Allogeneic Pancreas Transplant

Policy Number: MM.07.002
Original Effective Date: 03/23/2001
Line(s) of Business: HMO; PPO
Current Effective Date: 09/01/2013
Section: Transplants
Place(s) of Service: Inpatient

I. Description

Transplantation of a normal pancreas is a treatment method for patients with insulin-dependent diabetes mellitus. Pancreas transplantation can restore glucose control and is intended to prevent, halt, or reverse the secondary complications from diabetes mellitus.

Background

Achievement of insulin independence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. While pancreas transplantation is generally not considered a life-saving treatment, in a small subset of patients who experience life-threatening complications from diabetes, pancreas transplantation could be considered life-saving. Pancreas transplant alone (PTA) has also been investigated in patients following total pancreatectomy for chronic pancreatitis. In addition to the immune rejection issues common to all allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes. (1)

Pancreas transplantation occurs in several different scenarios such as: 1) a diabetic patient with renal failure who may receive a cadaveric simultaneous pancreas/kidney transplant (SPK); 2) a diabetic patient who may receive a cadaveric or living-related pancreas transplant after a kidney transplantation (pancreas after kidney, i.e., PAK); or 3) a non-uremic diabetic patient with specific severely disabling and potentially life-threatening diabetic problems who may receive a PTA. The total number of adult pancreas transplants (pancreas and pancreas/kidney) in the U.S. peaked at 1,484 in 2004; the number has since declined. (2) In 2011, there were 287 pancreas transplants and 795 pancreas/kidney transplants in the U.S.

According to International Registry data, the proportion of pancreas transplant recipients worldwide who have type 2 diabetes has increased over time, from 2% in 1995 to 7% in 2010. (3) In
2010, approximately 8% of SPK, 5% of PAK, and 1% of PTA were performed in patients with type 2 diabetes.

The approach to retransplantation varies according to the cause of failure. Surgical/technical complications such as venous thrombosis are the leading cause of pancreatic graft loss among diabetic patients. Graft loss from chronic rejection may result in sensitization, increasing both the difficulty of finding a cross-matched donor and the risk of rejection of a subsequent transplant. Each center has its own guidelines based on experience; some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

II. Policy

A. A combined pancreas-kidney transplant is covered (subject to Administrative Guidelines) in insulin-dependent diabetic patients with uremia.

B. Pancreas transplant after a prior kidney transplant is covered (subject to Administrative Guidelines) in patients with insulin dependent diabetes.

C. Pancreas transplant alone is covered (subject to Administrative Guidelines) in patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile insulin dependent diabetes that persists in spite of optimal medical management.

D. Pancreas retransplant is covered (subject to Administrative Guidelines) after a failed primary pancreas transplant.

III. Policy Guidelines

General:
Potential contraindications subject to the judgment of the transplant center:
1. Known current malignancy, including metastatic cancer
2. Recent malignancy with high risk of recurrence
3. Untreated systemic infection making immunosuppression unsafe, including chronic infection
4. Other irreversible end-stage disease not attributed to kidney disease
5. History of cancer with a moderate risk of recurrence
6. Systemic disease that could be exacerbated by immunosuppression
7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

Pancreas Specific:
Candidates for pancreas transplant alone should additionally meet 1 of the following severity of illness criteria:
1. Documentation of severe hypoglycemia unawareness as evidenced by chart notes or emergency room visits; OR
2. Documentation of potentially life-threatening labile diabetes as evidenced by chart notes or hospitalization for diabetic ketoacidosis.

In addition, the vast majority of pancreas transplant patients will have type 1 diabetes mellitus. Those transplant candidates with type 2 diabetes mellitus, in addition to being insulin-dependent, should also not be obese (body mass index [BMI] should be 32 or less). According to International Registry data, in 2010, 7% of pancreas transplant recipients had type 2 diabetes. (3)

Multiple Transplants

Although there are no standard guidelines regarding multiple pancreas transplants, the following information may aid in case review:

1. If there is early graft loss resulting from technical factors (e.g., venous thrombosis), a retransplant may generally be performed without substantial additional risk.
2. Long-term graft losses may result from chronic rejection, which is associated with increased risk of infection following long-term immunosuppression, and sensitization, which increases the difficulty of finding a negative cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

In addition, HMSA has the following requirements:
1. Adequate cardiopulmonary status
2. Absence of active infection
3. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
4. Documentation of patient compliance with medical management.

