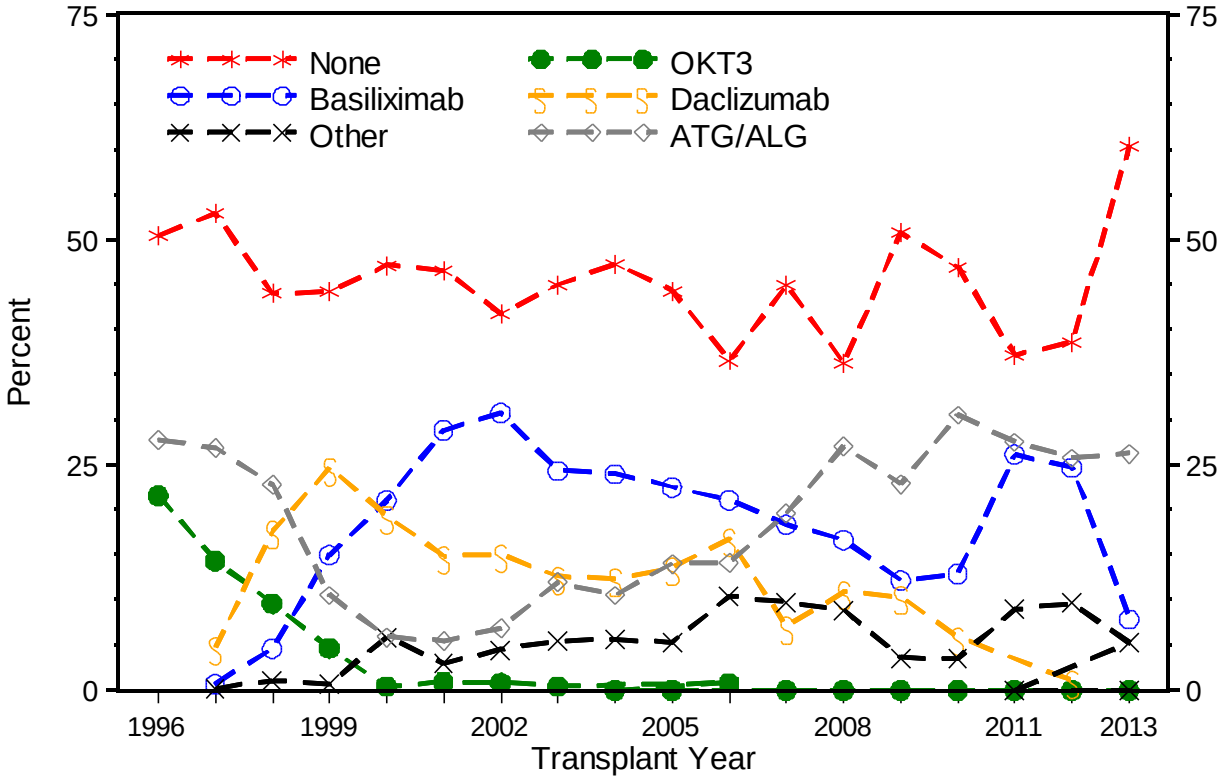


EXHIBIT 3.3
INDUCTION ANTIBODY USE BY WEEK 1 CALCINEURIN INHIBITOR

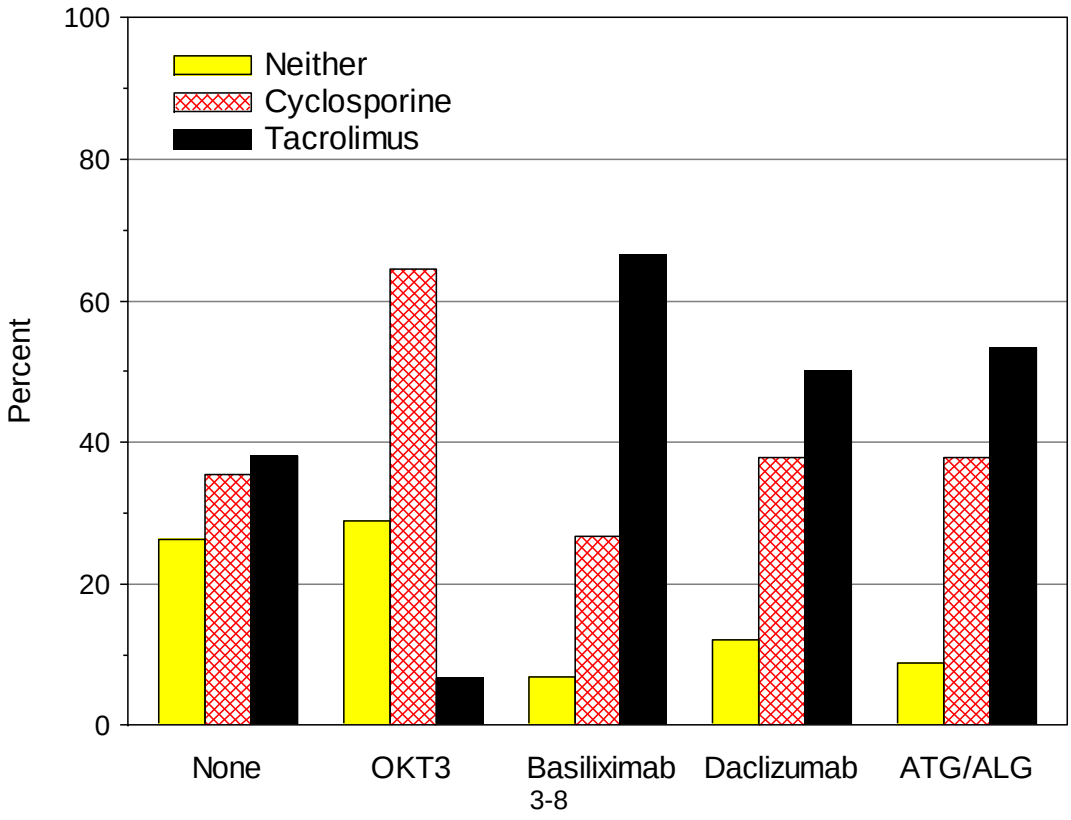


EXHIBIT 3.4
IMMUNOSUPPRESSIVE MEDICATION 30 DAYS POST TRANSPLANT
(patients with a functioning graft)

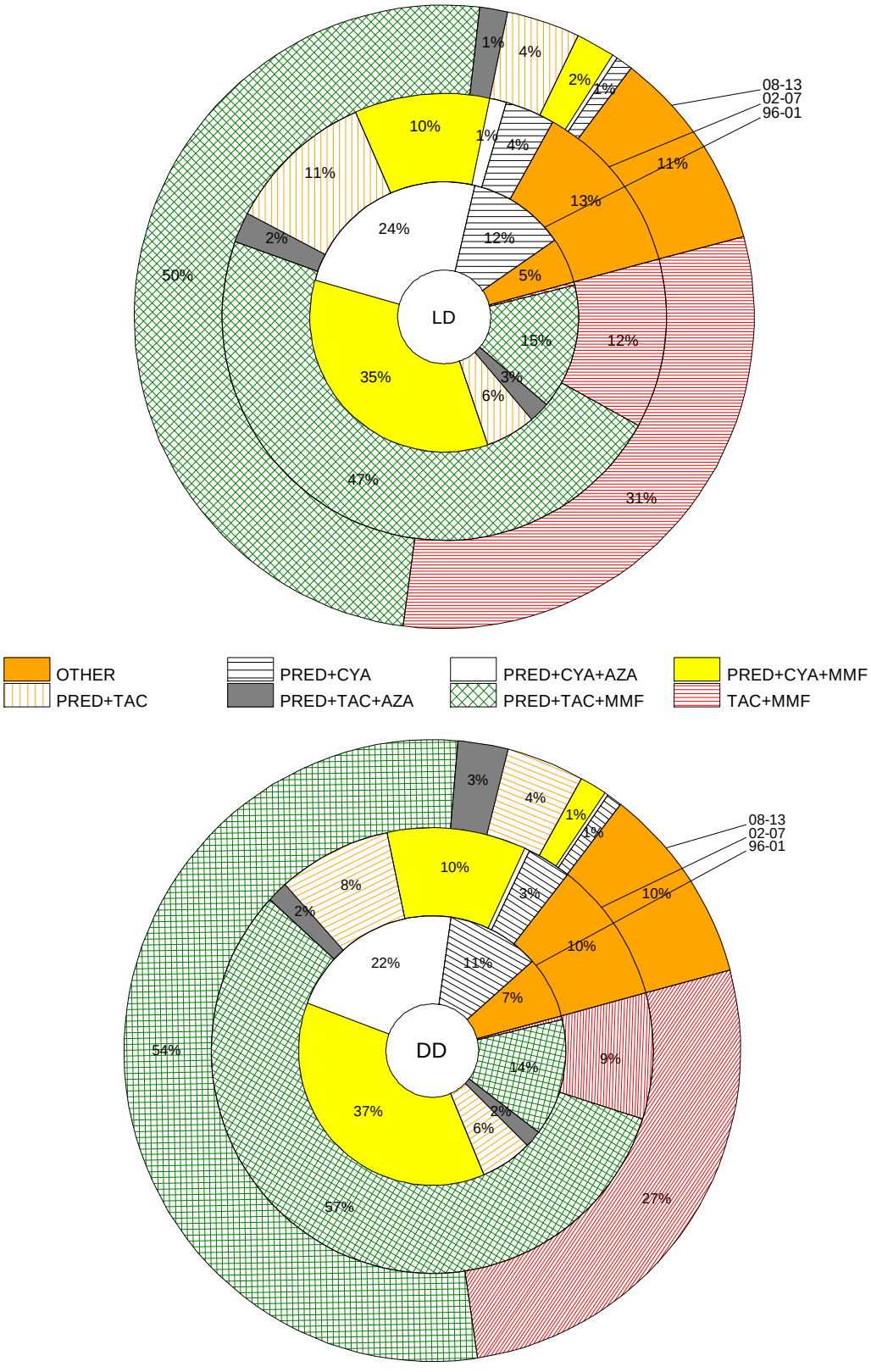


EXHIBIT 3.5
MEAN (±SE) DAILY DRUG DOSAGES BY FOLLOW-UP TIME

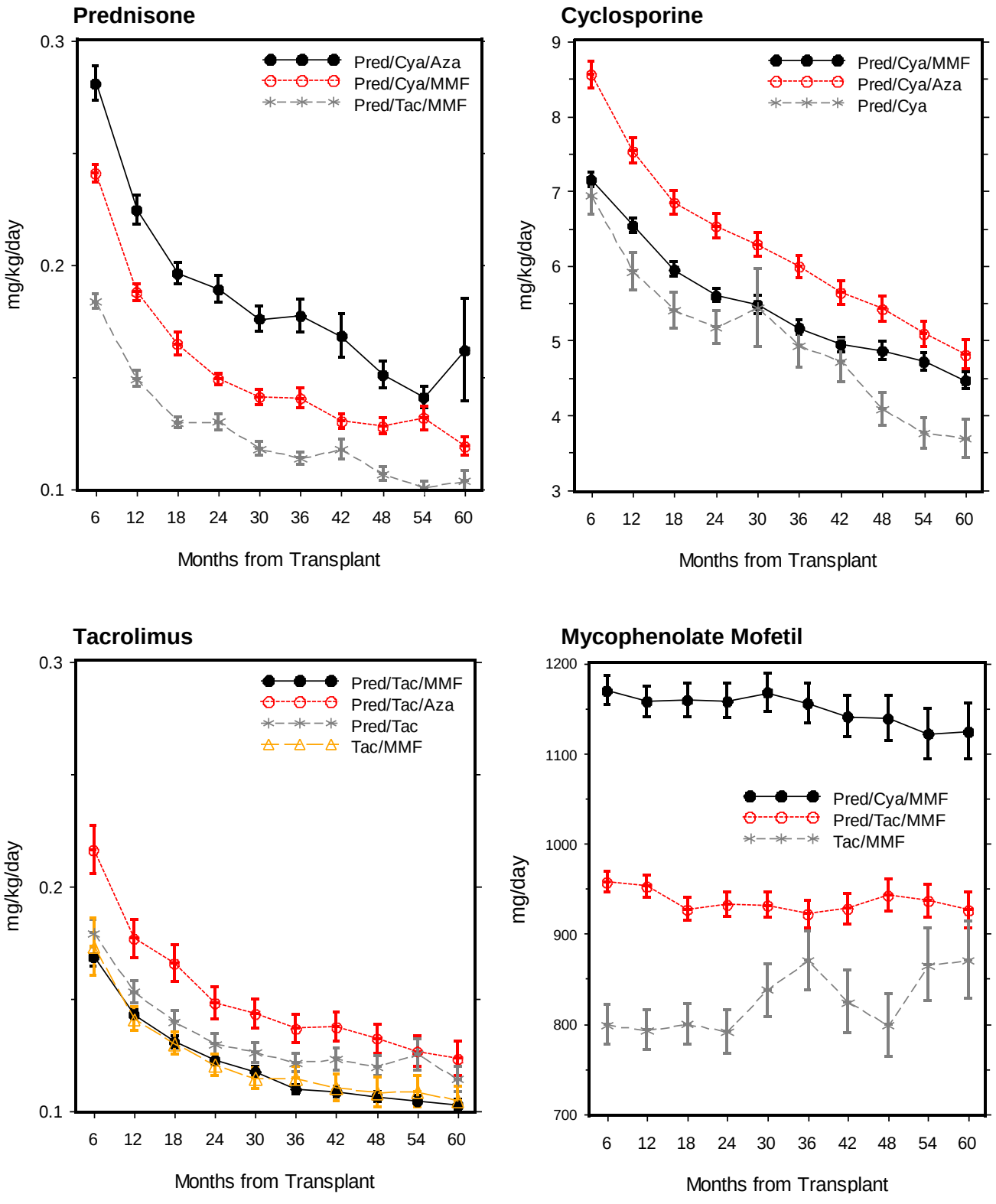


EXHIBIT 3.6
MAINTENANCE IMMUNOSUPPRESSION MEDICATION BY FOLLOW-UP TIME
(patients with a functioning graft)

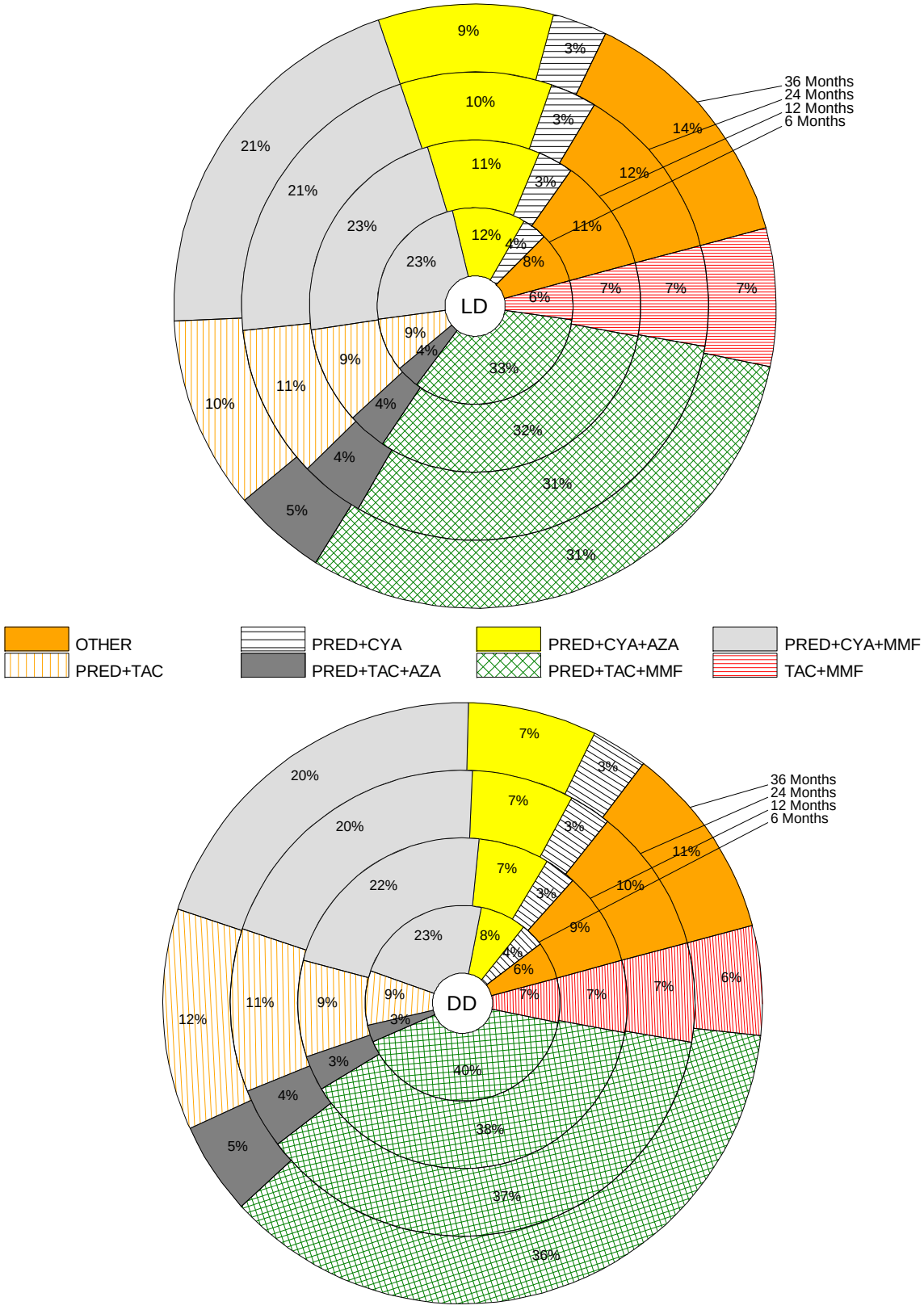
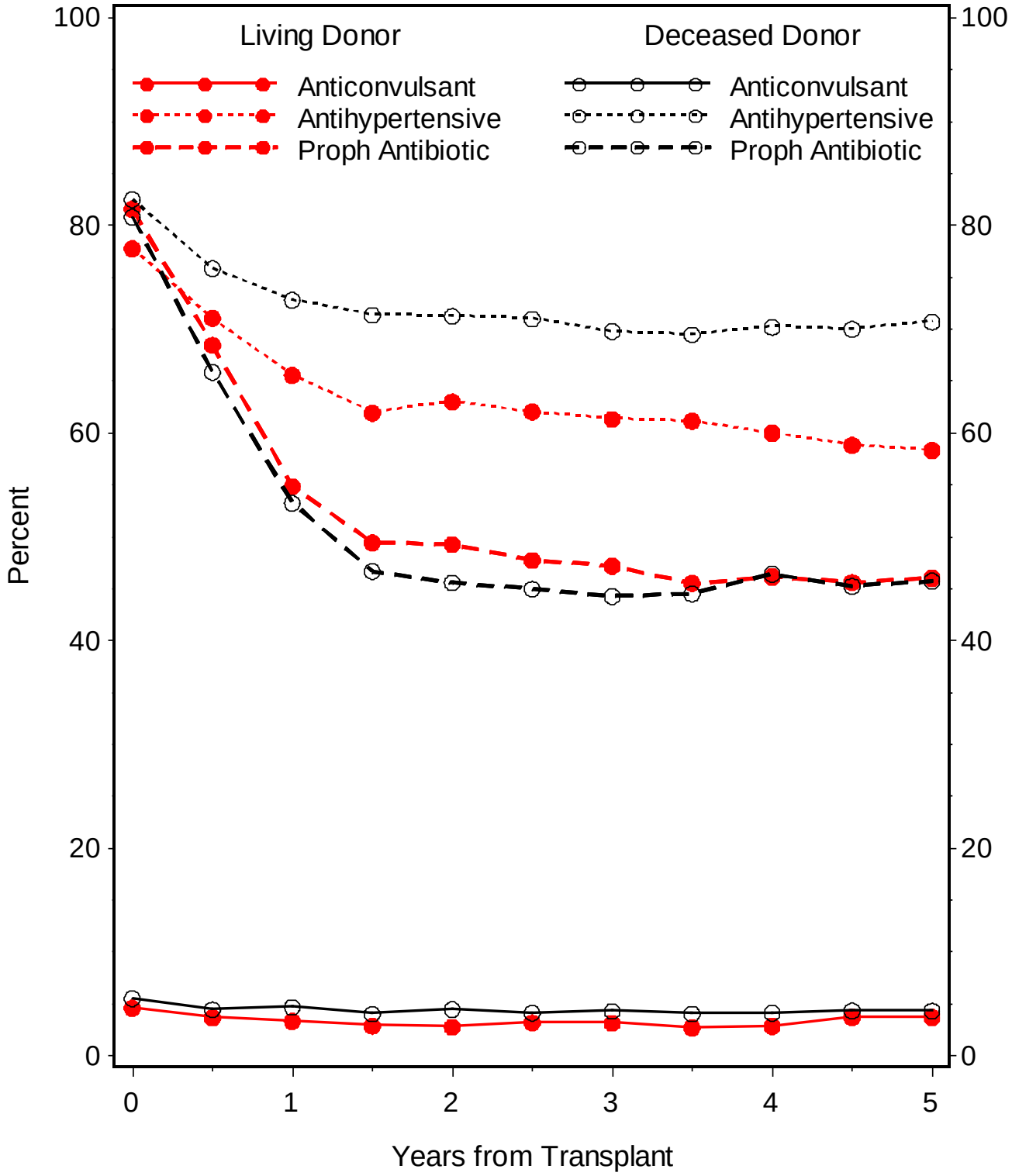


EXHIBIT 3.7
CONCOMITANT MEDICATIONS



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 83 episodes were included as such. As a result, a total of 10,653 episodes of rejection in the 12,116 transplants (with known donor source) were available for analysis, as described below. Acute rejection reversal outcome had not been established for 97 of the 10,653 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 12,116 transplants, no acute rejections were reported for 6717, exactly one rejection was reported for 2,801, two rejections for 1,285, three rejections for 665, and four or more rejections were reported for 648 transplants. 45% of the transplants had at least one rejection episode (40% in live donors and 49% in deceased donors). The number of rejections per transplant ranged from 0 to 12. Rejection rates were 70% for the 1987-1991 transplant cohort and have decreased steadily for each cohort over time with a rejection rates of 55%, 37%, 26% and 16% for transplants during 1992-1996, 1997-2001, 2002-2006 and 2007-2013 cohorts respectively. Acute rejection ratios (number of rejections/number of transplants) are shown in Exhibit 4.1B for transplant era 1987 – 1995, 1996 – 2004 and 2005 – 2013. On average, 0.75 acute rejections were reported for each living donor transplant, a ratio of 1.19 for 1987 – 1995, 0.53 for 1996 – 2004 and 0.22 for 2005-2013 transplants. On average there were 1.01 rejections for each deceased donor transplant, 1.50 in the 1987 – 1995 cohort, 0.75 in the 1996 – 2004 cohort and 0.34 in the 2005 – 2013 cohort. Age-specific ratios vary with the lowest rates in the 0-1 year olds in all eras. The highest rates in the 1987-1995 era are in the 6-12 year old age group, in 2005-2013 era the highest rejection ratios are in the >12 year old group. The 1996-2004 era has the highest rejection ratios in the >12 year old for living donor recipients and in the 6-12 year olds for deceased donor recipients. The biopsy rates of reported acute rejections over time are shown in Exhibit 4.1C. Biopsy rates have increased from 45% in 1987 and continue to rise to an average of 94% over the past 5 years.

Exhibit 4.2 displays the cumulative distribution of times to first rejection by allograft source and transplant era 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.

PROBABILITY OF FIRST REJECTION AT 12 MONTHS				
	Living Donor		Deceased Donor	
Transplant Year	%	SE	%	SE
1987-1991	52.8	1.5	67.4	1.3
1992-1996	40.8	1.3	54.7	1.4
1997-2001	25.3	1.2	30.6	1.6
2002-2006	13.9	1.1	18.2	1.3
2007-2013	9.3	1.4	13.8	1.4

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 Exhibit 4.3.

For living donor transplantation in the early (1987 – 1995) cohort, the incidence of first rejection was increased for black patients, for children over 24 months 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 1996-2004 transplant cohort, the relative hazard of rejection was significantly lower for children under 24 months and for children receiving induction therapy. There was an approximate 8% reduction in the hazard of rejection with each increasing transplantation year ($p<0.001$). In addition, in the 1996 - 2004 cohort of living donor transplant recipients, the previously identified race effect was not observed.

The transplant era 2005-2013 found children ≥24 months to have an increased hazard rate for first rejection. Effect of induction therapy and transplant year is no longer significant in this cohort.

The importance of acute tubular necrosis (ATN) on subsequent acute rejection was evaluated by restricting the analysis to recipients of living donor transplants 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 all 3 cohort eras (RH=1.94, p<0.001, RH=1.69, p=0.004 and RH=4.77, p=<0.001, respectively).

For deceased donor transplantation in the 1987-1995 cohort, black patients had 27% higher hazard of first acute rejection (RH=1.27, p<0.001) than non-black patients. Additional risk factor included no induction therapy (RH=1.20, p<0.001). The effect of transfusion history and cold storage time were 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 during this era.

For deceased donor recipients in the 1996-2004 transplant era, black race was associated with a higher relative hazard of first rejection (RH=1.41, p<0.001) and there was a 7% reduction in the relative hazard of rejection with each increasing transplantation year (p<0.001).

The most recent cohort (2005-2013) found only transplant year to have a significant effect on the deceased donor hazard rate of first rejection. An analysis of ATN in deceased donors found a relationship in this cohort (HR=2.06, 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 at transplant, and ATN (log-rank p<0.001 for each); HLA-DR mismatches and race are also significant with the Log-rank p=0.01 for each. For deceased donor recipients, significant differences in time to first rejection are seen in age at transplant (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 59% 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 (63%). 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 52% in 2005. More recent years are still accruing data. Graft failure/death rates as a rejection outcome in living donors were 4% in 1987 and have remained fairly constant over the years. 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 6221 patients satisfying these criteria, 1210 (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. Outcome of late rejection was complete reversal in 458 (38%) rejections, partial reversal 653 (54%) rejections, and graft failures or death in 72 (6%) rejection episodes. Twenty-seven episodes did not have outcome determined at the time of database closure.

EXHIBIT 4.1A
FREQUENCY OF ACUTE REJECTIONS
1987-2013

	Total*		Living Donor		Deceased Donor	
	N	**%**	**N**	**%**	**N**	**%**
All Transplants	12116	100.0	6100	100.0	6016	100.0
Transplants with at Least 1 Rejection	5399	44.6	2449	40.2	2950	49.0
Number of Acute Rejections						
0	6717	55.4	3651	59.9	3066	51.0
1	2801	23.1	1329	21.8	1472	24.5
2	1285	10.6	606	9.9	679	11.3
3	665	5.5	270	4.4	395	6.6
≥4	648	5.4	244	4.0	404	6.7
Transplants with at Least 1 Rejection by Transplant Era						
1987-1991	1874/2692	69.6	780/1210	64.5	1094/1482	73.8
1992-1996	1754/3169	55.4	807/1603	50.3	947/1566	60.5
1997-2001	1000/2720	36.8	537/1599	33.6	463/1121	41.3
2002-2006	548/2151	25.5	249/1133	22.0	299/1018	29.4
2007-2013	223/1384	16.1	76/555	13.7	147/829	17.7

*Total with known donor source.

