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Kidney transplant practice patterns and outcome benchmarks over 30 years: The 2018 report of the NAPRTCS

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Abstract

The NAPRTCS has collected clinical information on children undergoing renal transplantation since 1987 and now includes information on 12 920 renal transplants in 11 870 patients. Since the first data analysis in 1989, NAPRTCS reports have documented marked improvements in patient and allograft outcomes after pediatric renal transplantation in addition to identifying factors associated with both favorable and poor outcomes. The registry has served to document and influence practice patterns, clinical outcomes, and changing trends in renal transplantation and also provides historical perspective. This report highlights current practices in an era of major changes in DD kidney allocation and continuing steroid minimization. This report presents outcomes of the patients in the NAPRTCS transplant registry up to end of 2017. In particular, an increase in the cumulative incidence of late first AR has occurred in the most recent cohort, while all prior cohorts had a lower cumulative incidence of late first AR.

KEYWORDS
acute rejection, graft survival, infections, kidney, malignancies, pediatric, transplantation

1 | INTRODUCTION

The NAPRTCS has collected clinical information on children undergoing renal transplantation since 1987[1] and now includes information on 12 920 renal transplants in 11 870 patients. The NAPRTCS dataset remains a unique resource for the pediatric renal transplant community to document changes in practice, improvements in outcomes, and to generate hypotheses for future studies.

Changes the registry have documented over time include a steady increase in patient and allograft survival across both living and DD kidney transplant, a reduction of the graft survival gaps between living vs DD kidneys, a marked decrease in early AR, improvements in linear growth, the emergence of opportunistic infections and malignancies, and changes in donor source with changes in allocation schemes.[2]

The NAPRTCS registry is now also a resource to establish covariate-adjusted benchmarks against which pediatric transplant programs are measuring their standards of practice and outcomes.

This analysis reports on the outcomes of the patients in the NAPRTCS transplant registry up to the end of December 2017, with special emphasis on most recent data and comparisons to the entire 30-year cohort.

2 | PATIENTS AND METHODS

For the transplant registry, data are submitted on patients transplanted before their 21st birthday, at the time of transplant, 1 and 6 months post-transplant, and every 6 months thereafter. The initial transplant information consists of recipient age, gender, race, primary disease, type and duration of dialysis, type of transplant, degree of HLA-A, B and DR mismatch, ischemia time, height, and weight. At 30 days, data collected include graft outcome, initial immunosuppressive therapy, complications, and days of hospitalization during the first 30 days. Thereafter, information is collected every 6 months regarding height, weight, serum creatinine, allograft and patient survival, type and dose of immunosuppressive therapy, and the use of other medications. Information is collected with each AR episode to document treatment and response to treatment. An AR episode is defined by the physician's decision to initiate specific antirejection therapy. The registry has not collected data on BK viremia or BK virus nephropathy, but started to collect these data in 2018 with recently implemented updates to the data elements.

Pediatric transplant centers that are actively contributing data are included in the establishment of short-term and longer-term clinical benchmarks. Benchmark reports include data from the past 6 years, are updated nightly, and are available to the centers on a secure website. Short-term benchmarks include stratified rates of AR in the first year and freedom from AR at 1 year, catch-up growth in the first 2 years after transplantation, and hospitalization rates in months 1-6 and the subsequent 18 months post-transplantation. Longer-term benchmarks include stratified 1- and 5-year allograft survival, 5-year allograft function (estimated creatinine clearance), 3-year rates of malignancy, and 5-year patient survival.

Multivariable linear regression analysis of repeated measures was used to identify factors associated with eGFR decline over time (data was included to 7 years post-transplant). An unstructured covariance matrix was used to model the repeated measures within subjects. Variables included in the model were baseline creatinine clearance at Day 30, age-group at transplant, sex, race (black vs not black), primary diagnosis (hypo/dysplasias vs FSGS vs other), donor
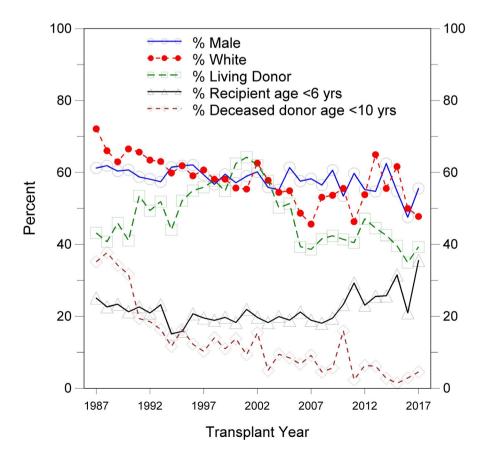

FIGURE 1 Recipient and donor demographics

TABLE 1 Recipient characteristics by age at transplant

	Age at transplantation				
	0-1 y (%)	2-5 y (%)	6-12 y (%)	13-17 y (%)	>18 y (%)
Gender					
Male	70.0	65.2	58.0	56.0	54.3
Female	30.0	34.8	42.0	44.0	45.7
Race					
White	73.1	62.3	60.0	55.7	50.9
Black	7.9	14.6	14.9	19.7	24.5
Hispanic	12.7	16.1	17.8	17.9	16.8
Other	6.3	7.0	7.2	6.7	7.7
Primary diagnosis					
Renal plasias	27.5	23.3	16.4	11.4	9.8
Obstructive uropathy	19.6	20.2	15.6	13.2	9.9
Other	52.4	48.7	55.6	62.3	63.9
FSGS	0.6	7.7	12.4	13.1	16.4

source, ATN, history of previous transplant, history of dialysis prior to transplant, use of antihypertensive medications at day 30, initial immunosuppression, rejection in the first 30 days, and transplant era. The SAS PROC mixed software package (Version 9.4) was used for theses analyses. All statistical tests were two-sided, and a *p*-value of <.05 was considered significant.

Standardized *z*-scores are computed following an age- and sex-specific formula based on the NHANES III 2000 growth chart dataset. 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.

