

PANCREAS- KIDNEY SIMULTANEOUS TRANSPLANTS, PANCREAS AFTER
KIDNEY TRANSPLANTS AND PANCREAS RETRANSPLANTS - Data CYE 2005- CYE
2008

PANCREAS-KIDNEY, PANCREAS AFTER KIDNEY AND PANCREAS RETRANSPLANTATION	AHCCCS Data for Cases Members >21 years			
	2005	2006	2007	2008
Listed During year	4 Pancreas after Kidney (PAK); 2 Simultaneous Pancreas/ Kidney (SPK)	2 PAK; 4 SPK	1 SPK	2 Pancreas retransplantation would be treated as PAK; 2 SPK
# listed Dual or TPL	unk	0	0	0
Total Member on Wait list who are AHCCCS primary	4 PAK; 7 SPK 2 members removed	3 PAK; 3 SPK	3 PAK; 3 SPK	1 PAK; 1 PAK
Transplanted	2 PAK; 3 SPK	1 PAK; 4 SPK	2 SPK	1 PAK; 2 SPK
Mortality	0	0	0	0
Approved Costs for Components during contract year	\$145,578.00	\$546,384.00	\$102,692.00	\$1,064,965.00

Note- 2005 a transplant log of all members was not maintained

SUMMARY OF FINDINGS:

This abstract will review patient selection for and immunologic aspects relating to combined or sequential kidney-pancreas transplantation in patients with diabetes mellitus and end stage renal disease. Additionally, the criteria for retransplantation of failed pancreatic organs that have been previously transplanted will not be addressed, as retransplantation as an overall policy decision will be addressed in context of policy. The roles of pancreas transplantation alone and islet transplantation are not a current service/ covered benefit under the AHCCCS Medical Policy Manual. The following criteria and outcome data must be considered along with the kidney criteria, mortality and morbidity and abstract.

Criteria for listing:

Many institutions offer combined kidney-pancreas transplantation as an established definitive treatment for selected type 1 diabetic patients with end-stage diabetic nephropathy. Of the more than 20,000 pancreas transplants performed worldwide since 1966, over 90 percent were performed as simultaneous pancreas-

kidney (SPK) transplants, with the remainder performed most often as sequential pancreas after kidney (PAK) procedures.

This trend has changed over time. Among 1,328 pancreas transplants performed in the United States in 2003, 66, 25, and 8 percent were SPK, PAK, and pancreas transplantation alone (PTA), respectively. Nearly 70 percent of those undergoing PAK had a previous living donor (LD) kidney. The Institute for Clinical Systems reports that in 2003 94% of all SPK transplants, 94% were for patients with Type I diabetes mellitus.

While SPK most often employs grafts procured from a single deceased donor (DD) after brain death, some are simultaneous LD kidney and DD pancreas, and a few are LD for both organs. Rarely, SPK is also procured from a DD after cardiac death.

PAK typically involves transplantation of a cadaveric pancreas graft into a recipient with a functioning living or deceased donor kidney allograft. Some patients without substantial renal disease may be candidates for pancreas transplantation alone (PTA). In a report from the University of Minnesota, which has the largest experience, 1000 pancreas transplants had been performed as of 2002: 498 SPK, 404 PAK, and 292 alone for nonuremic diabetic patients. Of note is that the leading research physician of this report is Dr. Rainer Gruessner, who now heads the University of Arizona's HepatoPancreaticBiliary (HPB) Center.

When all risk factors and outcome data are taken into account, the best candidates for pancreas transplantation are younger (age<45 years) type 1 diabetics without cardiac risk factors who are to receive SPK transplants. Recipients **over age 45 carry a twofold greater risk of graft loss**, most often due to technical failure, and a **threefold greater risk of dying than younger patients**.

However, some highly selected individuals may do as well as younger individuals. In the International Pancreas Transplant Registry (IPTR) reports, for example, there was little difference in pancreas allograft survival rate between SPK recipients 30 to 40 years of age and those older than 40 years of age.