IV. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, complete HMSA’s Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>48550</td>
<td>Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation</td>
</tr>
<tr>
<td>48551</td>
<td>Backbench standard preservation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery</td>
</tr>
<tr>
<td>48552</td>
<td>Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each</td>
</tr>
</tbody>
</table>
V. Scientific Background

Literature Review

This policy was created in 1996 and updated regularly with searches of the MEDLINE database. The most recent search was performed for the period December 2011 through January 14, 2013. Much of the published literature consists of case series reported by single centers and registry data. The extant randomized controlled trials (RCTs) compare immunosuppression regimens and surgical techniques and therefore do not address the comparison of pancreas transplantation to insulin therapy, or simultaneous pancreas/kidney (SPK) transplant to insulin therapy and hemodialysis.

This policy is based in part on a 1998 TEC Assessment, which focused on pancreas graft survival and health outcomes associated with both pancreas transplant alone (PTA) and pancreas after kidney transplant (PAK). (4) A 2001 TEC Assessment focused on the issue of pancreas retransplant. (5) The assessments and subsequent evidence offer the following observations and conclusions:

Pancreas after Kidney (PAK) Transplant

PAK transplantation allows the uremic patient the benefits of a living-related kidney graft, if available and the benefits of a subsequent pancreas transplant that is likely to result in improved quality of life compared to a kidney transplant alone. Uremic patients for whom a cadaveric kidney graft is available, but a pancreas graft is not simultaneously available benefit similarly from a later
pancreas transplant. Based on International Pancreas Registry data, at 5 years post-transplant, the patient survival rate after PAK is 83%. (3)

In 2009, Fridell and colleagues reported a retrospective review (n=203) of a single center’s experience with PAK and SPK since 2003, when current induction/tacrolimus immunosuppressive strategies became standard. (6) Of the cases studied, 61 (30%) were PAK and 142 (70%) were SPK. One-year patient survival rates were 98% and 95% (PAK and SPK, respectively; p=0.44). Pancreas graft survival rates at 1 year were observed to be 95% and 90%, respectively (p=0.28). The authors concluded that in the modern immunosuppressive era, PAK should be considered as an acceptable alternative to SPK in candidates with an available living kidney donor.

In 2012, Bazarbachi and colleagues reviewed a single center’s experience with PAK and SPK. (7) Between 2002 and 2010, 172 pancreas transplants were performed in diabetic patients; 123 SPK and 49 PAK. The median length of time between kidney and pancreas transplantation in the PAK group was 4.8 years. Graft and patient survival rates were similar in the 2 groups. Death-censored pancreas graft survival rates for SPK and PAK were 94% and 90% at 1 year, 92% and 90% at 3 years, and 85% and 85% at 5 years (all respectively, p=0.93). Patient survival rates (calculated beginning at the time of pancreas transplantation) in the SPK versus PAK groups were 98.3% and 100% after 1 year, 96.4% and 100% after 3 years, and 94.2% and 100% after 5 years (all respectively, p=0.09).

Kleinclauss and colleagues retrospectively examined data from diabetic kidney transplant recipients (n=307) from a single center and compared renal graft survival rates in those who subsequently received a pancreatic transplant to those who did not. (8) The comparative group was analyzed separately depending on whether they were medically eligible (KTA-E) for pancreas transplant, but chose not to proceed for financial or personal reasons, or were ineligible (KTA-I) for medical reasons. The KTA-I (n=57) group differed significantly at baseline from both the PAK group (n=175) and the KTA-E group (n=75) with respect to age, type of diabetes, and dialysis experience; kidney graft survival rates were lower than either of the other groups, with 1-, 5-, and 10-year rates of 75%, 54%, and 22%, respectively (p<0.0001). The PAK and KTA-E groups were similar in age, race, type of diabetes, and dialysis experience. The authors compared 1-, 5-, and 10-year kidney graft survival rates in PAK patients with those in the KTA-E group: 98%, 82%, and 67% versus 100%, 84%, and 62%, respectively, and concluded that the subsequent transplant of a pancreas after a living donor kidney transplant does not adversely affect patient or kidney graft survival rates.