3 | RESULTS

3.1 | Centers

At the time of the 2018 Transplant Annual Report, 136 centers contributed data to the transplant registry from 1998 to 2018. For the
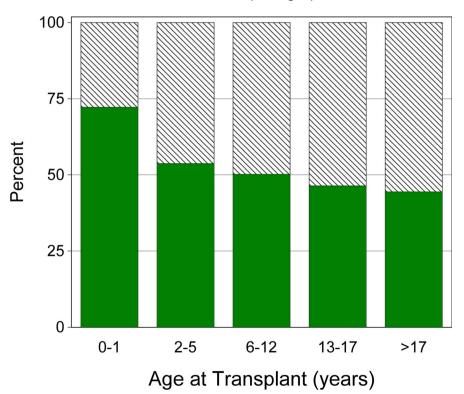

FIGURE 2 Donor source by recipient age at transplant

TABLE 2 Percent drug utilization—day 30 post-transplant (patients with functioning grafts)

	Transplant era 1996-2001	Transplant era 2002-2007	Transplant era 2008-2017
Prednisone	97.8	82.4	59.7
Cyclosporine	71.8	15.5	3.1
TAC	23.9	78.9	92.7
MMF	52.5	77.0	87.7
Aza	26.6	3.1	4.9
Sirolimus	3.6	13.4	0.5

most recent period (between January 1, 2012, to December 31, 2017), 40 centers have contributed transplant data.

3.2 | Patient characteristics

Since 1987, data have been collected on a total of 12 920 renal transplants in 11 870 pediatric patients. This report represents 1317 new transplants and 1238 new patients entered into the transplant registry since the 2010 Annual Report published in 2014. Of the 12 920 transplants, 10 032 were primary transplants and 2888 were repeat transplants. Preemptive transplants were performed in 2437/10032 (24.3%). DDs <10 years of age were used in less than 20% of pediatric recipients (Figure 1). Patient demographics in the cohort have changed over the course of the registry with a decrease in the percentage of white recipients from a high of 72% in 1987 to under 50% in the most recent cohort (Figure 1). The gender distribution has remained stable with approximately 60% male recipients. The age distribution of recipients has not changed significantly with 13- to 17-year-olds being the most common age at transplantation (38.8%) followed by 6- to 12-year-olds (32.3%), 2- to 5-year-olds (15.3%), and 0- to 1-year-olds (5.5%). The most common primary diagnosis remains aplastic/hypoplastic/dysplastic kidneys in 15.7% and obstructive uropathy in 15.2% of recipients. FSGS is the third most common (11.5%) and represents the leading cause of acquired renal disease. The etiology of ESRD varies by ethnicity with FSGS

TABLE 4 Probability of first rejection within first (a) 12 mo and (b) 6 mo

	LD		DD	
Transplant year	%	SE	%	SE
(a) Probability of first rejection at 12 mo				
1987-1991	52.9	1.5	68.1	1.3
1992-1996	41.6	1.3	55.6	1.3
1997-2001	25.4	1.1	31.3	1.5
2002-2006	14.3	1.1	18.3	1.3
2007-2011	11.1	1.4	15.3	1.4
2012-2017	12.7	2.1	13.2	1.8
(b) Probability of first rejection at 6 mo				
1987-1991	48.4	1.5	63.7	1.3
1992-1996	38.5	1.2	50.0	1.3
1997-2001	20.3	1.0	26.0	1.4
2002-2006	9.8	0.9	12.2	1.1
2007-2011	8.4	1.2	9.4	1.1
2012-2017	7.1	1.5	6.3	1.2

being the most common in black recipients (22.6%) and aplasia/hypoplasia/dysplasia and obstructive uropathy the most common in white (33.3%) and Hispanic recipients (28.7%). In addition, the etiology of ESRD changes by age at transplant (Table 1).

3.3 | Donor characteristics

LD recipients peaked at 64% in 2001, with the current cohort consisting of <50% LDs (Figure 1). Parents account for the majority of LDs to the pediatric recipient (4957 of 6413; 77.3%). There has been an increase in the number of unrelated LDs from 1.3% of LD transplants in 1987 to 31.4% in 2017. LDs are most common for recipients aged 0-5 years (Figure 2).

In June 2015, NAPRTCS revised how missing HLA alleles were counted (from non-matching to missing); hence, donor-recipient HLA mismatch in the post-2015 period cannot be compared to prior reports.

TABLE 3 Percent drug utilization—post-transplant (patients with functioning grafts)

	Transplant era 1996-2001				Transplant era 2002-2007				Transplant era 2008-2017			
	30 d	1 y	3 y	5 y	30 d	1 y	3 y	5 y	30 d	1 y	3 y	5 y
Prednisone/CsA/MMF	35.4	38.1	30.6	22.4	9.7	8.6	7.9	7.5	1.7	1.9	0.5	0.7
Prednisone/CsA/Aza	23.1	17.7	14.2	8.9	0.8	0.8	0.6	0.7	0.1	0.2	0.3	0.4
Prednisone/CsA	10.7	4.4	3.8	3.5	1.5	0.8	0.3	0.8	0.4	0.3	0.2	0.0
Prednisone/TAC/MMF	14.3	19.6	24.4	30.1	51.3	49.6	44.2	42.1	48.9	41.7	38.6	33.1
Prednisone/TAC/Aza	2.3	4.9	6.5	6.9	1.7	2.4	2.7	3.9	2.0	2.3	4.3	6.3
Prednisone/TAC	4.2	5.0	6.7	6.9	4.1	5.8	6.7	6.2	2.9	8.2	8.0	6.7
TAC/MMF	0.4	1.1	1.7	2.5	10.7	9.4	11.5	13.1	33.8	27.3	26.5	27.5
Other combination	9.5	9.2	12.0	17.3	20.1	22.7	26.0	25.8	10.1	18.1	21.6	25.3