Cardiac risk factors, defined by prior myocardial infarction, coronary bypass, or percutaneous coronary angioplasty, are associated (independent of age) with 20 percent one-year mortality in SPK and PAK recipients, **four times greater than in diabetic recipients without cardiac risk factors**. In comparison, blindness, hypertension, peripheral vascular disease (including limb amputation, peripheral bypass procedures, and cerebrovascular complications), and duration of diabetes have no significant impact on patient or graft outcome. For patients with cardiac disease, the long term mortality risk is higher with continued dialysis.

Some centers advocate PAK, particularly for recipients with a well-matched highly functioning kidney allograft from a living donor. The main disadvantage of this regimen is that the patient has to wait for a well-matched pancreas. Since the median time to transplant for kidney transplants ranges from 1100 to 1200 days, the time frame for a PAK would further extend this timeframe. In comparison, HLA matching

does not appear to influence the success rate in SPK at one year. As a result, SPK candidates do not need to wait for a better match for a longer period than they would for a deceased donor renal allograft alone. .

Post Transplant Mortality and Morbidity:

The technical failure rate for all bladder-drained pancreas recipients in the United States, regardless of the presence of a kidney allograft, is 8 percent. Technical failure consists of irreversible graft loss due to thrombosis, hemorrhage, graft pancreatitis, or local infection necessitating graft removal.

Simultaneous Pancreas/ Kidney transplantation (SPK): Patient survival is similar with both SPK and living donor kidney transplantation alone. However, survival is higher with SPK versus that observed with deceased donor kidney transplantation alone. Nevertheless, there may be **no survival benefit with SPK versus deceased donor kidney transplantation among young diabetic recipients** of kidneys from young donors.

With newer surgical techniques and current potent immunosuppressive regimens, one and five year pancreas graft survival in SPK recipients is currently 86 and 70 percent, respectively. In a 2006 report, the one and five year patient survival for SPK recipients was 95 and 86 percent, respectively. Ten year survival reportedly ranges from 65 to 85 percent. The range in reported pancreas graft survival rates reflects a number of factors; these include center-based differences, the method of duct management, patient selection, and the inclusion or exclusion of technical failures and death with a functioning graft. Although the technical failure rate decreased markedly during the 1990s, it was still seven percent in the pancreas transplants performed in the United States between 1998 to 2000.

Kidney allograft survival rates in diabetic recipients of SPK are comparable to those seen with living donor kidney allografts alone. There are also some retrospective data suggesting that SPK performed prior to the need for dialysis (eg, preemptive transplantation) may be associated with improved renal allograft survival versus SPK after the initiation of dialysis. Preemptive SPK transplantation may also be associated with improved long-term patient survival.

Thus, SPK is an attractive option for suitable type I diabetic patients who are candidates for renal transplantation. However, the main drawback of an SPK is the long waiting time for Deceased Donor (DD) organs in some organ procurement organizations where no priority is given in allocation to pancreas-kidney versus kidney alone candidates. Given that the wait times for an SPK can be three to five years, many waitlist candidates die without ever being transplanted.

Survival for SPK recipients is superior to that observed with patients who continue to receive dialysis. In a retrospective review of 351 dialysis patients with type I diabetes, survival rates were evaluated among 130 who subsequently underwent SPK, 25 who underwent kidney transplantation alone, and 190 who remained on the waiting list. At seven year follow-up, survival was significantly higher for those who underwent

SPK versus those never transplanted (77, 56, and 40 percent for SPK, kidney alone, and waiting list groups, respectively, with $P = 0.01$ for SPK versus waiting list).

In general, patient survival is similar with both SPK and living donor transplantation alone, but survival is higher versus that observed with deceased donor kidney transplantation alone. As examples:

- A small ten year study evaluated outcomes after SPK in 14 patients with type 1 diabetes and end-stage diabetic nephropathy versus 15 diabetics subjected to deceased donor kidney transplantation alone. Mortality was significantly lower among those who underwent SPK (20 versus 80 percent).
- A retrospective study of 18,549 patients with type 1 diabetes reported that eight year survival was similar for SPK (72 percent) and living donor kidney recipients (72 percent), which was higher than that observed for deceased donor kidney recipients (55 percent).
- Patient survival was evaluated among 130, 379, and 296 recipients of living related donor kidneys, SPKs, and deceased donor kidneys, respectively. Patient survival was significantly lower for the deceased donor group versus that observed with recipients of living related donor kidneys and SPKs.