EXHIBIT 4.1B
ACUTE REJECTION RATIOS

	Living Donor			Deceased Donor		
	No. of Transplants	No. of Rejections	Rejection Ratio	No. of Transplants	No. of Rejections	Rejection Ratio
Transplant Era 1987-1995						
Total	2465	2942	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	1184	1.36	963	1522	1.58
> 12 years	990	1160	1.17	1315	1940	1.48
Transplant Era 1996-2004						
Total	2728	1435	0.53	2003	1494	0.75
Recipient age						
0-1 years	205	53	0.26	37	13	0.35
2-5 years	435	195	0.45	249	156	0.63
6-12 years	874	475	0.54	651	510	0.78
> 12 years	1214	712	0.59	1066	815	0.76
Transplant Era 2005-2013						
Total	907	202	0.22	1250	429	0.34
Recipient age						
0-1 years	76	4	0.05	55	14	0.25
2-5 years	125	23	0.18	163	41	0.25
6-12 years	250	51	0.20	344	105	0.31
> 12 years	456	124	0.27	688	269	0.39

EXHIBIT 4.1C
BIOPSY RATE OF REPORTED ACUTE REJECTIONS

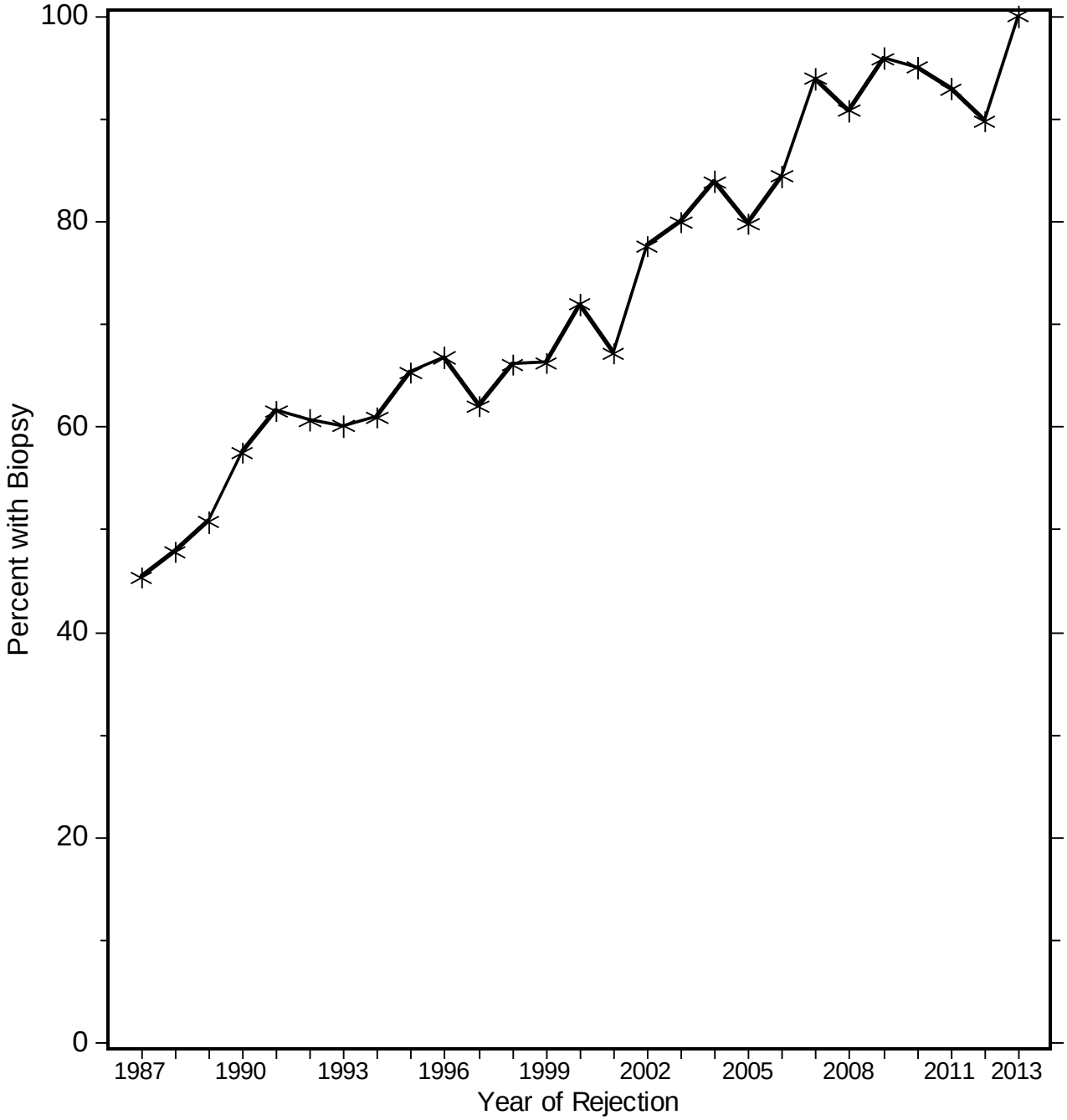
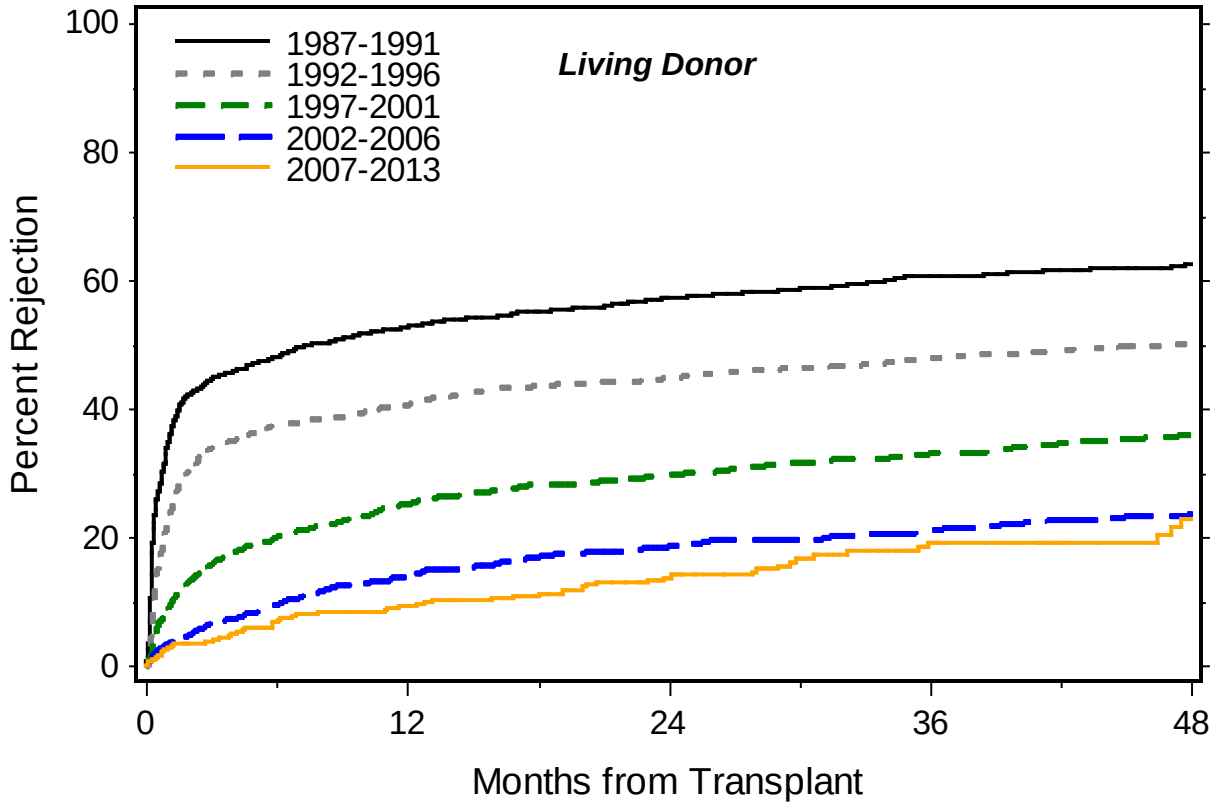


EXHIBIT 4.2
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS



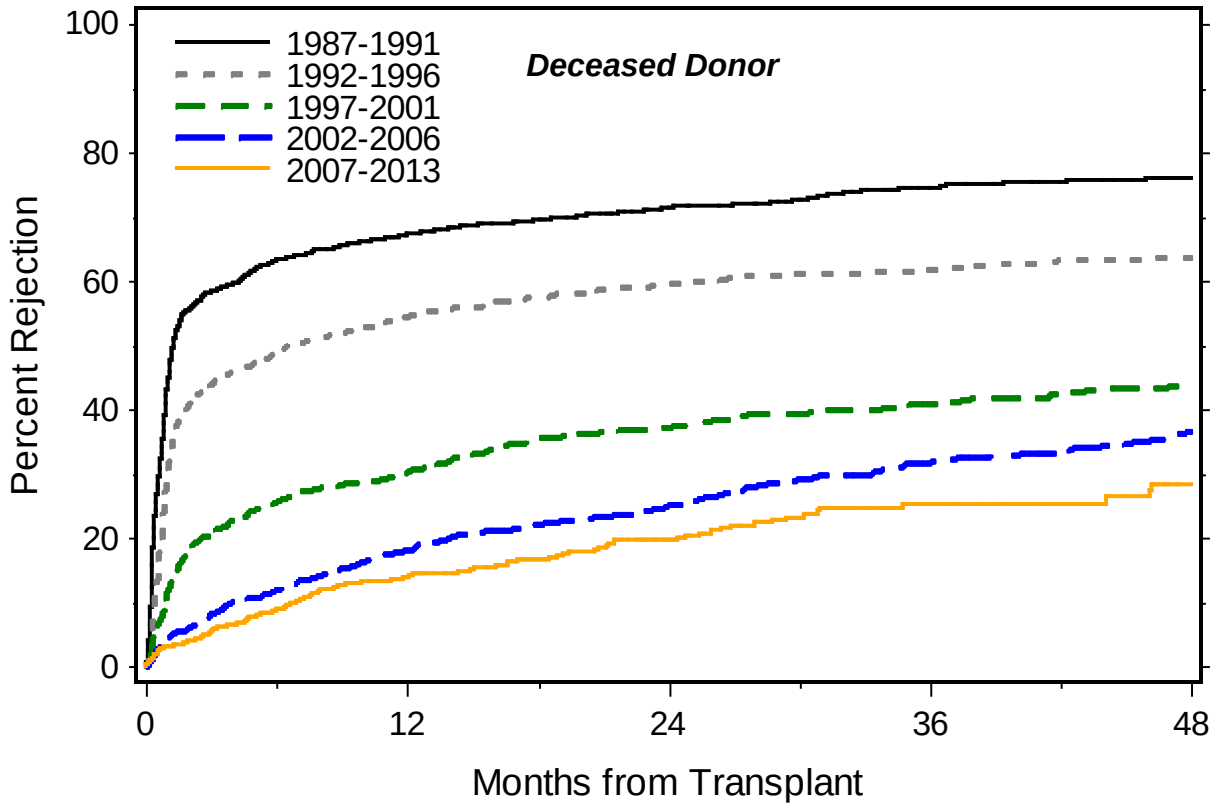


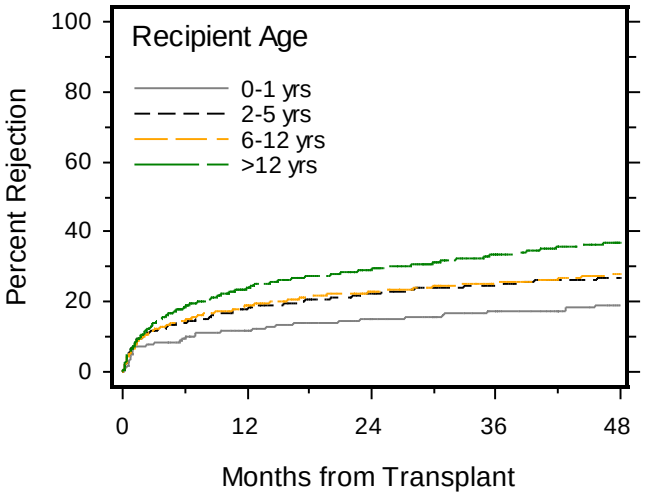
EXHIBIT 4.3
RELATIVE HAZARD (HR) OF FIRST REJECTION EPISODE
INDEX TRANSPLANTS

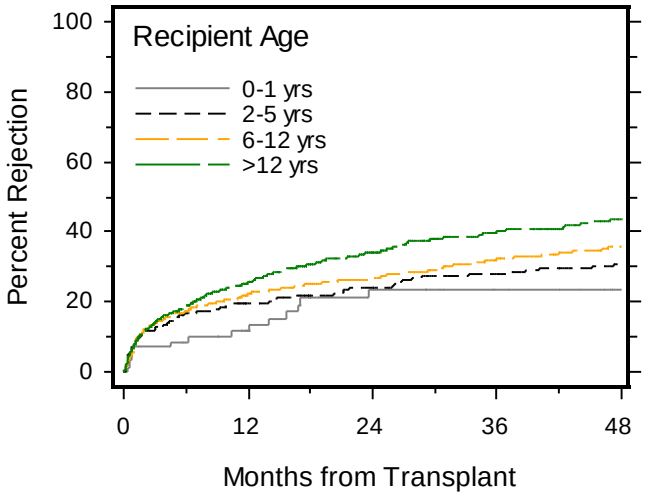
Characteristic	Comparison Group	Reference Group	Living Donor		Deceased Donor	
			RH	p-value	RH	p-value
Transplant Era 1987-1995						
Recipient Race	Black	Non-black	1.33	<0.001	1.28	<0.001
Recipient Age	<24 months	≥24 months	0.73	0.006	1.15	0.380
Induction therapy	No	Yes	1.22	<0.001	1.20	<0.001
Prior random transfusions	1-5 >5	None	0.95 1.08	0.405 0.350	0.91 0.96	0.194 0.588
Donor specific transfusions	Yes	No	0.91	0.277	--	--
Pre-op Immunotherapy	Yes	No	0.96	0.497	--	--
Cold storage time	>24 hours	≤24 hours	--	--	0.98	0.711
Transplant year	1987-1995		0.94	<0.001	0.93	<0.001
Transplant Era 1996-2004						
Recipient Race	Black	Non-black	1.09	0.432	1.41	<0.001
Recipient Age	<24 months	≥24 months	0.53	<0.001	0.42	0.087
Induction therapy	No	Yes	1.14	0.075	0.85	0.095
Prior random transfusions	1-5 >5	None	1.04 0.97	0.646 0.811	0.98 0.90	0.853 0.513
Donor specific transfusions	Yes	No	0.52	0.063	--	--
Pre-op Immunotherapy	Yes	No	1.06	0.455	--	--
Cold storage time	>24 hours	≤24 hours	--	--	1.12	0.375
Transplant year	1996-2004		0.92	<0.001	0.90	<0.001
Transplant Era 2005-2013						
Recipient Race	Black	Non-black	1.17	0.601	1.31	0.099
Recipient Age	<24 months	≥24 months	0.30	0.040	1.50	0.247
Induction therapy	No	Yes	0.82	0.339	1.04	0.824
Prior random transfusions	1-5 >5	None	0.75 1.36	0.295 0.388	1.32 1.10	0.127 0.769
Donor specific transfusions	Yes	No	2.21	0.277	--	--
Pre-op Immunotherapy	Yes	No	0.81	0.298	--	--
Cold storage time	>24 hours	≤24 hours	--	--	1.05	0.880
Transplant year	2005-2013		0.96	0.382	0.83	<0.001

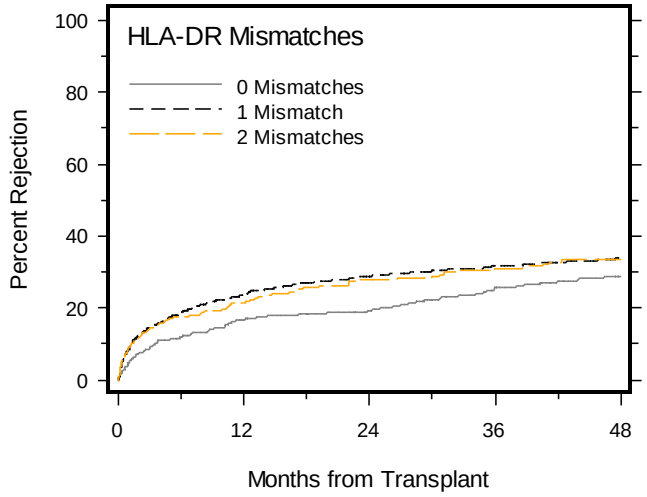
Note: HLA-DR Mismatches have been excluded from the model due to the number of missing values.

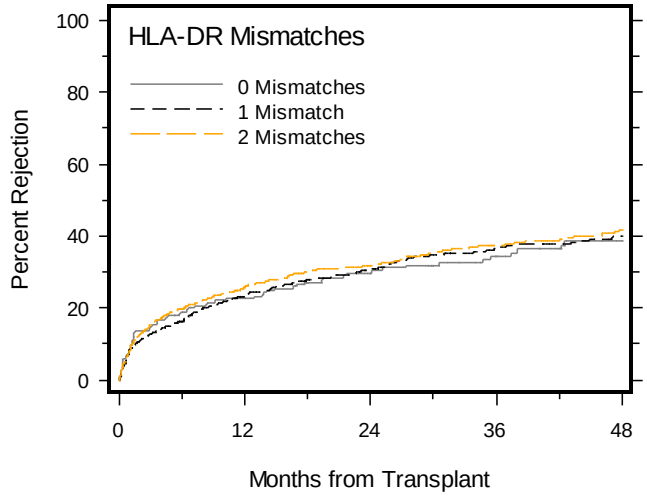
EXHIBIT 4.4
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS 1996-2013

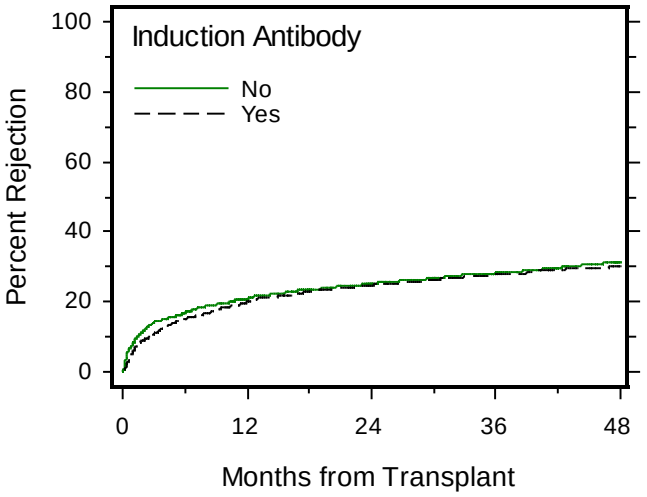
Living Donor | ***Deceased Donor***











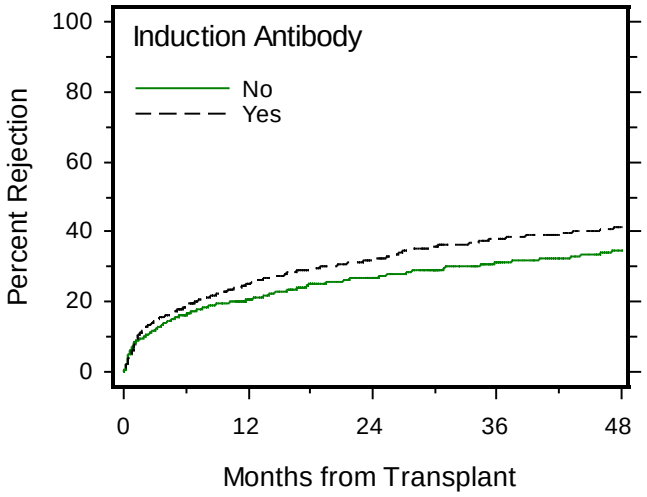
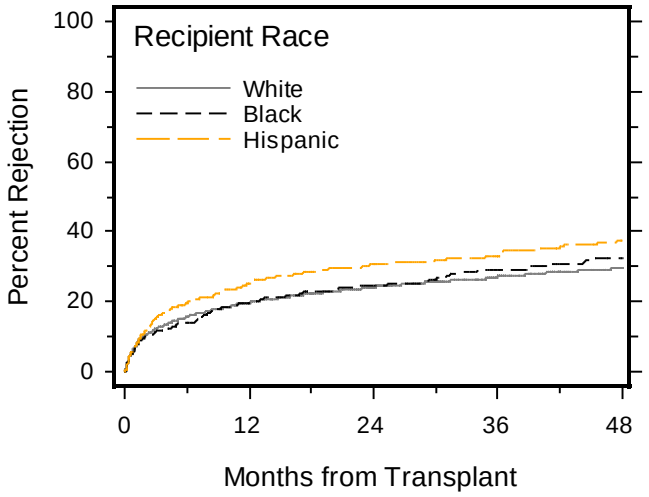
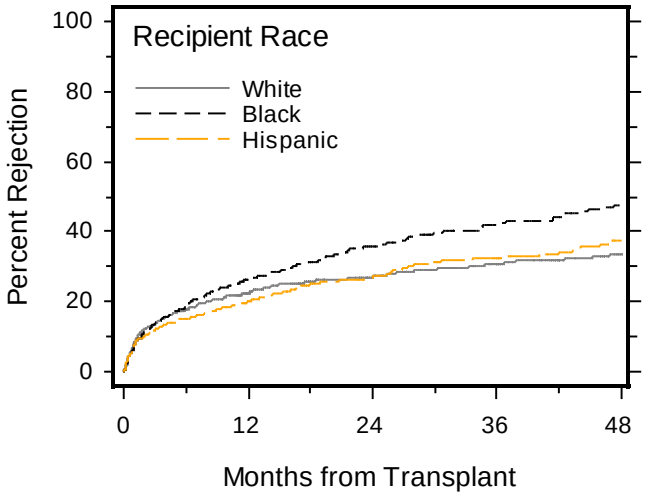
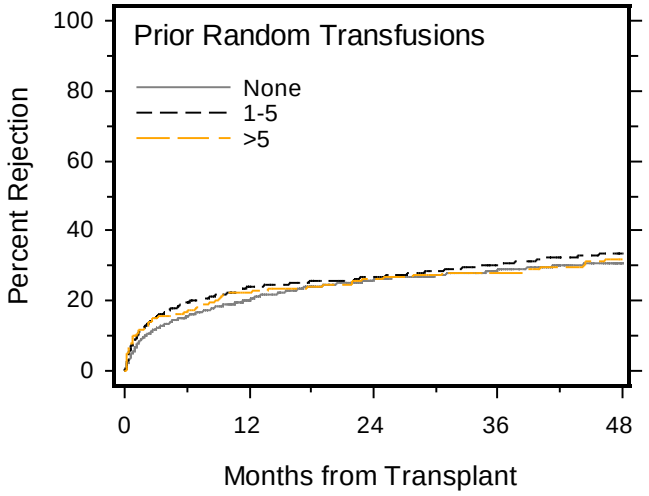


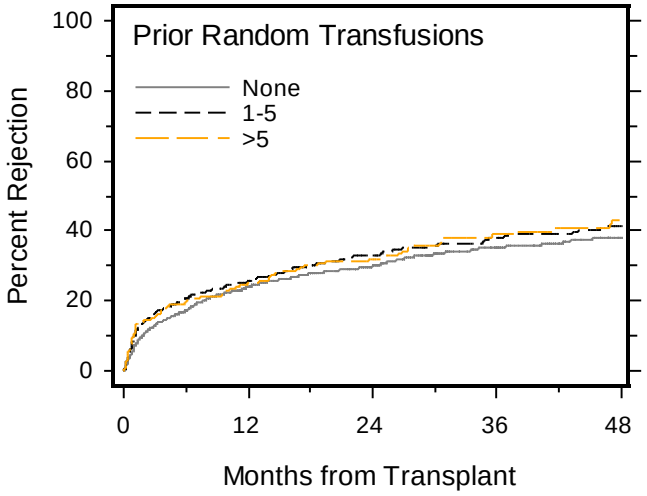
EXHIBIT 4.4 (continued)
TIME TO FIRST REJECTION FOR INDEX TRANSPLANTS 1996-2013

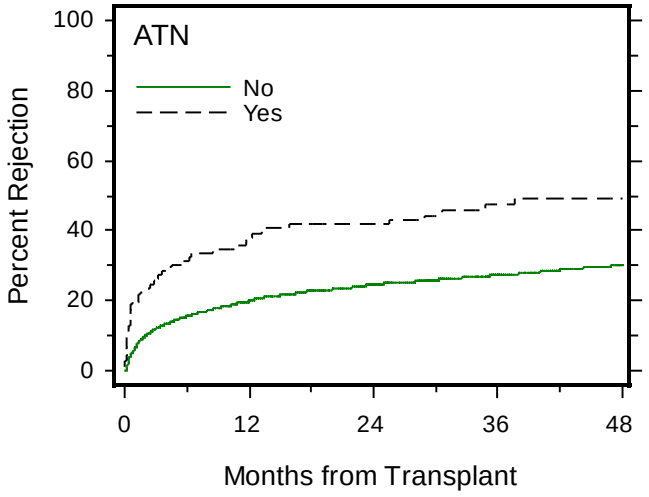
Living Donor | ***Deceased Donor***

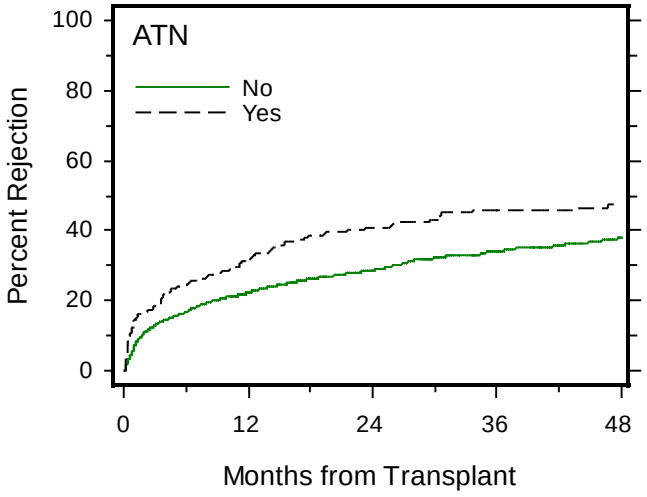












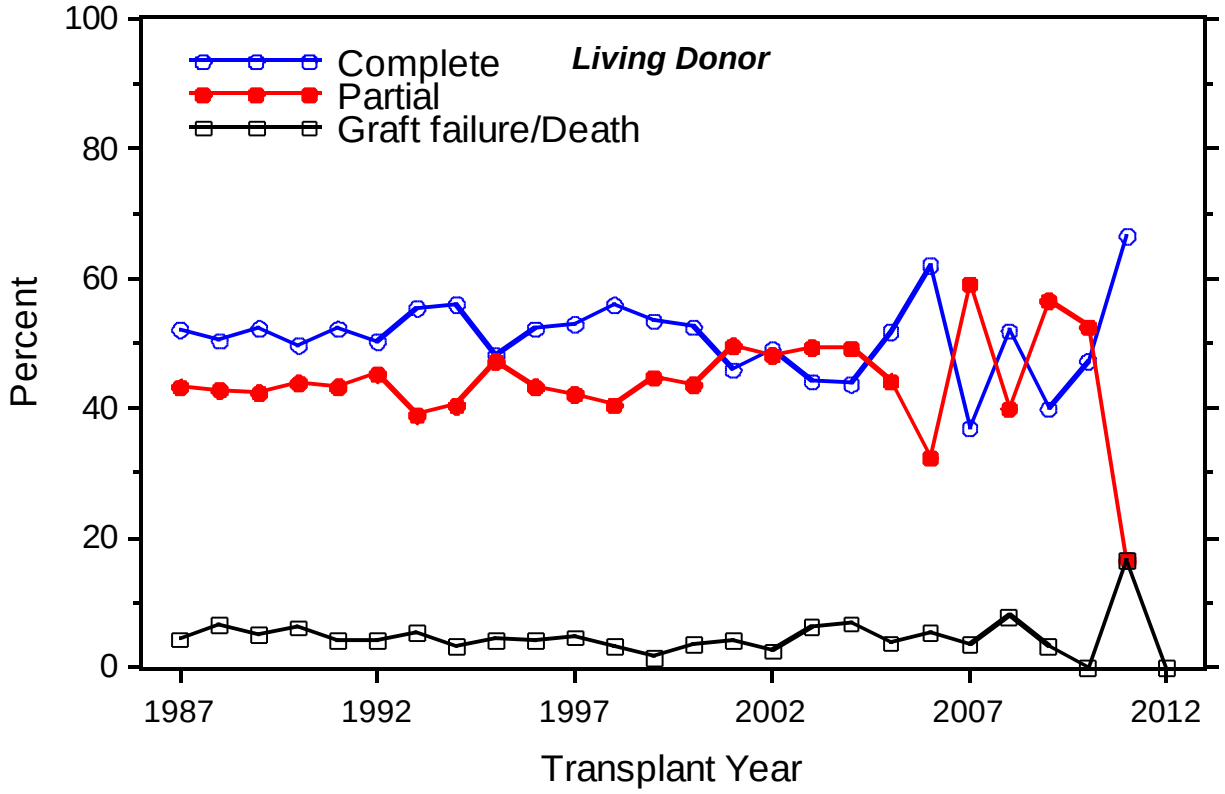
EXIHIBIT 4.5A
REJECTION REVERSAL OUTCOME BY PATIENT CHARACTERISTICS

	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	4544	51.6	43.8	4.6	6012	45.0	48.3	6.7
Rejection Number								
1	2435	59.1	36.1	4.8	2924	53.9	38.0	8.1
2	1110	45.4	49.8	4.8	1465	44.2	50.6	5.2
3	508	42.7	53.9	3.3	790	32.9	61.6	5.4
≥4	491	37.7	58.2	4.1	833	26.9	67.9	5.2
Recipient Age								
0-1 years	195	63.1	27.9	7.2	114	54.4	33.3	12.3
2-5 years	670	57.9	37.6	4.5	793	55.0	38.7	6.3
6-12 years	1697	51.3	44.8	3.9	2115	45.5	47.8	6.8
> 12 years	1982	48.6	46.5	4.9	2990	41.7	51.8	6.5
Biopsy								
No	1504	58.5	38.1	3.4	2182	48.2	46.9	4.9
Yes-needle	1455	48.1	48.2	3.6	1630	40.1	53.9	6.0
Yes-tissue	1548	49.2	46.0	4.8	2131	46.8	46.8	6.4
D-R Antigen								
0 mismatch	661	51.9	43.6	4.5	703	45.4	49.2	5.4
1 mismatch	3058	52.6	43.0	4.4	2372	44.1	49.6	6.2
2 mismatch	429	44.1	51.7	4.2	2379	44.7	48.0	7.4
Missing	396	51.3	42.2	6.6	558	49.8	43.2	7.0
Induction Antibodies								
No	2590	51.7	43.1	5.3	2394	45.4	47.7	6.9
Yes	1954	51.5	44.8	3.7	3618	44.8	48.7	6.5
Transplant Era								
1987-1995	2938	51.9	43.2	4.9	4143	46.8	46.1	7.1
1996-2004	1409	51.1	44.9	4.0	1462	40.7	53.6	5.7
2005-2013	197	50.3	45.2	4.6	407	42.8	51.6	5.7