TABLE 5 Relative hazard of first rejection episode, index transplants, 1987-2017

Characteristic	Comparison group	Reference group	LD RH	LD P-value	DD RH	DD P-value
Transplant era 1987-1996						
Recipient race	Black	Non-black	1.36	<.001	1.28	<.001
Recipient age	<24 mo	≥24 mo	0.72	.003	1.08	.603
Induction therapy	No	Yes	1.21	<.001	1.19	<.001
Prior random transfusions	1-5	None	0.95	.424	0.91	.156
	>5		1.05	.539	0.95	.510
Donor-specific transfusions	Yes	No	0.90	.226	–	–
Preop immunotherapy	Yes	No	0.97	.556	–	–
Cold storage time	>24 h	≤24 h	–	–	0.99	.793
Transplant year	1987-1995		0.93	<.001	0.92	<.001
Transplant era 1997-2006						
Recipient race	Black	Non-black	0.98	.87	1.48	<.001
Recipient age	<24 mo	≥24 mo	0.47	<.001	0.78	.525
Induction therapy	No	Yes	1.14	.097	0.82	.057
Prior random transfusions	1-5	None	1.05	.613	1.02	.820
	>5		1.04	.799	0.98	.919
Donor-specific transfusions	Yes	No	0.41	.032	–	–
Preop immunotherapy	Yes	No	1.09	.262	–	–
Cold storage time	>24 h	≤24 h	–	–	1.18	.220
Transplant year	1997-2006		0.92	<.001	0.93	<.001
Transplant era 2007-2017						
Recipient race	Black	Non-black	2.00	.012	1.36	.079
Recipient age	<24 mo	≥24 mo	0.78	.490	0.66	.363
Induction therapy	No	Yes	0.81	.287	1.03	.852
Prior random transfusions	1-5	None	0.73	.213	1.31	.164
	>5		0.95	.868	0.65	.216
Donor-specific transfusions	Yes	No	1.95	.367	–	–
Preop immunotherapy	Yes	No	1.05	.793	–	–
Cold storage time	>24 h	≤24 h	–	–	0.91	.809
Transplant year	2007-2017		1.03	.332	1.01	.745

3.4 | Preemptive transplantation

Twenty-four percent of primary transplants in the transplant registry were preemptive. The rate of preemptive transplantation differs significantly between recipients of living (33%) and DD (13%) organs (P < .001); between males (27%) and females (19%, P value <.001); and among the various age-groups (p value <.001) with the highest percentage (28%) occurring in 6- to 12-year-old age-group. Preemptive transplantation differs across races and occurs most commonly in white recipients (30%) followed by other race (17%), Hispanic (16%), and black (13%) recipients (P < .001).

3.5 | Immunosuppression

Tables 2 and 3 shows the maintenance immunosuppression regimens used, either as individual drugs at Day 30 post-transplant (panel A) or as immunosuppressive regimens at different time points by era (panel

B), in LD transplants. Prednisone use has declined to under 50% at Day 30 in the most recent era (Table 2). By era, in the most recent 2008-2017 period, a TAC-MMF-prednisone or TAC-MMF combination is the most common immunosuppressive regimen used (Table 3). Similar trends are seen in the DD transplants, data not shown.

3.6 | Acute rejection

The 1-year probability rate (± SE) of a first AR episode in the 2007-2011 time period was 11.1 ± 1.4% for LDs and 15.3 ± 1.4% in DDs (Table 4). In the most recent transplant period 2012-2017, the probability of an AR declined further in DD source to 13.2 ± 1.8%, but the rate for LD went up slightly to 12.7 ± 2.1%. This is the first time that a 12-month first AR rate has been higher in a more recent cohort. The 12-month post-transplant time point is the time period used in all prior NAPRTCS reports. In contrast, when looking at the 6-month post-transplant time point (Table 4), the first AR rates continue to drop, indicating that any
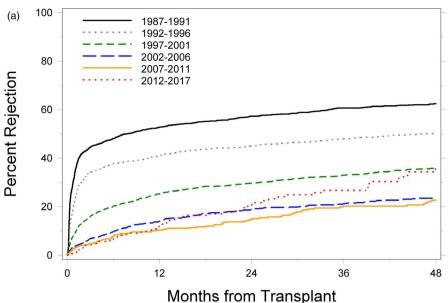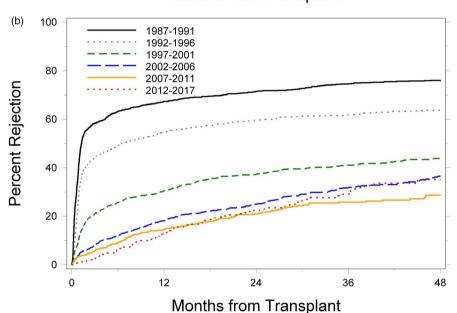
FIGURE 3 First rejection rates, by donor type and era, showing steady decrease in early AR rates in more recent eras, but a change in slope of first late AR in most recent era (red dotted line = 2012-2017 cohort). Panel A, LD; Panel B, DD

increases in 12-month rates occur in the latter parts of that time period. Data are still accruing in this latest cohort. Table 5 depicts that a more recent transplant year is no longer associated with a significantly lower risk of AR. The use of renal biopsy for histological confirmation has steadily increased to an average of 94% in the past 5 years reported. The registry does not collect information on whether the biopsy was performed for cause or as surveillance.

Several other changes in risk factors for first episode AR have occurred over time (Table 5). Several risk factors that significantly increased or decreased AR risk for both living and DD transplants in older eras, such as use of induction therapy, or more recent transplant year, are now no longer significant. Recipient black race has retained significance only in LD transplants.

While early AR (occurring within first 12 months) incidence has significantly decreased over the years in each more recent cohort, late ARs, which had a steady parallel slope in all prior cohorts, now show a markedly higher slope in the most recent cohort (Figure 3, LDs panel A and DDs panel B). Thus, the cumulative 48 month AR rate of nearly 40% is now higher in the most recent cohort than in the prior two cohorts for LD transplants, and to the most recent cohort for DD transplants, though few participants in this cohort have 48 month data. For LD transplants, this AR curve in the 2012-2017 cohort was significantly different than the prior 2007-2011 cohort (log rank *P* value = 0.038). For DD transplants, this AR curve in the 2012-2017 cohort is not significantly different than the prior 2007-2011 cohort (log rank *P* value = 0.664). The population at risk for these data is shown in Table 6.

3.7 | Renal function

Younger recipients begin with a higher calculated creatinine clearance post-transplant and are subject to greater absolute declines over time compared with older recipients (Figure 4, panel A: LD

and panel B: DD). These differences in function by age at transplant become negligible over time in long-term renal allograft survivors, with the exception of the youngest (0-1 years) LD recipients who continue to have better function at 7 years post-transplant. Table 7 presents the results of multivariable linear regression analyses of repeated measures to identify factors associated with creatinine clearance decline over time. Many factors impact the creatinine clearance decline slope. Age at transplant remains independently significant.

