CHAPTER IV
Kidney and Pancreas Transplantation in the United States, 1996-2005

OVERVIEW

- Kidney and pancreas transplantation in 2005 improved in quantity and outcome quality, despite the increasing average age of kidney graft recipients, with 56% aged 50 or older.
- Overall, 6% more deceased donor kidney transplants were performed in 2005 with slight increases in standard criteria donors (SCD) and expended criteria donors (ECD). Geography and ABO blood type contribute to the discrepancy in waiting time among the deceased donor candidates.
- The largest increase (39%) was in donation after cardiac death (DCD) from non-ECD donors. These DCD, non-ECD kidneys had equivalent outcomes to SCD kidneys. One-, three-, and five- year unadjusted graft survival was 91%, 80%, and 70% for non-ECD-DD transplants, 82%, 68%, and 53% for ECD-DD grafts, and 95%, 88%, and 80% for living donor kidney transplants.
- In 2005, 27% of kidney transplant recipients were discharged without steroids compared to 3% in 1999. Acute rejection decreased to 11% in 2004.
- There was a slight increase in the number of simultaneous pancreas-kidney transplants (895), with fewer pancreas after kidney transplants (343 from 419 in 2004), and a stable number of pancreas alone transplants (129). Pancreas underutilization appears to be an ongoing issue.

KIDNEY TRANSPLANTATION

Introduction

With 91,441 renal transplant recipients entering 2005 with a functioning graft, the care of the renal transplant recipient is now an important concern for all physicians in the United States *[Table 5.16]*. As the average age and comorbidities of these recipients increases, so does their need for coordinated care between the transplant center and community physicians from all specialties. In this chapter, based on the 2006 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) Annual Report, we review the standard kidney and pancreas transplant candidate and recipient data tables, and provide an update on OPTN policies affecting kidney and pancreas transplantation in 2005. The Health Resources and Services Administration (HRSA) Organ Donation Breakthrough Collaborative and its impact on renal–pancreas transplantation are also discussed.

OPTN Policy Changes in 2005

Recent modifications to the system for kidney allocation in the U.S. include: (1) changes in the priority assigned to pediatric candidates (i.e., less than 18 years old), and (2) implementation of a study to start candidate waiting time accrual from the initiation of dialysis.

(1) On September 28, 2005, the kidney allocation system was modified to provide priority for the allocation of standard criteria deceased donor kidneys from donors less than 35 years to pediatric candidates (listed prior to age 18) at each of the local, regional, and national levels of organ distribution. The intent of this modification is to allocate donor kidneys better suited to children immediately to address established goals of rapid transplantation for pediatric candidates, with minimal impact on adult transplantation. The modified pediatric candidate priority falls in the allocation algorithm after zero antigen mismatched candidates, sensitized candidates (PRA ≥ 80%) who otherwise would rank highest in allocation priority, combined kidney/non-renal organ candidates, and prior living organ donors, but before kidney paybacks. The system no longer uses pediatric allocation points, except in the allocation of zero antigen mismatched kidneys, and to maintain the current one point preference for younger pediatric versus adolescent candidates in allocating mismatched kidneys from donors less than 35 years.

(2) On April 29, 2006, the OPTN implemented a voluntary pilot study to assess the impact on kidney allocation from permitting kidney waiting time accrual to commence from the time of initiation of chronic maintenance dialysis once listed as an active transplant candidate, even if this time pre-dates the date of listing, and for repeat transplant candidates, from the date the candidate returns to chronic maintenance dialysis after graft failure once re-listed, even if this time pre-dates the date of re-listing. The intent of the study is to test the

effect of a change in the definition of waiting time on access to transplantation within participating Donation Service Areas (DSAs). The study still allows adult candidates to begin accumulating their waiting time prior to their initiation of dialysis once listed and with a creatinine clearance (CrCl) <20 mL/min. Waiting time is not granted retrospectively to the date of measured or calculated CrCl < 20mL/min. Pediatric candidates continue to accrue waiting time from time of listing if they have not started dialysis and regardless of their creatinine clearance level. Two DSAs are presently participating in the study; a third DSA will be enrolled pending computer programming. Other DSAs using the standard, national system for kidney allocation and distribution that wish to participate in the study may do so with the agreement of all kidney transplant programs served by the DSA and submission of a request to participate to the OPTN.

Definitions of Donor Type

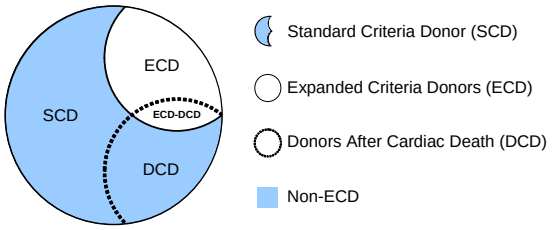
With the increase in use of kidneys from both expanded criteria donors (ECD) and donors after cardiac death (DCD), there has developed uncertainty regarding the usage of these terms in kidney transplantation. While a common nomenclature has appeared to evolve, the precise meaning of these terms in common usage often depends upon the context in which they are used.

Expanded Criteria Donors (ECD) are any donor age 60 years or older, or over 50 years old with at least two of the following conditions: hypertension history, serum creatinine > 1.5 mg/dl, or cause of death from cerebrovascular accident. Donors after cardiac death (DCD) are distinguished from donors with brain death. These may be referred to as donors after brain death (DBD) or non-DCD donors. Standard Criteria Donors (SCD), the most common type, are those who neither meet the criteria for ECD nor DCD. DCD donors may be divided into those who would otherwise fit into the ECD or SCD categories based on the ECD definition, and these donors are frequently designated as ECD-DCD and DCD/non-ECD, respectively (Figure IV-1). These four categories are outlined in Table IV-1 and also in Table 5.4.

In the SRTR Annual Report data tables for kidney transplantation, other than Table 5.4, donors are separated into living donor, non-ECD, and ECD. For these tables, non-ECD includes any donor that does not meet ECD criteria (all SCD and DCD/non-ECD). Transplants from DCD donors who meet the ECD criteria (ECD-DCD) are counted as ECD transplants.

It is, however, important to note that this nomenclature is not uniform in practice or in the literature. As stated above, the distinction between ECD/non-ECD

Figure IV-1. Categories Within the Deceased Kidney Donor Pool: SCD, ECD, DCD



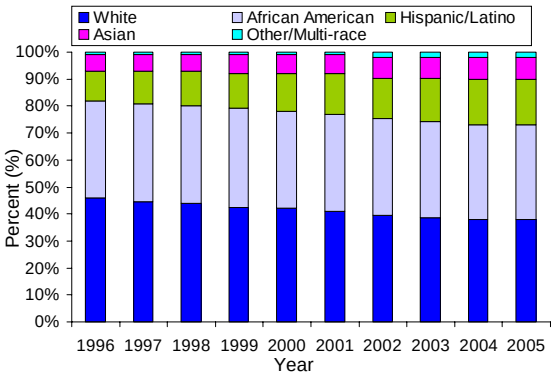
Note: Not drawn to scale. Source: SRTR.

commonly provides for the inclusion of appropriate DCD transplants in both groups, and analyses of DCD versus non-DCD transplants similarly include ECD transplants in the appropriate groups. However, it is also common, especially when examining utilization patterns, to split deceased donors by SCD, ECD, and DCD (for an example, see discussion of the HRSA Collaboratives, below). In these cases the ECD-DCD donors are usually included among the DCD cohort; thus the use of "ECD" differs from those comparisons where the distinction is between ECD/non-ECD.

The Kidney Transplant Waiting List

Although the number of active patients on the deceased donor kidney waiting list has increased by 61% between 1996 and 2005, the increase from year to year has slowed from a high of 10% between 1996 and 1997 to a low of 0.3% between 2003 and 2004 *[Table 5.1a]*. There was a small increase in the number of active waiting list patients in the past two years, from 45,340 candidates in 2004 to 46,351 in 2005 (roughly a 2% increase). The age distribution of the active registrants

Figure IV-2. Race of Active Kidney Waiting List Patients at Year-End, 1996-2005



Source: *2006 OPTN/SRTR Annual Report*, Table 5.1a.

Table IV-1. Kidneys Transplanted by Donor Type, Organ Type, and Year of Transplant

Donor Type	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Living Donor	3,668	3,927	4,419	4,716	5,488	6,035	6,240	6,470	6,647	6,563
Deceased Donor	7,729	7,774	8,032	8,042	8,123	8,230	8,538	8,666	9,357	9,914
Standard Criteria Donor (SCD)	6,558	6,519	6,707	6,680	6,786	6,806	7,018	6,929	7,442	7,554
Expanded Criteria Donor (ECD)	1,076	1,137	1,219	1,218	1,174	1,177	1,230	1,344	1,378	1,609
Donation After Cardiac Death, non ECD (DCD non-ECD)	82	111	100	127	153	231	264	341	476	677
ECD-DCD	13	7	6	17	10	16	26	52	61	74
Multi-Organ Transplants										
Kidney-Pancreas	848	841	967	930	908	886	902	866	880	895
Kidney-Heart	21	20	35	26	29	26	40	29	46	57
Kidney-Liver	112	118	98	99	135	134	210	246	279	339
Other	4	7	4	5	3	3	5	5	3	12

', Tables 1.7, 1.8, 5.4

on the kidney waiting list has continued to skew towards the older age groups, with decreases observed in the pediatric and young adult age groups. This aging of the waiting list is important to the discussion of Net Benefit below. The percentage of older adults (ages 50+) on the waiting list has increased steadily from 39.4% in 1996 to 55.8% in 2005, while the percentages of pediatric and young adult candidates have declined over the same time period (1.8% to 1.1% for pediatrics and 59% to 43% for adults ages 18-49). The percentage of active Hispanic/Latino candidates on the deceased donor kidney waiting list has increased in the past ten years from a low of 11% in 1996 to a high of 17% in 2005 (Figure IV-2). In comparison, the percentage of white candidates has slowly declined from a high of 46% in 1996 to 38% in 2005. The gender distribution of active waiting list registrants has remained constant over the past ten years with a higher percentage of male registrants than female registrants (in 2005, 58% males and 42% females).