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	2435	59.1	36.1	4.8	2924	53.9	38.0	8.1
Rejection Number								
1	2435	59.1	36.1	4.8	2924	53.9	38.0	8.1
Recipient Age								
0-1 years	130	64.6	25.4	10.0	72	61.1	22.2	16.7
2-5 years	369	65.9	28.5	5.7	376	62.0	28.5	9.6
6-12 years	865	59.2	35.8	5.0	1025	53.5	37.7	8.9
> 12 years	1071	56.0	40.1	3.8	1451	51.7	41.5	6.8
Biopsy								
No	787	69.6	27.7	2.7	969	60.7	33.5	5.8
Yes-needle	804	55.2	41.3	3.5	830	47.8	46.1	6.0
Yes-tissue	813	54.7	40.3	4.9	1062	55.4	37.7	7.0
D-R Antigen								
0 mismatch	343	58.6	36.4	5.0	316	56.6	36.1	7.3
1 mismatch	1627	60.5	35.0	4.5	1121	54.3	38.9	6.8
2 mismatch	214	51.9	43.9	4.2	1155	52.3	38.1	9.6
Missing	251	56.6	35.9	7.6	332	55.1	36.4	8.4
Induction Antibodies								
No	1364	59.3	34.8	5.9	1171	55.9	35.6	8.5
Yes	1071	58.8	37.6	3.5	1753	52.5	39.6	7.9
Transplant Era								
1987-1995	1443	60.4	34.0	5.7	1894	56.1	34.7	9.2
1996-2004	855	57.8	38.9	3.3	775	49.0	44.9	6.1
2005-2013	137	54.0	40.1	5.8	255	52.2	41.6	6.3

EXHIBIT 4.6
REJECTION REVERSAL OUTCOME



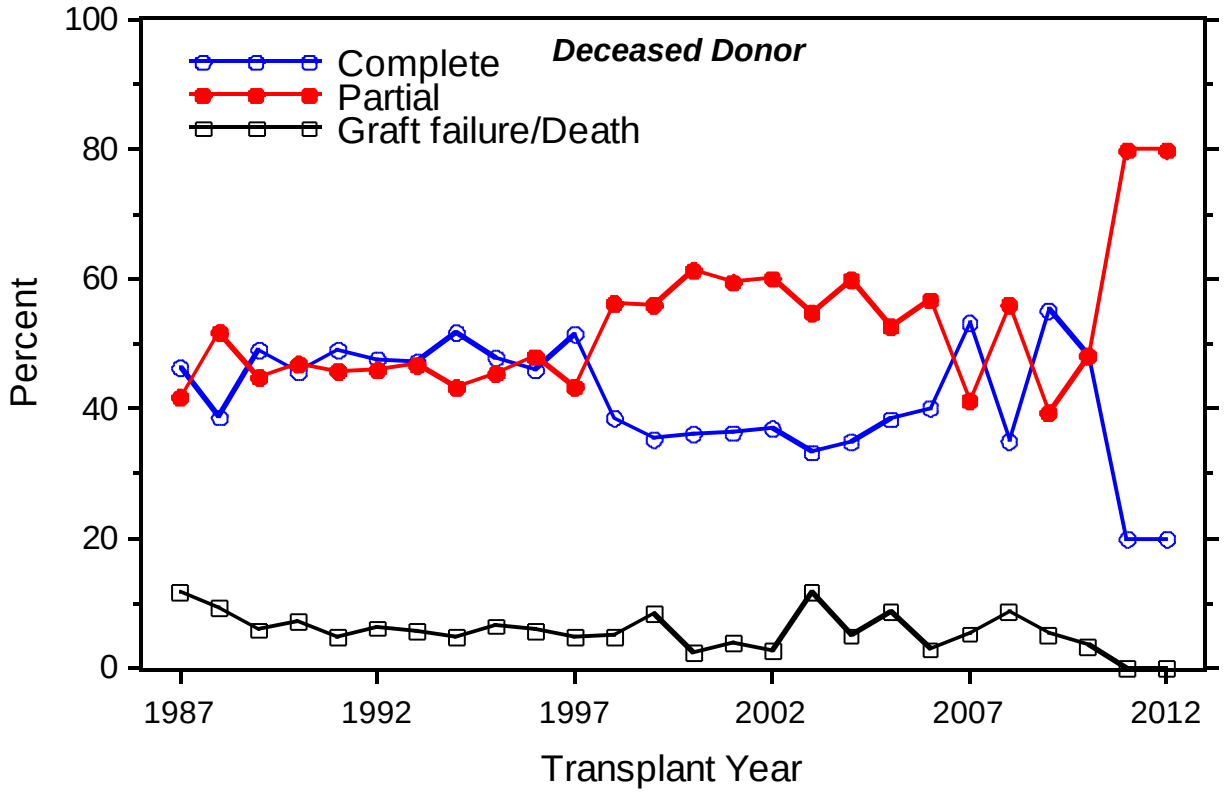


EXHIBIT 4.7
LATE FIRST REJECTIONS BY SELECTED CHARACTERISTICS

Patient Characteristics	No. of Transplants	No. of Rejections	Percent Rejection
Total	6221	1210	19.5
Donor source			
Living Donor	3460	611	17.7
Deceased Donor	2719	595	21.9
Age			
0-1 years	380	43	11.3
2-5 years	957	170	17.8
6-12 years	2102	476	22.6
> 12 years	2782	521	18.7
Sex			
Male	3668	697	19.0
Female	2553	513	20.1
Race			
White	3767	671	17.8
Nonwhite	2454	539	22.0

Late Rejection Outcome	No. of Rejections	Percent
Total	1210	100.0
Rejection outcome		
Unknown	27	2.2
Complete	458	37.9
Partial	653	54.0
Graft failure/Death	72	6.0

SECTION 5: GRAFT FUNCTION

A total of 3,045 graft failures among 12,189 (25.0%) transplants have occurred. This includes 307 patients who have lost 2 or more grafts since the study's start, of which 30 subjects had 3 graft failures and 3 had 4 graft failures. Of index transplants, 2,702 of 11,186 (24.2%) transplants have failed, while 343 of 1,003 (34.2%) subsequent transplants have failed. Of these 3,045 failures, 276 (9.1%) were deaths with functioning graft. In the remaining failures (with known determination), graft failure was determined by a return to dialysis in 84% and a retransplant in 8%. Exhibit 5.1 provides the distribution of graft failure causes. Note that tissue confirmation of cause was obtained in 1,670 (60%) failures. Of the index graft failures occurring since January 1, 2000, chronic rejection accounted for 40.5% (412/1,018) while 104 (10.2%) were acute rejection graft failures, (plus 2 hyper acute and 3 accelerated acute rejections), 58 (5.7%) cases discontinued medication, 67 (6.6%) failed from graft thrombosis, 79 (7.8%) had disease recurrences, and 85 (8.4%) 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, 50.7% of all graft failures are caused by rejection, with chronic rejection accounting for 35.8% and acute rejection accounting for 13.0% of the failures. Recurrence of original disease as a cause of graft failure has been observed 212 times as follows: focal segmental glomerulosclerosis (102), membranoproliferative glomerulonephritis Type II (18), hemolytic uremic syndrome (18), oxalosis (10), chronic glomerulonephritis (7), others (57). Vascular thrombosis remains a major cause of failure; 390 graft failures are attributed to primary non-function, vascular thrombosis, or miscellaneous technical causes, suggesting that such problems will occur in 3.2% 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 7.4% of living donor versus 10.5% of deceased source transplants and respective failure rates due to primary non-function are 0.4% versus 0.7% while those for thrombosis are 1.8% versus 3.0%.

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 4.6 and 3.9 years. Estimated graft survival probabilities are 94%, 88%, 83% and 77% 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 88%, 78%, 71% and 63%. Notice from Exhibit 5.2, that deceased donor source transplants in the 1996-2004 cohort have a graft survival experience very similar to that of living donor transplant from the 1987-1995 era and the more recent deceased donor transplants (2005-2013) do even better. The graft survival in 1996-2004 and 2005-2013 cohorts are significantly better than the 1987-1995 cohort for both deceased donor source ($p<0.001$) and living donor grafts ($p<0.001$). Deceased donor grafts continue to show improvement from 1996-2004 to 2005-2013, while the living donor transplants graft survival experience is similar in these 2 cohorts. 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 for graft failure in the presence of other factors in multivariate proportional hazards models.

Graft Failure
Multivariate Proportional Hazards Regression Model

Characteristic	Comparison Group	Reference Group	Living Donor		Deceased Donor	
			HR	p-value	HR	p-value
Recipient Age	≥ 24 months	<24 months	1.24	0.054	0.70	0.009
Transplant History	Prior transplants	No prior tx's	1.51	<0.001	1.45	<0.001
Induction Therapy	Induction	No induction	0.82	0.001	0.94	0.225
Transfusion History	>5	≤ 5	1.22	0.016	1.23	0.001
Recipient Race	Black	Non-black	1.89	<0.001	1.60	<0.001
Dialysis History	Prior dialysis	No prior dialysis	1.17	0.028	1.20	0.048
Cold Storage Time	>24 hours	≤ 24 hours	--	--	1.14	0.029
Native Nephrectomy	Not removed	Tissue removed	0.86	0.025	0.93	0.235
Gender	Male	Female	0.88	0.034	0.84	0.002
Transplant Year	Per year 1987-2010		0.96	<0.001	0.95	<0.001

Note: HLA-B and HLA_DR Mismatches have been excluded from the model due to the number of missing values.
HR=hazard ratio

For recipients of living donor grafts, the most influential prognostic variables (of index transplant graft survival) are race (black vs. non-black; HR=1.89, $p<0.001$), prior transplant (HR=1.51, $p<0.001$) and induction antibody therapy (HR=0.82, $p=0.001$). A linear trend in improvement in graft retention with later year of entry is also observed (HR=0.96 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; HR=1.60, p<0.001), prior transplant (HR=1.45, p<0.001), transfusion history (HR=1.23, p=0.001) and male gender (HR=0.84, p=0.002). The model includes a linear term for year of transplant, whose estimated relative risk increase implies a decreasing hazard (HR=0.95 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 seen from the earliest 1987-1991 cohort to the 1992-1996 cohort and from 1992-1996 to 1997-2001 in both living and deceased donor transplants. Not much improvement is seen in graft survival after 1997 with the 2002-2006 and 2007-2013 cohorts showing graft survival similar to the 1997-2001 cohort in living donor transplants. Deceased donor transplants also show similar rates in the 1997-2001 and 2002-2006 cohorts, but while follow-up is shorter and data is still accruing the results show some improvement in the 2007-2013 cohort. The following table displays graft survival percentages for the various cohorts. (Standard errors range from 0.5% to 1.0% at 1 year and 1.1% to 1.4% at 5 years for living donor, and from 0.8% to 1.2% at 1 year and 1.4 to 1.8% 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
1987-1991	90.3	82.4	76.3	76.4	65.3	56.9
1992-1996	92.1	87.0	81.6	87.0	77.9	70.9
1997-2001	95.4	91.4	86.3	93.1	84.5	78.3
2002-2006	96.3	92.0	86.4	94.4	84.1	79.2
2007-2013	96.4	93.4	--	95.8	90.4	--

Exhibit 5.7 shows graft survival for HLA-A, HLA-B and HLA-DR mismatches for living and

deceased donors. Living donors and deceased donors show a graft survival advantage for patients with no HLA-B mismatches. Living donors show also show a slight advantage for patients with no HLA-DR 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 71% and patients with GN have a 5 year rate of 77%. All other shown categories of primary diagnoses for living donors have a 5 year graft survival rate above 84%. In the deceased donor group, 5 year graft survival rates are between 63% and 67% for GN, FSGS, CNS and HUS and between 73% and 74% for congenital/structural, renal infarct, and cystinosis. Familiai nephritis diagnosis has 5-year graft survival rate around 69%.

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 5.0% of index living donor transplants which is significantly less than the ATN rate reported for deceased donor source transplants (15.2%). Living donor transplants report little change in ATN rates over the life of the registry (5.1% in 1987-1995, 5.1% in 1996-2004 and 4.2% in 2005-2013), while deceased donor transplants show a decrease in rates over time with 17.9% in 1987-1995, 14.5% in 1996-2004 and 10.3% in 2005-2013.

Among the living donor transplants, increased rates of ATN are noted with >5 prior transfusions (10.8%), black race (7.8%), infants <24 months (7.6%), prior transplants (7.4%), children with a native nephrectomy (7.1%) and children receiving prior dialysis (6.8%). These factors continue to be significant in a multivariate logistic regression model with prior dialysis (OR=4.3) and >5 prior transfusions (OR=1.9) highly significant at $p<0.001$. Black race (OR=1.7, p=0.003), history of prior transplant (OR=1.5, p=0.016) and native nephrectomy (OR=1.3, p=0.039) are also still important risk factors. Infants <24 months (OR=1.5, p=0.054) is of borderline significance in the multivariate model.

For transplants with deceased donor source organs, the ATN rate increases significantly with several factors: >5 transfusions (27.5%), cold ischemia times >24 hours (23.9%), prior transplant (21.6%), native nephrectomy (21.3%), and black recipients (20.4%). Donor (Age <2 years, 23.2%), donor age ($\geq$50 years, 28.3%) and prior dialysis (17.3%) also had higher rates of

ATN. The ATN rate differs for Collins iced electrolyte solution (21.3%) versus Wisconsin solution (15.2%), but not with use of machine perfusion (14.5%). In a multivariate logistic regression analysis, the following variables were significantly predictive of ATN risk in deceased donor graft recipients: prior dialysis (OR=15.9, p<0.001), older donor age (OR=2.1, p<0.001), cold time ≥ 24 hours (OR=1.9, p<0.001), >5 prior transfusions (OR=1.9, p<0.001), black race (OR=1.8, p<0.001), prior transplant (OR=1.5, p<0.001) and native nephrectomy (OR=1.3, p=0.008).

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 85.2% for grafts without ATN and 64.3% for grafts with ATN (log-rank p<0.001). ATN is significant in the multivariate proportional hazards regression analysis (RH=2.25, p<0.001) along with race, recipient age <24 months, transplant history, induction therapy and transplant year. Transfusion history, HLA-B matches, dialysis history, native nephrectomy and gender are no longer predictive after adjustment for first week results. Among functioning deceased donor grafts at 1 week, 75.5% of subjects without first week dialysis are estimated to be functioning at 5 years as opposed to 56.6% 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=1.65, p<0.001), race, transplant history, recipient age <24 months, HLA-B matches, gender, and transplant year. Transfusion history is a borderline significance (p=0.046) and HLA-DR mismatches, cold storage time and dialysis history are not predictive 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.)

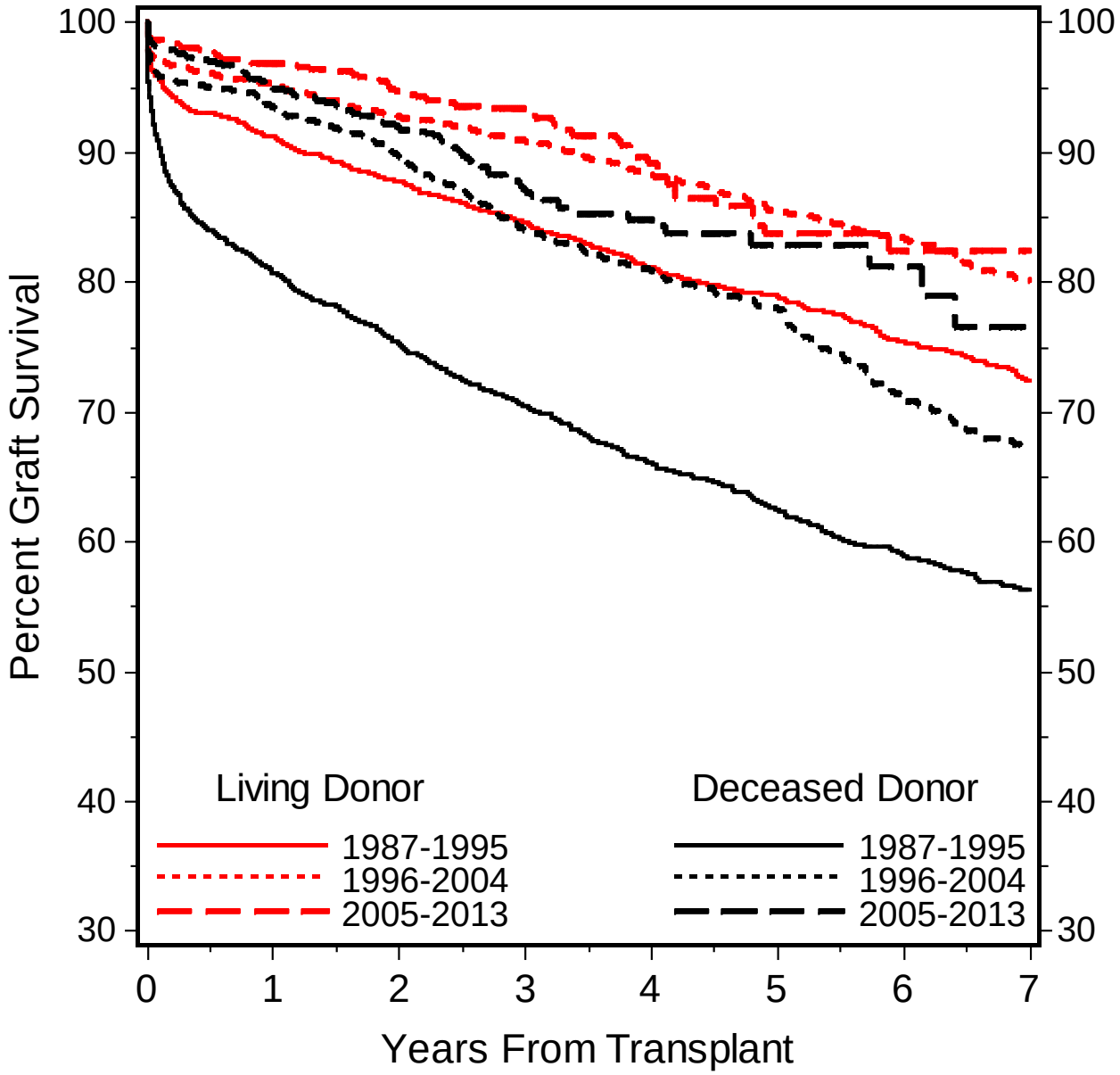
In Exhibits 5.12 - 5.14, graft survival percentage and mean calculated clearance values for subjects with functional grafts are plotted at each annual follow-up visit for various groups, including donor source, transplant year, race and induction antibody therapy use. Continued decreases in both graft survival and graft function are seen through the first five post-transplant years. Temporal improvements in median creatinine clearance accompany the improvements seen in graft survival. In Exhibit 5.12, improvements in calculated clearance levels are evident in the post 2005 cohort, relative to earlier cohorts.

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	2702	100.0	343	100.0	3045	100.0
Cause of Graft Failure						
Death with functioning graft	249	9.2	27	7.9	276	9.1
Primary non-function	63	2.3	2	0.6	65	2.1
Vascular thrombosis	252	9.3	39	11.4	291	9.6
Other technical	30	1.1	4	1.2	34	1.1
Hyper-acute rejection	15	0.6	4	1.2	19	0.6
Accelerated acute rejection	33	1.2	8	2.3	41	1.4
Acute rejection	352	13.0	44	12.8	396	13.0
Chronic rejection	960	35.5	129	37.6	1089	35.8
Recurrence of original kidney disease	179	6.6	33	9.6	212	7.0
Renal artery stenosis	15	0.6	0	0.0	15	0.5
Bacterial/viral infection	47	1.7	6	1.8	53	1.7
Cyclosporine toxicity	13	0.5	0	0.0	13	0.4
De novo kidney disease	8	0.3	2	0.6	10	0.3
Patient discontinued medication	125	4.6	8	2.3	133	4.4
Malignancy	34	1.3	2	0.6	36	1.2
Other/Unknown	327	12.1	35	10.2	362	11.9

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
LD: 1987 - 1995	91.2	0.59	84.6	0.76	78.9	0.89	72.4	1.05
LD: 1996 - 2004	95.2	0.43	90.9	0.61	85.6	0.84	80.2	1.11
LD: 2005 - 2013	96.9	0.62	93.4	1.02	83.8	2.32	82.4	2.65
DD: 1987 - 1995	80.7	0.81	70.5	0.96	62.4	1.06	56.3	1.15
DD: 1996 - 2004	93.5	0.61	84.1	0.99	78.1	1.23	67.3	1.73
DD: 2005 - 2013	95.0	0.68	87.3	1.34	83.0	1.92	76.6	3.99

EXHIBIT 5.3
GRAFT FAILURE SUMMARY BY SELECTED TRANSPLANT CHARACTERISTICS

	Living Donor (N=5819)				**Deceased Donor** (N=5298)			
	% 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	20.1	82.7	0.58	100.0	28.8	70.8	0.75
Sex								
Male	60.3	19.5	83.8	0.72	57.7	27.9	72.7	0.97
Female	39.7	21.1	80.9	0.96	42.3	30.1	68.1	1.20
Race								
White	68.7	19.8	84.1	0.67	48.7	28.2	74.3	0.99
Black	11.0	30.7	72.5	2.05	23.8	34.1	60.8	1.75
Hispanic	15.8	16.0	83.1	1.54	18.3	26.1	69.7	1.94
Other	4.5	13.7	85.8	2.74	9.3	23.5	76.3	2.31
Transplant History								
No prior tx	88.7	19.1	83.0	0.61	83.0	26.9	72.5	0.81
Prior tx	11.3	28.1	80.6	1.80	17.0	38.3	62.8	1.91
Dialysis History								
No prior dialysis	33.0	16.3	86.5	0.93	13.1	22.0	79.5	1.80
Prior dialysis	67.0	22.0	80.8	0.73	86.9	29.8	69.4	0.82
Recipient Age								
0-1 years	8.1	20.8	84.2	1.81	3.3	39.0	62.5	4.38
2-5 years	16.2	24.1	85.9	1.23	13.8	34.7	74.5	1.77
6-12 years	32.9	22.1	84.4	0.92	32.8	32.1	73.0	1.19
>12 years	42.8	17.0	78.7	1.08	50.1	24.3	67.5	1.25
Donor Age								
<2 years	--	--	--	--	1.4	55.1	51.4	6.41
2-17 years	--	--	--	--	36.5	33.2	68.0	1.27
18-49					56.5	25.9	73.2	1.04
≥50 years	--	--	--	--	5.6	40.8	57.9	3.70
Cold Ischemia Time								
≤24 hours	--	--	--	--	75.1	27.2	71.5	0.94
>24 hours	--	--	--	--	24.9	40.9	62.6	1.59

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

	Living Donor (N=5819)				Deceased Donor (N=5298)			
	% 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	--	--	--	--	75.6	30.2	70.2	0.88
Yes	--	--	--	--	11.9	36.2	62.1	2.44
Unknown	--	--	--	--	12.5	20.3	78.3	2.11
HLA-A Mismatches								
0	16.5	20.4	82.7	1.41	8.3	29.9	72.7	2.45
1	63.6	22.1	82.0	0.72	33.5	31.6	69.4	1.27
2	5.2	20.4	79.6	2.83	41.7	30.9	69.0	1.19
Missing	14.6	11.2	87.3	1.46	16.5	17.4	77.7	1.91
HLA-B Mismatches								
0	11.7	18.5	85.3	1.56	7.3	26.0	75.7	2.52
1	66.5	22.0	82.0	0.71	27.1	32.3	70.0	1.41
2	7.2	23.3	75.7	2.69	49.1	31.1	68.4	1.09
Missing	14.6	11.2	87.3	1.46	16.6	17.5	77.5	1.90
HLA-DR Mismatches								
0	15.7	20.0	84.7	1.38	10.0	30.3	70.5	2.34
1	59.7	21.9	81.6	0.76	35.9	30.5	69.8	1.25
2	7.9	22.5	80.1	2.25	36.4	31.4	69.6	1.23
Missing	16.7	12.7	86.4	1.37	17.7	19.2	76.0	1.87
Pre-operative immunosuppression								
No	51.1	18.3	83.9	0.81	--	--	--	--
Yes	48.1	22.8	81.0	0.86	--	--	--	--
Native Nephrectomy								
No	73.3	18.6	83.3	0.68	79.9	27.6	71.4	0.85
Yes	26.7	24.7	80.9	1.13	20.1	35.8	66.4	1.72
Lifetime Transfusion								
0	53.9	16.6	84.2	0.83	43.4	21.6	75.9	1.19
1-5	34.9	22.4	83.6	0.95	36.3	30.2	71.9	1.24
>5	11.2	33.6	72.1	1.97	20.3	46.7	57.4	1.73

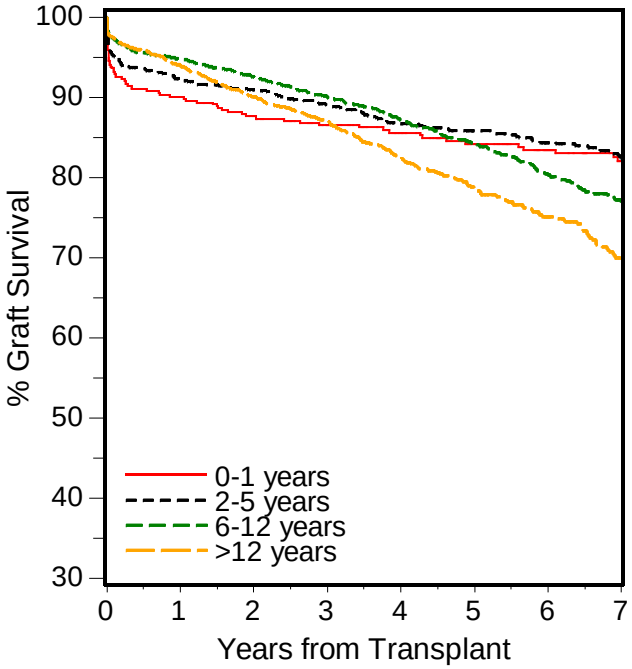
EXHIBIT 5.3 (continued)
GRAFT FAILURE SUMMARY BY SELECTED TRANSPLANT CHARACTERISTICS

	Living Donor (N=5819)				**Deceased Donor** (N=5298)			
	% of Total	% Failing	5 year Graft Survival	5 year rate SE	% of Total	% Failing	5 year Graft Survival	5 year rate SE
Induction Antibody								
No	52.7	21.9	80.8	0.83	42.3	29.3	69.1	1.18
Yes	47.3	18.1	84.9	0.80	57.7	28.4	71.9	0.98

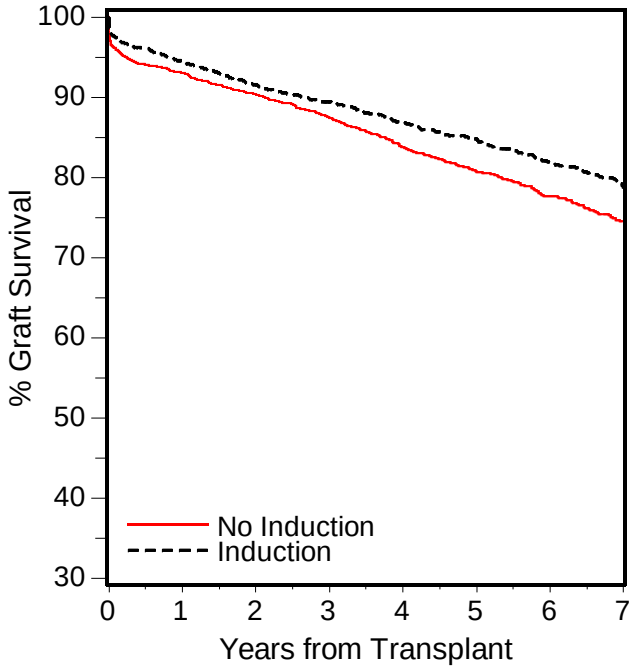
EXHIBIT 5.4
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Living Donor