However, there may be no survival benefit with SPK versus deceased donor kidney transplantation among young diabetic recipients of kidneys from young donors. As an example, survival outcomes were examined in a retrospective study of 3642 SPK and 2374 deceased donor renal transplant recipients. Although overall five year patient survival was superior among those who received SPK (85 versus 76 percent), there was no difference in survival between the two groups among recipients less than 41 years of age who received a kidney from a donor under the age of 36 years.

Pancreas after kidney transplantation (PAK): Data suggest that pancreas graft survival in PAK transplantation with zero to one HLA mismatches in the pancreas transplant is similar to that achieved with SPK. As noted in the latest International Pancreas Transplant Registry (IPTR) analysis, however, the match will frequently be for one A or B antigen if a young donor is involved, given that the HLA effect is much weaker.

The relative effect of PAK on patient survival is unclear. As examples:

- In a retrospective study of over 11,000 diabetics on the waitlist between 1995 to 2000, mortality within four years of transplantation was evaluated among those who underwent PAK, SPK, and Pancreas Transplant Alone (PTA) versus patients waiting for the same procedure. Overall relative risk of all-cause mortality at four years was significantly higher for those who underwent PAK versus those on the waitlist for PAK (RR of 1.42, 95% CI 1.03 to 1.94), with one year survival rate also being relatively lower (95 versus 97 percent) for PAK and PTA. On

the other hand, overall relative risk at four years was significantly lower for those who underwent SPK, the procedure used most frequently. In interpreting these data, it is important to realize the limitations of this report. Some patients were wait-listed on more than one list and therefore counted more than once, while others on the waitlists withdrew from the lists because they were so ill they needed to have a kidney transplant. Both of these unaccounted for variables would have the effect of biasing the data towards better outcomes for those on the waitlist.

- In a study using data from 1995 through 2003, mortality was assessed among 2942 diabetics waitlisted for PAK. With univariate analysis, four year survival was significantly lower in those who underwent PAK (82 versus 88 percent). However, mortality was not increased after multivariate analysis, suggesting that survival after PAK is similar to that observed with waitlisted patients.

Thus, Living Donor (LD) kidney followed by DD pancreas may be a better option as far as survival and the wait-no wait for the kidney. After a kidney is transplanted, the wait for a pancreas alone is weeks to months and nearly always less than a year.

Morbidity:

Complications related to transplant are the same as kidney transplants, with addition of the following pertaining to the pancreas:

The morbidity of **SPK** can be appreciated by the following observations:

- One study compared 88 technically successful SPK and 65 first cadaveric Kidney Transplants Alone (KTA) performed in diabetic patients with end-stage renal disease. SPK recipients had an increased risk of early death, most often due to myocardial infarction, sepsis (26 versus 13 percent of all deaths), and surgical complications.
- Many studies have documented a significantly greater morbidity associated with SPK than KTA, reflected by longer initial hospital stay (23 days), more frequent rehospitalization (75 percent) during the first year posttransplant, and greater severity of illness requiring rehospitalization (19 percent requiring operative intervention).

Common nonimmunologic complications encountered following SPK include wound problems (23 percent), gross hematuria (15 percent), urinary leak (14 percent), reflux pancreatitis (11 percent), recurrent urinary tract infection (10 percent), abdominal abscess (5 percent), small bowel obstruction (5 percent), and vascular thrombosis (0.2 to 2 percent). A retrospective review of 276 SPK and 1833 KTA recipients revealed a significant increase in the risk of deep venous thrombosis (18 versus 6 percent, $p<0.001$) and pulmonary thromboembolism (4.7 versus 1.7 percent, $p<0.01$) following SPK [56]. Among SPK recipients, DVT tended to occur more often on the side of the pancreas than the kidney (57 versus 43 percent, $p=0.10$), and the risk of DVT was greatest during the first month post-transplant.