**Pancreas Transplant Alone (PTA)**

PTA graft survival has improved in recent years. According to International Registry data 1-year graft function increased from 51.5% in 1987-1993 to 77.8% in 2006-2010 (p<0.0001). (3) One-year immunologic graft loss remains higher (6%) after PTA than PAK (3.7%) or SPK (1.8%). In carefully selected patients with insulin dependent diabetes mellitus (IDDM) and severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile diabetes that persists despite optimal medical management, the benefits of PTA were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression.
The majority of patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where nonuremic IDDM patients have significant morbidity risks due to secondary complications of diabetes (i.e., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because there is virtually no published evidence regarding outcomes of medical management in this very small group of exceptional diabetic patients, it is not possible to generalize about which circumstances represent appropriate indications for pancreas transplantation alone. Case-by-case consideration of each patient’s clinical situation may be the best option for determining the balance of risks and benefits.

Noting that nephrotoxic immunosuppression may exacerbate diabetic renal injury after PTA, in 2008 Scalea et al. reported a single institutional review of 123 patients who received 131 PTA for development of renal failure. (9) Mean graft survival was 3.3 years (range, 0–11.3), and 21 patients were lost to follow-up. Mean estimated glomerular filtration rate (eGFR) was 88.9 pre-transplantation versus 55.6 post-transplantation, with mean follow-up of 3.7 years. All but 16 patients had a decrease in eGFR, and mean decrement was 32.1 mg/min/1.73. Thirteen developed end-stage renal disease, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA. Future updates of this policy will continue to follow this clinical topic.

**Simultaneous Pancreas/Kidney (SPK) Transplant**

According to International Registry data through 2005, recent 5-year graft survival rates for SPK transplants are 72% for the pancreas and 80% for the kidney. (10) Ten-year graft survival rates have reached almost 60% for SPK transplants.

In 2010, Mora and colleagues described the long-term outcome of 12 patients 15 years following SPK transplant. (11) Metabolic measures of glucose control were measured at 1, 5, 10, and 15 years following the procedure. Of this subset of patients, 6 (50%) had non-diabetic glucose challenge tests. Basal serum insulin levels declined over this period as well, from 24 mU/L to 16 mU/L at 1 and 15 years, respectively. The authors conclude that in a select group of patients whose pancreatic graft continued to function after 15 years, some glycemic control continued, albeit in a diminished fashion. It should be noted that this represents a small fraction of the 367 patients receiving the SPK transplant at this single center (12 of 367 SPK; 3.3%). The number of allograft survivals at 5 or more, and 10 or more years in this study was 43 (11.7%) and 28 (7.6%), respectively.

The improved glycemic control that may occur in SPK transplant patients, principally in those with labile disease while on medical therapy alone, is purported to reduce risk of complications from the diabetic disease. In 2009, Davenport and colleagues published results of a registry review (n=58) on cardiovascular risk factors in an Irish study of SPK transplant recipients. (12) Glycosylated hemoglobin values fell from a mean of 8.1 to 5.2 (p<0.0001) from pre-transplant levels. Similar statistically significant declines were seen in total cholesterol, triglycerides, and creatinine. Systolic and diastolic blood pressures were likewise improved but with a greater range of pre- and post-
transplant variability. These endpoints are commonly accepted as surrogates for cardiovascular risk. The authors compared both a surgical method (bladder vs. enteric drainage) and mode of immunosuppression (cyclosporine vs. tacrolimus) on changes to blood pressure and cholesterol. No significant differences were found in either measure based on surgical drainage method, nor did immunosuppressive therapy have an impact on blood pressure reduction. Cholesterol reduction was greater in the cyclosporine than the tacrolimus group (-1.3 to -0.2, respectively), favoring the less contemporary strategy. The authors note that this is in contrast to other recently published studies favoring both enteric drainage and tacrolimus. While this single-arm study suggests beneficial cardiovascular effects from transplant, other factors such as rejection rates are more likely to influence the conditions under which transplantations take place, and this study’s data do not lead to conclusions that would change the policy statement.