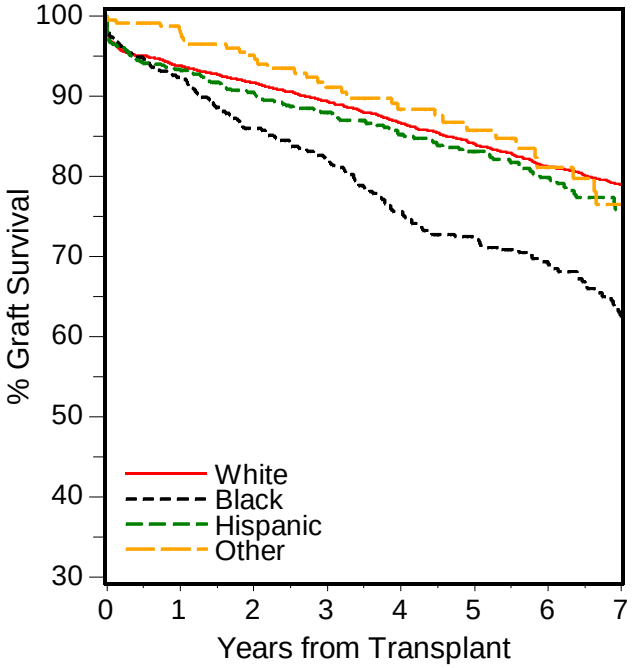
Recipient Age



Induction Antibody



Recipient Race



Transfusion History

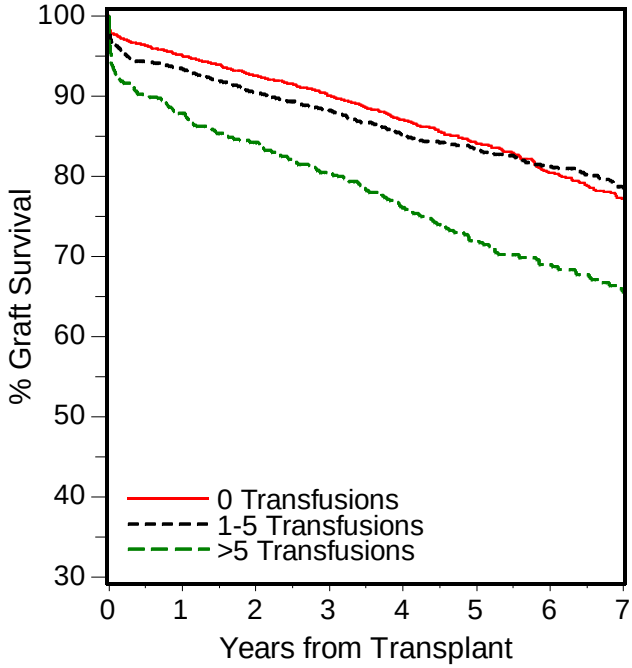
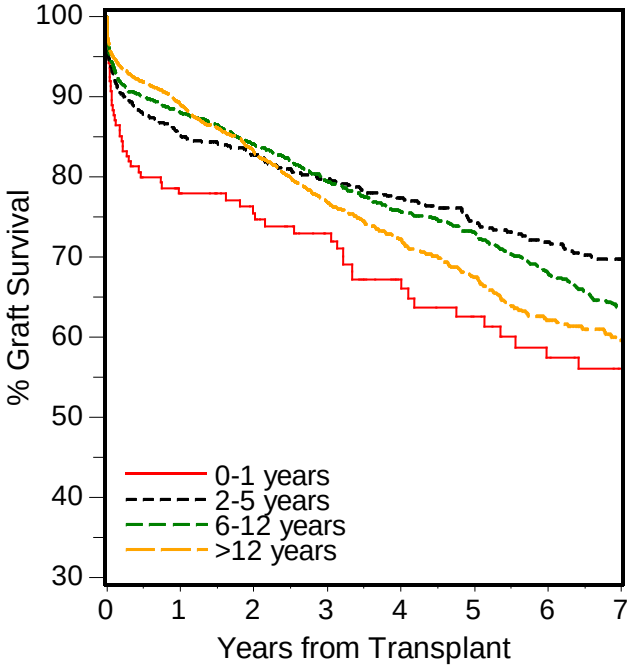


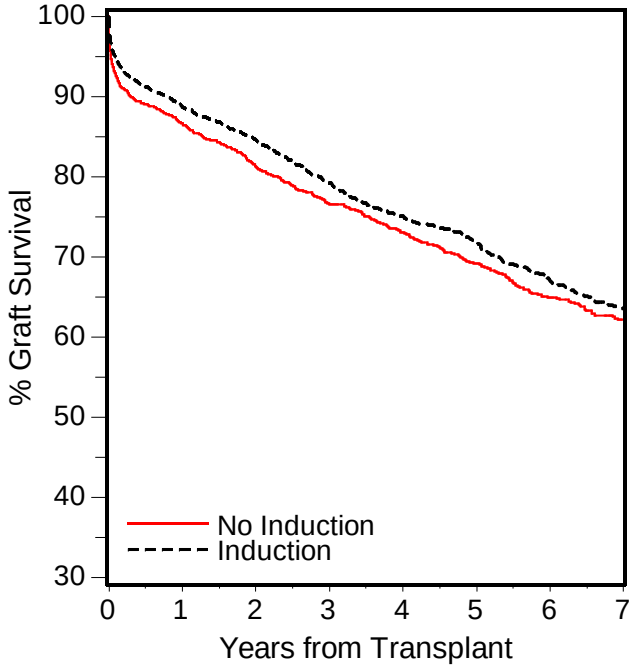
EXHIBIT 5.5
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Deceased Donor

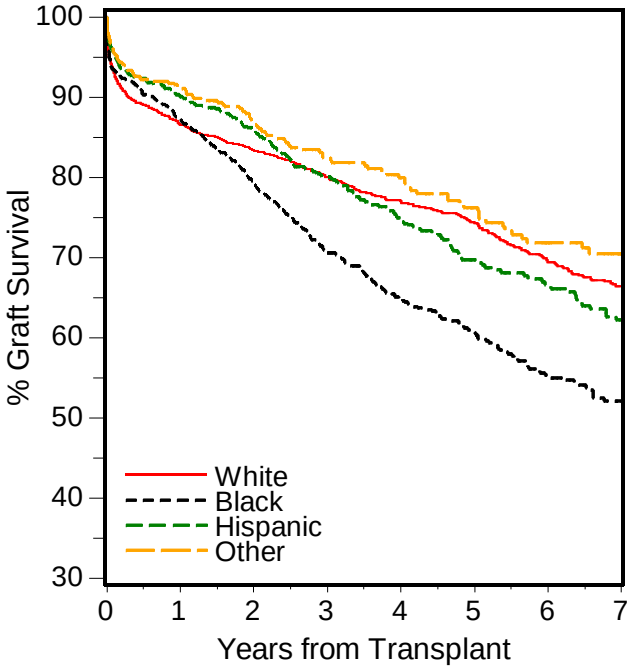
Recipient Age



Induction Antibody



Recipient Race



Transfusion History

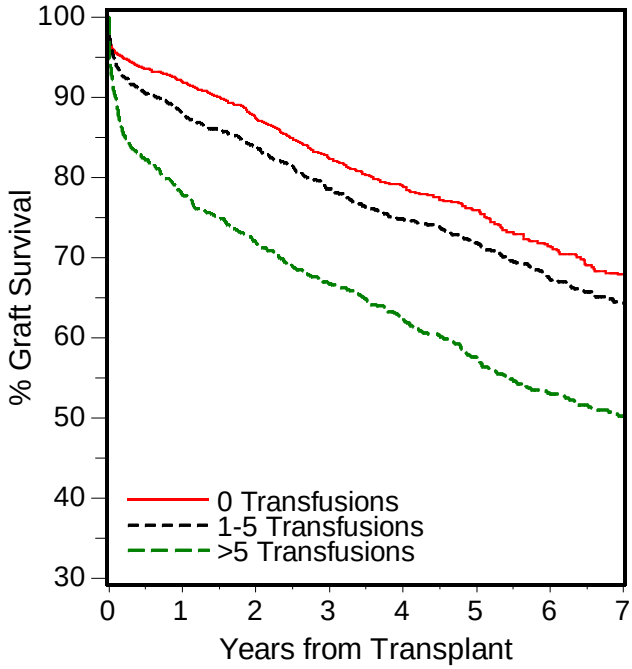
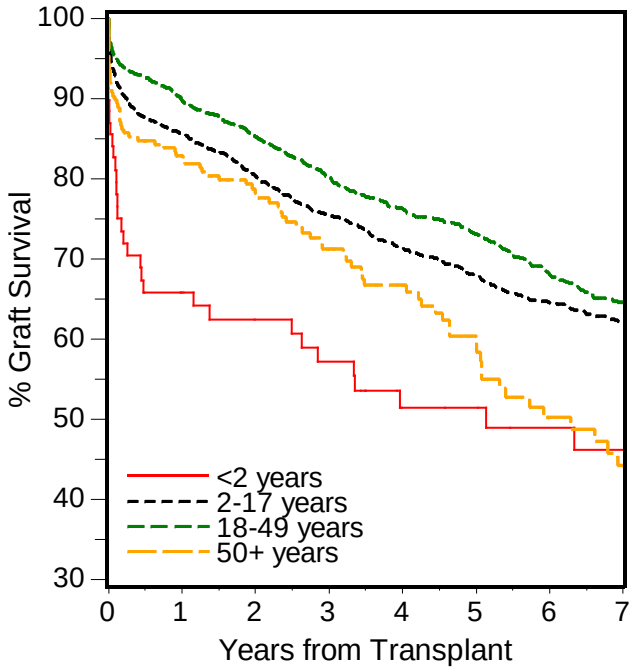


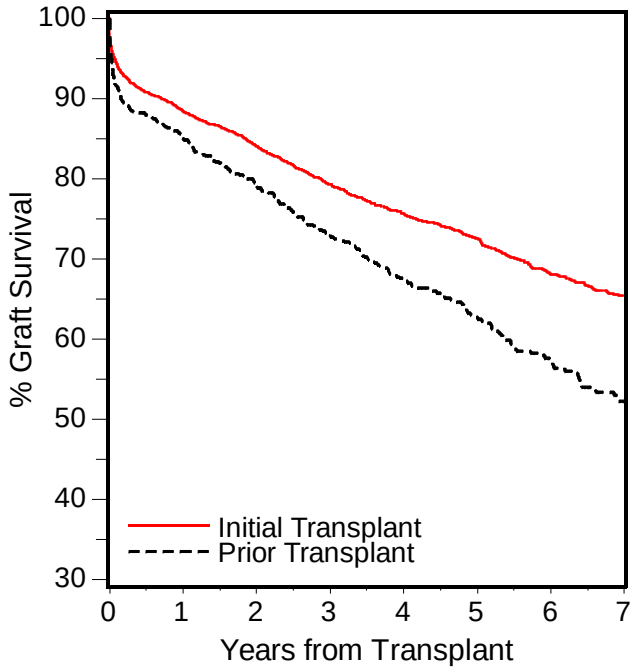
EXHIBIT 5.5 (continued)
GRAFT SURVIVAL BY SELECTED CHARACTERISTICS

Deceased Donor

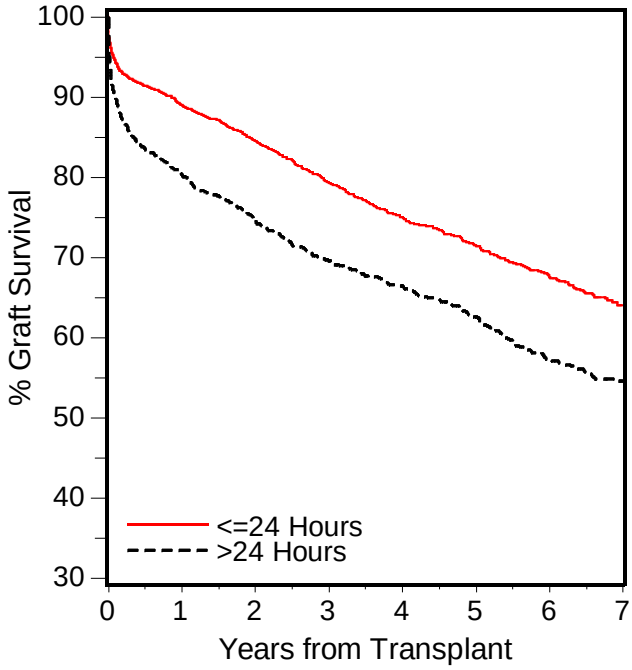
Donor Age



Transplant History



Cold Ischemia Time



Dialysis History

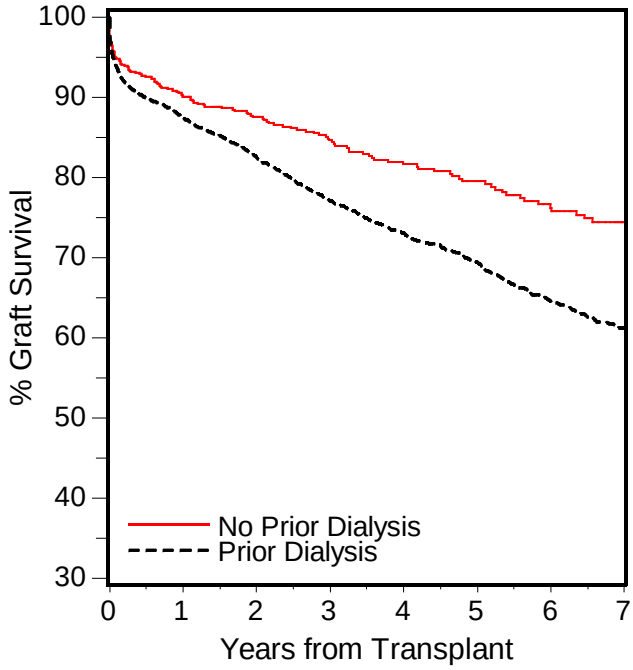
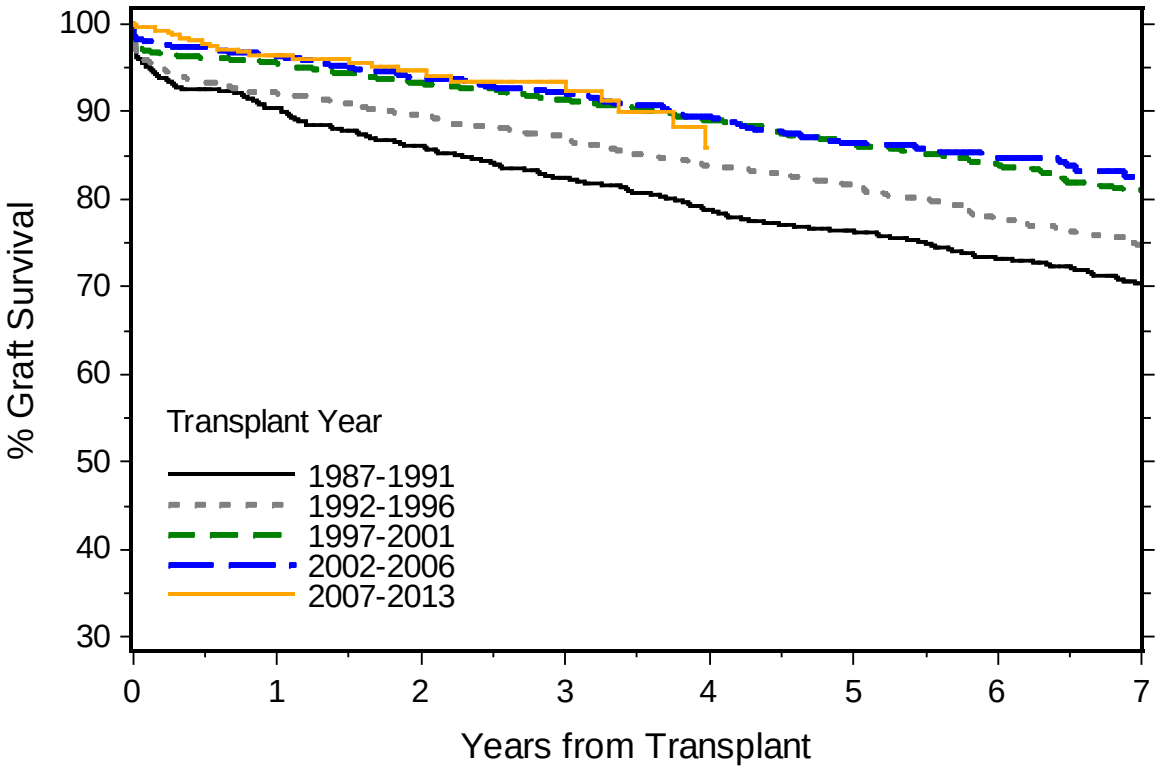


EXHIBIT 5-6
GRAFT SURVIVAL BY TRANSPLANT YEAR

Living Donor



Deceased Donor

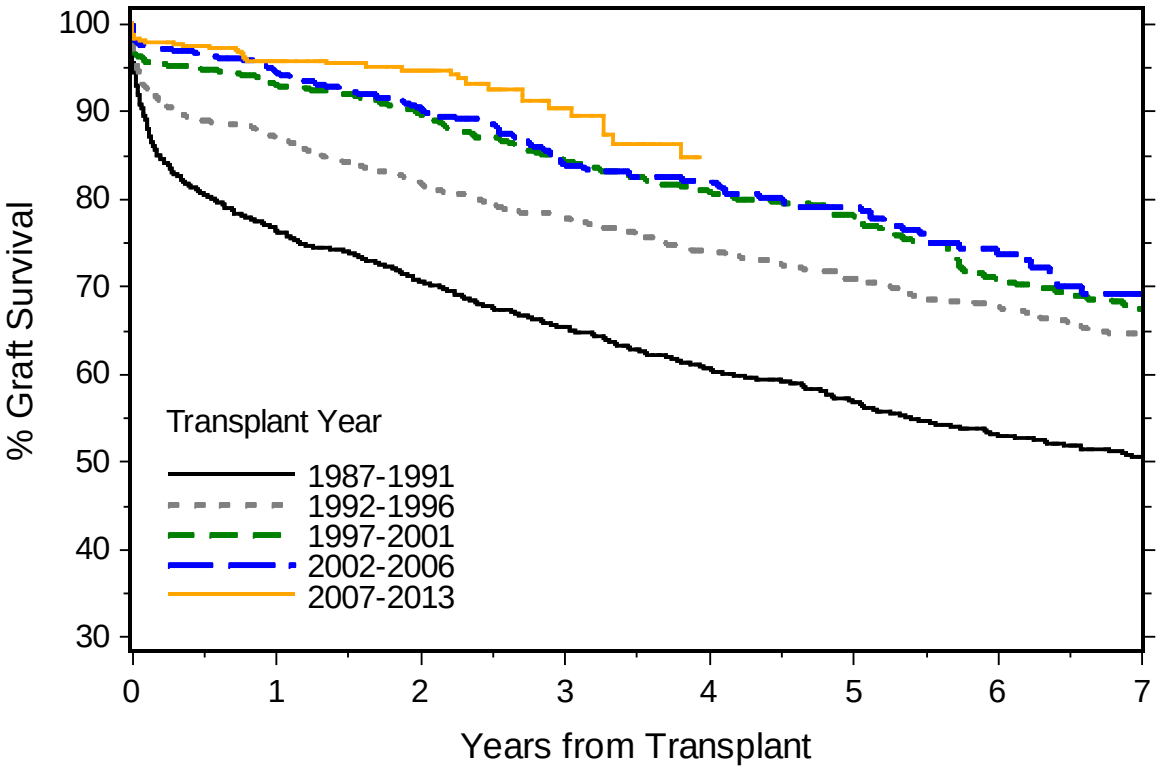
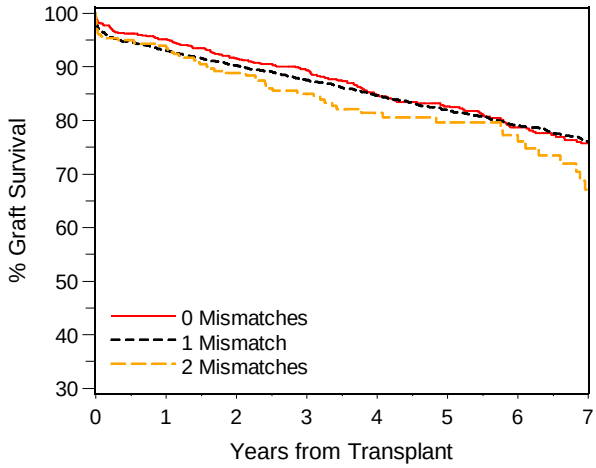


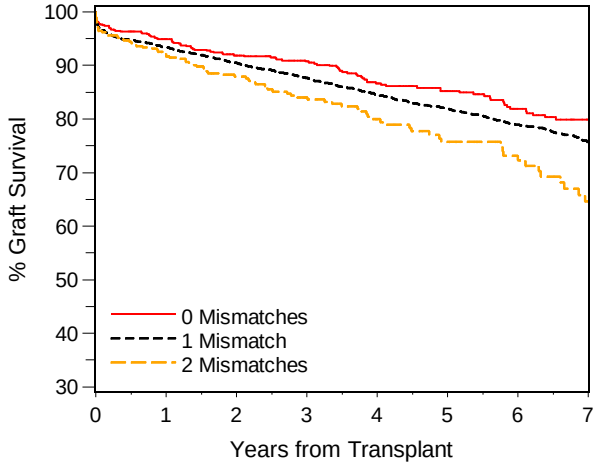
EXHIBIT 5.7
HISTOCOMPATIBILITY DATA

Living Donor

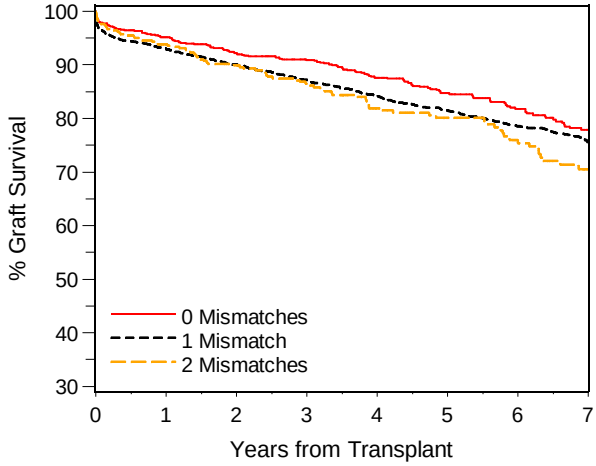
HLA-A



HLA-B

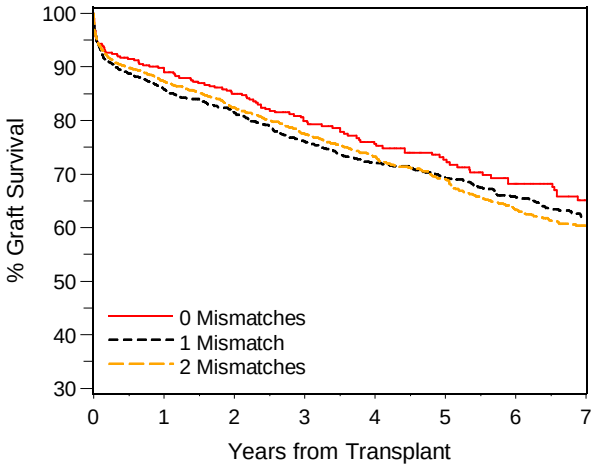


HLA-DR

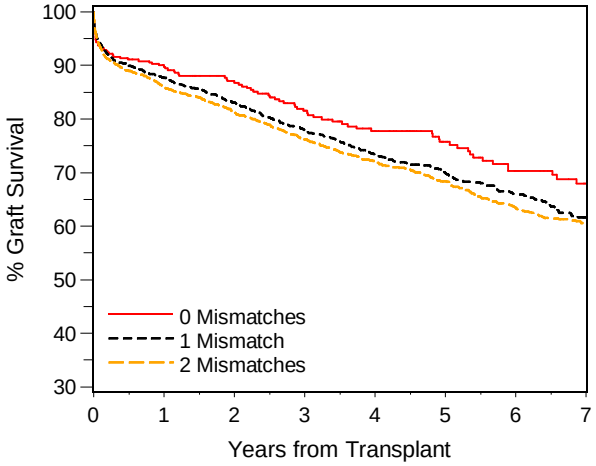


Deceased Donor

HLA-A



HLA-B



HLA-DR

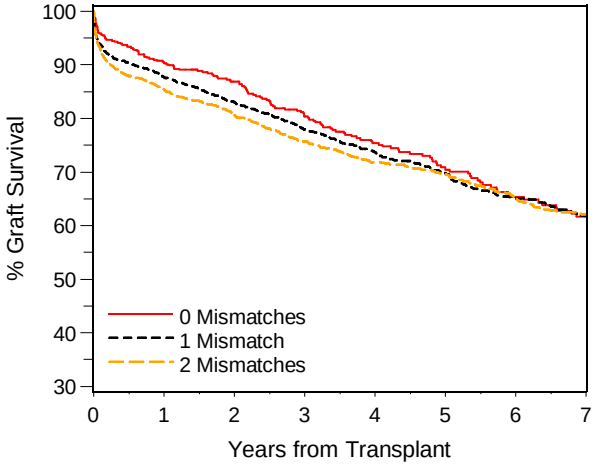
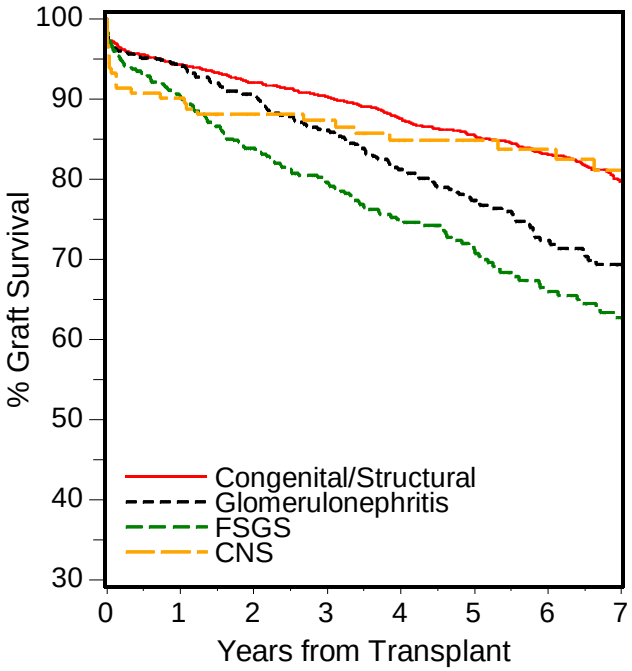
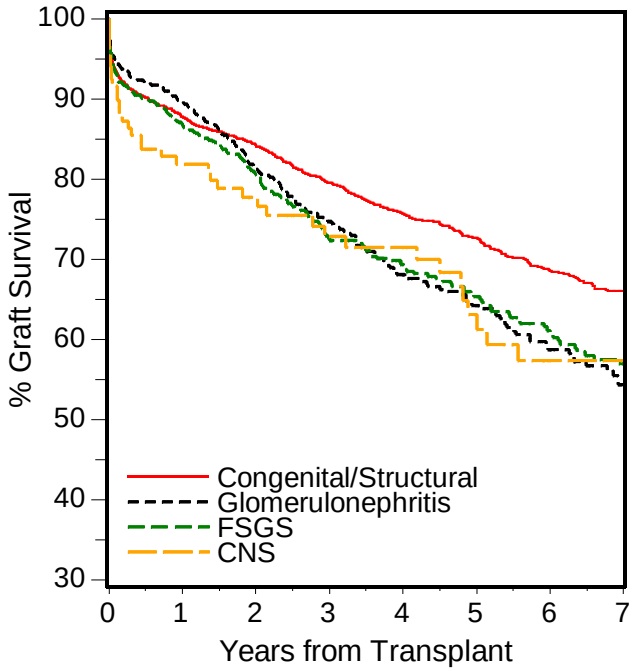


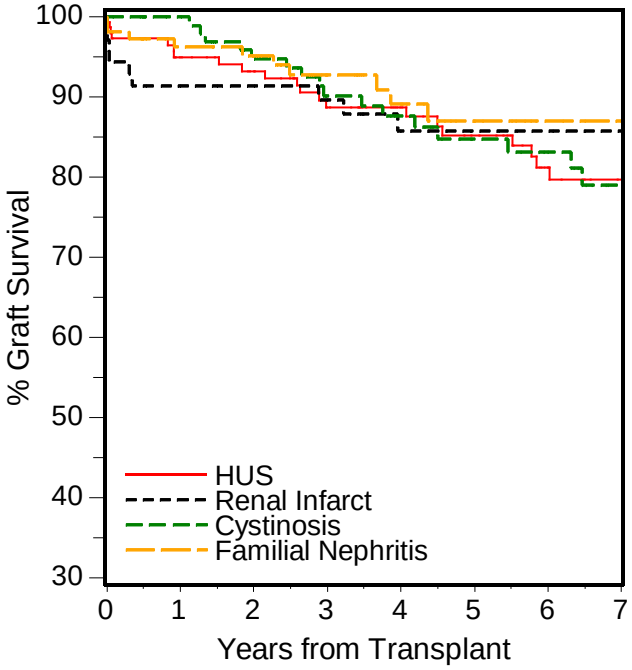
EXHIBIT 5.8
GRAFT SURVIVAL BY PRIMARY DIAGNOSIS