3.8 | Graft survival

The 1-, 3-, and 5-year allograft survival continues to improve for each more recent cohort. In the 2012-2017 cohort, the 1-year allograft survival is now very high at >99% and >97% for living or DD recipients (Table 8). In the 2012-2017 cohort, the 5-year allograft survival now exceeds 90% for both LD and DD recipients.

Table 9 demonstrates the causes of graft failure among both index and subsequent transplants over the lifetime of the registry. Chronic rejection (35.6%) and AR (13.0%) in index transplants as attributed by the reporting site remain the most important cause of allograft failure. When limiting to the 2008-2017 cohort (Table 9), primary non-function is now a smaller proportion of graft failure causes. Death with a functioning graft remains a low proportion of graft failure cause.

Table 10 shows the results of a univariable model of risk factors for graft loss in the recent 2008-2017 era and contrasts LD and DD recipient characteristics. For LD recipients, significant covariates include history of prior dialysis (worse survival) and more recent transplant year (better survival). For DD recipients, the only significant covariate was male gender (better survival). Notably, recipient age <24 months, black recipient race, and prolonged cold storage time do not impact graft survival in recent years.

3.9 | Recurrence of primary disease

Recurrence of the primary native kidney disease accounts for 7% of allograft failure in the index graft. MPGN type 1 and type 2 were the primary renal disease in 201 and 90 patients, respectively. The 5-year patient survival is similar (92% and 94% respectively), but the 5-year allograft survival is significantly different. Patients with type 1 have a 74% 5-year allograft survival vs 50% 5-year allograft survival for type 2. The entire NAPRTCS cohort consists of 1367 cases of FSGS. The 5-year patient survival for LD and DD is 96% and 94%, respectively. The 5-year allograft survival is 71% and 66%, respectively, much lower than the 5-year allograft survival of 83% (LD) and 82% (DD) for the entire cohort.

3.10 | Hypertension

The use of antihypertensive medications at 30 days after transplant has decreased slightly with time, from 81% in 1996 to 73% in 2017 in LD recipients and from 87% in 1996 to 72% in DD recipients in 2017.

TABLE 6 At-risk population by donor source and time post-transplant

| Transplant year	Transplant Number at risk	6 mo Number at risk	12 mo Number at risk	18 mo Number at risk	24 mo Number at risk	30 mo Number at risk	36 mo Number at risk	42 mo Number at risk	48 mo Number at risk
(a) Time to first transplant LD numbers at risk									
1987-1991	1173	586	515	481	449	429	397	370	350
1992-1996	1519	875	779	714	664	613	567	520	470
1997-2001	1530	1084	941	857	800	722	658	596	533
2002-2006	1085	868	770	689	620	547	491	419	362
2007-2011	501	393	350	302	258	221	194	168	152
2012-2017	299	218	179	140	109	88	65	42	25
(b) Time to first transplant DD numbers at risk									
1987-1991	1318	436	361	333	293	275	241	223	208
1992-1996	1323	607	506	451	406	366	343	290	262
1997-2001	956	633	546	465	423	369	329	288	255
2002-2006	920	715	599	519	469	385	310	255	204
2007-2011	719	541	449	343	279	224	186	159	134
2012-2017	428	303	243	191	153	117	86	50	33
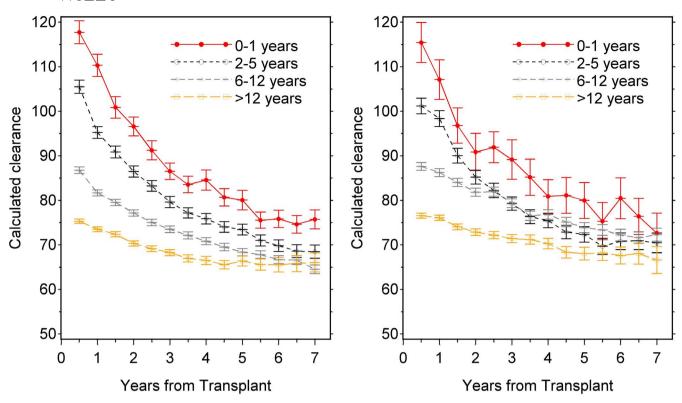
FIGURE 4 Creatinine clearance (mean ± SE) by age among LDs (left panel) and DDs (right panel)

3.11 | Growth

At the time of transplantation, the mean height deficit for all patients is 1.72 SDs below the age- and sex-adjusted height level. This deficit is greater for males (−1.74) than females (−1.67). The younger patients (2-5 years) and those with prior transplants have greater height deficits at transplant. This deficit has been improving steadily over the registry reporting period (Figure 5, panel A) with a mean deficit of −2.43 in 1987 which has improved to a mean deficit of −1.62 in 2017. The mean change in height *z*-score at 12 months is 0.12 from transplant. Growth patterns post-transplant vary by age with the youngest patients experiencing the most *z*-score improvement (age 0-1: 0.54, age 2-5: 0.38, age 6-12: 0.07, age ≥13: 0.03) in their mean height deficit (Figure 5, panel B). A rapid increase in standardized weight scores is observed for all age-groups in the first 6 months post-transplant. Patients gain an average of 0.81 SD in weight in the first year post-transplant with relative stability in average standardized weight scores over the next 5 years.

3.12 | Re-hospitalization rates after the initial post-transplant period

In the registry reporting period, LD recipients were less frequently hospitalized during months 1-5 post-transplantation (45% vs 51%). The most common reason for hospitalization in this period was treatment of rejection, which was the reason in 21% and 16% in DD and LD recipients respectively. Viral (13% vs 12%) and bacterial (13% vs 12%) infections and treatment of hypertension (5% vs 3%) were other major causes of early re-hospitalization. Hospitalization stays during months

1-5 from 1997 to 2006 showed a decrease in frequency (43%) and duration (median 6 days, range 1-124) compared with the 1987-1996 period (53%, median 10 days, range 1-153), but then have not shown any further drop in the 2007-2017 period (frequency 45%, median 6 days, range 1-180). This trend was true for both LD recipients (1987-1996: 48%, median 8 days; 1997-2006: 42%, median 6 days, 2007-2017: 47%, median 5 days) and for DD recipients (1987-1996: 58%, median 11 days; 1997-2006: 44%, median 7 days and 2007-2017: 44%, median 6 days). The initial decline is principally attributable to a decline in hospitalization for rejection in both LD (23% to 11% to 5%) and DD (33% to 13% to 7%) recipients.