At the end of 2005, approximately 74% of the kidney registrants were actively listed on the deceased donor waiting list and 26% were listed with inactive status *[Table 5.1b]*. That this percentage is greater than the corresponding percentage for the interval of 2001 to 2004 (18%), is an apparent consequence of the policy modification that permits accrual of waiting time while listed as inactive.

Between 1996 and 2005, the number of new kidney waiting list registrations increased from 18,330 to 29,135 (a 59% increase) *[Table 5.2]*. Between 1997 and 2000, the average annual increase of new kidney waiting list registrations was between 4% and 6%. From 2003 to 2004, the increase was 11% (24,419 new registrants to 27,126 new registrants) with an increase of 7% between 2004 and 2005. The median time to transplant of 1,136 days for those candidates listed in 2002 (the most recent year for which median times to transplant may be calculated) actually decreased compared with those registered in 2000 (1,198 days). However, the 25th percentile of time to transplant increased from 338 days in 2002 to 355 days in 2005, which presumably reflects the more recent accelerated increase in new registrations.

Among new kidney waiting list registrants, large discrepancies in median times to transplants were observed among ABO blood types. In 2000 (the most recent year with sufficient follow-up information available for all blood groups), the median times to transplant for O, A, B, and AB registrants were 1,463

days, 792 days, 1,848 days, and 469 days, respectively. Because of these discrepancies in time to transplant, some Organ Procurement Organizations (OPOs) have adopted a variance in kidney allocation policy that allocates kidneys from A2 donors to other blood groups. In 2005, 24 of these transplants were performed, with 11 going to B recipients, 10 going to AB recipients, and 3 going to O recipients. In recent years, graft survival for these limited numbers of transplants has been reported to be excellent (1-3).

It is noteworthy that the median time to transplant has decreased for pediatric and adolescent registrants ages 6-17 between 2003 and 2005, which may be a result of allocation policy modifications designed to decrease waiting times for these candidates.

Donor Source

The overall number of kidney donors has increased annually from 8,717 in 1996 to 13,266 in 2005 *[Table 1.1]*. In 2000, the number of deceased kidney donors was approximately equal to the number of living kidney donors (5,489 deceased donors compared with 5,493 living donors). Between 2001 and 2004, the number of living kidney donors exceeded the number of deceased kidney donors. In 2005, the number of deceased kidney donors surpassed the number of living kidney donors by 134 donors.

The total number of kidney transplants increased from 14,857 to 15,674 transplants (roughly 5%) between 2003 and 2004. Between 2004 and 2005, the number of kidney transplants increased by a smaller percentage of 2% or from 15,674 to 16,072 transplants *[Table 1.7]*. Increases were observed in all categories of deceased donor kidney transplants with a modest increase of 2% observed in SCD kidney transplants *[Table 5.4]*. A larger increase was observed in DCD, non-ECD transplants. From 2003 to 2005, the number of DCD, non-ECD transplants increased at an annual rate of approximately 40% per year. ECD kidney transplants increased from 1,378 transplants in 2004 to 1,609 transplants in 2005 or a 17% increase. Likewise, the number of ECD-DCD kidney transplants increased by 21% (from 61 to 74) from 2004 to 2005. After an average annual increase of approximately 3% in living donor kidney transplants from 2002 to 2004, a slight decrease of 1%, or 84, in living donor transplants was observed between 2004 and 2005 *[Table 1.7]*. Although definitive interpretations cannot be made from data covering one year, following the trend in living donation over the next several years will be important, especially given the increases in transplants from deceased donors.

Living donation accounted for 40.8% of kidney transplants in 2005. The high rate of living donation has increased attention to the issues of living donor safety in the US. The OPTN addresses safety issues through several committees, including Membership and Professional Standards. This committee developed standards for transplant programs to perform living donor kidney transplants (4). These criteria establish the requirements for open and laparoscopic donor nephrectomy surgeons and mandate that a surgeon experienced in open nephrectomy be available on-site during laparoscopic nephrectomy. The OPTN's authority to monitor compliance with these standards and address instances of non-compliance was clarified in a notice published in the Federal Register on June 16, 2006. This notice states that OPTN living donor guidelines will receive the same status of other OPTN policies; therefore, non-compliance with such guidelines will subject the offending OPTN member to the same consequences as non-compliance with policies concerning deceased organ donors and deceased organ donor recipients developed under the Final Rule for operation of the OPTN.

In an effort to expedite reporting of serious events that affect the well-being of living donors, the OPTN Living Donor Committee recently recommended a requirement for all transplant centers to report living donor deaths and, for living liver donors, failure of the liver donor's native organ function within 72 hours of becoming aware of such events. This supplements the current routine living donor follow-up at six months and one year. The recommendation was approved by the OPTN Board of Directors for implementation simultaneously with distribution for public comment (5). It is currently being implemented.

Over the last several years, living donation has been advanced using both HLA antibody and ABO isoaglutinin desensitization / removal techniques. Large series of successful transplants of recipients with HLA donor specific alloantibody and/or ABO incompatibly to their intended living donor have been described with protocols utilizing plasmapheresis and low dose IVIG, with occasional use of Rituximab (anti-Cd20) (6, 7). High dose IVIG protocols have also been successful in recipients with prior positive crossmatches due to HLA alloantibody against both living donors and deceased donors.

Non-directed kidney living donation has also increased in volume through both paired donation, formerly known as kidney donor exchange, list paired donation, or list exchange, and simple non-directed donation, usually resulting in the selection of a recipient with the highest allocation priority on the local OPTN deceased

donation waiting list. The OPTN Kidney Transplantation Committee has developed for public comment the concept of a proposed national Kidney Paired Donation system, as these systems are most dependent on a large number of participants for their success. Actual implementation of a Kidney Paired Donation system through the OPTN would first require authorization from the Health Resources and Services Administration (HRSA), within the Department of Health and Human Services (HHS), to proceed with such a program.

The increases in deceased donation have been aided by the HRSA sponsored Organ Donor and Transplantation Collaboratives. The Organ Donor Breakthrough Collaborative (http://www.organdonor.gov/collaborative.htm) has concentrated on improving relationships between donor hospitals and OPOs, to increase prompt notification of potential organ and tissue donors, and to increase consent rates for organ donation. The Organ Transplantation Breakthrough Collaborative (http://www.organdonor.gov/bp_introduction.htm) brings in the transplant centers to help increase the "pull" for organs and thus organ utilization. It is hoped that improved end-of-life care with the active involvement of intensivists will improve organ function prior to procurement, and thus graft function after transplantation. The Collaboratives have set goals for organs per donor type (SCD vs. ECD vs. DCD) as detailed in Chapter II in this report.These goals per donor type help to spread best practices and have contributed to increased numbers of ECD and DCD donors across the country. Many OPOs did not previously have policies in place for DCD donors and have been assisted by other OPOs to implement DCD policies. One Collaborative goal is for all DSAs to have at least 10% of their donors be DCDs. Another area of concentration has been the use of pulsatile perfusion to evaluate kidney organ function, decrease delayed graft function, and increase the utilization of both ECD and DCD kidneys.

A major goal of the Organ Transplant Breakthrough Collaborative is to increase yearly donation from all sources by 7,000 kidneys over the current levels, with the objective of eliminating the kidney transplant waiting list in 10 years. This target has come to be known as the "7,000 Kidney Challenge." Dr. Alan Leichtman has challenged each DSA to perform ten more kidney transplants per month – from any combination of donor sources. With 58 DSAs in this country, this would translate into 580 more kidney transplants per month, and therefore 6,960 more kidney transplants per year for the country.

It appears currently that the "push" of organs from the Collaboratives has been matched, but not exceeded, by the "pull" from transplant centers. While ECD kidney transplantation is increasing, the significant discard rates for ECD kidneys have not changed, despite implementation of an ECD allocation algorithm designed to facilitate placement. Discard rates for ECD kidneys have not changed appreciably in this decade. In 2005, 2,912 ECD kidneys were recovered with 1,169 (40%) discarded. Twenty-five percent of DCD kidneys recovered were discarded (262 out of 1,051), and 16.6% of SCD kidneys. For the period of January 1, 2001 to July 31, 2004, 36% of recovered ECD kidneys were discarded, compared with 7% of SCD kidneys and 11% of DCD kidneys (8). The discard rates vary greatly by DSA, likely influenced by both transplant center practice as well as local DSA waiting times. There is a negative correlation between recovery rates and discard rates at the DSA level, i.e., those DSAs with high recovery rates tend to have lower discard rates.

This profound geographic variation in ECD utilization, which also exists for SCD and DCD kidneys, suggests that there are geographic differences in requirements for ECD or other marginal kidneys. This is consistent with other analyses that indicate there is substantial geographic variation in access to kidney transplantation from the waiting list. See Chapter VIII in this report on Geographic Variability in Access to Primary Kidney Transplantation for further details. Such variation in both access and utilization suggests that there are opportunities to distribute kidneys from areas of low utilization and high candidate access, to those with high utilization but low access. Efforts by the OPTN and the SRTR to identify kidneys with a high risk of local discard, and to develop methods to place these kidneys with centers that are likely to use them, are being undertaken to minimize these inefficiencies. This is also an opportunity for the development of better preservation techniques as well as means of evaluation of renal grafts ex vivo.

The renal transplant community, like all groups, needs clear terminology for communications of practices and to understand outcomes. The groupings into SCD, ECD, and DCD (defined above) serve this practical purpose; however, all agree that there is a great amount of heterogeneity within these groups. "Other Criteria Donor (OCD)" has been proposed by some in the transplant community as a way of dividing the SCD group into the average "standard" donor, one that should result in six to eight organs donated, versus those donors who are less than 50 years old, but have multiple chronic and/or acute medical issues that result in a one or two organ donation.