Living Donor



Deceased Donor





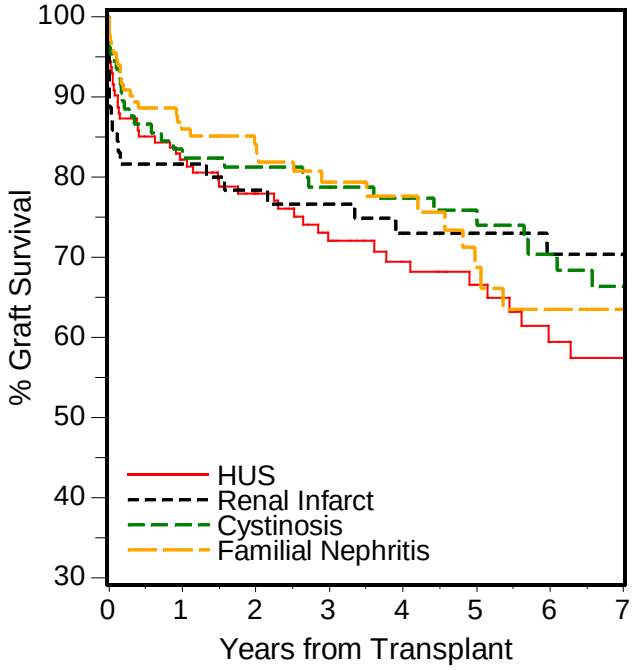
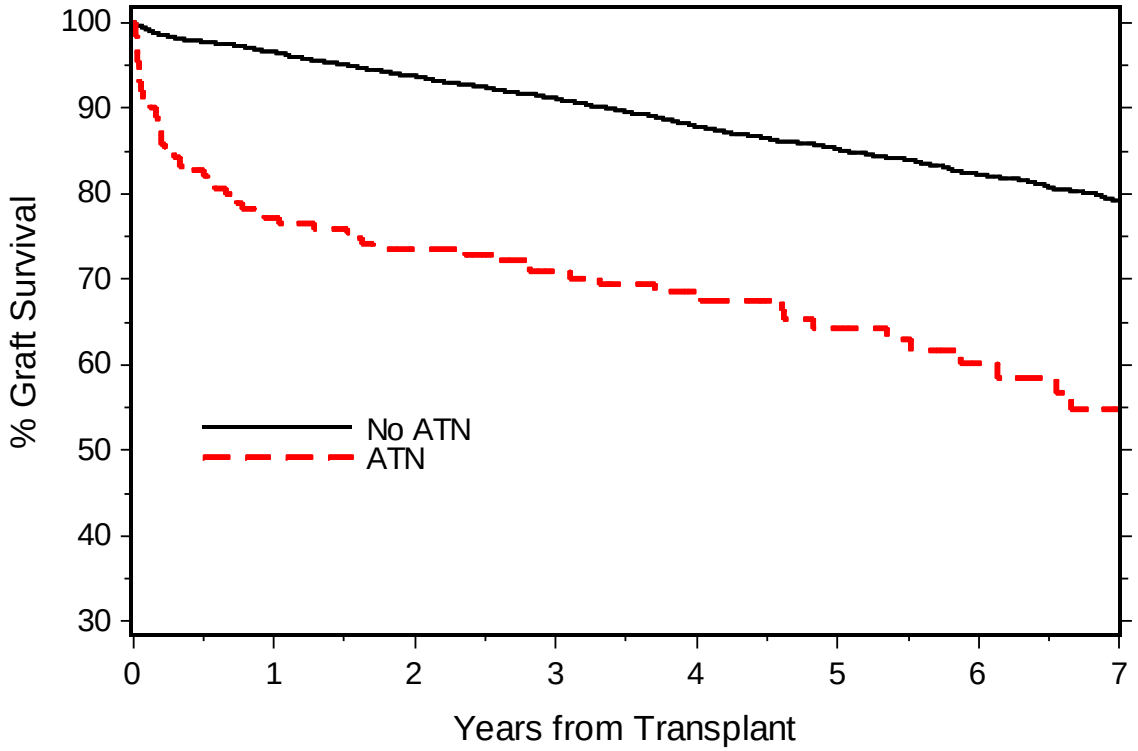


EXHIBIT 5.9
GRAFT SURVIVAL BY ACUTE TUBULAR NECROSIS STATUS
Grafts Surviving beyond 7 days

Living Donor



Deceased Donor

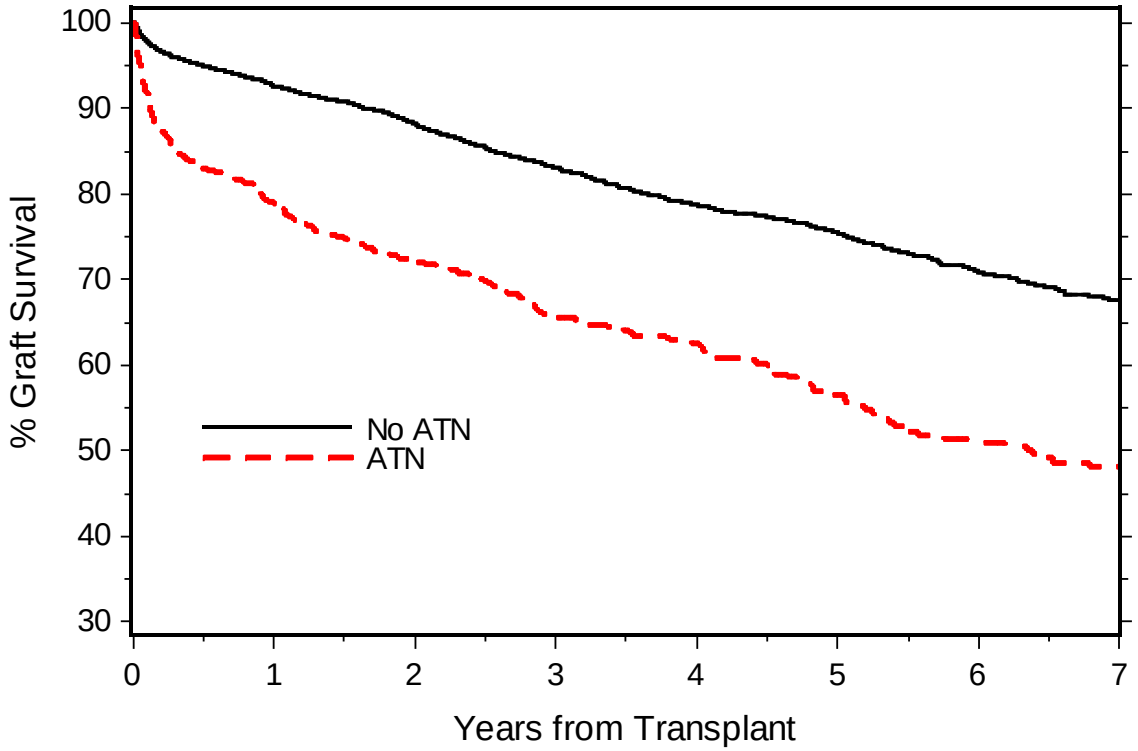
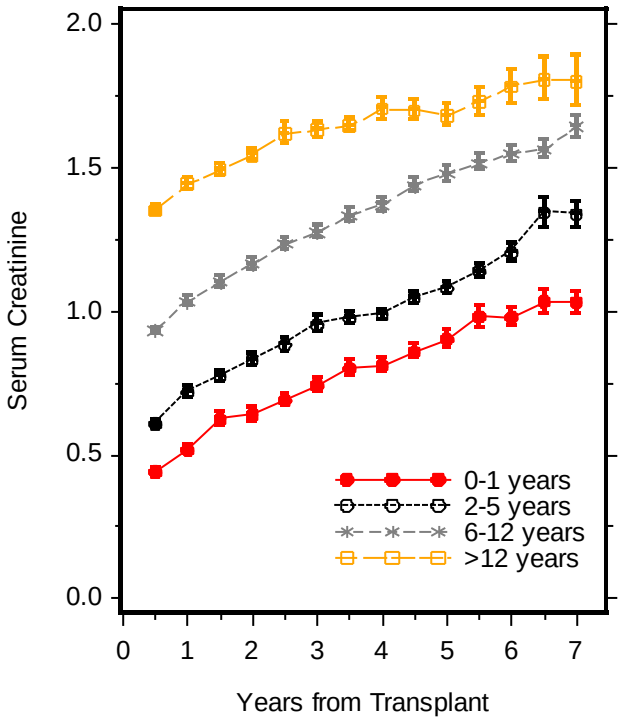


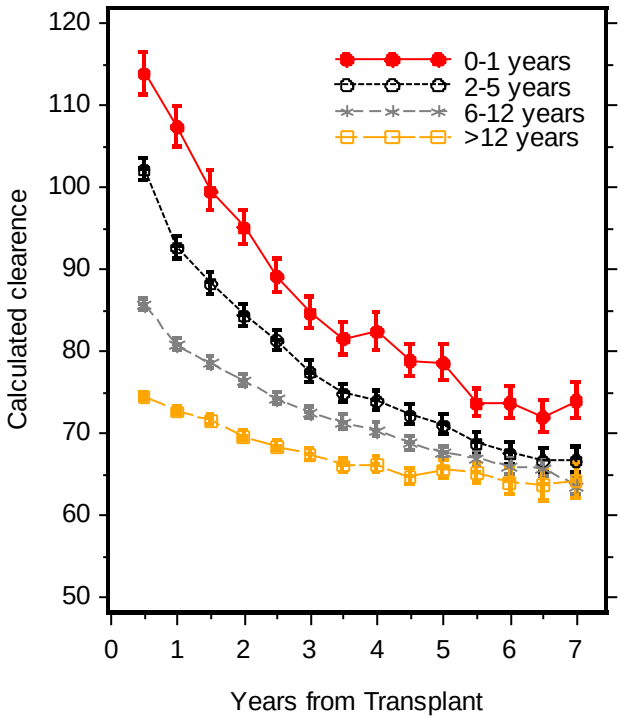
EXHIBIT 5.10
SERUM CREATININE AND CREATININE CLEARANCE (MEAN ± SE) BY AGE
(Index Transplants with Functioning Grafts)

Living Donor

Serum Creatinine

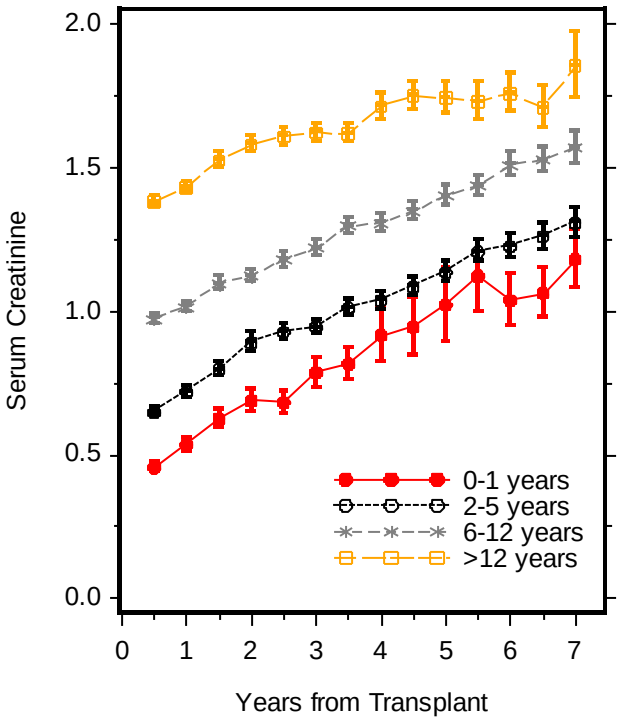


Creatinine Clearance



Deceased Donor

Serum Creatinine



Creatinine Clearance

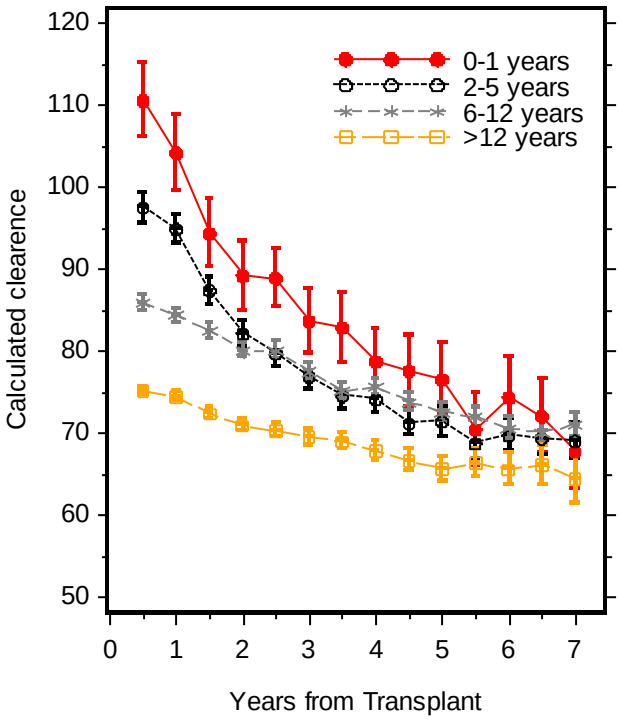
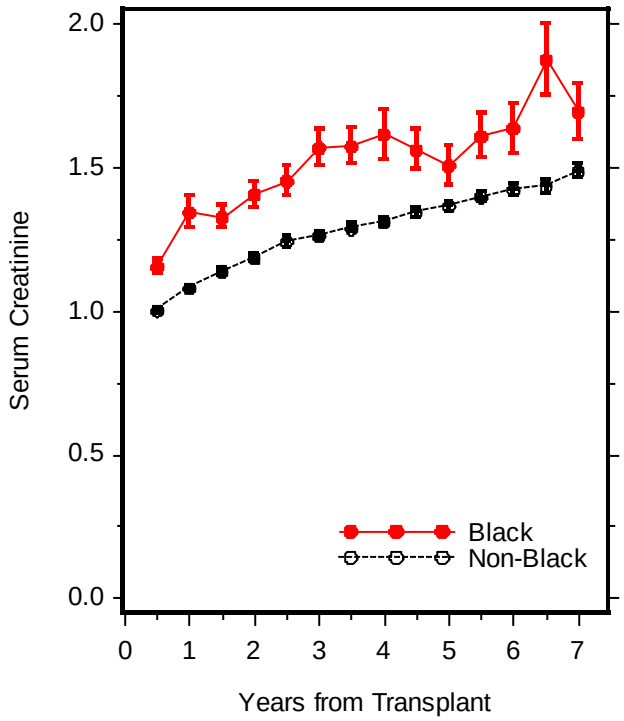


EXHIBIT 5.11
SERUM CREATININE (MEAN ± SE) BY RACE AND INDUCTION ANTIBODY
(Index Transplants with Functioning Grafts)

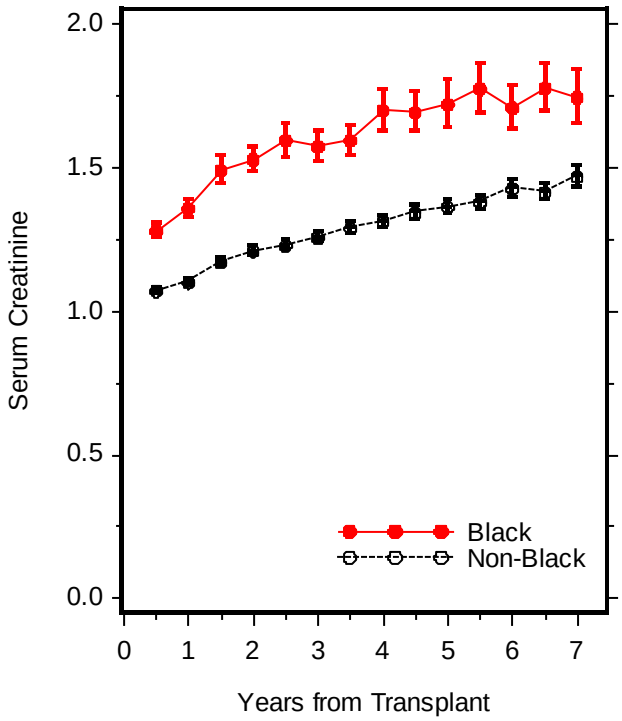
Living Donor

Race

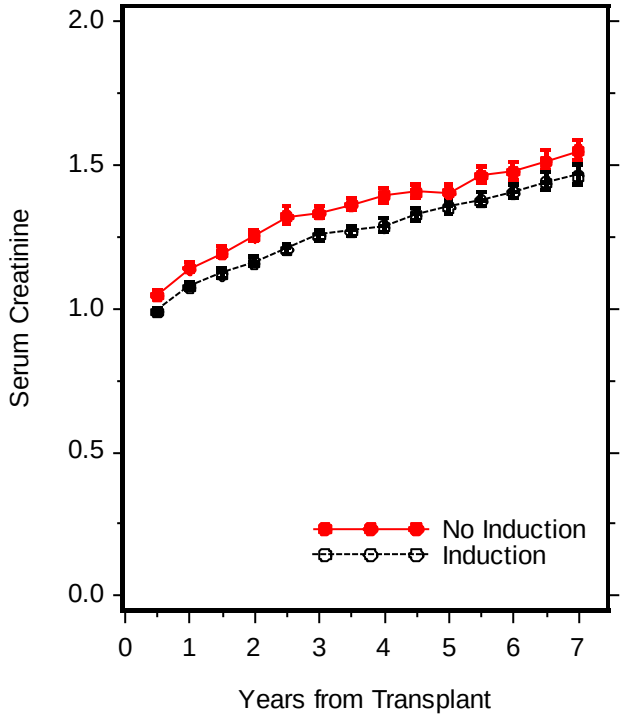


Deceased Donor

Race



Induction Antibody



Induction Antibody

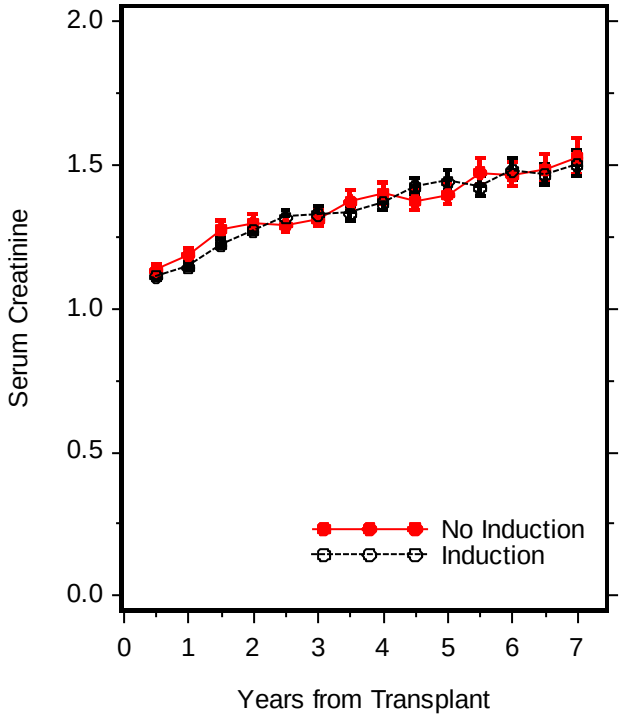
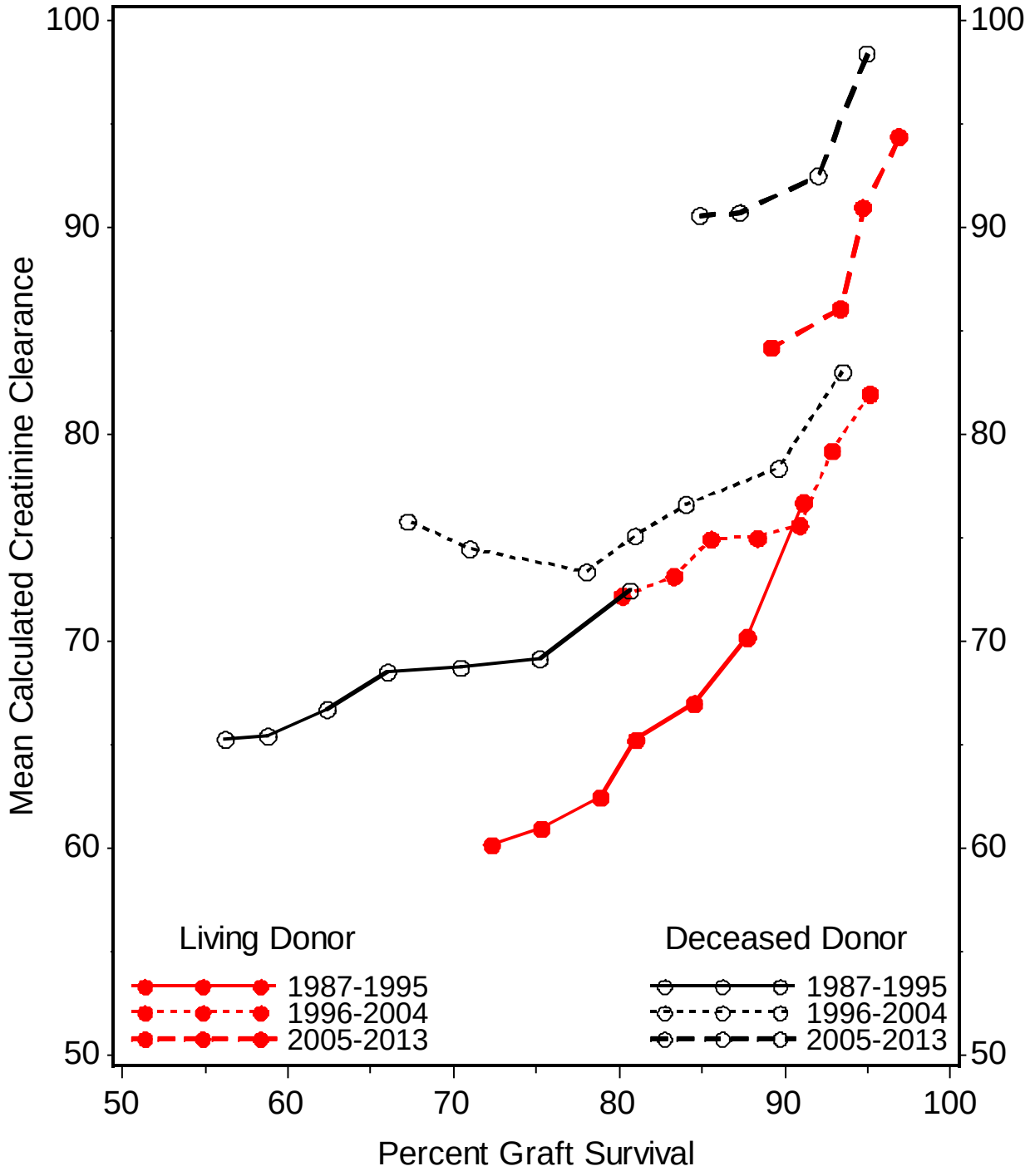


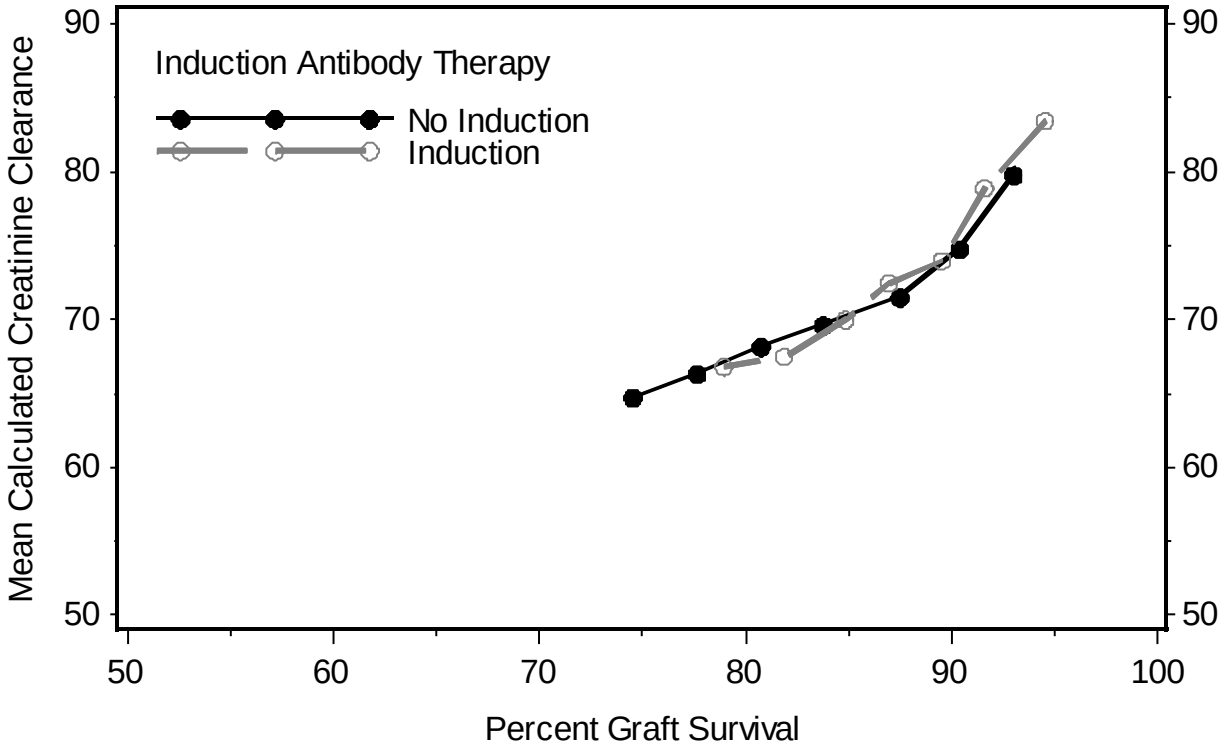
EXHIBIT 5.12
GRAFT FUNCTION
Graft Survival and Mean Calculated Clearance at Annual Follow-up



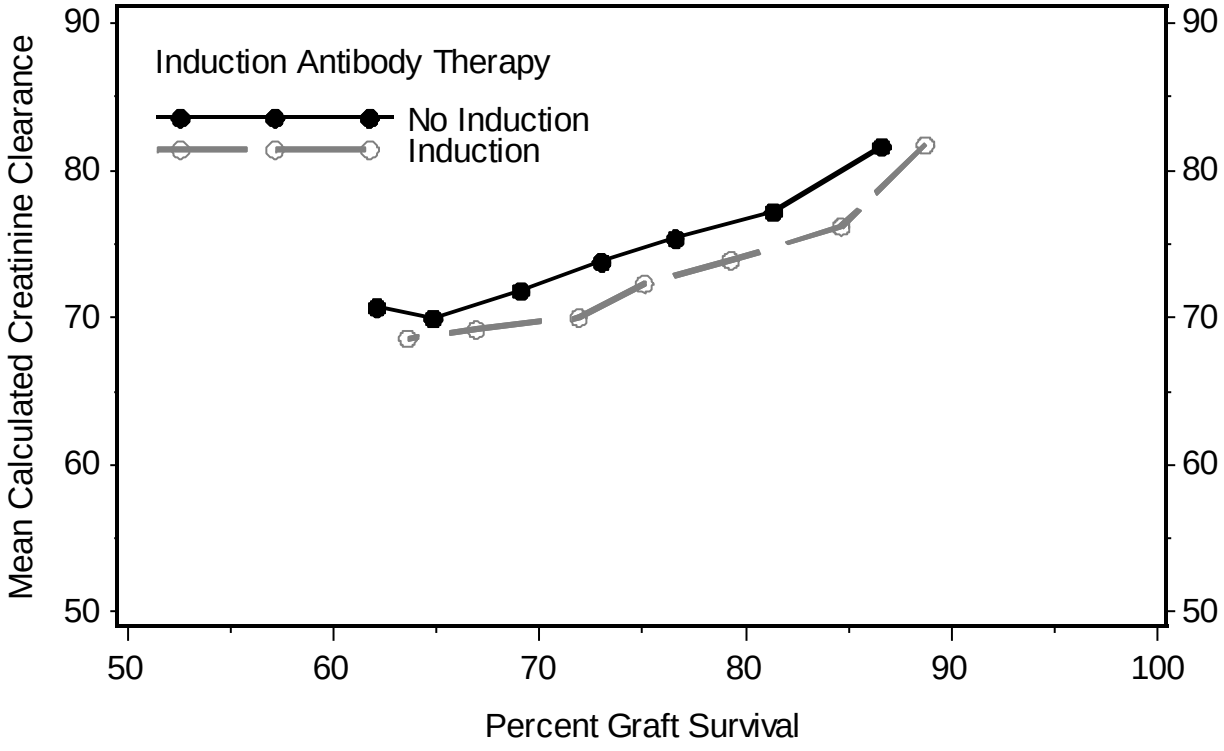
Note: Symbols represent annual follow-up. Year 1 is farthest right and year 7 is farthest left. The most recent era reports only 4 years of follow-up.