Table 11a (LD source) and b (DD source) shows the percent hospitalization, stratified by era, by time post-transplant, and by hospitalization cause. AR and hypertension have declined as the primary hospitalization reason, across the three eras. Consistent with our prior report,[3] with the decline in hospitalization for AR, the most common reason for hospitalization in the 6- to 24-month post-transplant period is infection (bacterial or viral). Further, in the latest cohort, bacterial infection has now overtaken AR as the most common cause of hospitalization in the 1- to 6-month post-transplant time period, for both LD and DD source.

3.13 | Patient survival

Over the time of the registry, both allograft survival and patient survival (Figure 6, panels A and B, respectively) have significantly improved for both LD and DD recipients. While a gap remains in 7-year allograft survival, the gap between LD and DD patient survival rates

TABLE 7 Multivariable model for factors associated with creatinine clearance decline over time

Parameter	Value	Estimate	SE	95% CI Lower	Upper	DF	t value	Pr > |t|
Intercept		70.1797	1.4624	67.3132	73.0463	9392	47.99	<0.0001
eGFR at 30 d	Continuous	0.2228	0.005891	0.2112	0.2343	9392	37.81	<0.0001
Age at transplant	0-1 y	20.4272	1.0829	18.3045	22.5499	9392	18.86	<0.0001
	2-5 y	12.1301	0.7146	10.7294	13.5308	9392	16.98	<0.0001
	6-12 y	6.5697	0.5316	5.5277	7.6116	9392	12.36	<0.0001
	>12 y	0	.	.	.	.	.	.
Sex	Female	3.2817	0.4757	2.3493	4.2142	9392	6.90	<0.0001
	Male	0	.	.	.	.	.	.
Race	Black	−7.2092	0.6385	−8.4607	−5.9577	9392	−11.29	<0.0001
	Other	0	.	.	.	.	.	.
Primary diagnosis	Plasias	−1.8651	0.5262	−2.8966	−0.8336	9392	−3.54	0.0004
	FSGS	−0.6260	0.7559	−2.1077	0.8558	9392	−0.83	0.4076
	Other	0	.	.	.	.	.	.
Donor source	DD	4.0578	0.4895	3.0983	5.0172	9392	8.29	<0.0001
	LD	0	.	.	.	.	.	.
ATN	No	4.1027	0.9607	2.2195	5.9859	9392	4.27	<0.0001
	Yes	0	.	.	.	.	.	.
Prior transplant	No	2.1306	0.6529	0.8509	3.4104	9392	3.26	0.0011
	Yes	0	.	.	.	.	.	.
Prior dialysis	No	−0.7549	0.5579	−1.8484	0.3386	9392	−1.35	0.1760
	Yes	0	.	.	.	.	.	.
Antihypertensive meds at day 30	No	−0.1065	0.5712	−1.2261	1.0132	9392	−0.19	0.8522
	Yes	0	.	.	.	.	.	.
Initial immunosuppression	None	−2.3704	1.0487	−4.4261	−0.3147	9392	−2.26	0.0238
	Cyclosporine	−10.0712	0.6967	−11.4368	−8.7055	9392	−14.46	<0.0001
	TAC	0	.	.	.	.	.	.
Rejection in first 30 d	No	1.9347	0.6462	0.6680	3.2014	9392	2.99	0.0028
	Yes	0	.	.	.	.	.	.
Transplant year	1987-1996	−15.4117	0.9251	−17.2250	−13.5983	9392	−16.66	<0.0001
	1997-2006	−10.4828	0.7618	−11.9760	−8.9895	9392	−13.76	<0.0001
	2007-2017	0	.	.	.	.	.	.
Follow-up visit in 6-mo intervals	Continuous (0.5 to 7)	−3.5868	0.07350	−3.7309	−3.4427	9392	−48.80	<0.0001

Note: Pr > t = *P* value.

has also narrowed substantially and now is clinically negligible in the cohort transplanted from 2007 to 2017.

The causes of death (total 602) are summarized in Table 12a (entire 30-year cohort) and b (transplants performed between 2005 and 2017) with infection accounting for 27.9% of deaths, cardiopulmonary 14.5%, malignancy 11.3%, and dialysis related complications 3% in the entire cohort. Almost half of the patients who died (48%) had a func graft.

3.14 | Malignancy rates

To date, 316 malignancies have been reported, of which the majority (85%) are post-transplant lymphoproliferative disorders. The median

TABLE 8 Graft survival rates by donor source and transplant era

Cohort group	Graft survival rates LD 1 y	3 y	5 y	DD 1 y	3 y	5 y
1987-1991	90.3	82.4	76.3	76.4	65.3	56.9
1992-1996	92.1	87.0	81.5	87.0	77.9	70.9
1997-2001	95.4	91.4	86.4	93.1	84.5	78.3
2002-2006	96.3	92.1	86.8	94.3	84.1	79.3
2007-2011	96.9	94.4	86.7	95.5	88.5	83.3
2012-2017	99.5	97.2	94.9	97.6	94.4	90.1