The concept of a continuous donor risk index for kidneys may help better define "the right organ for the right recipient." While it may be difficult for a predictive formula created from registry data to capture the experience and clinical judgment used in evaluating donor organs, a numerical indicator of risk that can be applied by anyone to any donor at any time may assist the clinician by providing a reasonable expectation based on past outcomes. A donor risk index may also be very useful in conveying clinical judgment of physicians to patients in simple terms, for it is the patient who ultimately accepts these organs. For organ placement efficiencies, it may allow for individual patient determination of the risk they are willing to accept at the time of their listing with alterations allowed over time. This then will allow the patient to be an active decision maker in choosing the organ that may be right for them while not adding cold ischemia time to a precious resource, the donated kidney. This index may also help to more accurately assess transplant program acceptance rates. A comparable liver DRI has already been published that includes donor risk factors to calculate the relative risk of graft failure: age, cause of death, race, DCD, partial/split, height, location, and cold ischemia time (9).

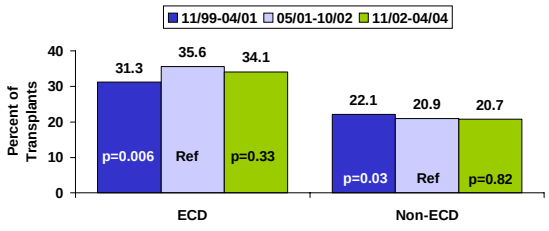
Kidney Transplant Recipients

In 2005, there was a 6% increase in the total number of deceased donor kidney transplants performed *[Table 5.4]*. Between 2004 and 2005, increasing numbers of transplants were observed in all deceased donor categories; SCD: 7,442 to 7,554 (2% increase), ECD: 1,378 to 1,609 (17% increase), DCD: 476 to 677 (42% increase), and ECD-DCD: 61 to 74 (21% increase) (Table IV-1). After a decade of an upward trend, the total number of living donor kidney transplants decreased slightly from 6,647 in 2004 to 6,563 in 2005 (1% decrease) *[Table 5.4c]*.

Recipients of Non-ECD Kidneys: The yearly increase in the number of deceased donor non-ECD transplants has recently accelerated, increasing from 7,270 in 2003 to 7,918 in 2004 (9% increase) and 8,231 in 2005 (4% increase) *[Table 5.4a]*. In the preceding seven years, the average increase was 3% or lower per year. The age of non-ECD recipients continues to increase. In 2005, approximately half of the non-ECD recipients were age 50 years or older at transplant, up from 37% in 1996. The percentage of recipients age 18 to 34 declined from 20% to 14% over the same time period. The percentage of white recipients decreased from 59% (3,882 recipients) in 1996 to 48% (3,972 recipients) in 2005, while the percentages of African American and Hispanic recipients increased from 26% (1,727 recipients) to 30% (2,477 recipients) and 10% (664 recipients) to 15% (1,192 recipients), respectively. The percentage of zero HLA mismatched kidneys remained relatively stable. The percentage of highly mismatched kidneys (four or more HLA mismatches) increased dramatically (48% in 1996 to 67% in 2005 compared with a decrease of 37% to 16% for transplants with one to three HLA mismatches), which reflects both the overall increase in accrued waiting time points and the decreased emphasis on HLA matching in allocation policy over the decade. After a decline between 1997 and 1999, the percentage of non-ECD kidneys transplanted with cold ischemia time (CIT) of 21 hours or less increased annually from 2000 to 2005.

Recipients of Expanded Criteria Donor Kidneys: The number of ECD kidney transplants increased steadily over the past decade, from 1,089 in 1996 to 1,683 in 2005 *[Table 5.4b]*. In 2005, 81% of ECD recipients were age 50 years and older, an increase from 55% in 1996. The race/ethnicity distribution of ECD recipients did not change dramatically over the past decade, although there was a decline of 8% in the percentage of white recipients. Between 1996 and 2005, the majority of ECD recipients were male (64% in 2005). Only 7% of ECD kidneys were transplanted to zero antigen mismatched recipients in 2005, compared with 10% in 2001. This probably reflects the 2002 change in allocation policy for ECD kidneys that decreased the allowable time interval to place zero-mismatched ECD kidneys nationally. CIT was under 22 hours in approximately 57% of recipients, which represents an increase of approximately 11% from 2000. Between 2001 and 2005, there was an improvement in the percentage of ECD kidneys transplanted with a CIT of less than 12 hours, from 11% to 18%. Decreases in CIT for ECD kidneys are also coincident with the implementation of the ECD allocation algorithm designed to expedite their placement. Unfortunately, these improvements in CIT do not appear to have affected the incidence of delayed graft function (10) (Figure IV-3).

Figure IV-3. Delayed Graft Function Pre- and Post-ECD Policy Implementation



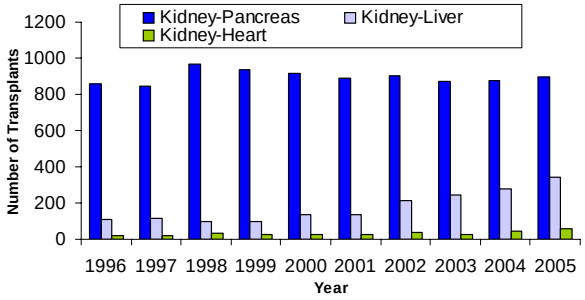
Source: Sung, et al. Impact of the expanded criteria donor kidney allocation system on the use of expanded criteria donor kidneys. Transplantation 2005; 79: 1257-61.

Recipients of DCD Kidneys: The number of DCD (including ECD-DCD) kidney transplants has increased from 95 in 1996 to 751 in 2005 *[Table 5.4]*. More than 50% of DCD kidney recipients are older than age 50, and only 1% went to pediatric recipients. The CIT for DCD kidneys has been decreasing; the percentage of DCD kidneys with CIT less than 21 hours was 58% in 2005 (SRTR Special Analysis, July 2006). This is likely a consequence of an increased number of DSAs that have DCD policies in place, and centers that are willing to transplant DCD kidneys, which make them easier to place.

Multi-Organ Transplants: The total number of kidneys transplanted with extrarenal organs continues to increase (Figure IV-4) (Table IV-1). Although the number of combined kidney-pancreas transplants has not changed appreciably, heart-kidney and liver-kidney transplants have increased substantially. The 150% increase in liver-kidney transplants since 2001 is undoubtedly a result of the adoption of MELD-based allocation, which gives priority to those candidates with renal dysfunction based on their high mortality rates. These candidates receive priority for donor kidneys over kidney-alone candidates in the allocation algorithm. Since the indications for liver-kidney transplantation are not well-defined, there is considerable debate about the necessity of diverting approximately 3.4% of transplanted deceased donor kidneys to liver-kidney recipients, and about whether some of these candidates without fixed renal disease might not experience recovery of native renal function (11, 12). Efforts to more clearly define the indications for liver-kidney are limited by the lack of large single-center experience, and by insufficient registry data regarding duration of pre-transplant dialysis and cause of renal disease in liver and liver-kidney candidates.

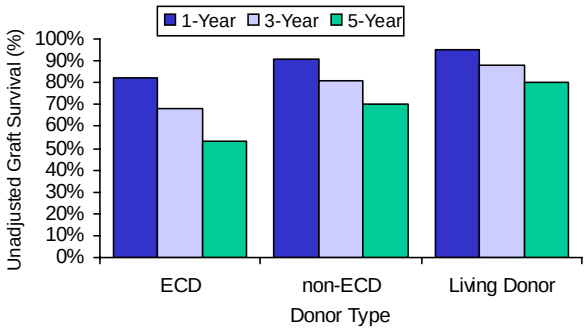
Recipients of Living Donor Kidneys: The number of living donor kidney transplants increased dramatically over the past decade, from 3,668 in 1996 to 6,563 in 2005, which represents a 79% increase *[Table 5.4c]*. As with other types of kidney transplants, the age distribution of living donor recipients has shifted towards older recipients; the largest growth was observed in the percentage of recipients who were age 50 or older at transplant (24% in 1996 to 43% in 2005). African Americans and Hispanics continue to be underrepresented in the population of living donor recipients (35% and 17%, respectively, of the active waiting list at the end of 2005 compared with 15% and 12% of living donor recipients in 2005) (Table IV-2). There continues to be an increase in the proportion of living donors who are unrelated to the recipient; the percentage of these donors increased from 16% in 1996 to 34% in 2005. This probably explains the decrease in living donor transplants that had two or fewer HLA mismatches (32% in 2005, compared with 45% in 1996).

Figure IV-4. Number of Combined Kidney Transplants, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 1.8.

Figure IV-5. Unadjusted 1-Year, 3-Year, and 5-Year Kidney Graft Survival, by Donor Type, for Transplants Received 1999-2004



Source: *2006 OPTN/SRTR Annual Report,* Tables 5.10a, b, c.

Deceased Donor Kidney Recipient - Graft Survival: One-year, three-year, and five-year unadjusted graft survivals were 91%, 80%, and 70%, respectively, for recipients of deceased donor, non-ECD kidney transplants *[Table 5.10a]*. For the same follow-up periods, unadjusted graft survival for ECD transplants was 82%, 68%, and 53% (Figure IV-5) *[Table 5.10b]*.

Among non-ECD recipients, older adults (age 65 years and older at transplant) had the poorest unadjusted five-year graft survival at 60%, followed by adolescents (age 11-17) with 64%, and adults age 50-64 with 69% *[Table 5.10a]*. Recipients aged 1-5 had the best long-term graft survival at 76%. African American recipients had the lowest unadjusted five-year graft survival rate of 62% compared with 72% for white recipients, 74% for Hispanic recipients, and 78% for Asian recipients. The five-year graft survival varied by primary diagnosis, from 53% for recipients with neoplasms to 80% for

recipients with polycystic kidneys. Diabetic recipients, hypertensive recipients, and recipients with renovascular and other vascular diseases had similar long-term graft survival at approximately 66%. The 22% of non-ECD kidney recipients who required dialysis within the first week after transplantation had a five-year graft survival of 55%, compared with 74% if dialysis was not needed. The five-year unadjusted graft survival of non-ECD kidneys decreased with increasing cold ischemia time and increasing number of total HLA mismatches.