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

Living Donor



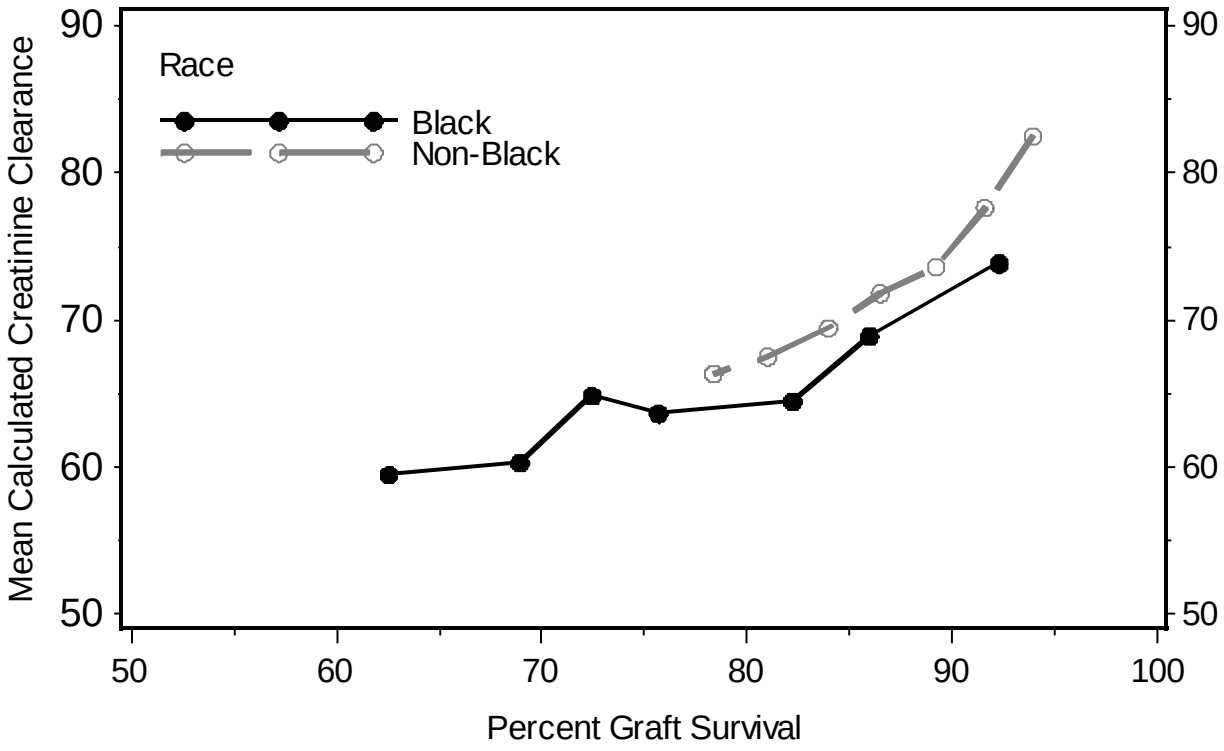
Deceased Donor



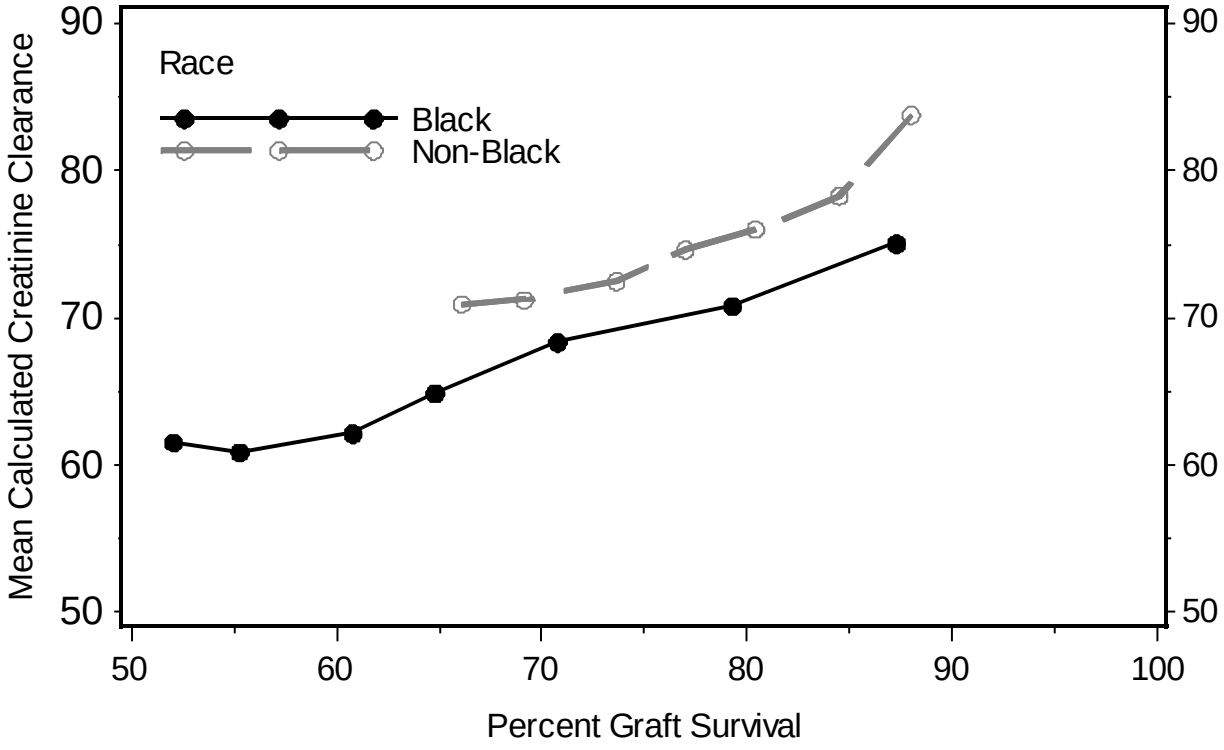
Note: Symbols represent annual follow-up. Year 1 is farthest right and year 7 is farthest left.

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 -1.73; that is, the average patient is 1.7 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 (-1.77) than females (-1.68). Younger subjects between 2 and 5 years at transplant (-2.22) and those with prior transplants (-2.09) also have greater height deficits at the time of transplantation. Overall, mean height Z scores remain relatively constant over the available follow-up period, increasing 0.1 SD every 2 years. 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 0.26 standard deviations is observed in the first six months post-transplant, which increases to 0.53 by 12 months and 0.70 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 0.57 at 2 years. For subjects aged 6-12, linear growth appears to be stable, at about 1.9 standard deviation below the normal population, and the older subjects also have no mean increase in Z-scores averaging about 1.4 SD below the normal population throughout.

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 0.83 standard

deviations in weight in the first year following transplantation and 0.90 SD by 2 years where there is relative stability in average standardized weight scores over the next 5 years.

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, is -1.37. Twenty-five percent of these patients have a Z-score of -2.20 or worse, and 10% are over 3.22 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; -1.06 for the 1997-2001 cohort, -0.98 for the 2002-2006 cohort and -0.89 for the most recent cohort. A box plot of final adult height by transplant cohort is shown in Exhibit 6-4.

	Final Adult Height Z Score				Final Adult Weight Z Score			
Cohort Group	N	Median	Mean	SE	N	Median	Mean	SE
1987-1991	597	-1.81	-1.93	0.07	241	-0.51	-0.88	0.15
1992-1996	757	-1.33	-1.51	0.06	294	-0.19	-0.29	0.09
1997-2001	572	-0.96	-1.06	0.06	231	-0.22	-0.23	0.11
2002-2006	453	-0.82	-0.98	0.07	186	0.37	-0.35	0.52
2007-2013	190	-0.87	-0.89	0.10	87	0.22	-0.02	0.21
Total	2569	-1.23	-1.37	0.03	1039	-0.10	-0.40	0.11

Exhibit 6.5 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 -1.17 for height and -0.60 for weight in the 2013 cohort. This increase is shown for age groups in Exhibit 6.6.

Besides age, donor source and use of antihypertensive medication are predictive of 2-year standardized height changes. Recipients of living donor organs had an average increase of 0.25 standard deviations and deceased donors increased by 0.13 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 0.37 standard deviations versus 0.15 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

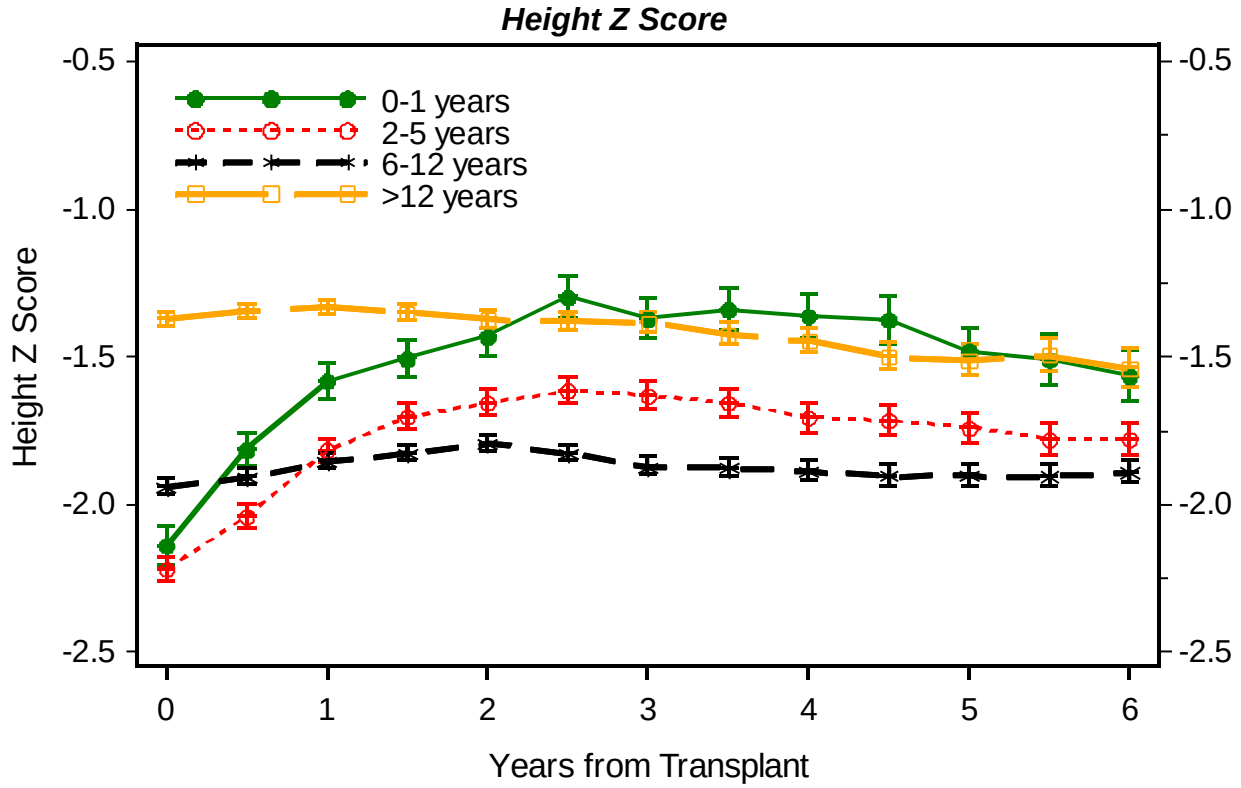
Height Z Score

	Baseline (N=10642)		**2 years** (N=6686)		**4 years** (N=4266)		**6 years** (N=2547)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Total	-1.73	0.02	-1.58	0.02	-1.68	0.02	-1.78	0.03
Sex								
Male	-1.77	0.02	-1.59	0.02	-1.71	0.03	-1.81	0.03
Female	-1.68	0.03	-1.56	0.03	-1.64	0.04	-1.72	0.05
Age								
0-1 years	-2.14	0.07	-1.43	0.06	-1.36	0.07	-1.57	0.09
2-5 years	-2.22	0.04	-1.66	0.04	-1.71	0.05	-1.78	0.06
6-12 years	-1.94	0.03	-1.79	0.03	-1.89	0.03	-1.89	0.04
>12 years	-1.37	0.02	-1.37	0.03	-1.45	0.04	-1.54	0.07
Prior Transplant								
No	-1.68	0.02	-1.53	0.02	-1.64	0.02	-1.74	0.03
Yes	-2.09	0.04	-1.84	0.05	-1.97	0.06	-2.03	0.08

Weight Z Score

	Baseline (N=10760)		**2 years** (N=6715)		**4 years** (N=4023)		**6 years** (N=2337)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Total	-1.09	0.02	-0.24	0.02	-0.29	0.03	-0.34	0.03
Sex								
Male	-1.07	0.02	-0.27	0.02	-0.32	0.03	-0.38	0.04
Female	-1.10	0.03	-0.21	0.03	-0.25	0.04	-0.28	0.05
Age								
0-1 years	-1.47	0.07	-0.42	0.07	-0.40	0.08	-0.38	0.08
2-5 years	-1.19	0.04	-0.31	0.04	-0.16	0.05	-0.16	0.06
6-12 years	-1.23	0.03	-0.17	0.03	-0.28	0.04	-0.41	0.05
>12 years	-0.90	0.02	-0.26	0.03	-0.39	0.06	-0.45	0.14
Prior Transplant								
No	-1.06	0.02	-0.23	0.02	-0.27	0.03	-0.31	0.03
Yes	-1.23	0.05	-0.35	0.05	-0.44	0.07	-0.55	0.10

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



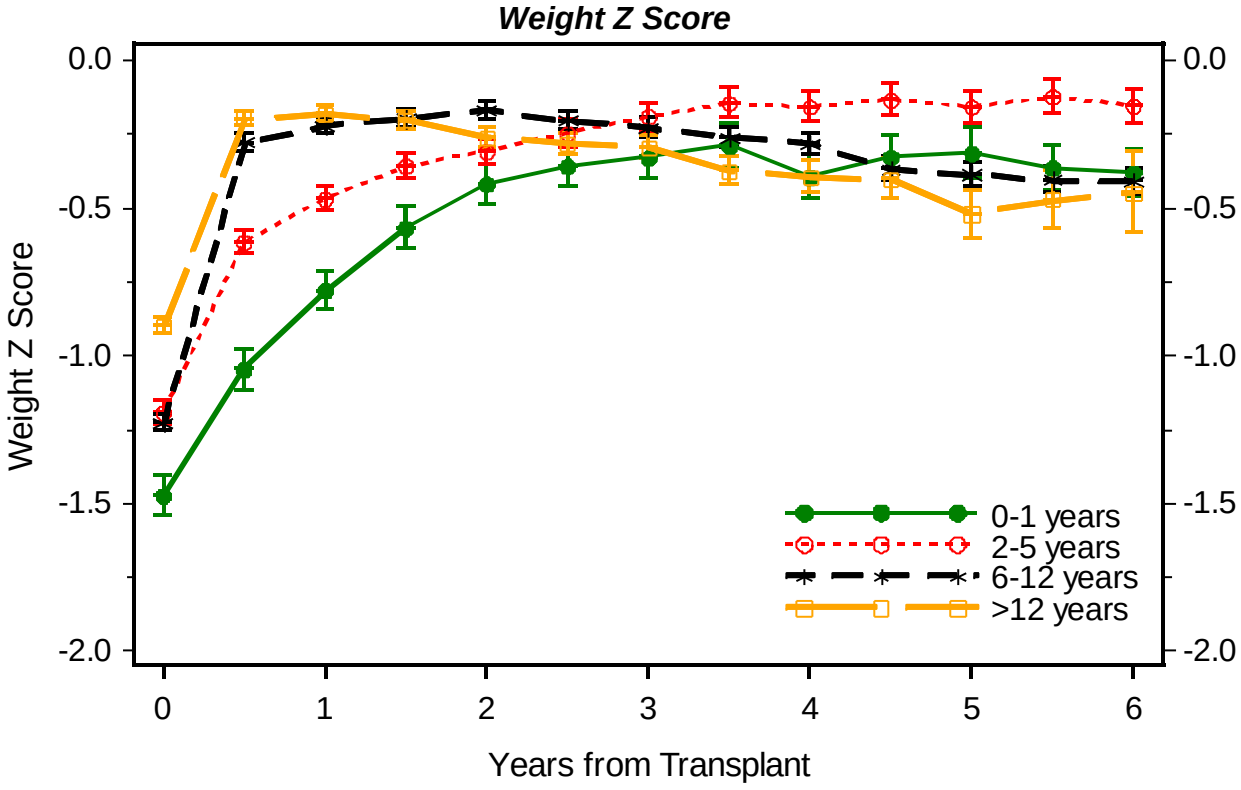
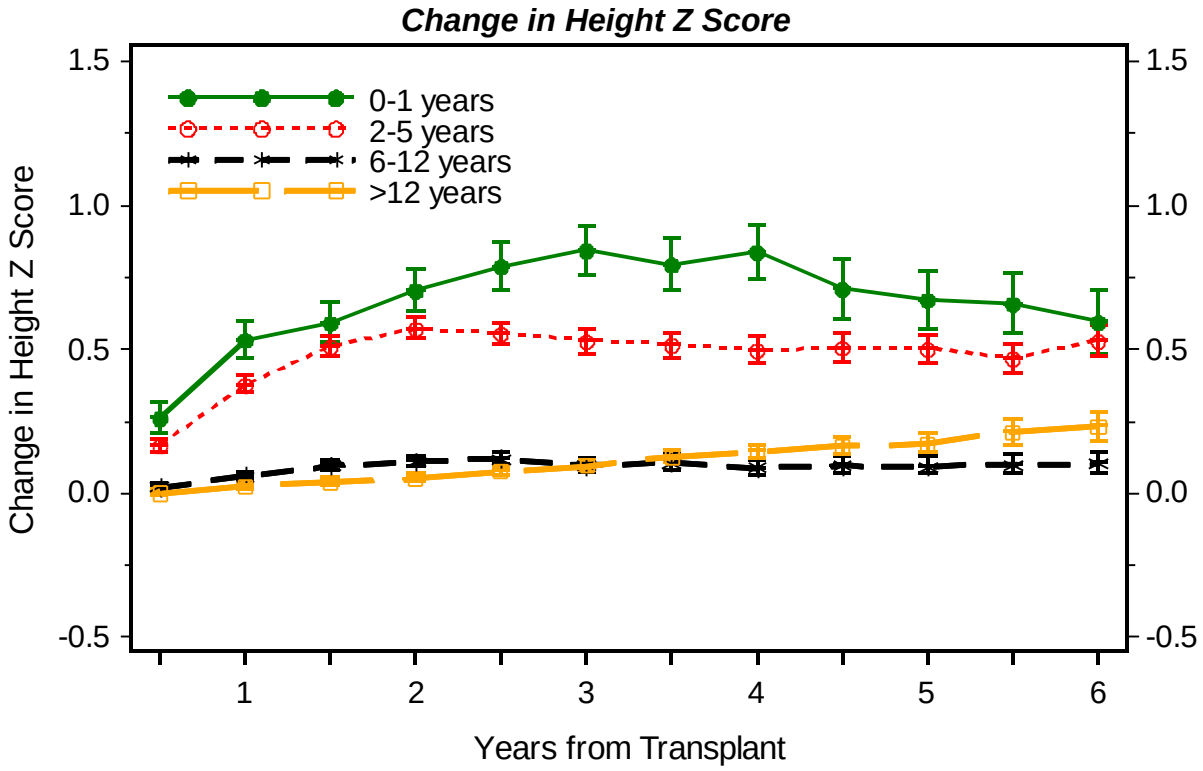


EXHIBIT 6.3
CHANGE FROM BASELINE IN STANDARDIZED SCORE (MEAN ± SE)
BY AGE AT TRANSPLANT
(Index transplants with functioning graft)



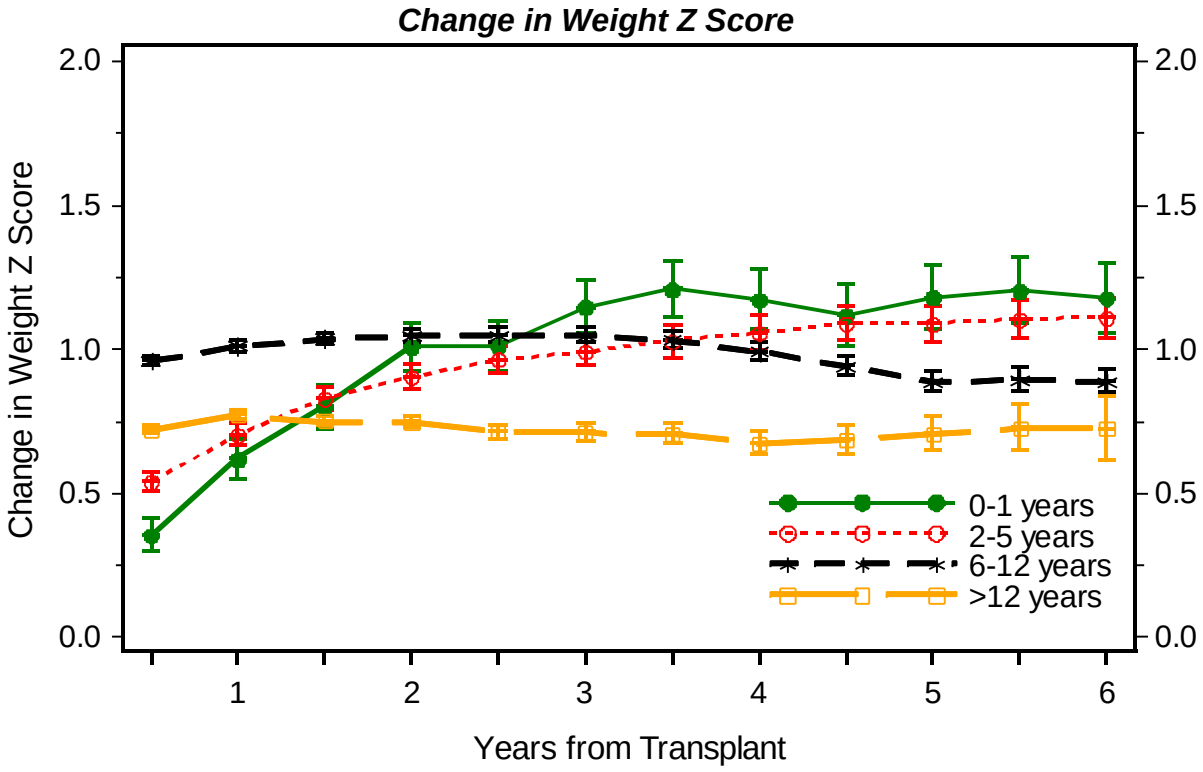
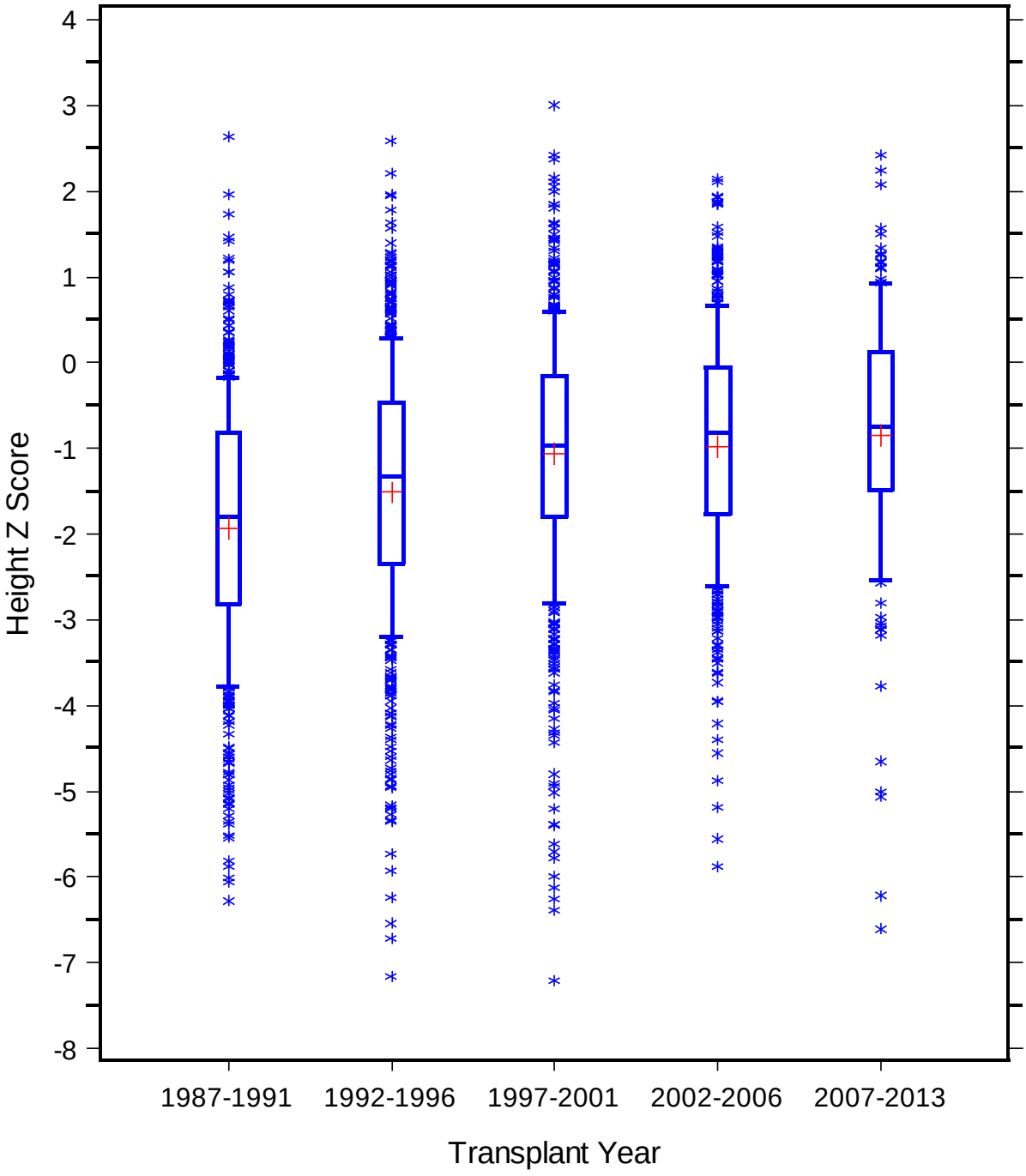


EXHIBIT 6.4
FINAL ADULT STANDARDIZED HEIGHT SCORE BY YEAR OF TRANSPLANT



NOTE: Box represents the 25th & 75th percentiles, whiskers the 10th & 90th percentiles, - is the median value ,+ is the mean value and * are values above and below the 10th & 90th percentiles.