The more aggressive prophylactic and antirejection immunosuppressive strategies used in SPK exposes the patient to a greater degree of overall immunosuppression. As a result, there is an increased risk of infection and possibly a lymphoproliferative disorder or cancer. Fungal infection is two to three times more common in SPK recipients; however, there is no evidence of a statistically significant increase in the incidence of CMV disease.

Viral infection — Hepatitis C virus (HCV) infection is an important source of morbidity and mortality among immunosuppressed transplant recipients. However, no prospective data exists concerning the effect of HCV infection on patients who have undergone SPK as compared with renal transplantation alone. A retrospective study examined the clinical course of 137 kidney-pancreas transplant recipients according to HCV status as determined by polymerase chain reaction. Compared to uninfected patients, those with HCV infection (8.7 percent) had a 3.7 and 3.4 fold increased risk of death and renal graft failure, respectively. These adverse results need to be confirmed in larger, better designed studies.

BK virus is an increasingly recognized cause of allograft loss in renal transplant recipients. The major diseases caused by BK virus are tubulointerstitial nephritis and ureteral stenosis in renal transplant recipients. This virus may also be a significant cause of renal graft loss in SPK recipients.

As with other immunosuppressed transplant recipients, cytomegalovirus (CMV) infection is among the most common viruses causing clinical significant infection in kidney-pancreas transplant recipients. In the Euro-SPK 001 study, for example, the rate of CMV infection among donor-minus (D-)/recipient-minus (R-), D-/R+, D+/R+, D+/R- pairs was 11, 40, 37, and 52 percent, respectively.

Metabolic disturbances — SPK with bladder drainage is often associated with the loss of large quantities of bicarbonate-rich pancreatic secretions into the urine, leading to a normal anion gap metabolic acidosis, hyponatremia, and volume depletion. The hyponatremia is presumably due to the combination of hypovolemia-induced stimulation of the release of antidiuretic hormone and the replacement of solute-rich pancreatic secretions with free water. As a result, many SPK recipients with bladder drainage require chronic sodium bicarbonate supplementation; the dose is often as high as 100 to 150 meq/day.

Problems with acidosis and volume depletion are greatly reduced with enteric exocrine drainage of the pancreas graft. In a single center report of 30 and 23 patients with bladder and enteric drainage, respectively, the incidence of metabolic acidosis was significantly lower in those with enteric drainage (zero versus 83 percent). Patient and allograft survival appears to be similar with either bladder or enteric drainage.

Hyperglycemia — Hyperglycemia can result from two different mechanisms after pancreas transplantation:

- Pancreatic dysfunction due to rejection, technical problems, or direct cyclosporine or tacrolimus toxicity.

- Recurrent autoimmune injury to the pancreas was originally described only in recipients of grafts from HLA-identical siblings who received no prophylactic immunosuppression. Immunosuppressive therapy in cadaver grafts is usually sufficient to prevent recurrent disease in the pancreas. However, recurrence has been reported, even in patients with poor HLA matches.

The morbidity of **PAK** was not addressed in the context of the PAK in the literature, but generalizations based the morbidity of both a renal / kidney transplant and that of a pancreas alone transplant should be considered due to the individual nature of each surgery. Generalizations as to the effects of immunosuppression are common to all solid organ transplants.

Quality Of Life after Transplantation:

Pancreas transplant candidates can be informed that the major benefits they can expect from the addition of a pancreas to a kidney transplant are an improved quality of life, stabilization of neuropathy and improvement in nephropathy, and protection of a simultaneously transplanted kidney from the adverse effects of hyperglycemia.

The rationale for performing pancreas transplantation in patients with diabetes mellitus is that persistent euglycemia will improve the quality of life by making the patient free of insulin therapy and may prevent progression of and even improve diabetic microvascular and macrovascular complications. However, the extent to which the latter occurs is variable.