For ECD kidney recipients, similar trends to non-ECD kidney recipients were seen, although the survival percentages are lower *[Table 5.10b]*. Among age groups, the worst graft outcomes were also observed in recipients over 65 years; their unadjusted graft survival was 46% at five years. African American patients continued to fare worse than other ethnic and racial groups, with 46% graft survival at five years compared with 55% for whites, 61% for Hispanics, and 66% for Asians. As with non-ECD kidney transplants, recipients

Table IV-2. Kidneys Transplanted by Donor Type, Race, and Year of Transplant

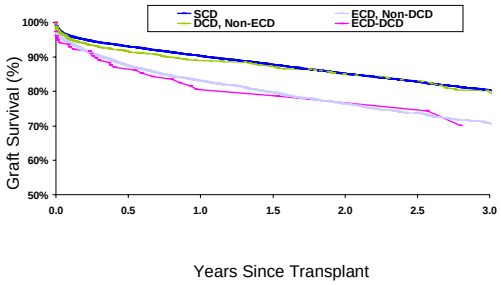
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Deceased Donor, Non-ECD										
Total	6,640	6,630	6,807	6,807	6,939	7,037	7,282	7,270	7,918	8,231
White	3,882	3,789	3,784	3,782	3,738	3,695	3,753	3,610	3,885	3,972
African American	1,727	1,832	1,852	1,861	1,977	2,072	2,120	2,148	2,340	2,477
Hispanic/Latino	664	636	759	769	811	882	970	1,015	1,110	1,192
Asian	294	321	347	313	340	335	357	407	464	483
Other/Multi-race	73	51	64	82	73	53	81	89	119	107
Unknown	-	1	1	-	-	-	1	1	-	-
Deceased Donor, ECD										
Total	1,089	1,144	1,225	1,235	1,184	1,193	1,256	1,396	1,439	1,683
White	614	644	667	656	627	633	633	699	679	822
African American	320	317	350	350	353	353	401	459	420	510
Hispanic/Latino	93	119	126	132	113	123	132	139	201	197
Asian	49	57	63	79	77	68	76	83	107	122
Other/Multi-race	13	7	19	18	14	16	14	16	32	32
Living Donor										
Total	3,668	3,927	4,419	4,716	5,488	6,035	6,240	6,470	6,647	6,563
White	2,589	2,746	3,065	3,216	3,778	4,117	4,278	4,343	4,257	4,312
African American	524	548	625	720	766	911	903	965	957	958
Hispanic/Latino	413	451	524	546	659	690	746	808	806	792
Asian	102	125	158	162	230	241	227	243	242	253
Other/Multi-race	31	41	27	44	37	60	57	69	75	73
Unknown	9	16	20	28	18	16	29	42	310	175

Tables 5.4a-c

with a diagnosis of polycystic kidney disease had the highest unadjusted five-year graft survival (69%). Diabetic recipients, hypertensive recipients, recipients with tubular and interstitial diseases, and recipients with renovascular and other vascular diseases had similarly low graft survival rates of approximately 48%-49%. Graft survival decreased with increasing CIT and increasing number of total HLA mismatches.

Graft survival for DCD kidney transplants was 92% at three months, 87% at one year, 77% at three years, and 65% at five years. These results are similar to non-DCD transplants. Even after adjusting for differences in donor and recipient characteristics, analyses by the SRTR and others have continued to demonstrate equivalent graft survival between DCD kidneys and those from brain dead (non-DCD) donors (Figure IV-6).

Figure IV-6. Adjusted* Graft Survival for DCD and ECD Kidneys, 2000-2004



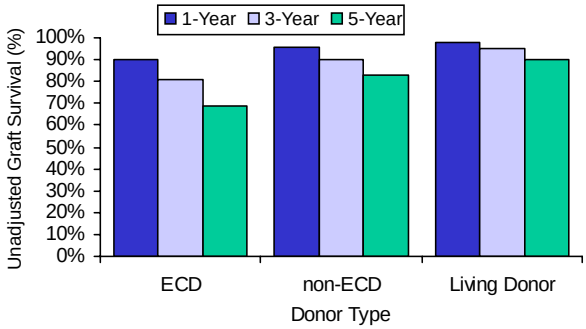
*Adjusted for recipient age, sex, race, PRA, ESRD cause, years of ESRD, HLA mismatch, year of transplant, previous transplant, transfusions and donor sex, race, diabetes, cold ischemia time

Source: SRTR Special Analysis, April 2005.

Deceased Donor Kidney Recipients - Patient Survival: The annual death rate following non-ECD kidney transplantation has dropped from a high of 60 deaths per 1,000 patient-years at risk in 2000 to 43 deaths per 1,000 patient-years at risk in 2004 *[Table 5.7a]*. For ECD transplants, the death rate has remained relatively stable over the past three years at approximately 100 deaths per 1,000 patient-years at risk *[Table 5.7b]*. Unadjusted patient survival rates at one, three, and five years following non-ECD and ECD kidney transplantation were 96%, 90%, 83%, and 90%, 81%, 69%, respectively (Figure IV-7) *[Tables 5.14a and 5.14b]*.

As expected, patient survival following non-ECD transplantation decreased with increasing recipient age at transplant. Hispanic and Asian recipients had the highest patient survival of 87% and 88%, respectively, while white and African American recipients had similar patient survival (approximately 82%). As with graft survival outcomes, non-ECD kidney recipients with diagnoses of neoplasms had the lowest patient survival (approximately 58%). Recipients of non-ECD kidneys

Figure IV-7. Unadjusted 1-Year, 3-Year, and 5-Year Kidney Patient Survival, by Donor Type, for Transplants Received 1999-2004



Source: *2006 OPTN/SRTR Annual Report,* Tables 5.14a, b, c.

with the longest cold ischemia times (42 or more hours) had worse five-year survival, 72%, compared with those with shorter CIT. Unlike non-ECD graft survival, five-year unadjusted patient survival did not appear to decrease with an increasing total number of HLA mismatches.

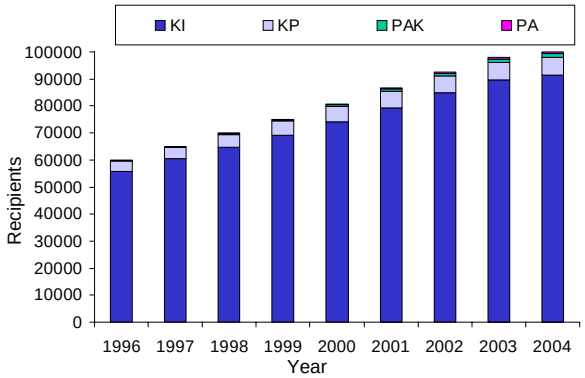
Unadjusted patient survival trends were similar in ECD transplant recipients *[Table 5.14b]*. Five-year patient survival decreased as recipient age at transplant increased. With an unadjusted five-year patient survival of 59%, diabetic recipients of ECD kidneys had the worst posttransplant patient survival outcomes. Recipients of ECD kidneys with shorter cold ischemia times had better unadjusted patient survival: 72% for kidneys with 0-21 hours of CIT, 68% for kidneys with 22-31 hours, and 61% for those with 32-41 hours. Recipients of ECD kidneys from donors aged 50-64 had better five-year patient survival than recipients of older donors aged 65 years and over (71% vs. 64%).

Living Donor Kidney Recipients - Graft Survival: Graft survival for living donor kidney recipients continues to be superior to those for recipients of deceased donor kidneys (Figure IV-5). Unadjusted graft survival rates at one, three, and five years following living donor kidney transplantation were 95%, 88%, and 80%, respectively *[Table 5.10c]*. Recipients aged 65 or older had the lowest five-year unadjusted graft survival (70%) compared with other adults aged 18-64 (80%, 82%, and 80%, respectively, for age groups 18-34, 35-49, and 50-64). African American recipients had the lowest five-year graft survival, at 72%, compared with approximately 81% for whites, 84% for Hispanics, and 87% for Asians. Recipients with a primary diagnosis of polycystic kidney disease had the highest five-year unadjusted graft survival of 88%. Recipients of older donor kidneys aged 65 or more years had lower five-year graft survival at approximately 70% compared with around 80% for other donor age groups. Five percent of

living donor recipients required dialysis within the first week following living donor kidney transplantation; these recipients had a five-year unadjusted graft survival rate of 51%. Unadjusted five-year graft survival following living donor (related or unrelated) transplantation did not vary dramatically by relation of the donor to the recipient (range of 77% for other non-first degree relative to 84% for sibling).

Living Donor Kidney Recipients - Patient Survival: After gradual increases between 1998 and 2001, death rates for recipients in the first year following living donor transplantation have decreased, from 26 per 1,000 patient-years at risk in 2001 to 21 per 1,000 patient-years at risk in 2004 *[Table 5.7c]*. Unadjusted patient survival rates at one, three, and five years following living donor kidney transplants were 98%, 94%, and 90%, respectively (Figure IV-7) *[Table 5.14c]*. Five-year unadjusted patient survival decreased with increasing recipient age. Compared with other primary diagnosis groupings, diabetic living donor recipients had the lowest five-year patient survival of 83% (other diagnoses ranged from 86% to 96%). Recipients who required dialysis within the first week following living donor kidney transplantation had a five-year unadjusted survival rate of 78% compared with 91% for recipients who did not require dialysis following transplantation. Recipients of kidneys from the oldest donors (65 years or older) had a lower patient survival rate (78%) than recipients of younger donor kidneys.