EXHIBIT 6.5
STANDARDIZED SCORES (MEAN ± SE) AT TRANSPLANT
BY YEAR OF TRANSPLANT
(Index transplants)

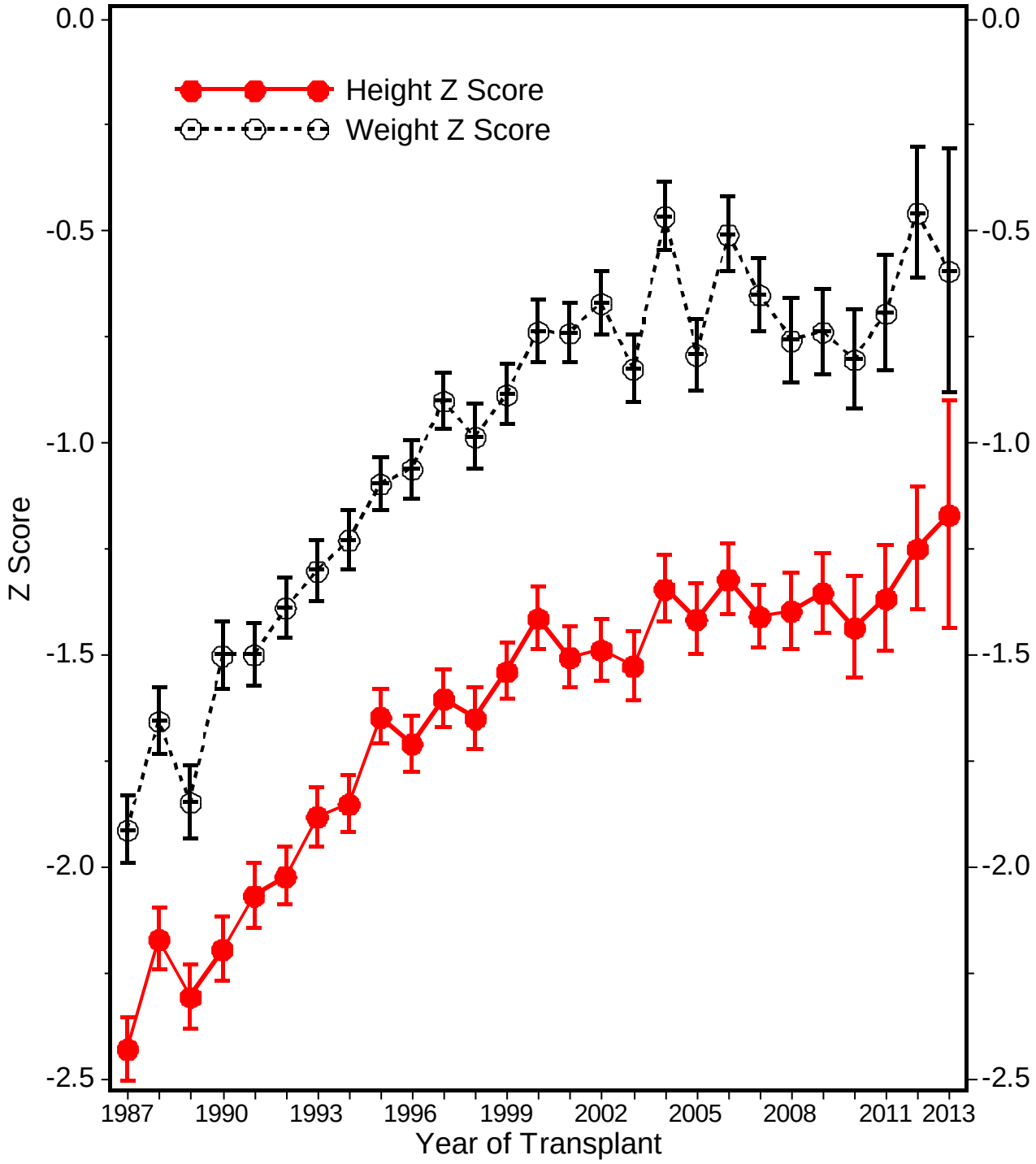
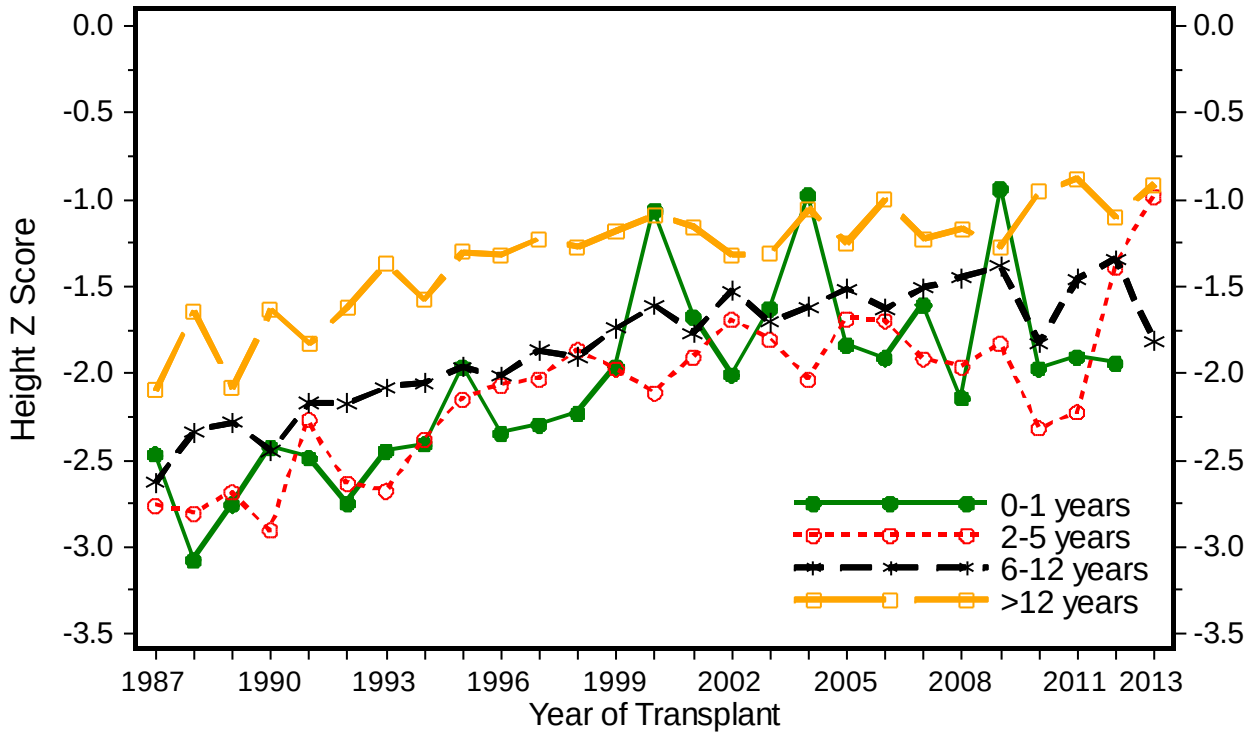
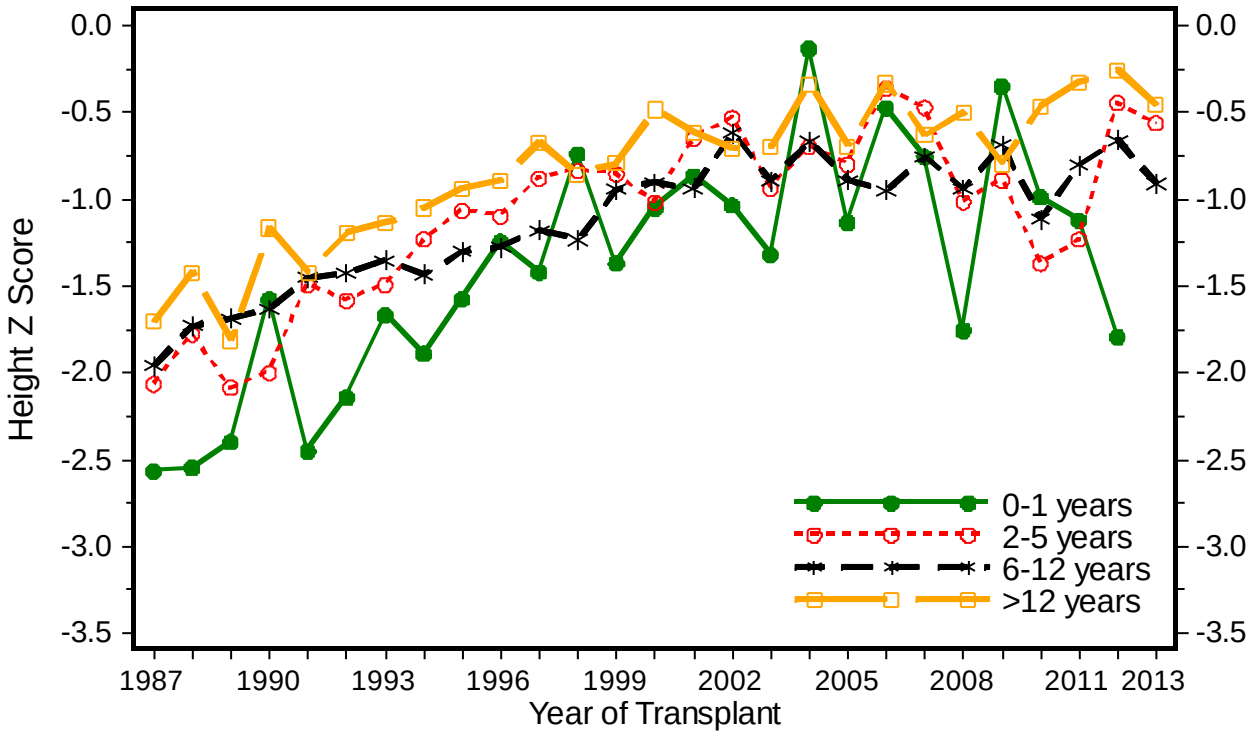


EXHIBIT 6.6
STANDARDIZED SCORES (MEAN) AT TRANSPLANT
BY AGE AT TRANSPLANT AND YEAR OF TRANSPLANT

Height Z Score



Weight Z Score


Height Z Score
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
1987
1990
1993
1996
1999
2002
2005
2008
2011
2013
Year of Transplant
0-1 years
2-5 years
6-12 years
>12 years

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 11 days, with lower and upper quartiles of 8 and 17 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 19 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 source specific mean (± SE) hospitalization days during 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. In 2002, mean hospital stays decreased to around 10 days for LD recipients where it remains constant. Deceased donor hospital stays in the first month post-transplant dropped to 10.8 days in 2000, it fluctuates from 9 to 12 days per month in the years since.

Exhibit 7.2A, 7.2B, 7.2C, and & 7.2D 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, 1996-2004 and 2004-2013) 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 seven days shorter in the most recent era (2005-2013) compared to the earliest 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, 46% of living donor graft recipients were re-hospitalized compared to 51% of deceased donor graft recipients. The most common reason for hospitalization in this interval was treatment of rejection, which occurred in 23% and 16% of DD and LD patients, respectively. Viral (14% versus 12%) and bacterial (13% versus 12%) infections and treatment of hypertension (5% versus 3%) were other major causes of hospitalization. Hospital stays decrease in both frequency and length by month 6 and beyond. In recent years (2005 - 2013), 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 9 days (1987-1995) versus 44% of the patients hospitalized for a median of 7 days in 1996-2004 versus 41% of the patients hospitalized for a median of 5 days in 2005-2013. Deceased donor recipients showed similar results with decreases in hospitalization rates from 61% to 46% to 42% and decrease in median days from 11 to 7 to 6 days for each era respectively. Hospitalization for rejection has also decreased from 24% in 1987-1995 to 13% in 1996-2004 to 5% in 2005-2013 in live donor recipients and 35% to 15% to 8% in deceased donor recipients in the first five months of follow-up.

Malignancy

To date, 316 malignancies have been reported of which 310 have confirmed diagnoses — 262 lymphoproliferative (LPD) and 48 non-lymphoproliferative (non-LPD). These malignancies have been reported in 311 patients. Four 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 three cases had two LPD's – one case had 2 PTLD's 21 months apart, one case had 2 PTLDs 30 months apart and one case had Hodgkins disease 1-year after PTLD. Exhibit 7.4 shows selected transplant characteristics for the cohort with malignancy. 2.6% of transplants are associated with development of malignancy during the follow-up period. The median time from transplant to first malignancy for those with a confirmed diagnosis of LPD was 14.9 months (range 0.9-161.8) and 33.0 months (range 2.4 – 123.7 for non-LPD 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	
Transplant Era	%	SE	%	SE
1987 – 1991	0.62	0.16	0.96	0.21
1992 – 1996	1.32	0.22	2.15	0.28
1997 – 2001	1.96	0.28	2.97	0.36
2002 – 2006	1.28	0.26	2.32	0.38
2007 – 2013	0.94	0.30	1.78	0.50

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 any upward trend has been arrested.

Mortality

To assess post transplant patient survival, we considered 11,117 index transplants (5,819 LD and 5,298 DD). Percent patient survival estimates (with standard errors) for all patients at 1, 2, 5 7, and 10 years post transplant are 98.0±0.1, 97.3±0.2, 95.1±0.2, 93.3±0.3, and 90.6±0.5 respectively. Exhibit 7.5A depicts patient survival by allograft source. Percent patient survival estimates for recipients of index living donor kidneys are 98.5±0.2, 97.8±0.2, 96.2±0.3, 94.5±0.4 and 92.7±0.6 percent, at 1, 2, 5, 7 and 10 years post transplant, respectively. Comparable values for recipients of deceased donor allografts are 97.5±0.2, 96.7±0.3, 93.8±0.4 and 91.8±0.5 and 88.0+0.8 percent (log-rank $p<0.001$). Exhibit 7.5B compares patient survival for transplants in 1987-1995 versus 1996 – 2004 versus 2005-2013, by primary allograft source. Patient survival has significantly improved for DD patients since 1996 ($p<0.001$). Their 5-year post transplant survival in the 1987-1995 era was 91.2±0.6, compared to 96.4±0.6 and 96.4±1.1for the 1996-2004 and 2005-2013 eras respectively. LD patients have also shown some improvement in survival rates with 5-year survival rate of 95.1±0.5 in the 1987-1995 era compared to 96.8±0.4 and 97.1±1.2 in the 1996-2004 and 2005-2013 eras (Log Rank $p<0.001$).

Patient survival for transplants in 1996-2013, 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 89 patients. The following table shows percent

survival at 36 months post transplant, by age at transplantation for patients transplanted between 1996 and 2013. 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 78.7% (SE=4.6%) between 1987 - 1995 to 94.8% (SE=2.6%) in 1996 and later. For infants receiving living donor grafts, their 3-year survival also improved from 89.9% (SE=2.2%) in 1987-1995 to 96.3% (SE=1.2%) in 1996 and beyond.

PATIENT SURVIVAL AT 3 YEARS POST TRANSPLANT BY AGE
Transplant Era 1996 – 2013

	Living Donor		Deceased Donor	
	%	SE	%	SE
All Patients	98.0	0.3	97.9	0.3
Age 0-1 years	96.3	1.2	94.8	2.6
Age 2-5 years	97.6	0.7	96.3	1.1
Age 6-12 years	98.3	0.4	99.0	0.4
Age >12 years	98.3	0.4	97.8	0.5

In total, death reports have been received for 591 of the 11,117 patients (5.3%). Crude donor source-specific mortality rates are 4.5% (260/5,819) for recipients of living donor index transplants and 6.3% (331/5,298) for recipient of deceased donor index transplants. Reasons for patient death are shown in Exhibit 7.7. Infection was the cause of death in 168 patients (28.4% of deaths). Other reported causes include cancer/malignancy (n=68, 11.5%), cardiopulmonary (n=86, 14.6%), and dialysis-related complications (n=18, 3.0%). Of the expired patients, 285 (48.2%) died with a functioning graft.

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

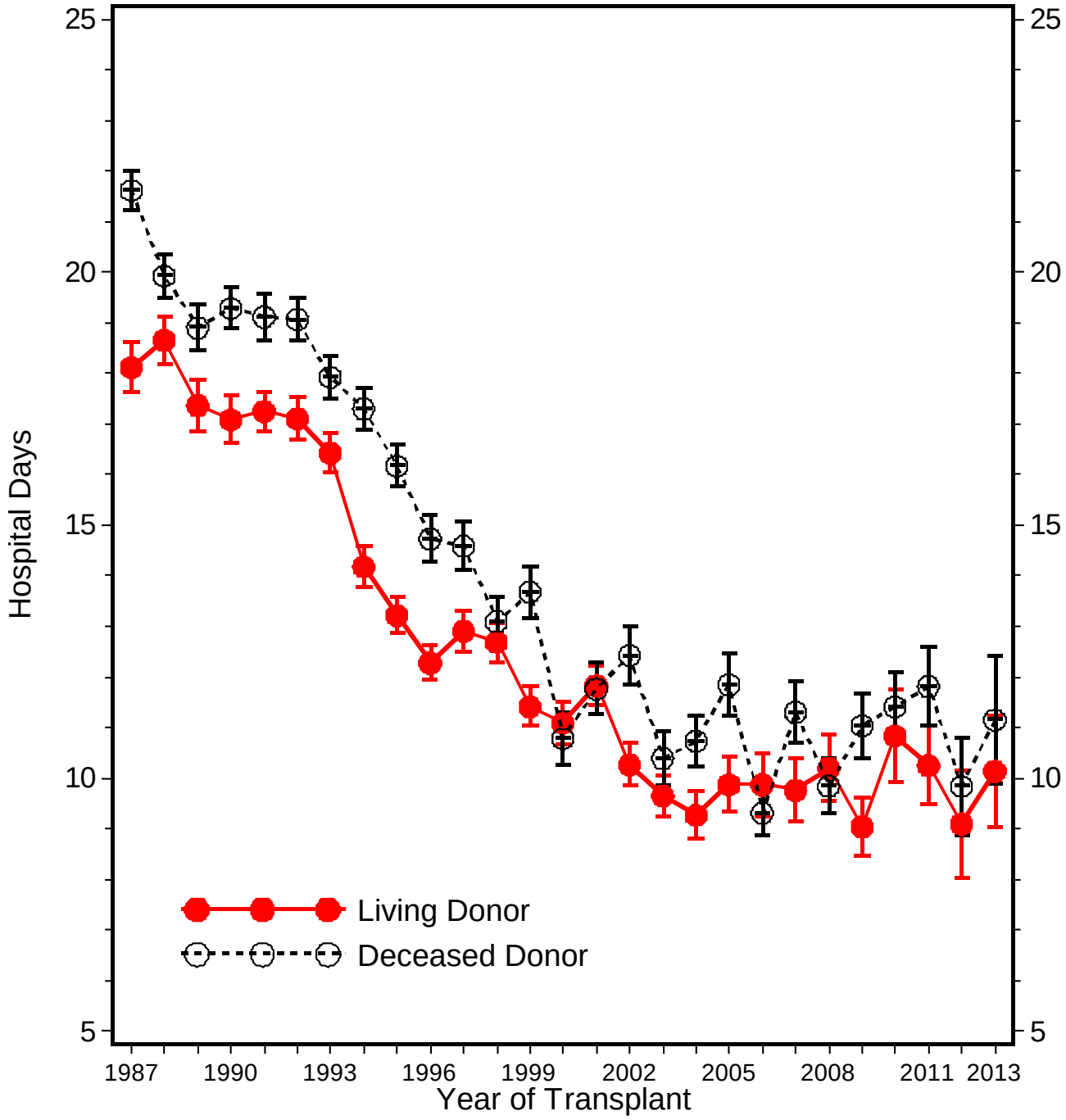


EXHIBIT 7.2A
HOSPITALIZATION DAYS DURING THE FIRST POST- TRANSPLANT MONTH

	Total (N=11744)			Living Donor (N=5905)			Deceased Donor (N=5839)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	Median
All transplants	14.2	0.07	13.0	13.3	0.10	12.0	15.2	0.11	14.0
Age at transplant									
0-1	18.6	0.35	18.0	18.1	0.39	17.0	19.9	0.78	22.0
2-5	16.8	0.21	16.0	16.1	0.27	15.0	17.7	0.32	17.0
6-12	14.5	0.13	13.0	13.4	0.17	12.0	15.7	0.19	14.0
>12	12.7	0.10	11.0	11.3	0.13	10.0	13.9	0.14	12.0
Transplant History									
No prior transplant	14.1	0.08	13.0	13.3	0.11	12.0	15.0	0.12	14.0
Prior transplant	14.6	0.17	13.0	13.0	0.27	11.0	15.5	0.22	14.0
ATN									
No	13.6	0.08	12.0	12.9	0.10	11.0	14.4	0.11	13.0
Yes	19.5	0.24	19.0	19.6	0.49	20.0	19.5	0.27	19.0
Rejection (during 1st month)									
No	12.6	0.08	11.0	11.9	0.10	10.0	13.3	0.11	12.0
Yes	20.6	0.15	21.0	19.7	0.24	19.0	21.3	0.20	22.0
Native Nephrectomy									
Tissue removed	13.6	0.08	12.0	12.5	0.11	10.0	14.7	0.12	13.0
No tissue removed	16.1	0.15	15.0	15.4	0.19	14.0	17.0	0.24	16.0
Dialysis History									
No prior dialysis	12.5	0.15	11.0	11.9	0.16	10.0	14.1	0.31	12.0
Prior dialysis	14.7	0.08	13.0	13.9	0.12	12.0	15.3	0.12	14.0
Transplant Era									
1987-1991	18.8	0.14	18.0	17.7	0.21	17.0	19.8	0.19	19.0
1992-1996	15.8	0.13	14.0	14.6	0.18	13.0	17.1	0.19	16.0
1997-2001	12.4	0.14	10.0	12.0	0.18	10.0	13.0	0.23	11.0
2002-2006	10.3	0.16	9.0	9.8	0.21	8.0	10.9	0.24	9.0
2007-2013	10.5	0.20	9.0	9.9	0.30	9.0	10.9	0.27	10.0

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 – 2004

	Total (N=4549)			**Living Donor** (N=2614)			**Deceased Donor** (N=1935)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	Median
All transplants	12.0	0.11	10.0	11.4	0.14	10.0	12.7	0.17	11.0
Age at transplant									
0-1	16.2	0.55	16.0	16.8	0.58	16.0	13.3	1.52	14.0
2-5	14.4	0.32	13.0	13.6	0.38	12.0	15.8	0.55	15.0
6-12	11.8	0.18	10.0	11.3	0.22	10.0	12.6	0.30	11.0
>12	10.9	0.14	9.0	9.9	0.18	8.0	12.1	0.23	10.0
Transplant History									
No prior transplant	12.0	0.12	10.0	11.5	0.15	10.0	12.7	0.20	11.0
Prior transplant	12.0	0.25	10.0	11.1	0.37	9.0	12.6	0.34	11.0
ATN									
No	11.3	0.11	10.0	11.1	0.13	9.0	11.7	0.17	10.0
Yes	17.9	0.40	17.0	18.0	0.74	17.0	17.9	0.48	17.0
Rejection (during 1st month)									
No	11.3	0.11	10.0	10.9	0.14	9.0	11.9	0.17	10.0
Yes	17.9	0.37	17.0	17.1	0.50	16.0	18.7	0.53	19.0
Native Nephrectomy									
Tissue removed	11.3	0.12	10.0	10.7	0.15	9.0	12.2	0.19	10.0
No tissue removed	14.1	0.23	13.0	13.6	0.29	12.0	14.8	0.38	13.0
Dialysis History									
No prior dialysis	10.0	0.19	9.0	9.8	0.21	8.0	10.5	0.46	9.0
Prior dialysis	12.6	0.13	11.0	12.2	0.17	10.0	13.0	0.18	11.0

EXHIBIT 7.2D
HOSPITALIZATION DAYS DURING THE FIRST POST- TRANSPLANT MONTH
TRANSPLANT YEARS 2005 – 2013

	Total (N=2004)			**Living Donor** (N=844)			**Deceased Donor** (N=1160)		
	Mean	SE	Median	Mean	SE	Median	Mean	SE	Median
All transplants	10.4	0.16	9.0	9.9	0.24	8.0	10.8	0.22	9.0
Age at transplant									
0-1	14.6	0.91	12.0	13.8	1.05	11.0	15.9	1.62	15.0
2-5	12.6	0.51	12.0	13.2	0.74	12.0	12.2	0.69	11.0
6-12	10.2	0.32	9.0	9.2	0.46	8.0	10.9	0.43	10.0
>12	9.5	0.19	8.0	8.8	0.28	8.0	10.0	0.26	9.0
Transplant History									
No prior transplant	10.6	0.19	9.0	9.9	0.28	8.0	11.0	0.26	10.0
Prior transplant	9.9	0.32	8.0	9.7	0.48	8.0	10.0	0.43	8.0
ATN									
No	9.8	0.16	9.0	9.4	0.23	8.0	10.1	0.22	9.0
Yes	17.2	0.75	17.0	20.1	1.59	20.5	16.4	0.84	16.0
Rejection (during 1st month)									
No	10.1	0.16	9.0	9.6	0.24	8.0	10.4	0.22	9.0
Yes	16.4	0.90	16.5	15.7	1.51	17.0	16.8	1.14	16.0
Native Nephrectomy									
Tissue removed	9.7	0.18	8.0	8.9	0.27	8.0	10.2	0.24	9.0
No tissue removed	12.4	0.38	11.0	12.5	0.51	11.0	12.3	0.57	10.5
Dialysis History									
No prior dialysis	9.2	0.28	8.0	8.8	0.33	8.0	10.0	0.52	9.0
Prior dialysis	10.8	0.20	9.0	10.5	0.33	9.0	10.9	0.24	10.0

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	5241	4901	4483	4154	3487	2852	2264
Median days hospitalized	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean days hospitalized	5.5	2.6	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	8.9	8.4	6.8	6.6	5.9	6.3
% Hospitalized	45.4	28.3	23.0	19.9	17.7	15.9	15.6
% Hospitalized for:							
Bacterial infection	11.8	7.6	6.8	5.9	4.3	4.4	5.3
Fungal infection	0.7	0.2	0.3	0.2	0.2	0.3	0.2
Viral infection	12.2	8.0	5.7	5.1	4.0	3.5	3.6
Rejection	16.4	7.6	5.4	4.7	4.1	3.1	3.0
Hypertension	3.2	1.5	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	4896	4465	4005	3542	2749	2110	1631
Median days hospitalized	1.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean days hospitalized	7.3	3.4	2.5	1.9	1.5	1.5	1.3
Hopitalized Transplants							
Median days hospitalized	9.0	6.0	5.5	5.0	4.0	4.0	4.0
Mean days hospitalized	14.0	10.5	9.7	7.9	7.2	7.7	7.3
% Hospitalized	51.4	31.6	25.9	23.8	21.1	18.8	18.3
% Hospitalized for:							
Bacterial infection	13.1	9.4	6.7	5.2	5.3	5.2	4.3
Fungal infection	1.0	0.5	0.3	0.1	0.2	0.1	0.2
Viral infection	13.7	7.5	5.9	5.7	4.7	4.1	3.9
Rejection	22.8	10.6	8.1	7.7	5.9	4.9	4.1
Hypertension	4.9	2.5	1.9	2.0	1.9	1.8	1.2

EXHIBIT 7.4
MALIGNANCY RATES BY SELECTED CHARACTERISTICS

	Malignancies	
	N	**%**
Transplants with malignancy	311	2.55
Donor Source		
Living Donor	157	2.57
Deceased Donor	152	2.53
Age at Transplant		
0-1 years	18	2.73
2-5 years	83	4.62
6-12 years	104	2.62
>12 years	106	1.84
Sex		
Male	191	2.65
Female	120	2.41
Race		
White	230	3.16
Black	33	1.59
Hispanic	34	1.67
Other	14	1.73
Transplant Year		
1987-1991	56	2.08
1992-1996	102	3.21
1997-2001	91	3.32
2002-2006	46	2.11
2007-2013	16	1.14

Note: Transplants with multiple malignancies are only counted once.