Kidney-Pancreas and Pancreas Alone Patient Care Cost Analysis:

According to Milliman, the average total cost of a kidney- pancreas transplant in 2007 was \$368,600 and \$439,000 in 2008. This figure includes the cost of obtaining donor organs and does not specify the difference in cost of a cadaveric or living donor. The average cost of procurement was \$124,500 and \$122,300 in 2008; hospitalization was \$120,300 in 2007 and \$171,100 in 2008; additional costs for 2007 were \$14,700 for the transplant evaluation and in 2008 the data is reported as the cost for the 30 days pre-transplant which was \$18,400; physician fees in 2007 were \$24,600 and \$32,000 in 2008; post-operative care in 2007 was \$48,300 in 2008 the post care is reported as the 180 days after transplant at \$73,800; and immunosuppressive prescription and medications are reported as \$36,200 for 2007 and \$21,400 for 2008. These totals do not differentiate between a SPK or PAK.

The reported totals for Pancreas alone were \$297,300 in 2007 and \$275,500 in 2008. This figure includes the cost of obtaining the pancreas and does differentiate the between cadaveric pancreas or islet cell transplantation. The cost of organ procurement was listed as \$66,200 in 2007 and \$68,400 in 2008; hospitalization cost of \$107,100 in 2007 and \$93,400 in 2008; Physician fees in 2007 were \$24,600 and \$16,300 in 2008; in 2007 the evaluation is reported as \$14,700 while in 2008 Milliman reports the 30 days

pre-transplant as \$16,500; in 2007 post transplant care is listed at \$48,300 while in 2008 the data is reported as the 180 days post transplant admission at \$58,700; outpatient immunosuppressants and prescriptions are listed as \$36,400 in 2007 and \$22,200 in 2008.

AHCCCS Experience with Pancreas after Kidney Transplants (based on Data Warehouse numbers eff. 5/09)

	Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant	Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant	Average Cost of member during transplant year	Average Cost per member for 1 st year post transplant	Average Cost per member for 2 nd year post transplant
Billed Amount	\$622.38	\$95,339.17	\$461,210.33	\$25,893.49	\$149,895.52
Allowed Amount	\$561.06	\$21,702.65	\$89,673.02	\$11,851.20	\$32,415.43
Paid Amount	\$90.00	\$15,072.23	\$62,024.23	\$9,609.39	\$14,713.63
Health Plan Paid Amount	\$90.00	\$17,895.35	\$91,865.03	\$8,446.21	\$13,394.47
Simultaneous Kidney-Pancreas	Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant	Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant	Average Cost of member during transplant year	Average Cost per member for 1st year post transplant	Average Cost per member for 2nd year post transplant
Billed Amount	\$98,121.47	\$200,532.60	\$316,490.27	\$49,429.08	\$151,062.32
Allowed Amount	\$19,632.79	\$41,236.59	\$73,514.37	\$25,933.65	\$21,742.48
Paid Amount	\$15,992.26	\$31,967.38	\$56,771.44	\$12,185.90	\$5,446.16
Health Plan Paid Amount	\$18,308.65	\$36,574.17	\$59,485.64	\$11,936.36	\$4,772.60

Insurance Coverage Summary: Medicare covers pancreas alone and pancreas/kidney transplants

(http://www.cms.hhs.gov/CertificationandCompliance/20_Transplant.asp#TopofPage) If you have ESRD and need a **pancreas/kidney** transplant, Medicare covers this type of transplant if one of the following applies:

- It's done at the same time you get a kidney transplant
- It's done after a kidney transplant

If you have Medicare only because of kidney failure, and you have the pancreas transplant after the kidney transplant, Medicare will only pay for your immunosuppressive drug therapy for 36 months after the month of the kidney transplant. If you already had Medicare because of age or disability before you got ESRD, or if you became eligible for Medicare because of age or disability after getting a transplant, Medicare will continue to pay for your immunosuppressive drugs with no time limit

Medicare coverage of Pancreas alone transplants to induce an insulin-independent, euglycemic state in diabetic patients. The procedure is generally limited to those patients with severe secondary complication of diabetes, including kidney failure, and is sometimes performed on patients with labile diabetes who experience hypoglycemic unawareness.