Figure IV-8. Prevalence of People Living with a Functioning Transplant at End of Year, 1996-2004



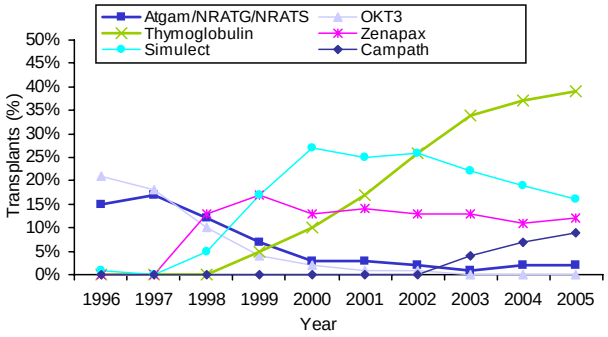
Source: *2006 OPTN/SRTR Annual Report,* Table 5.16, 6.16,7.16,8.16.

Prevalence of People Living with a Functioning Graft: There were 91,441 renal transplant recipients that entered 2005 with a functioning graft *[Table 5.16]*. A continually increasing proportion of these recipients had functioning grafts from living donors (41%), which reflects the impact of kidney donor quality on patient survival after transplantation. For example, one-year unadjusted patient survival for SCD recipients was 96% in 2004, a slight improvement from 2003, but still below that of living donor recipients at 97.9% *[Tables 5.15a, b]*. In contrast, ECD recipients posted a much lower (90%) one-year unadjusted patient survival *[Table 5.15]* (Figure IV-8).

Immunosuppression and Acute Rejection

Induction Immunosuppression: Induction therapy with biological agents continued a nine-year trend of increasing utilization to 74% of kidney transplants in 2004-2005 *[Table 5.6a]* (Figure IV-9). Antithymocyte

Figure IV-9. Immunosuppression Agents Used for Induction in Kidney Transplantation, 1996-2005



Source: *2006 OPTN/SRTR Annual Report,* Table 5.6a.

globulin (rabbit) (Thymoglobulin, manufactured by Genzyme Polyclonals S.A.S., Lyon, France, distributed by Genzyme Corporation, Cambridge, MA) was used in 39% with the two interleukin-2 receptor (IL2-R) antagonists, daclizumab (Zenapax Roche, Nutley, NJ) and basiliximab (Simulect, Novartis, East Hanover, NJ) totaling 28%. Alemtuzumab (Campath, manufactured by Genzyme, Cambridge, MA, distributed by Berlex, Montville, NJ) was used in 9% with the remaining agents, mostly antithymocyte globulin (equine) (ATGAM, Pharmcia & Upjohn Company, Kalamazoo, MI) and muromonab-CD3 (OKT3, Ortho Biotech Products, L.P., Bridgewater, NJ) totaling less than 2%. The practice trend is clearly toward anti-lymphocyte depleting antibody induction with both Thymoglobulin and Campath being the only two agents that have increased in use over the last three years. The interleukin-2 receptor (IL-2R) antagonists, Zenapax and Simulect, have declined from a combined 40% usage in 2000 to 2002, to 28% in 2005.

Sixteen percent of the combined recipients from 2001 to 2005 were discharged without maintenance steroids *[Table 5.6c]*. The rate of steroid-free maintenance regimens has increased rapidly in the last six years. In 1999, only 3% of recipients were without steroids at discharge, versus 26% in 2005 *[Table 5.6e]*. In the 2001 to 2005 recipients, 76% were reported to have induction therapy with most receiving Thymoglobulin (43.6%),

Campath (14%), or IL2-R antagonists (19%, made up of Simulect 12% + Zenapax 7%) *[Table 5.6c]*. Over the last three years, several protocols have been published and presented that describe the use of Thymoglobulin or Campath with five or less doses of steroids. These protocols have been referred to as "rapid steroid discontinuation." Most protocols use the steroids as pre-medication for the Thymoglobulin or Campath infusions to decrease the chance of cytokine release syndrome. Campath use was first reported in 2003 when it was used as induction in 10.9% of the steroid-free maintenance recipients (SRTR special analysis, June 2006). In 2004 and 2005, Campath use in these steroid-free recipients increased to 17.5% and 20%, respectively. Thymoglobulin use remains steady at 46% + 5% for the last three years in these steroid-free maintenance regimens. Approximately 20% of steroid-free maintenance regimen recipients are reported to have received no induction therapy from 2003 through 2005.

For 2001 through 2005 discharged patients taking steroids, Thymoglobulin was the most common single induction agent (28%), but the two IL2-R antagonists combined were more frequent at 38% (Simulect 24% and Zenapax 14%) *[Table 5.6c]*. Campath was used in only 2.1% of these steroid regimens. Thymoglobulin use has doubled in these steroid maintenance patients from 16.1 % in 2001 to 35.9% in 2005.

Maintenance Immunosuppression: Only 6% of patients discharged with a functioning graft were not taking calcineurin inhibitors (CNI) in 2005, with 7% in 2004 *[Table 5.6e]*. For grafts functioning at one year, only 1% were not on a CNI *[Table 5.6g]*. This difference from the time of discharge to one year could be due to: 1) patients with delayed graft function being started on CNIs as outpatients to allow renal function to return without nephrotoxic drugs, 2) CNIs added later due to acute rejection on a calcineurin free regimen, and/or 3) graft loss in recipients not treated with CNIs. In 2004, 23% of patients were discharged without maintenance steroids, with 20% of these patients remaining off steroids one year later *[Tables 5.6e,g]*.

For all 2005 recipients at the time of discharge, cyclosporine (Neoral®, Novartis, East Hanover, NJ) was used in 15% of recipients, with tacrolimus (Prograf, Astellas Pharma US, Deerfield, IL) used in 79% of patients *[Table 5.6e]*. The ten-year trend for the two CNIs has completely reversed. A Mycophenolic Acid (MPA; Cellcept®, Roche, Nutley, NJ) was used in 87% of recipients at the time of discharge in 2005, a trend that has continued to increase over the last ten years. In 2004, 82% of recipients were on a MPA at the time of discharge with that number increasing to 85% one year after transplantation *[Table 5.6g]*. mTOR inhibitor (Rapamune, Wyeth Pharmaceuticals Inc, Collegeville, PA or Certican, Novartis AG, Basel, Switzerland) use declined at the time of discharge to 9% in 2005, down from 13% in 2004 and a high of 17% in 2001 *[Table 5.6e]*. However, the use of mTOR inhibitors at one year posttransplant is greater than that at discharge, with 18% of 2004 transplanted patients on mTOR inhibitors *[Table 5.6g]*. This later introduction of mTOR inhibitors suggests a practice of transition to lesser nephrotoxic maintenance regimens as an outpatient once a recipient stabilizes after transplant. This delayed introduction of mTOR inhibitors could also minimize side effects as lower CNI, steroid, MPA, and/or valganciclovir doses may allow for better tolerability of the mTOR in regards to hyperlipidemia and bone marrow suppression.

For patients transplanted in 2004, 81% of patients discharged on tacrolimus plus mycophenolate mofetil with or without steroids remained on this regimen at one year *[Table 5.6h]*. For tacrolimus plus sirolimus, this persistency was 60% at one year. Cyclosporine plus azathioprine was maintained in 85% of patients with cyclosporine plus mycophenolate mofetil at 76% and cyclosporine plus sirolimus at 71%.

For maintenance regimens without steroids, most patients were given tacrolimus and a mycophenolic acid. This was 19% of all transplant recipients at discharge in 2005, up from 14% in 2004 *[Table 5.6d]*. At one year, 14% of all patients transplanted in 2004 were on only tacrolimus and a mycophenolic acid *[Table 5.6f]*.

Acute Rejection: For patients transplanted in 2004, 12% were treated for rejection within a year of transplant *[Table 5.6i]*. The acute rejection incidence has continued to decrease from 1996 through 2003 with rejection incidences of: 51%, 29%, 21%, 19%, 17%, 17%, 15%, and 13% in each year, respectively. Steroids were used in 70% of recipients with rejection; antibodies were used in 48% with 33% receiving Thymoglobulin (69% of all antibodies used). The trend of decreasing steroid use and increasing antibody use that started in 2001 continued. Eight percent of recipients with acute rejection were treated with an IL2-R antagonist, though there is little in the literature to support this.

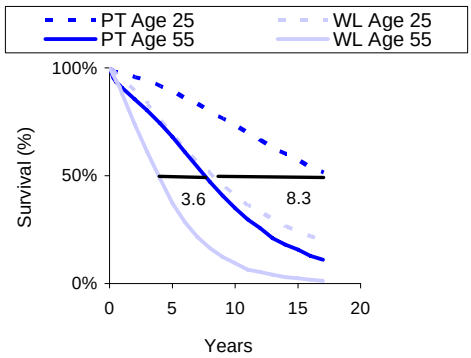
Anticipation of a Revised Allocation System: Net Lifetime Survival Benefit

Kidney and kidney-pancreas transplant recipients receive a survival benefit from transplant compared to remaining on dialysis. Using separate patient survival models for expected lifetimes following transplant or continuing on dialysis, this benefit can be calculated for individual patients based on their characteristics. These lifetime calculations use the survival curves for patients with similar characteristics based on Cox regression

models. These models contain patient (and donor, for posttransplant models) factors used to estimate median life expectancy with and without transplant. The models to date have considered adult candidates and recipients, and SCD organs only. Lifetimes can be recalculated for each candidate based on the current donor whenever a new organ becomes available. Aside from active/inactive status and PRA, changes in a candidate's condition while on the waiting list are not factored into the modeling, since there is no follow-up reporting mechanism for kidney waiting list registrants.

Net lifetime survival benefit (NLSB) is calculated by the expression PT – WL, where PT is posttransplant lifespan (with transplant), and WL is waiting list lifespan (without transplant). In the figure shown, this difference in median survival is 8.3 years for a 25 year-old diabetic candidate, compared with 3.6 years for a 55 year-old diabetic candidate (Figure IV-10).