EXHIBIT 7.5A
PATIENT SURVIVAL BY ALLOGRAFT SOURCE

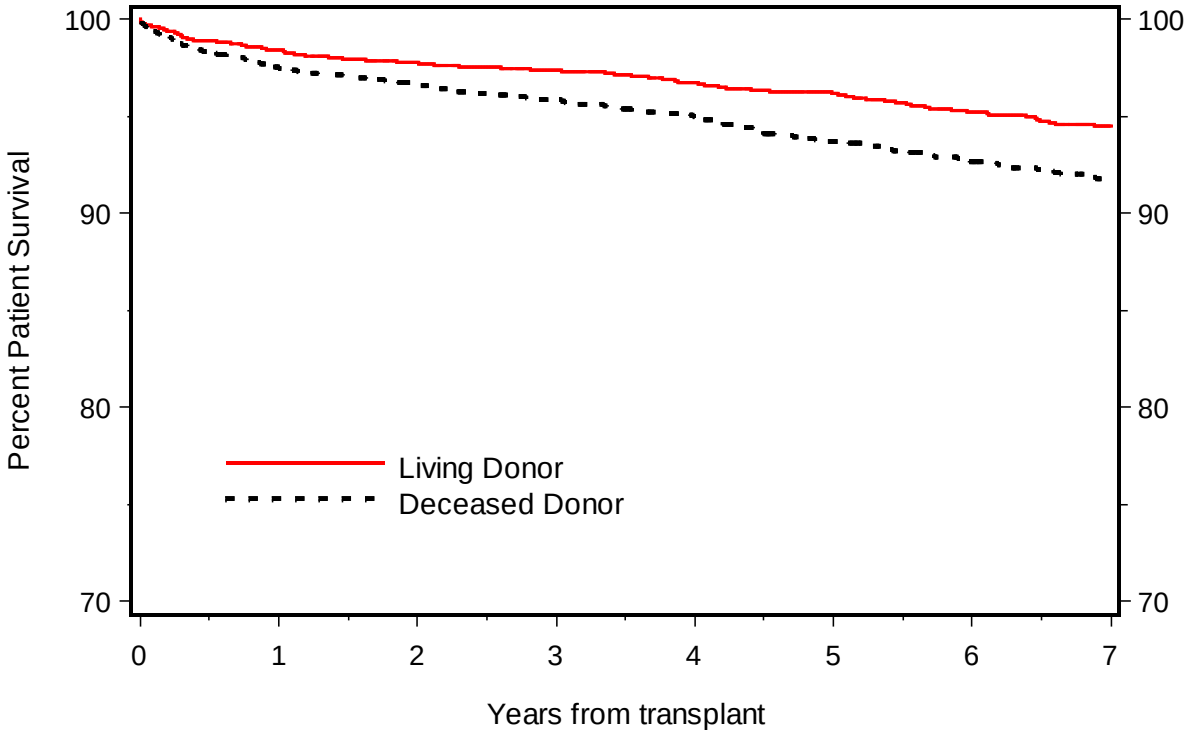


EXHIBIT 7.5B
PATIENT SURVIVAL BY TRANSPLANT ERA AND ALLOGRAFT SOURCE

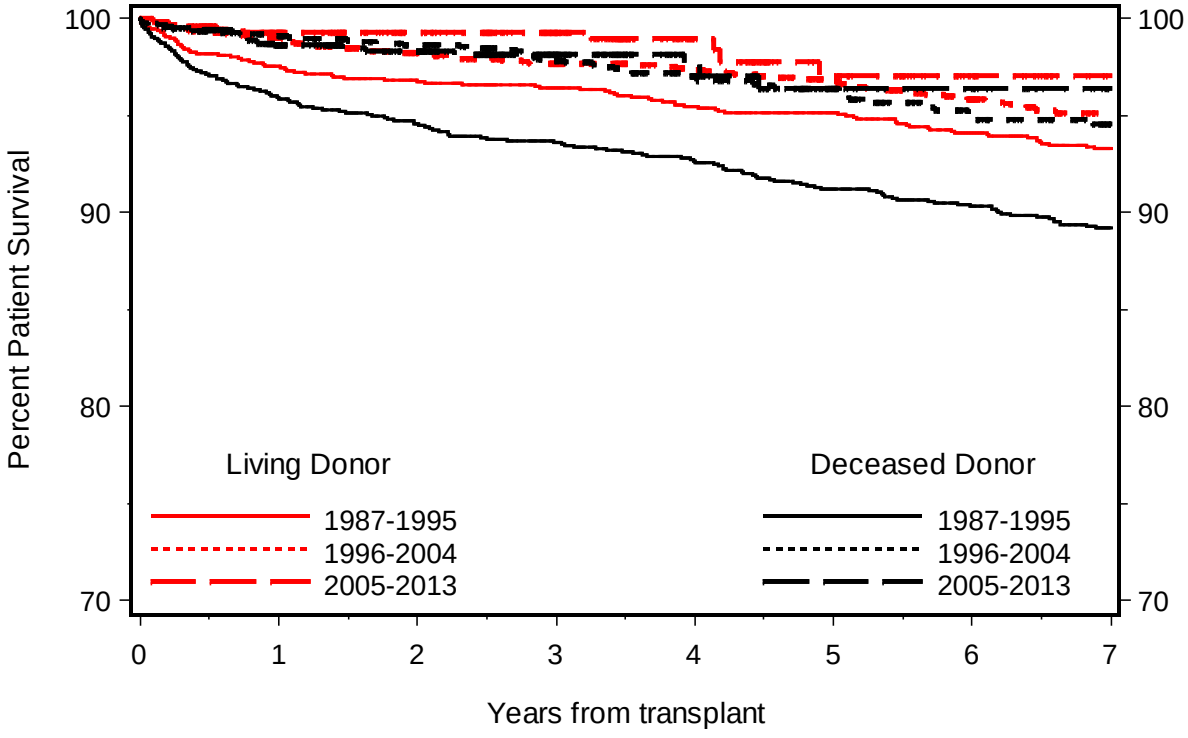
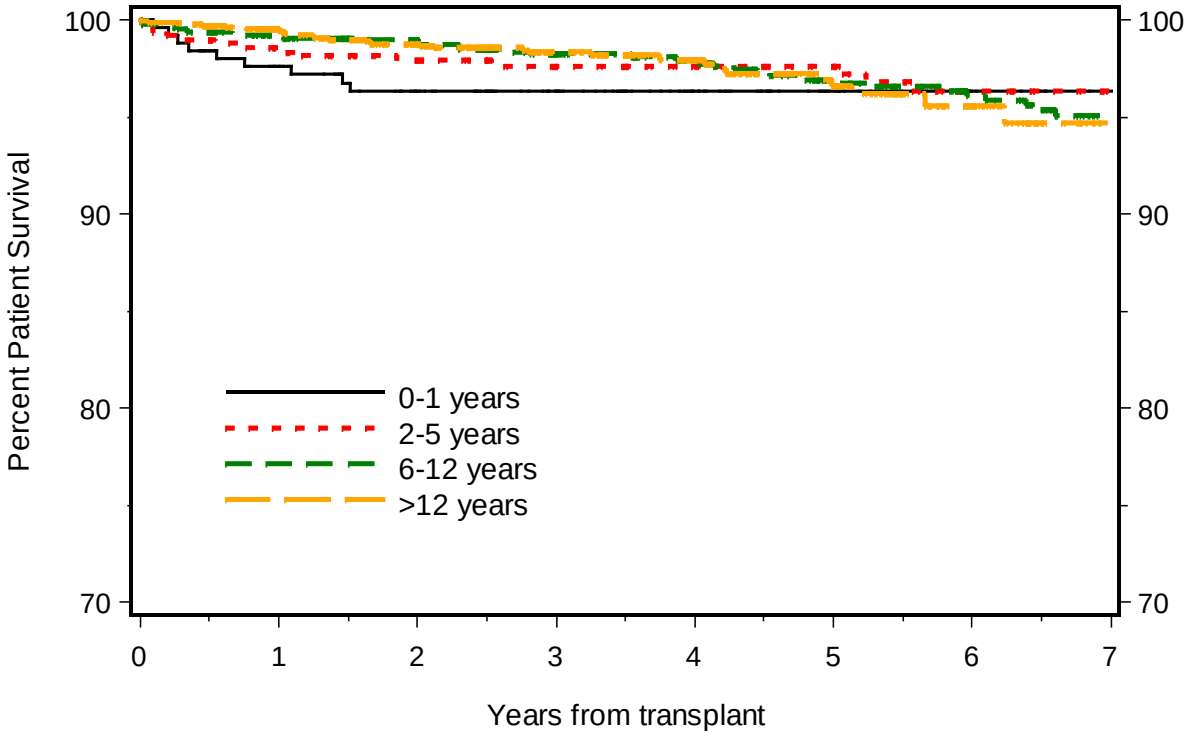


EXHIBIT 7.6
PATIENT SURVIVAL BY AGE AT TRANSPLANT
TRANSPLANT ERA 1996-2013

Living Donor



Deceased Donor

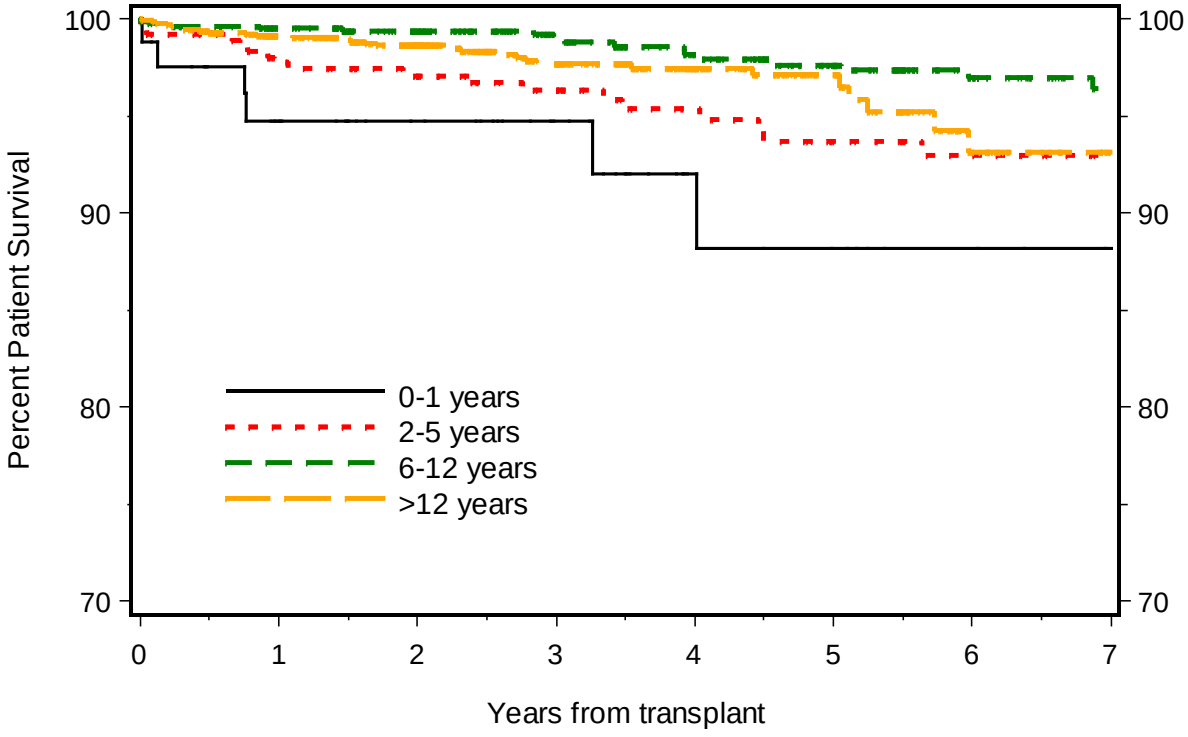


EXHIBIT 7.7
CAUSES OF DEATH FOLLOWING INDEX RENAL TRANSPLANTATION

	Total			Living Donor			Deceased Donor		
	N	%	Func graft	N	%	Func graft	N	%	Func graft
All deceased patients	591	100.0	285	260	100.0	131	331	100.0	154
Cause of Death									
Infection,Viral	47	8.0	25	26	10.0	14	21	6.3	11
Infection,Bacterial	75	12.7	38	35	13.5	16	40	12.1	22
Infection, Not Specified	46	7.8	15	23	8.8	8	23	6.9	7
Cancer/malignancy	68	11.5	49	38	14.6	28	30	9.1	21
Cardiopulmonary	86	14.6	39	31	11.9	15	55	16.6	24
Hemorrhage	33	5.6	12	9	3.5	2	24	7.3	10
Recurrence	10	1.7	1	4	1.5	1	6	1.8	0
Dialysis-related Complications	18	3.0	0	8	3.1	0	10	3.0	0
Other	149	25.2	76	64	24.6	35	85	25.7	41
Unknown	59	10.0	30	22	8.5	12	37	11.2	18

SECTION 8: SUPPLEMENTAL ANALYSES

Machine Perfusion and Cold Storage Time

Of the 5298 deceased donor index transplants, 594 have used machine perfusion for the preservation of the donor kidney, 3782 have not. There are 922 transplants where 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 18% average in the last 3 years (2011, 2012, 2013) (Exhibit 8.1), the rate of unknown/missing data shows a marked increase in more recent years with 3% in 1987 up to 19% in 1996 and to 35% in 2001 where it remains high (average of 24% over the last 3 years). The cold storage time of the deceased donor kidneys (Exhibit 8-2) has been decreasing over the life of the registry with 45% >24 hours in 1987 (mean±SE, 24.4±0.6 hours), 18% >24 hours in 1996 (18.3±0.5 hours) and <2% averaged over the last 3 years (11.8±0.5 hours).

Primary Disease Sub-analyses

The NAPRTCS registry now spans more than 25 years and has collected information on the transplants of over 11,186 children. There is a special opportunity to evaluate patient and graft survival in some of the more rare primary renal diseases as shown in Exhibit 8-3.

Membranoproliferative glomerulonephritis (MPGN) Type I has occurred in 191 patients and Type II has occurred in 87 patients. While there is no statistical difference in patients survival (92% vs. 94% at 5 years for Type I and Type II respectively), graft survival is significantly higher in Type I (74% at 5 years) than Type II (50% at 5 years), log-rank p=0.003. Causes of graft failure for the 53 Type I cases that failed included 5 vascular thrombosis, 27 rejection, (8 acute, 1 accelerated acute and 18 chronic). Disease recurrence was quite common in Type II disease, occurring in 15 of the 36 patients with graft failure.

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 901 cases with specific diseases of: Congenital nephrotic syndrome (n=289), MPGN Type I (n=191), Idiopathic cresentic glomerulonephritis (n=195), Berger's nephritis (IgA) (n=139) and MPGN Type II (n=87). Patient survival at 5 years is 94% and graft survival at 5 years is 73%.

There are currently 1308 cases with Focal segmental glomerulosclerosis as the primary cause of kidney failure. 556 of these patients received living donor grafts, with patient survival of 97% and graft survival of 71% at 5 years. Patients receiving deceased donor grafts (n=748) had patient survival rates of 94% and graft survival rates of 65% at 5 years. The most common causes of the 408 graft failures are chronic rejection (n=119, 9.1% of all FSGS patients) and recurrence of original kidney disease (n=95, 7.3%).

Metabolic diseases include 225 cases with cystinosis and 58 cases with oxalosis. There are significant differences between cystinosis and oxalosis, with 5 year rates of graft survival of 80% and 56% 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 78% for patients with oxalosis (log-rank p=<0.001).

Genetic disease comprises 116 patients, 59 Wilm's tumor and 57 Drash syndrome. There was no statistical difference in patient (96% and 87% respectively at 5 years) or graft (87% and 78% respectively at 5 years) survival between the 2 groups. The most common causes of the 26 graft failures included death with a functioning graft (n=9), chronic rejection (n=7) and acute rejection (n=5).

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

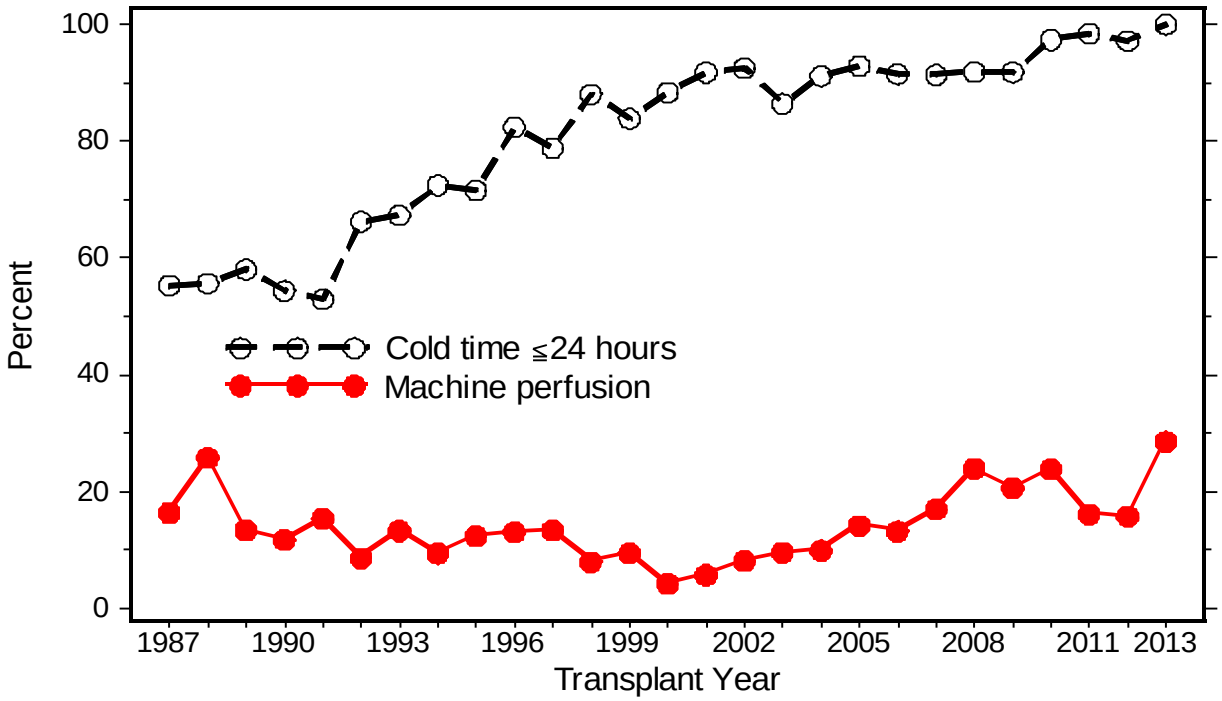


EXHIBIT 8.2
DECEASED DONOR INDEX TRANSPLANTS
COLD ISCHEMIA TIME (MEAN ± SE) BY TRANSPLANT YEAR

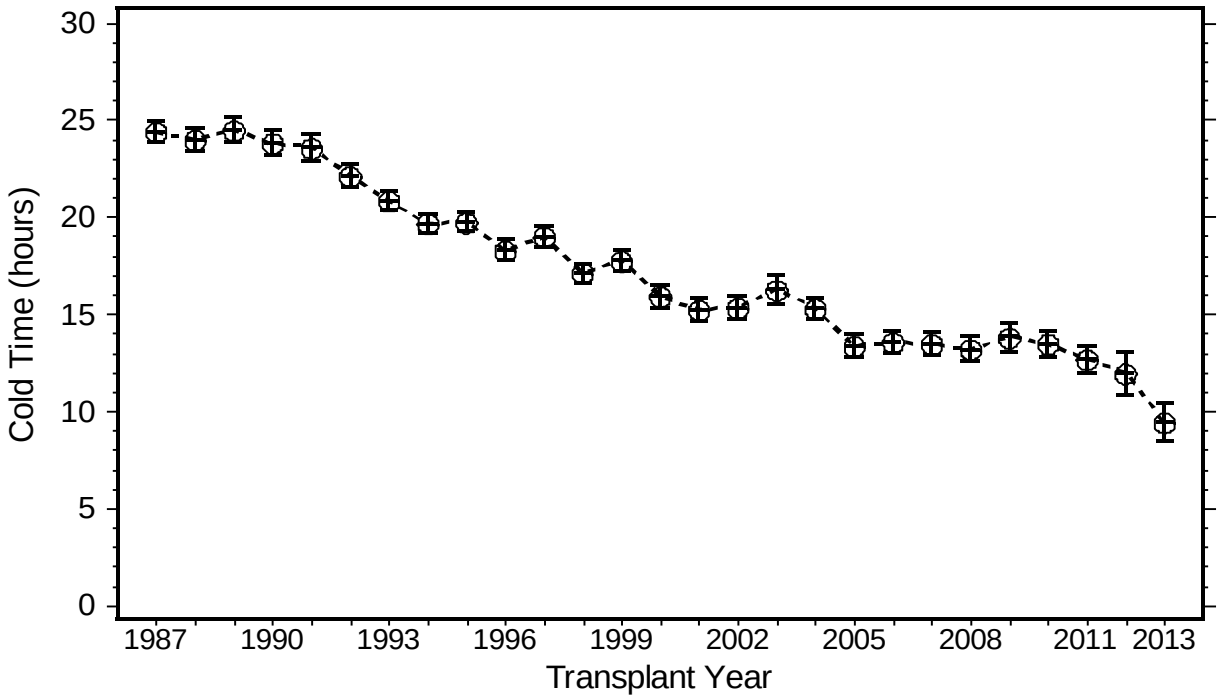
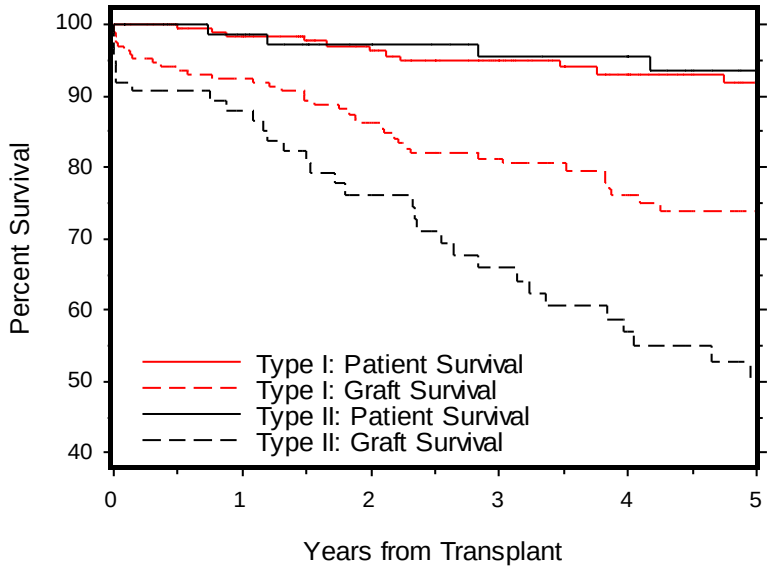


EXHIBIT 8-3
RARE PRIMARY DISEASES

MPGN Type I and Type II

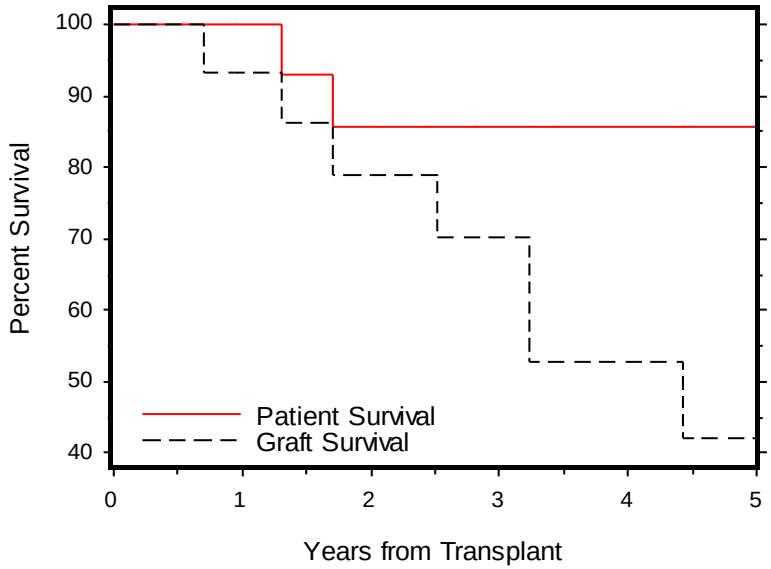
Type I						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1995	62	88.1±4.3	45	65.3±7.3	107	78.2±4.1
1996-2013	49	89.4±5.1	33	76.8±9.3	84*	85.1±4.7
Total	111	88.8±3.2	78	70.1±5.7	191*	81.3±3.1
Type II						
Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1996	22	78.6±9.6	25	43.1±10.7	47	59.5±7.7
1997-2013	21	78.1±11.8	19	73.2±11.9	40	75.4±8.5
Total	43	79.0±7.2	44	54.4±8.4	87	65.9±5.8

*2 Type I cases from 1997-2010 are missing donor source.



Sickle Cell Nephropathy

Era	LD (n)	DD (n)	Total (n)
1987-1996	3	6	9
1997-2004	3	3	6
2005-2013	1	0	1
Total	7	9	16



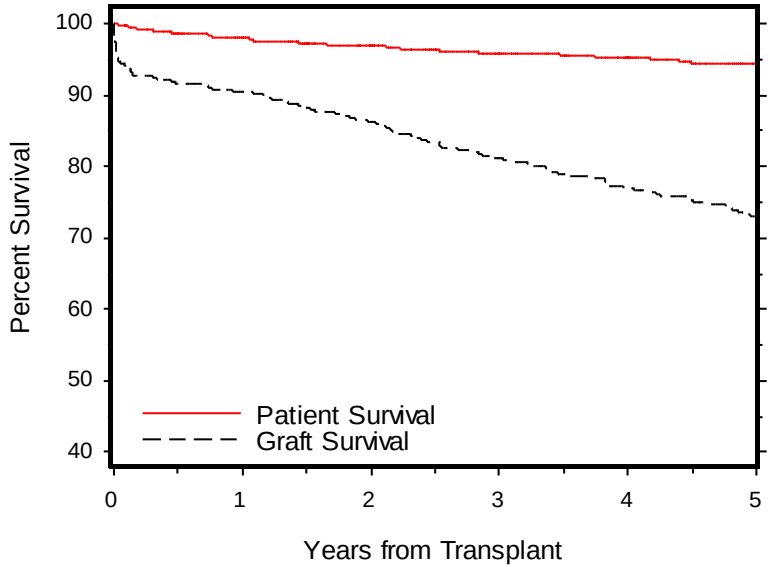
LD=Living donor; DD=Deceased donor; GS=Graft Survival; se=standard error;

EXHIBIT 8-3 (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
1987-1995	232	83.3±2.5	195	62.8±3.6	428	74.0±2.2
1996-2004	217	89.5±2.3	126	84.1±3.7	347	87.5±2.0
2005-2013	54	97.0±3.0	70	83.0±6.6	126*	90.1±3.5
Total	503	87.2±1.6	391	72.8±2.5	901*	81.1±1.4

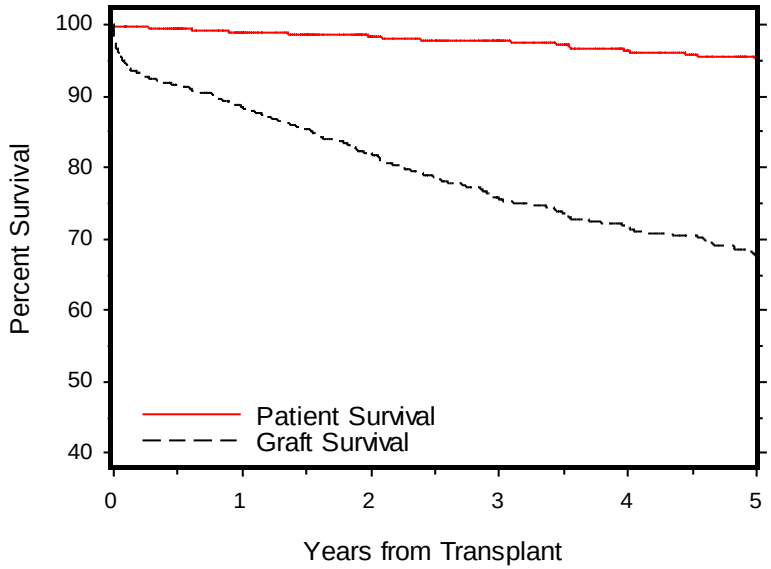
*1 case from 1987-1995 is missing donor source.
4 cases from 1996-2004 are missing donor source
2 cases from 2005-2013 are missing donor source.



Focal Segmental Glomerulosclerosis

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1995	246	73.7±2.9	329	65.5±2.7	575	69.1±2.0
1996-2004	230	83.4±2.8	241	78.5±3.0	474	80.7±2.1
2005-2013	80	91.4±3.8	178	79.3±4.3	259*	82.8±3.2
Total	556	79.7±1.9	748	72.6±1.8	1308*	75.6±1.3

*3 cases from 1996-2024 are missing donor source
1 case frp, 2005-2013 is missing donor source



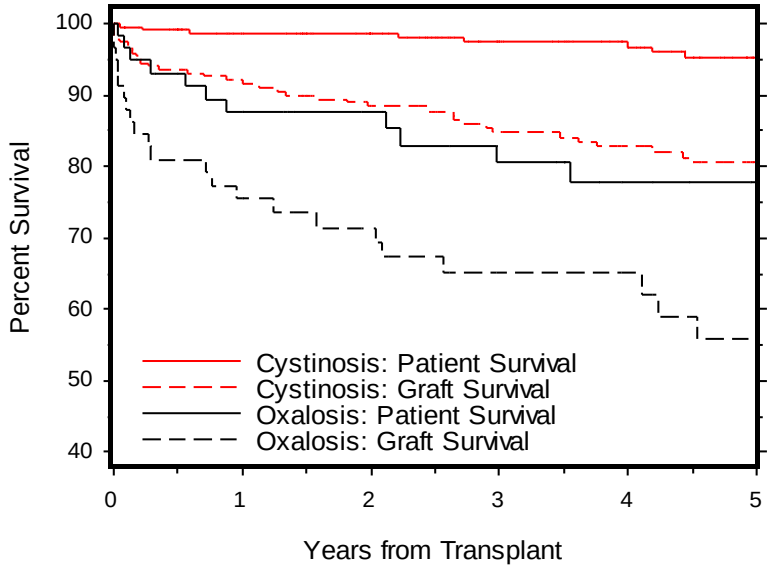
LD=Living donor; DD=Deceased donor; GS=Graft Survival; se=standard error;

EXHIBIT 8-3 (continued)
RARE PRIMARY DISEASES

Metabolic Disease

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
Cystinosis						
1987-1995	43	89.3±5.1	66	70.6±5.7	109	77.9±4.1
1996-2013	73	90.9±3.9	43	92.9±5.0	116	91.6±3.1
Total	116	90.2±3.1	109	78.8±4.2	225	84.7±2.6
Oxalosis						
1987-1995	14	35.7±12.8	22	58.0±10.7	36	49.0±8.4
1996-2013	6	--	15	93.3±6.4	22*	95.5±.4.4
Total	20	51.4±11.8	37	72.0±7.6	58*	65.1±6.6

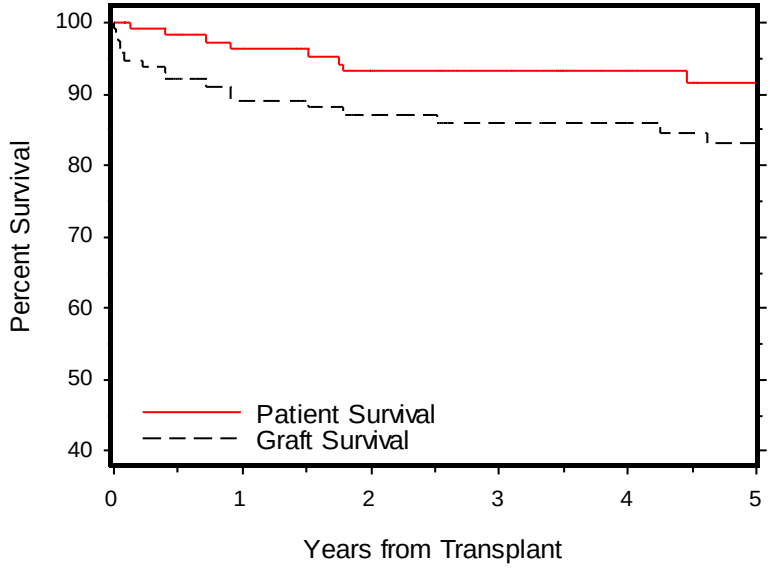
1 oxalosis case from 1996-2013 is missing donor source.



Genetic Disease

Era	LD (n)	3 yr GS±se	DD (n)	3 yr GS±se	Total (n)	3 yr GS±se
1987-1995	30	76.4±7.8	25	79.8±8.1	55	78.0±5.6
1996-2013	41	96.6 ±3.4	19	87.8±8.1	61	93.4±3.7
Total	71	87.8±4.1	44	83.2±5.8	116	86.0±3.4

*1 case from 1996-2013 is missing donor source



LD=Living donor; DD=Deceased donor; GS=Graft Survival; se=standard error;