Aetna covers pancreas kidney transplants only if a member has end-stage renal disease (ESRD) and requires dialysis or is expected to require dialysis in the next 12 months: AND the member's creatinine clearance using the Cockcroft-Gault formula is less than 20 mL/min, or has a directly glomerular filtration rate of less than 20 ml/min.

Aetna coverage of Pancreas alone transplantation is limited to the patient meeting all four of the following criteria: 1. member must have satisfactory kidney function (creatinine clearance greater than 40 mL/min; 2. member has adequate cardiac status (no angiographic evidence of significant coronary artery disease, ejection fraction greater than or equal to 40%, no myocardial infarction in the last 6 months, and a negative stress test) 3. Absence of ongoing or recurrent active infections that are not effectively treated 4. Absence of uncontrolled HIV/AIDS infection.

Blue Cross / Blue Shield of Florida only covers pancreas transplantation when it is considered life-saving including re-transplantation, SPK and PAK are covered when criteria met.

Medicaid: **Kansas** covers kidney-pancreas transplants but does not reimburse at an additional rate from the rate for kidney alone; **Oregon** covers up to one transplant (PAK or SPK are covered) and has criteria that the member must have irreversible kidney and/or pancreatic disease which has advanced to the point where conventional treatment offers no prospect for prolonged survival and the member's 5 year survival rate is at least 20% as supported by medical literature ; **Florida** does not cover kidney/pancreas transplants for recipients \geq 21 years ; **Hawaii** does not cover kidney-pancreas and pancreas alone transplants; **Oklahoma** simply states they cover all medically necessary transplants with prior authorization.

Recommendations: Eliminate all Pancreas retransplants and Pancreas after Kidney (PAK) transplants. Cover Simultaneous Pancreas- Kidney (SPK) transplants only. SPK transplants actually showed a decreased cost both in the year of transplant and annually for the 2 year timeframe post transplant compared with Kidney only transplant members. This is due to the more stringent criteria adopted by transplant centers for approving SPK transplants. A SPK transplant is reserved for members considered highly motivated, are \leq 45 years of age, have no comorbidities, and have Type I diabetes. These patients

are not generally on dialysis at the time of transplant and studies show that this is the optimal scenario for the best long term outcome. AHCCCS will implement the criteria into policy.

- The average number of PAK transplants over a 4 year period average allowed costs for this transplant = \$89,673.02/transplant year. The frequency of this transplant type is 1 per year.
- The average number of SPK transplants over a 4 year period average allowed costs of a SPK transplant = \$73,514.37/transplant year

Average annual cost of medical management of these members post transplant is:

- SPK: \$ 25,933.65 for the first year post transplant based on the 9 members profiled for the time period from 2005 through 2008, there is no data for the second year post transplant.
- PAK: Year 1 post transplant = \$11,851.20 and Year 2 post transplant = \$32,415.43 based on 3 members profiled.
- The potential savings in post transplant costs could not be conducted based on the limited number of long term members post transplant and lack of second year data for SPK, although the literature implies that there are long term cost savings with the use of SPK transplants over PAK transplants. SPK carries less risk since a second surgery is not required and is more cost effective at transplant than a PAK. The criteria and patient profiles for SPK and PAK patients are comparative.

Total savings projected is the difference between a SPK and a PAK based on 1 transplant annually is the difference in the cost during the transplant year between these transplant types: \$89,673.02(PAK) -\$73,514.37(SP) = \$16,158.65

(1)<http://www.milliman.com/expertise/healthcare/publications/rr/pdfs/2007-US-Organ-Transplant-RR11-01-07.pdf>

(2)Medicare Coverage criteria

(3)The following state Medicaid programs: Oregon, Kansas, Utah, Hawaii, Oklahoma and Florida

- (4) Up to Date: **Patient selection for and immunologic issues relating to kidney-pancreas transplantation in diabetes mellitus, Last literature review version 17.1:** January 2009, **This topic last updated:** February 11, 2009

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