Figure IV-10. Median Survival Curves for Diabetic Kidney Transplant Candidates and Recipients, Age 25 and 55



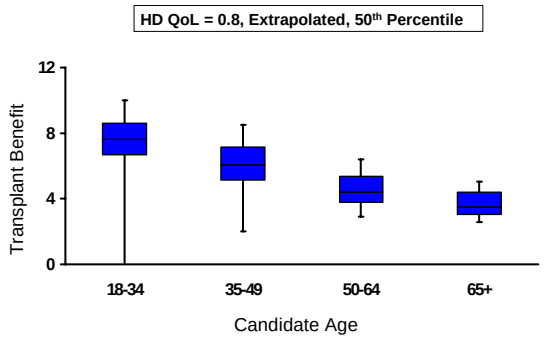
Source: SRTR Special Analysis, June 2006.

Quality of life (QoL) considerations are more relevant to the assessment of kidney transplant benefit than for other transplants for which prevention of imminent death is the primary benefit. Thus, an adjustment is included to account for the enhancement of quality of life provided by a kidney transplant. This quality of life adjusted estimated net lifetime survival benefit (QENLSB) values dialysis years (both waiting list and post-graft failure) less than years with a functioning graft by a factor of 0.8. Separate studies in published literature each estimated time-tradeoff factors very close to 0.8 for time spent without versus with a functioning graft (13, 14). All candidates receive the same QoL modifier.

QENLSB can be integrated into a kidney and kidney-pancreas allocation system, which may maximize the potential benefits of each kidney. Younger candidates tend to have greater QENLSB scores, but there is a wide range within each age category (Figure IV-11).

Otherwise, the distribution of QENLSB is similar across DSA at listing, sex, race/ethnicity, insurance status, and non-diabetic status. Diabetic kidney recipients tend to have lower benefit compared with non-diabetics, although the benefit to diabetic kidney-pancreas recipients is on average greater.

Figure IV-11. Distribution of QENLSB from Transplantation with Average SCD Kidney, by Candidate Age (Age=32 yrs)



Source: SRTR Special Analysis, November 2005.

Getting Back to Basics: Supply and Demand

This review of renal transplantation in 2005 continues many of the trends from prior years. Positive trends are improving or maintaining already excellent patient and graft survival rates, declining acute rejection rates, and increasing maintenance regimens without steroids. The "white elephant in the room" has been growing larger each year – the obvious problem of supply and demand of a precious resource – donor kidneys. The manifestation of the organ shortage is the continued growth of the deceased donor waiting list, leading to longer waiting times and more deaths on the waiting list for adults. Nevertheless, efforts to help improve the organ shortage, focused on both deceased and living donation, have helped to mitigate this increase in the growth of the waiting list.

The HRSA Organ Donation Breakthrough Collaborative has already increased organ donation throughout the country. The number of standard criteria donors has slightly increased, with greater growth potential in older donors (ECD) and donors after cardiac death (DCD). Kidney, pancreas, liver, and lung grafts from younger DCD donors have excellent function and are an excellent addition to the organ pool, though so far low in absolute numbers. While the aging of the population in the U.S. is a triumph of modern public health and medicine, it also has led to the rapid aging of organ donors over the last ten years. Since the average ECD kidney transplant has a shorter potential half-life than a non-ECD (either SCD or DCD/non-ECD) kidney transplant, a more precise approach is needed to

accurately estimate graft survival when making decisions for candidates. The development of a continuous donor risk index may help clinicians select the appropriate ECD kidneys for their patients.

In addition to maximizing timely referrals, consent, and conversion rates for all potential standard criteria donors, living donation is the remaining practical answer for kidney candidates. Living donor transplantation results in greater patient and graft survival, and longer graft half-lives, with fewer readmissions and lower levels of immunosuppression use in many programs. The annual death rate per 1,000 patient-years at risk is less than half for living donor recipients compared to SCD recipients (21 vs. 43), and one-fifth for those who receive an ECD graft (21 vs. 104) *[Tables 5.7a- c]*.

In the last ten years, the number of living donor renal transplants increased from 3,668 in 1996 to 6,563 in 2005, a 79% increase *[Table 1.7]*. During the same period, deceased donor transplantation increased from 7,595 to 9,509, a 25% increase. There are several obvious causes leading to the increase in living donors: the greater acceptance of unrelated living donors, including spouses and friends; the widespread availability of laparoscopic donor nephrectomy from the late 1990s; the increasing public awareness of living kidney donation; and the rapidly increasing waiting time on the deceased donor renal transplant waiting list. The national median time to transplant has not been able to be calculated since 2002, when it was 1,135 days *[Table 1.5]*. The annual death rate on the waiting list remains about 70 per 1,000 patient-years at risk *[Table 1.6]*. In 2005, over 4,000 people died on the kidney alone transplant waiting list versus 3,000 patient deaths for all the other solid organs combined *[Table 1.6]*.

With 62,294 patients on the waiting list at the end of 2005, it is imperative that every effort be made to ensure that every potential willing living donor who is found to be psychosocially fit to donate be allowed to benefit his/her intended recipient *[Table 1.3]*. If this is truly the goal of the healthcare system / transplant community, transplant professionals must not only work toward a national Kidney Paired Donation program (donor exchange program), but also seek appropriate funding for desensitization programs for both alloantibody incompatible pairs, as well as ABO incompatible pairs. These programs currently exist in only a few programs around the country, and growth has historically been limited by funding constraints.

The next set of goals, to once again increase living donation rates, must be met by focusing more on the living donor. While discussion about monetary compensation for living donors is both controversial and considered by many to be a violation of the National Organ Transplant Act, there is an, as yet, unaddressed and growing concern about the long-term safety of living donors in the U.S. which threatens to undermine the growth in living donor transplantation. Measures to address this could include the establishment of a database to study long-term living donor outcomes, lifetime organ-specific health insurance for donors, coverage of all reasonable expenses related to organ donation and testing for donation, financial coverage of post-donation renal function evaluation, and coverage for all follow-up and long-term care related to the donation. Adequately addressing these concerns will require cooperation and involvement of transplant medical professionals, government regulators, and private health insurance payers. For the transplant centers, there will be a need to create a risk fund to cover the rare, but mathematically expected, complications that will come from living donation events.

The commitment to the care of the living donor is much more difficult for physicians and transplant centers already faced with financial and logistic obstacles to patient care. However, it is important to remember that, compared with dialysis, kidney transplantation not only extends life years lived and quality of years lived, it also financially benefits the government, healthcare providers, and insurance companies. To have some of those savings invested in the future health of living donors is ethically correct, and would increase confidence in the process, potentially increasing living donation rates.

PANCREAS TRANSPLANTATION

CMS Policy Changes

On May 19, 2006, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination that stated that Medicare would now pay for pancreas transplantation alone (PTA). This appears in section 260.3 of Pub. 100-03 and can be downloaded at: http://www.cms.hhs.gov/transmittals/downloads/R56NCD.pdf.

CMS will cover PTA performed on or after April 26, 2006 that are reasonable and necessary for Medicare beneficiaries in the following limited circumstances: (1) facilities must be Medicare approved for kidney transplantation, (2) patients must have a diagnosis of type I diabetes made by the documentation of beta cell autoantibody or fasting C-peptide less than or equal to

110% of the laboratory's lower limit of normal, and with a concurrently obtained fasting glucose < 225 mg/dl, (3) patients must have a history of medically-uncontrollable labile insulin dependent diabetes mellitus (IDDM) with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization, (4) patients must have been optimally and intensively managed by an endocrinologist for at least 12 months, (5) patients must have the emotional and mental capacity to understand the risks associated with surgery and the lifelong need for immunosuppression; and, (6) patients must otherwise be a suitable candidate for transplantation.

This CMS coverage determination specifically states that transplantation of partial pancreatic tissue or islet cells is not covered at this time. CMS has been covering simultaneous kidney-pancreas transplantation since July 1, 1999. Starting October 1, 2004, CMS covered islet cell transplantation ONLY in the context of an NIH-sponsored clinical trial.

The coverage decision discussed the improvement in graft survival rates in recent years and notes the improvements in immunosuppressive regimens and surgical techniques, which have resulted in a decrease in rejection and technical failure rates (15). Since PTA is generally performed on patients much less than 65 years old and those not in end-stage renal diseases, it is unclear how many patients who would qualify for a PTA are Medicare beneficiaries. However, this coverage decision may influence more private payers to cover PTA.

Pancreas Utilization

The change in OPTN pancreas allocation policy that went into effect in February 2005 directs pancreata from donors older than age 50 or with a BMI greater than 30 kg/m2 for islet transplantation processing if the whole organ is not placed locally. This allocation change was based on data that demonstrated low placement rates of such organs for whole pancreas transplantation outside of the local DSA. This policy change is designed primarily to expedite placement and decrease cold ischemia times for pancreata recovered for islet transplantation, resulting in better utilization of these organs. The first year under the new policy did not appear to make a large difference in the number of pancreata recovered for islet processing (70 in 2005 compared with 73 in 2004) *[Table 3.4]*. The reason for this may be independent of allocation issues as financial constraints may have also affected islet transplant volume nationally.

A major issue in pancreas transplantation in the United States at the current time appears to be the relative underutilization of deceased donor pancreata and the disparate procurement rates for pancreata from deceased donors. In 2005, pancreata were not recovered from 65% of deceased donors. This rate has been relatively stable from 2000 to 2005. The pancreas was recovered and transplanted in 19% of all deceased donors in 2005, with an additional 5% recovered for transplant but discarded, 2% recovered for transplant but used for research, and 0.9% recovered for whole organ transplant but used for islets. An additional 3% were recovered primarily for islets and 5% were recovered for research only. This whole organ transplant rate of 19% was slightly down from a high of 24% in 2002 (OPTN Analysis, April 2006). This may reflect the increasing proportion of older donors mentioned previously.

Among OPTN regions, the percentage of pancreata recovered and transplanted ranged from a low of 10% to a high of 24%, with a national average of 21% between 2000 and 2005. Regional differences in donor quality could account for the differences, as well as the number of candidates awaiting pancreas transplantation (OPTN Analysis, April 2006). The overall number of pancreas transplants ranged from 231 to 1,947 across the eleven OPTN regions for a total of 8,456 whole organ pancreas transplants from 2000 to 2005.