TABLE 9 Causes of graft failure in (a) entire cohort over the 30 y, (b) the most recent 2005-2017 cohort

|	Index graft failures		Subsequent graft failures		All graft failures	
	N	%	N	%	N	%
(a)						
Total transplants with graft failure	2810	100.0	351	100.0	3161	100.0
Cause of graft failure						
Death with func graft	71	2.5	28	8.0	281	8.9
Primary non-function	257	9.2	2	0.6	73	2.3
Vascular thrombosis	30	1.1	39	11.1	296	9.4
Other technical	71	2.5	4	1.1	34	1.1
Hyper AR	15	0.5	4	1.1	19	0.6
Accelerated AR	33	1.2	8	2.3	41	1.3
AR	366	13.0	44	12.5	410	13.0
Chronic rejection	995	35.4	131	37.3	1126	35.6
Recurrence of original kidney disease	187	6.7	34	9.7	221	7.0
Renal artery stenosis	15	0.5	0	0.0	15	0.5
Bacterial/viral infection	49	1.7	6	1.7	55	1.7
Calcineurin inhibitor nephrotoxicity	13	0.5	0	0.0	13	0.4
De novo kidney disease	9	0.3	2	0.6	11	0.4
Patient discontinued medication	127	4.5	10	2.9	137	4.3
Malignancy	35	1.3	2	0.6	37	1.2
Other/unknown	355	12.6	37	10.5	392	12.4
(b)						
Transplant era 2008-2017						
Total transplants with graft failure	122	100.0	11	100.0	133	100.0
Cause of graft failure						
Death with func graft	14	11.5	2	18.2	16	12.0
Primary non-function	6	4.9	0	0.0	6	4.5
Vascular thrombosis	13	10.7	1	9.1	14	10.5
Other technical	1	0.8	0	0.0	1	0.8
Hyper AR	1	0.8	0	0.0	1	0.8
Accelerated AR	0	0.0	0	0.0	0	0.0
AR	20	16.4	0	0.0	20	15.0
Chronic rejection	26	21.3	3	27.3	29	21.8
Recurrence of original kidney disease	13	10.7	0	0.0	13	9.8
Renal artery stenosis	0	0.0	0	0.0	0	0.0
Bacterial/viral infection	2	1.6	1	9.1	3	2.3
Calcineurin inhibitor nephrotoxicity	0	0.0	0	0.0	0	0.0
De novo kidney disease	0	0.0	0	0.0	0	0.0
Patient discontinued medication	2	1.6	2	18.2	4	3.0
Malignancy	0	0.0	0	0.0	0	0.0
Other/unknown	24	19.7	2	18.2	26	19.6
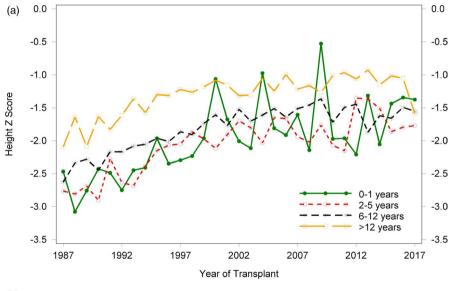
time from transplant to malignancy diagnosis was 15.2 months for lymphoproliferative malignancies and 31.4 months for non-lymphoproliferative malignancies. The 1- and 3-year malignancy rates had peaked in the 1997-2001 cohort, decreased thereafter, but now show significant increases again in the most recent 2012-2017 cohort (P < .001, Table 13).

4 | DISCUSSION

Results after pediatric kidney transplantation have shown significant improvements over the last three decades.[4-6] The sequential NAPRTCS registry reports have served to track changes in pediatric renal transplantation over time and provided impetus for future

TABLE 10 Univariable model of graft survival, for transplant years 2008-2017

| Characteristic | Comparison group | Reference group | Graft failure Univariable proportional hazards regression model | | | |
| | | | LD | | DD | |
			HR	P-value	HR	P-value
Recipient age	≥ 24 mo	<24 mo	0.82	.712	0.83	.683
Transplant history	Prior transplants	No prior tx's	0.68	.274	1.15	.559
Induction therapy	Induction	No induction	1.00	.992	0.87	.523
Prednisone at 30 d	Prednisone	No prednisone	1.82	.105	0.73	.160
Recipient race	Black	Non-black	1.82	.210	1.25	.357
Dialysis history	Prior dialysis	No prior dialysis	3.62	.007	1.04	.898
Cold storage time	>24 h	≤ 24 h	–	–	1.63	.346
Gender	Male	Female	0.90	.750	0.65	.049
Transplant year	Per year 2008-2017		0.79	.008	0.90	.041

Note: LD N = 680
DD N = 719.
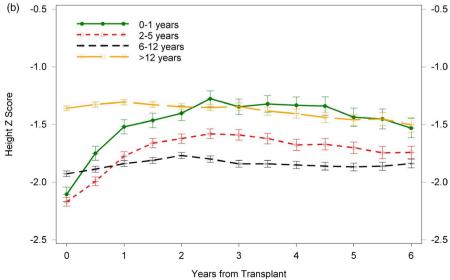
FIGURE 5 Height z-score by age at transplant—stratified by year of transplant (panel A) or years post-transplant (panel B)

TABLE 11 Hospitalization post-transplant frequency and reason: (a) LD, (b) DD

| | 1987-1996 | 1997-2006 | 2007-2017 |
	Percent hospitalized	Percent hospitalized	Percent hospitalized
(a)			
Time post-transplant (mo)			
1-6	48	42	47
6-12	27	30	30
12-18	21	24	29
18-24	19	20	27
Bacterial infection (mo)			
1-6	11	12	12
6-12	7	8	9
12-18	7	7	9
18-24	6	5	8
Viral infection (mo)			
1-6	13	11	10
6-12	7	9	10
12-18	5	6	8
18-24	5	6	5
Fungal infection (mo)			
1-6	0.8	0.7	0.6
6-12	0.2	0.3	0.3
12-18	0.2	0.4	0.6
18-24	0.2	0.3	0.0
Rejection (mo)			
1-6	23	11	5
6-12	9	6	4
12-18	6	5	4
18-24	6	3	6
Hypertension (mo)			
1-6	4.3	2.2	2.0
6-12	2.1	1.0	0.3
12-18	1.5	1.3	0.6
18-24	1.2	0.5	0.4
(b)			
Time post-transplant (mo)			
1-6	58	44	44
6-12	30	31	37
12-18	26	25	29
18-24	23	23	26
Bacterial infection (mo)			
1-6	13	12	15
6-12	8	10	11
12-18	6	8	7
18-24	4	5	7

(Continues)