In 2011, Sampaio and colleagues published an analysis of data from the United Network for Organ Sharing (UNOS) database. The investigators compared outcomes in 6,141 patients with type 1 diabetes and 582 patients with type 2 diabetes who underwent SPK between 2000 and 2007. In adjusted analyses, outcomes were similar in the 2 groups. After adjusting for other factors such as body weight; dialysis time; and cardiovascular comorbidities, type 2 diabetes was not associated with an increased risk of pancreas or kidney graft survival, or mortality compared to type 1 diabetes.

Pancreas Retransplantation

The U.S.-based Organ Procurement Transfer Network (OPTN) reported data on transplants performed between 1997 and 2004. Patient survival rates after repeat transplants were similar to survival rates after primary transplants. For example, the 1-year survival rate was 94.0% (95% confidence interval [CI]: 92.6 to 95.3%) after a primary pancreas transplant and 95.6% (95% CI: 92.7 to 98.5%) after a repeat pancreas transplant. The numbers of patients transplanted was not reported, but the OPTN data stated that 1,217 patients were alive 1 year after primary transplant and 255 after repeat transplants. Three-year patient survival rates were 89.5% (95% CI: 87.8 to 91.2%) after primary transplants and 89.7% (95% CI: 85.9 to 93.5) after repeat transplants. One-year graft survival rates were 78.2% (95% CI: 76.0 to 80.5%) after primary pancreas transplants and 70.4% (95% CI: 64.8 to 76.0%) after repeat transplants.

Data are similar for patients receiving combined kidney/pancreas transplants, but follow-up data are only available on a small number of patients who had repeat kidney/pancreas transplants so estimates of survival rates in this group are imprecise. Three-year patient survival rates were 90.0% (95% CI: 89.0 to 91.0%) after primary combined transplant and 79.9% (95% CI: 63.8 to 95.9%) after a repeat combined transplant. The number of patients who were living 3 years after transplant was 2,907 after a primary combined procedure and 26 after a repeat combined procedure.

In 2013, Buron and colleagues reported on their experience with pancreas retransplantation in France and Geneva. Between 1976 and 2008, 568 pancreas transplants were performed at 2 centers, including 37 repeat transplants. Patient survival after a repeat pancreas transplant was 100% after 1 year and 89% after 5 years. Graft survival was 64% at 1 year and 46% at 5 years.
Among the 17 patients who underwent a second transplant in a later time period i.e., between 1995 and 2007, graft survival was 71% at 1 year and 59% at 5 years. In this more recently transplanted group, graft survival rates were similar to primary pancreas transplants, which was 79% at 1 year and 69% at 5 years.

**Immunosuppressive Regimen**

Pancreas transplantation requires T cell autoantibody induction, which most solid organ transplantations do not. As a consequence, a variety of studies, including RCTs, have examined various immunosuppressive regimens. (15-20) This high-quality evidence adds to our understanding of transplant management but does not compare pancreas transplant to alternatives and therefore does not contribute to the evidence base for this policy.

**HIV+ Transplant Recipients**

The Organ Procurement Transfer Network (OPTN) policy on Identification of Transmissible Diseases in Organ Recipients states: “Potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy.” (21)

In 2006, the British HIV Association and the British Transplantation Society Standards Committee published guidelines for kidney transplantation in patients with human immunodeficiency virus (HIV) disease. (22) As described above, these criteria may be extrapolated to other organs. The guidelines recommend that any patient with end-stage organ disease with a life expectancy of at least 5 years is considered appropriate for transplantation under the following conditions:

- CD4 count greater than 200 cells/microliter for at least 6 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- Demonstrable adherence and a stable HAART [highly active antiretroviral therapy] regimen for at least 6 months
- Absence of AIDS [acquired immunodeficiency syndrome]-defining illness following successful immune reconstitution after HAART.

**Age**

Several 2011 studies addressed pancreas transplantation in individuals 50 years of age or older. A study by Afaneh and colleagues reviewed data on 17 individuals at least 50 years-old and 119 individuals younger than 50 years who had a pancreas transplant at a single institution in the U.S. (23) The 2 groups had similar rates of surgical complications, acute rejection and non-surgical infections. Overall patient survival was similar. Three- and 5-year survival rates were 93% and 90% in the younger group and 92% and 82%, all consecutively, in the older group. Schenker and colleagues in Germany compared outcomes in 69 individuals at least 50 years-old and 329 individuals younger than 50 years who had received a pancreas transplant. (24) Mean duration of follow-up was 7.7 years. One-, 5-, and 10-year patient and graft survival rates were similar in the 2 groups. For example, the 5-year patient survival rate was 89% in both groups. The 5-year pancreas grant survival rate was 76% in the older group and 72% in the younger group. The authors of both
studies, as well as the authors of a commentary accompanying the Schenker article, (25) agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