The age range of the donor clearly affects the pancreas utilization rate. From 2000 through 2005, 34% of pancreata from donors less than 18 years old were transplanted, and 39% from donors age 18 to 40 were transplanted. This rate drops dramatically with only 13% utilized from 41 to 50 year-old donors and 4% from donors aged 51 to 55. Surprisingly, 1% of donor pancreata from donors aged 56 to 60 were transplanted (OPTN Analysis, April 2006). Donor BMI had a similar effect on pancreas utilization, with 26% of donors with BMI <28 having their pancreata transplanted. Utilization decreased with increasing BMI, as those with 28 to 30 had a transplant rate of 15%, 30 to 35 had a rate of 11%, 35 to 40 had 6%, and 40+ was 6%.

Reasons for non-recovery of consented organs in 2005 were 36% due to "Poor Organ Function," 20% due to "Other," 17% for "Donor Medical/Social History," and 11% for "No Recipient Found" *[Table 3.6]*. Nine percent of pancreata were damaged or had anatomic abnormalities that precluded transplantation. Although the categories above are very subjective, there is clearly opportunity for increased utilization of the 11% of organs in the category "No Recipient Found" as these could have been used outside of the local DSA. The 36% of organs listed as "Poor Organ Function" may offer the opportunity of increased transplantation by improved and consistent donor management, as well as

cooperative donor management with high volume regional pancreas centers.

Of pancreata recovered in 2005, 11% were not used due to "No Recipient Found" with 27% not used due to "Other;" these two reasons account for nearly 40% of the pancreata recovered and not used *[Table 3.5]*. "Organ Unsatisfactory" was listed in 29% of discards, with "Poor Organ Function/Infection" listed in 14%. Increasing regional and national use of pancreata through DonorNet2007 may assist in decreasing discard and nonrecovery rates due to the inability to find an appropriate recipient. Increased training of procurement surgeons will undoubtedly also assist the increased recovery and decreased anatomic injuries reported during pancreas procurement.

In 2005, 52% of recovered pancreata were transplanted locally with only 20% of pancreata shared outside of the local area *[Table 3.4]*. However, 13% of the organs recovered for local transplantation were not used while only 5% of those shared were not used. The relatively low demand for pancreata in some geographic areas allows the pancreas transplant centers to be very selective in evaluating pancreas donors. Local variations in pancreas allocation reflect the diversity of opinion on whether local candidates for simultaneous pancreas-kidney (SPK) transplants should be prioritized over kidney-only candidates. As a result, differences in waiting time among DSAs can be several years. Gruessner et al (16) have previously reported that nearly half the SPK candidates will die on the waiting list by four years if not transplanted. Type I diabetic recipients of SPK transplants receive a survival advantage equivalent to a living donor kidney, and superior to that of a deceased donor kidney alone (17, 18). These observations have convinced many DSAs to preferentially allocate kidneys to SPK candidates in the same manner as for other combined transplants (liver-kidney, heart-kidney) independent of their priority on the kidney waiting list.

The Pancreas Waiting List

The waiting list for a SPK transplant increased from 1,193 active candidates in 1996 to 1,194 candidates in 2000 *[Table 8.1a]*. Between 2000 and 2002, the number of active candidates on the SPK waiting list was just over 2,000. This was followed by an annual decline in the number of active candidates to a low of 1,536 in 2005. The number of older candidates (age 50-64) increased from 86 (7%) candidates in 1996 to 310 (20%) in 2005. The percentages of African American registrants (16%) and Hispanic/Latino registrants (11%) also increased over the past decade.

The number of patients active on the waiting list at the end of the year for isolated pancreas transplants has decreased from the highs of 534 listed for Pancreas After Kidney (PAK) and 303 listed for PTA in 2003 to 330 for PAK candidates and 209 for PTA candidates in 2005 *[Tables 6.1a and 7.1a]*. The majority of patients awaiting isolated pancreas transplants are white (83% for PAK, 90% for PTA). Although the percentage of PAK candidates aged 50-64 increased dramatically over the past decade (from 7% in 1996 to 22% in 2005), a more modest increase was observed in the percentage of PTA candidates aged 50-64 (11% to 14%). The percentage of PAK candidates with previous pancreas/kidney-pancreas transplants decreased from 43% in 1996 to 26% in 2005.

Overall waiting times continued to increase, with 45% of the SPK registrants active on the list at the end of 2005 having waited for a year or longer. This was an increase from 31% at the end of 1996. At the end of 2005, 38% of candidates on the SPK waiting list were inactive, including 26% of those aged 50 years or older *[Table 8.1b]*. In 2005, almost 44% of the inactive waiting list patients had been waiting for two or more years, while only 21% of the active waiting listing had been waiting for two or more years. In contrast, a majority of candidates wait-listed for PAK (66%) and PTA (60%) at the end of 2005 were not active *[Tables 6.1b, 7.1b]*. A disproportionate percentage of inactive wait-listed PAK and PTA candidates had been waiting one or more years at the end of 2005 (72% and 75% inactive vs. 50% and 44% active patients).

The median time to SPK transplant increased to a peak of 543 days for registrants listed in 2000 from 375 days for registrants listed in 1996 *[Table 8.2]*. Since 2000, the median time to transplant has decreased to 428 for registrants listed in 2004. The median time to transplant for registrants listed in 2004 increased with increasing age, from 374 days for registrants aged 18-34 years to 432 days for patients aged 35-49 years and 519 days for those aged 50-64. Median time to SPK transplant was also longer for African American registrants (505 days) and Hispanic registrants (614 days) compared with white registrants (396 days), and registrants with blood types O and B (535 and 520 days, respectively, in 2004) compared with those with blood types A and AB (324 and 214 days, respectively). The annual death rate on the SPK waiting list decreased slightly from 95 per 1,000 patient-years at risk in 2004 to 87 per 1,000 in 2005.

In 2004, median time to transplant among new PAK registrations was 575 days while median time to transplant among new PTA registrations was 376 days *[Tables 6.2 and 7.2]*. In 2003, white candidates on the PAK waiting list had shorter median waiting times (461

days) than did African American (740 days) or Hispanic candidates (863 days). Female PAK and PTA candidates had longer median waiting times in 2004 (616 and 449 days vs. 486 and 307 days for males). In 2004, PAK and PTA candidates with blood type O had the longest median waiting times among ABO blood types. Among candidates on the waiting list for PTA in 2005, the death rate was 61 per 1,000 patient-years at risk, while the death rate among waiting list candidates for PAK was 24 per 1,000 patient-years at risk *[Tables 6.3, 7.3]*.

Characteristics of Pancreas Transplant Recipients

Although the number of SPK transplants performed in 2005 was 7% lower than the peak of 972 in 1998, the number of SPK transplants increased over the past two years from 871 in 2003 to 881 in 2004 and 903 in 2005 *[Table 8.4]*. The percentage of SPK recipients who were 50 years of age or older decreased slightly from 19% in 2004 to 15% in 2005. The majority of SPK recipients in 2005 were white (73%), although the percentage of African American recipients increased from a low of 9% in 2000 to 16% in 2005. SPK transplant recipients were more often male (62%) in 2005 and only 2% received a zero mismatch transplant. Fewer than 2% had received a previous kidney-pancreas transplant.

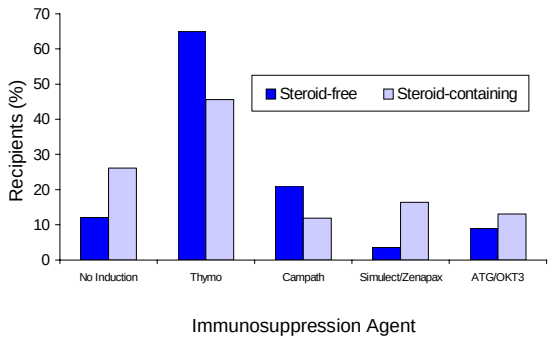
In 2005, 344 PAK transplants and 195 PTA transplants were performed. This represents an 18% decrease in PAK transplants and a 6% increase in PTA since 2004 *[Tables 6.4, 7.4]*. The percentage of PAK and PTA recipients who were age 50-64 years has increased dramatically from 2% and 4%, respectively, in 1996 to 17% and 19% in 2005. The percentage of African American PAK recipients has also increased in the past decade from 3% in 1996 to 10% in 2005. In contrast, the percentage of African American PTA recipients increased by only 3% from 1996 to 2005. Increasing numbers of solitary pancreata were transplanted with cold ischemia times under 12 hours (35% for PAK and 49% for PTA in 2005 vs. 17% for PAK and 21% for PTA in 1998).

Pancreas Transplant Immunosuppression

A majority of pancreas transplant recipients in 2005 (89% SPK, 85% PAK, 92% PTA) received tacrolimus-based immunosuppression for maintenance prior to discharge *[Tables 6.6e, 7.6e, 8.6e]*. Similarly, most recipients (81% SPK, 83% PAK, 58% PTA) had mycophenolate (Cellcept or Myfortic) included in their maintenance regimen. The use of steroids in maintenance immunosuppression has decreased from 93% for SPK and PAK in 2001 to 71% for SPK and 67% for PAK in 2005. Steroid use is less frequent in PTA recipients, and decreased from 77% in 2001 to 52% in 2005.

The overall use of induction agents in pancreas transplant immunosuppression is increasing, from 62% in SPK recipients and 26% in PAK recipients in 2001, to 88% in SPK and 83% in PAK in 2005 (SRTR special analysis, August 2006). This may reflect the increasing use of steroid-free maintenance regimens, as induction is more frequently used than with steroid-containing regimens (Figure IV-12). For example, in 2005, 88% of

Figure IV-12. Induction Immunosuppression for SPK Recipients, 2005



Source: *2006 OPTN/SRTR Annual Report*, Table 8.6a

SPK recipients on steroid-free regimens received induction; 65% received Thymoglobulin and 21% received Campath. Campath use in SPK steroid-free recipients has actually demonstrated a decline in use from a high of 43.1% in 2004. In contrast, 74% of SPK recipients with steroid-containing regimens received induction, with 46% receiving Thymoglobulin and 12% receiving Campath. The use of anti-CD25 antibodies (Simulect and Zenapax) was less frequent in steroid-free regimens (4%) than steroid containing regimens (17%).