TABLE 11 (Continued)
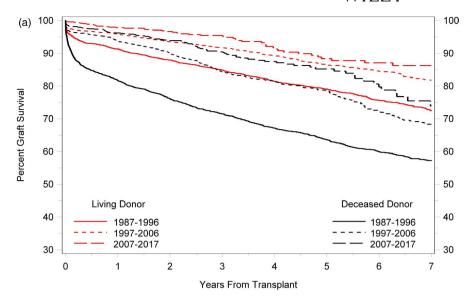
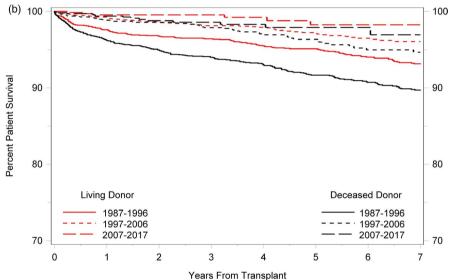| | 1987-1996 | 1997-2006 | 2007-2017 |
	Percent hospitalized	Percent hospitalized	Percent hospitalized
Viral infection (mo)			
1-6	17	11	9
6-12	6	8	7
12-18	6	6	6
18-24	5	5	5
Fungal infection (mo)			
1-6	1.3	0.7	0.6
6-12	0.5	0.5	0.4
12-18	0.4	0.2	0.6
18-24	0.2	0.2	0.5
Rejection (mo)			
1-6	33	13	7
6-12	12	9	9
12-18	9	8	7
18-24	8	7	8
Hypertension (mo)			
1-6	7.4	3.2	1.2
6-12	3.1	2.3	0.9
12-18	2.3	1.6	1.0
18-24	2.1	1.7	1.3

research questions. This report is the first time that DD 5-year allograft survival has reached 90%. However, this report is also the first time that a 12-month first AR rate has been higher in a more recent cohort. Uniquely and unlike other registry reports, NAPRTCS is designed to address pediatric specific outcomes, with input from pediatric community. The unique data in NAPRTCS relate to growth, hypertension, re-hospitalization, and recurrent disease. NAPRTCS registry data remain an important resource to establish national benchmarks against which individual pediatric transplant programs can measure their center's outcome and design quality improvement projects.

This report represents a cohort that overlaps a change in DD allocation in the United States, from the prior Share 35 policy implemented in October 2005, to the new KAS schema since December 2014, which is based on donor organ quality. Under the Share 35 policy, children received DD kidneys faster than previously, but with a corresponding drop in LD percentages[7] and relatively higher HLA mismatches. Several publications have highlighted the pros and cons of this allocation. Higher HLA mismatch still confers a risk of worse allograft survival even in the post-Share 35 era.[8,9] Other publications have addressed the impact of these KAS criteria in allowing highly sensitized patients to receive a kidney transplant, and the temporary effect of diverting some DD kidneys from children <6 to the highly sensitized.[10] To

FIGURE 6 Graph and patient survival by transplant era, stratified by donor source, showing steady improvement of graft survival in each more recent era (panel A) and continuing very high patient survival (panel B)

our knowledge, the effect of these policies in affecting *recent late first AR rates* has not been examined in detail. Follow-up data beyond the first year tends to be less complete in the OPTN registry. NAPRTCS may have more complete and more granular late first AR data, and this area is the focus of a new special study that we will be undertaking. It is also possible that changes to the patient characteristics or case mix from different centers may explain some of the dramatic changes in late first AR rates that we see in the most recent cohort.

The racial distribution of pediatric renal transplant recipients has changed over time with decrease in white race recipients, which is in keeping with demographics changes in the United States. While the remainders of the recipient characteristics (sex and age distribution and causes of ESRD) have not changed, FSGS continues to affect black recipients disproportionately. While the proportion of children receiving preemptive transplants has remained unchanged, they continue to occur more commonly in males and whites and less commonly in blacks. This finding is consistent with

a study by Patzer et al[11] that noted both Hispanic and black patients were less likely to be preemptively transplanted as compared to whites (14.2% and 8.7% vs 27.4%). This offers an insight into sexual and racial disparities and thus opportunities for intervention. The lack of improvement in allograft survival in patients with FSGS indicates a lack of optimal therapies to treat recurrent FSGS, another future opportunity.

There has been underutilization of donors younger than 5 years of age which account for less than 10% donors. A few years ago, NAPRTCS data showed comparable patient and graft survival in recipients of young donor kidneys (<5 years) to those who received kidneys from donors ≥5 years of age[12] indicating potential to use this group of donors.

The use of maintenance immunosuppression has not changed significantly since the last NAPRTCS report.[2] NAPRTCS registry data clearly show continuing decrease in the incidence of AR occurring during the first 12 months of transplant in DD transplants, but the rate increased in LD transplants in this most recent cohort.

TABLE 12 Causes of death in (a) entire cohort over the 30 y and (b) the most recent 2005-2017 cohort

	Causes of death, following primary renal transplantation								
	Total			LD			DD		
	N	%	Func graft	N	%	Func graft	N	%	Func graft
(a)									
All transplant patients									
All deceased patients	602	100.0	289	264	100.0	132	338	100.0	157
Cause of death									
Infection, viral	47	7.8	25	26	9.8	14	21	6.2	11
Infection, bacterial	75	12.5	38	35	13.3	16	40	11.8	22
Infection, not specified	46	7.6	15	23	8.7	8	23	6.8	7
Cancer/malignancy	68	11.3	49	38	14.4	28	30	8.9	21
Cardiopulmonary	87	14.5	40	31	11.7	15	56	16.6	25
Hemorrhage	34	5.6	12	10	3.8	2	24	7.1	10
Recurrence	10	1.7	1	4	1.5	1	6	1.8	0
Dialysis-related complications	18	3.0	0	8	3.0	0	10	3.0	0
Other, specify	151	25.1	77	64	24.2	35	87	25.7	42
Unknown/missing	66	11.0	32	25	9.5	13	41	12.1	19
(b)									
Patients transplanted from 2005 to 2017									
All deceased patients	36	100.0	25	11	100.0	8	25	100.0	17
Cause of death									
Infection, viral	3	8.3	2	2	18.2	1	1	4.0	1
Infection, bacterial	4	11.1	4	1	9.1	1	3	12.0	3
Infection, not specified	2	5.6	1	1	9.1	1	1	4.0	0
Cancer/malignancy	2	5.6	2	2	18.2	2	0	0	0
Cardiopulmonary	5	13.9	3	1	9.1	1	4	16.0	2
Hemorrhage	1	2.8	0	1	9.1	0	0	0	0
Other, specify	12	33.3	9	2	18.2	1	10	40.0	8
Unknown/missing	7	19.4	4	1	9.1	1	6	24.0	3