Summary
The literature, consisting primarily of case series and registry data, demonstrate graft survival rates comparable to other solid organ transplants, as well as attendant risks associated with the immunosuppressive therapy necessary to prevent allograft rejection. No randomized controlled trials have compared any form of pancreas transplant to insulin therapy. Pancreas transplant may be considered medically necessary in patients who are undergoing, or have undergone, kidney transplantation for renal failure. It may also be considered medically necessary as a stand-alone treatment in patients with hypoglycemia unawareness and labile diabetes despite optimal medical therapy and in whom severe complications have developed.

Practice Guidelines and Position Statements
In 2010, the Board of Directors of OPTN/UNOS approved changes to address concerns related to local variations in the allocation system for pancreas transplant. (26) The policy changes attempt to reduce the discarding of pancreas donations that have been declined in the context of PTA but which may have been utilized if offered in the setting of SPK. The effect of the policy changes on availability of pancreas donations for transplant alone or in combination with kidney transplants is unknown.

A technology assessment was produced by the Canadian Agency for Drugs and Technology in Health in 2007. (27) The authors did not identify any studies that would contribute additional evidence to this policy. The assessment states: “Given that pancreas transplantation has been widely disseminated for years, it is unlikely that well-designed RCTs that examine pancreas transplantation will occur because ethical and logical complications will prevent this...Pancreas transplantation is an accepted treatment for patients with type I diabetes and end-stage renal disease (ESRD). This has occurred despite the absence of high quality, robust evidence.”

Medicare National Coverage
Allogeneic pancreas transplant is covered under Medicare when performed in a facility that is approved by Medicare as meeting institutional coverage criteria. (28) The Centers for Medicare and Medicaid Services (CMS) has made the following national coverage decision regarding pancreas transplant for Medicare recipients:

A. General
   Pancreas transplantation is performed to induce an insulin-independent, euglycemic state in diabetic patients. The procedure is generally limited to those patients with severe secondary complications of diabetes, including kidney failure. However, pancreas transplantation is sometimes performed on patients with labile diabetes and hypoglycemic unawareness.

B. Nationally Covered Indications
Effective for services performed on or after July 1, 1999, whole organ pancreas transplantation is nationally covered by Medicare when performed simultaneous with or after a kidney transplant. If the pancreas transplant occurs after the kidney transplant, immunosuppressive therapy begins with the date of discharge from the inpatient stay for the pancreas transplant.

Effective for services performed on or after April 26, 2006, pancreas transplants alone (PA) are reasonable and necessary for Medicare beneficiaries in the following limited circumstances (29):

1. PA will be limited to those facilities that are Medicare-approved for kidney transplantation.
2. Patients must have a diagnosis of type I diabetes:
   - Patient with diabetes must be beta cell autoantibody positive; or
   - Patient must demonstrate insulinopenia defined as a fasting C-peptide level that is less than or equal to 110% of the lower limit of normal of the laboratory’s measurement method. Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose <225 mg/dL;
3. Patients must have a history of medically-uncontrollable labile (brittle) insulin-dependent diabetes mellitus with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization. Aforementioned complications include frequent hypoglycemia unawareness or recurring severe ketoacidosis, or recurring severe hypoglycemic attacks;
4. Patients must have been optimally and intensively managed by an endocrinologist for at least 12 months with the most medically-recognized advanced insulin formulations and delivery systems;
5. Patients must have the emotional and mental capacity to understand the significant risks associated with surgery and to effectively manage the lifelong need for immunosuppression; and,
6. Patients must otherwise be a suitable candidate for transplantation.

C. Nationally Non-Covered Indications

The following procedure is not considered reasonable and necessary within the meaning of section 1862(a)(1)(A) of the Social Security Act:

Transplantation of partial pancreatic tissue or islet cells (except in the context of a clinical trial (see section 260.3.1 of the National Coverage Determinations Manual)

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References


29. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination (NCD) for 

Manual. 7.03.02. Revised February 14, 2013.