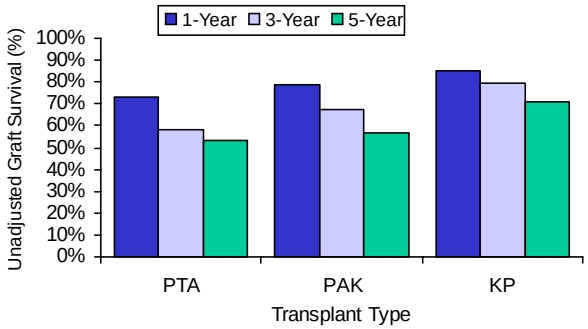
Graft Survival

Simultaneous Pancreas-Kidney Graft Survival - Kidney: Unadjusted kidney graft survival rates at one year, three years, and five years after SPK transplantation were 92%, 85%, and 76%, respectively *[Table 8.10]*. At 79%, unadjusted five-year kidney graft survival was highest for recipients who were age 35-49 years at transplant compared with 18-34 year-old recipients (72%) and 50-64 year-old recipients (74%). African American kidney-pancreas recipients had lower five-year kidney graft survival (65%) compared with white (78%), Hispanic (80%), and Asian recipients (77%). Unadjusted five-year kidney graft survival was lower for kidney-pancreas recipients who had received a previous kidney transplant (65% versus 77% for those who had not received a previous kidney transplant). The difference in unadjusted five-year kidney graft survival was even

larger for kidney-pancreas recipients who had received a previous pancreas transplant (44% versus 77% for those who had not received a previous pancreas transplant). Unadjusted five-year kidney graft survival decreased with increasing donor age (78% for 18-34 year-old donors, 73% for ages 35-49, and 66% for ages 50-64).

Simultaneous Pancreas-Kidney Graft Survival - Pancreas: Unadjusted pancreas graft survival rates at one, three, and five years following SPK transplantation were 85%, 79%, and 71%, respectively (Figure IV-13)

Figure IV-13. Unadjusted 1-Year, 3-Year, and 5-Year Pancreas Graft Survival by Transplant Type for Transplants Received 1999-2004

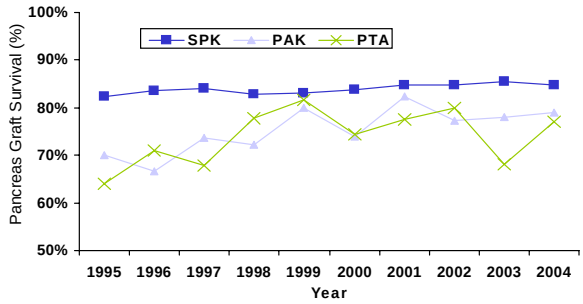


Source: *2006 OPTN/SRTR Annual Report,* Tables 6.10, 7.10, 8.10.

[Table 8.10]. African American kidney-pancreas recipients had poorer five-year pancreas graft survival (63%) than white (72%), Hispanic (77%), and Asian (74%) recipients. Unadjusted five-year pancreas graft survival was very similar amongst recipient age groups (68% for recipients aged 18-34 years, 72% for ages 35-49, and 71% for ages 50-64). As noted above for kidney graft survival rates, recipients with any previous transplant (kidney, pancreas, or both) had worse pancreas graft outcomes. Five-year pancreas graft survival after transplants from older adult donors (60% for donors aged 50-64 years) was substantially lower than after transplants from younger adult donors (73% for donors aged 18-34).

Graft Survival - PAK and PTA: Unadjusted graft survival rates at one year, three years, and five years following PAK transplantation were 79%, 68%, and 56%, respectively *[Table 7.10]*. The unadjusted graft survival rates for PTA at one, three, and five years following transplantation were moderately lower at 73%, 58%, and 53%, respectively (Figure IV-13) *[Table 6.10]*. Five-year graft survival was somewhat better in older PAK and PTA recipients (age 50-64 years: 61% for PAK and 62% for PTA, vs. age 18-34 years: 48% for PAK and 42% for PTA). Surprisingly, no clear trends in PAK and PTA graft survival were observed by donor age except for the suggestion of slightly decreased survival for PTA grafts from donors 35-49 as compared to all other donors *[Table 6.10]*.

Figure IV-14. Unadjusted One-Year Pancreas Graft Survival, by Year of Transplant, 1995-2004



Source: *2006 OPTN/SRTR Annual Report,* Tables 6.11, 7.11, 8.11b.

Short-term graft survival following solitary pancreas transplantation has improved over the decade, with outcomes now closer to those for SPK transplants (Figure IV-14). This may be a consequence of improved immunosuppression and improved diagnosis of rejection with increasing use of biopsy for solitary pancreas transplants. Despite these improvements, long-term outcomes of solitary transplants remain worse than for SPK transplants; conditional five-year survival (that is, survival of those transplants that were functioning at one year after transplant) for PAK and PTA were 72% and 70%, respectively, compared with 84% for SPK transplants (SRTR special analysis, August 2006).

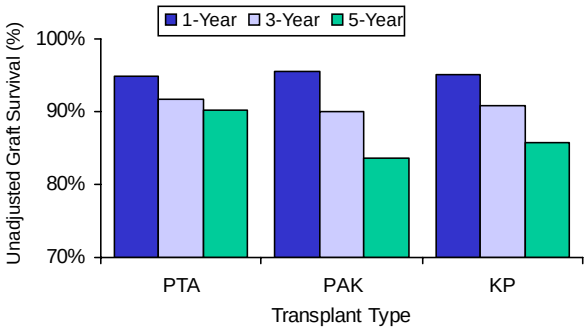
Patient Survival Following Pancreas Transplant

At the end of 2004, there were 6,535 SPK, 1,347 PAK, and 639 PTA recipients alive with functioning grafts *[Tables 6.16, 7.16, and 8.16]*. Over the past nine years, death rates for recipients in the first year following SPK transplant have decreased, from 63 per 1,000 patient-years at risk in 1996 to 56 per 1,000 in 2004 *[Table 8.7]*. This contrasts with death rates of 96 per 1000 on the SPK waiting list in 2004 *[Table 8.3]*. The annual death rate per 1,000 patient-years at risk for recipients in the first year following PAK transplantation was at a ten-year low of 41 in 2004, which was greater than those on the PAK waiting list (24 per 1000 patient-years at risk) *[Tables 7.3, 7.7]*. The greater death rate at one year after PAK transplantation versus PAK waiting list is probably due to short follow up time. Furthermore, small numbers of deaths in PTA recipients in the first year following transplantation makes interpretation of annual death rates difficult *[Table 6.7]*. Gruessner et al have demonstrated a probable benefit in patient survival in the PAK recipients versus those on the PAK waiting list

with longer follow up (16). Venstrom et al fail to demonstrate a benefit at four years (19).

Patient survival rates following all types of pancreas transplantation are excellent. Unadjusted patient survival rates at one, three, and five years following SPK transplantation were 95%, 91%, and 86%, respectively *[Table 8.14]*. The unadjusted patient survival rates for PAK recipients at one year, three years, and five years were 96%, 90%, and 84%, respectively (Figure IV-15)

Figure IV-15. Unadjusted 1-Year, 3-Year, and 5-Year Patient Survival by Transplant Type for Transplants Received 1999-2004



Source: *2006 OPTN/SRTR Annual Report,* Tables 6.14, 7.14, 8.14.

[Table 7.14]. Similar unadjusted patient survival rates were observed in PTA recipients with one-, three-, and five-year patient survival at 95%, 92%, and 90% *[Tables 6.14]*. African American SPK recipients had only minimally lower unadjusted five-year patient survival (83%) compared with white (86%) and Hispanic recipients (89%) *[Table 8.14]*. SPK recipients aged 50-64 years had slightly lower patient survival (82%) compared with younger recipients (88% for ages 18-34). Only a slight decrease in patient survival following SPK was observed with increasing donor age (patient survival of 87% for donors aged 18-34 to 84% for ages 35-49 to 82% for ages 50-64).

CONCLUSION

Kidney and pancreas candidates have unique challenges in the US today. The large deceased donor kidney waiting list comprised of increasingly older candidates allows both the opportunity to use ECD grafts due to the shorter life expectancy of the candidates, while presenting more ill patients with less physiological reserve after surgery and immunosuppression. The superiority of living donor grafts continues and offers the best overall outcomes. The greatest challenge to candidates on the DD waiting list is the increasing median time to transplantation.

The pancreas DD waiting list has slowly decreased since 2000. This may be due to local allocation policies. Type I diabetics who need to wait more than a couple of years on a lengthy DD waiting list have a high death rate. Therefore, many traditional SPK candidates may have turned to life-saving LD kidney transplantation followed by elective DD pancreas after kidney (PAK) transplantation. The pancreas whole organ grafts appear to be available throughout parts of the country, but the potential supply and demand are not ideally geographically matched.

Children have benefited from recent allocation policy changes with decreased medial waiting times. The rapid trend toward steroid-free maintenance immunosuppression has not resulted in decreased short term outcomes as many may have feared. The current struggle with allocation policy is the attempt to ration a scare resource wisely - the DD kidney graft. This problem has been mounting annually despite increases in the numbers of deceased donor kidney transplants last year, due in large part to the efforts of all those involved in the HRSA sponsored Collaboratives. The evaluation of concepts such as Net Lifetime Survival Benefit is attempting to make optimal use of the donor's precious gifts, while leaving opportunity for transplantation to most candidates. In long median waiting time donor service areas, older candidates have a reasonable possibility for a kidney transplant via the ECD allocation system.

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