TABLE 13 Post-transplant malignancy rate by transplant era

	Post-transplant malignancy rate by transplant era					
			1 y		3 y	
Transplant era	N Transplants	N Malignancies	%	SE	%	SE
1987-1991	2692	37	0.62	0.16	0.96	0.21
1992-1996	3173	86	1.32	0.22	2.15	0.28
1997-2001	2747	76	1.96	0.28	2.97	0.36
2002-2006	2197	40	1.21	0.25	2.23	0.37
2007-2011	1327	18	0.83	0.28	1.51	0.41
2012-2017	784	11	1.03	0.42	2.31	0.77

Moreover, late ARs continue to occur over the life of the allograft such that the 48-month AR rate has now increased. In analyses of the OPTN data,[7] ARs are more common in children >12 years of age and in black recipients of DDs, with lower allograft survival in adolescents.[13-15] Similarly, health disparities have been shown to be magnified in adolescents in another OPTN data analysis.[16] Recognition of late ARs is important as these are often associated with non-adherence and development of de novo donor-specific antibodies and have negative impact on the graft survival.[17] Indeed, data from USRDS have demonstrated that graft survival is lower for blacks compared to both Hispanics and whites with 5-year graft survival for DD transplant recipients being 63% compared to 82.8% for Hispanics and 80.8% for whites. This finding persists with LD transplant recipients with 5-year graft survival being 92.2% for whites, 90.8% for Hispanics, and 78.8% for blacks.[11]

Hypertension remains an important complication after transplant. However, the use of antihypertensive medications after transplant has decreased over time. This may have been secondary to younger donors being allocated for pediatric recipients, decrease in the use and dose of chronic steroids, and TAC replacing cyclosporine. Recent randomized controlled trials in pediatric transplant recipients have shown a wide range of incidence of hypertension of 21%-61%,[18-22] but trending toward the lower end of the range in more recent trials.

Growth has improved over time, in particular, in youngest recipients indicating growth advantage of undertaking transplant in younger children. Successful use of steroid withdrawal/avoidance protocols and use of alternate day steroids may also have provided a growth advantage, as shown by others.[18,23]

While other OPTN studies have shown that improvement in allograft survival over time is mostly restricted to the early first year post-transplant and minimally better in subsequent years,[24] the NAPRTCS data show a continuing improvement in 7-year allograft survival and also in patient survival.

In summary, NAPRTCS transplant registry data provide a unique opportunity to document long-term changes in practice patterns and outcomes in pediatric renal transplantation. These results are encouraging since they show improvement in patient and graft survival, reduced rates of early ARs, and improvement in growth and hypertension. Challenges remain in preventing late ARs particularly in blacks and adolescents, as well as in devising effective therapies for recurrent FSGS.

In September 2018, NAPRTCS has also implemented many data element updates and a newer more modern web data capture system, which will allow capture of data related to donor-specific antibodies and key viral infections.

AUTHORS' CONTRIBUTIONS

Annabelle Chua, Carl Cramer, Asha Moudgil, Karen Martz, Jodi Smith, Tom Blydt-Hansen, Alicia Neu, and Vikas R. Dharnidharka: contributed to study design, data interpretation, manuscript writing; and Karen Martz: performed the statistical data analyses.

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APPENDIX

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12	University of California Los Angeles	Isidro Salusky, Ora Yadin
13	University of California San Francisco	Marsha Lee
14	Lurie Children's Hospital	Craig Langman
15	Johns Hopkins University	Meredith Atkinson
16	Emory University	Laurence Greenbaum
18	Children's Mercy Kansas City	Bradley Warady
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32	University of Missouri	Laura Hesemann
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APPENDIX (Continued)

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73	Penn State University	Deborah Kees-folt
74	University of Louisville	Sushil Gupta
77	Cleveland Clinic	Katherine Dell
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79	Texas Children's Hospital	Poyyapakkam Srivaths
81	University of Vermont	Sarah Twichell, Elizabeth Hunt
82	Indiana University	Sharon Andreoli
84	Rainbow Babies Children's Hospital	Tamar Springel
88	Cedars-Sinai	Dechu Puliyanda
91	Children's Hospital of Philadelphia	Benjamin Laskin
96	Rhode Island Hospital	Mohammed Faizan
98	Alfred DuPont Institute	Joshua Zaritsky
101	Nemours Orlando	Robert Mathias
107	University of Maryland	Susan Mendley
111	New England Medical Center	Lawrence Milner

(Continues)

APPENDIX (Continued)

Center #	Center name	Current PI
112	Stanford University	Cynthia Wong
113	Carolinas Med. Ctr.	Susan Massengill
114	SUNY Stony Brook	Robert Woroniecki
122	Children's Hospital of Winnipeg	Patricia Birk
123	University of Rochester	Patrick Brophy
125	Northwest Pediatric Kidney Specialists	Randall Jenkins
127	University of South Florida	Alfonso Campos
136	Children's Hospital New Orleans	Diego Aviles
138	Connecticut Children's Medical Center	Cynthia Silva
139	Montreal Children's Hospital	Lorraine Bell
142	Rush Presbyterian Medical Center	Sara Jandeska
143	St. Barnabas Medical Center	Shefali Vyas
146	University of New Mexico	John Brandt
148	Children's Hospital of Austin	Kartik Pillutla
153	Hackensack University	Kenneth Lieberman
154	Children's Hospital of Eastern Ontario	Janusz Feber
156	Driscoll Children's Kidney Center	Samhar Al-Akash
157	Arnold Palmer Children's Hospital	Jorge Ramirez
158	Children's Specialty Center	Randall Jenkins
159	Pediatric Nephrology of Alabama	Mark Benfield
161	St. Vincent Hospital	Daniel McKenney
162	Memorial Health System	Alexandru Constantinescu
163	Legacy Research Institute	Sharon Su
164	Children's Kidney Center of Florida	Deogracias Pena
167	Helen De Vos Children's Hospital	Alejandro Quiroga, Julia Steinke