Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Transplant-Pancreas (Allogeneic)

Description/Background

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[2.] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Allogeneic Pancreas Transplant

Allogeneic pancreas transplants, meaning a pancreas transplant from another person, are considered relatively rare compared to other organ transplants, with only a few hundred performed annually in the United States, primarily as part of a simultaneous pancreas-kidney transplant. The rarity of pancreas transplants are due to the complexity of the procedure, the need for a suitable donor match, strict criteria that limits eligibility for many donors and the recovery process as well as other available treatments that are less invasive than a transplant.

Pancreas transplantation occurs in several different scenarios such as (1) a diabetic patient with renal failure who may receive a simultaneous cadaveric pancreas plus kidney transplant; (2) a diabetic patient who may receive a cadaveric pancreas transplant after a kidney transplantation (pancreas after kidney); or (3) a nonuremic diabetic patient with specific severely disabling and potentially life-threatening diabetic problems who may receive a pancreas transplant alone.

Data from the United Network for Organ Sharing and the International Pancreas Transplant Registry indicate that the proportion of simultaneous pancreas plus kidney transplant recipients

worldwide who have type 2 diabetes has increased over time, from 6% of transplants between 2005 and 2009 to 9% of transplants between 2010 and 2014.[4,] Between 2010 and 2014, approximately 4% of pancreas after kidney transplants and 4% of pancreas alone transplants were performed in patients with type 2 diabetes. In 2022, patients with type 2 diabetes accounted for 22.4% of all pancreas transplants, according to data from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients.[5,]

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Pancreas transplants are included in these regulations.

Medical Policy Statement

Pancreatic transplantations are established. It is considered a useful therapeutic option for patients meeting selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Indications for a pancreas transplant include but are not limited to:

- A combined pancreas-kidney transplant (SPK) for insulin-dependent diabetic individuals with uremia.
- Pancreas transplant after a prior kidney transplant (PAK) for individuals with insulin dependent diabetes.
- Pancreas transplant alone (PTA) may be for individuals 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.
- Pancreas retransplant after a failed primary pancreas transplant in carefully selected individuals who meet criteria for pancreas transplantation.

The consideration for risk-reducing procedure (e.g., CABG) performed at the same time as the organ transplant is a consideration based on the medical consultation review.

Exclusions:

- Pancreas transplantation not meeting the above criteria.

Potential Contraindications for Transplant/Retransplant:
Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

Potential contraindications represent situations where proceeding with transplant is not advisable in the context of limited organ availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan should demonstrate that attending staff at the transplant center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

- Known current malignancy, including metastatic cancer;
- Recent malignancy with high risk of recurrence;
- Untreated systemic infection making immunosuppression unsafe, including chronic infection;
- Other irreversible end-stage disease not attributed to kidney disease;
- History of cancer with a moderate risk of recurrence;
- Systemic disease that could be exacerbated by immunosuppression;
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

All transplants must be prior authorized through the Human Organ Transplant Program

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

48550 48551 48552 48554 S2065

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

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.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function--including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable

intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Much of the published literature consists of case series reported by single centers and registry data. The extant randomized controlled trials compare immunosuppression regimens and surgical techniques and therefore do not compare pancreas transplantation with insulin therapy, or simultaneous pancreas and kidney (SPK) transplant with insulin therapy and hemodialysis.

PANCREAS TRANSPLANT AFTER KIDNEY TRANSPLANT

Clinical Context and Therapy Purpose
The purpose of a PAK transplant in individuals who have insulin-dependent diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with insulin-dependent diabetes.

Interventions
The therapy being considered is a PAK transplant.

PAK transplantation permits patients with insulin-dependent diabetes to benefit from a living-related kidney graft, if available, and to benefit from a subsequent pancreas transplant that is likely to improve quality of life compared with a kidney transplant alone. Patients with insulin-dependent diabetes for whom a cadaveric kidney graft is available, but a pancreas graft is not simultaneously available, benefit similarly from a later pancreas transplant.

Comparators
The following therapy is currently being used to make decisions about insulin-dependent diabetes: insulin therapy.

Outcomes
The general outcomes of interest are overall survival (OS), disease progression, graft failure, and adverse events. In the short-term (post-surgery), follow-up monitors for graft failure. Long-term follow-up has extended to ten years as survival improves.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample sizes and longer duration were preferred.
- Studies with duplicative or overlapping populations were excluded.

Registry Studies and Retrospective Studies

As reported by Gruessner and Gruessner (2016), according to United Network for Organ Sharing (UNOS) and International Pancreas Transplant Registry data, patient survival rates after PAK conducted from 2010 to 2014 was 97.9% after 1 year and 94.5% after 3 years.[4] This compares with 1-year (96.4%) and 3-year (93.1%) patient survival rates for transplants conducted from 2005 to 2009.

Parajuli et al (2019) described a single center's experience with 635 pancreas and kidney transplant patients (611 SPK, 24 PAK).[8] Transplants were performed between 2000 and 2016. The mean length of time between kidney transplant and pancreas transplant was 23.8 months in the PAK group. Pancreas rejection rates at 1 year post-transplant were 4% and 9% with PAK and SPK respectively (p=0.39). During the entire study period, PAK patients were more likely to experience pancreas rejection (38% vs. 16%; p=0.005). Kidney and pancreas graft survival rates did not differ between groups at 1 year or at last follow-up. Pancreas graft survival rates for PAK and SPK at 1 year were 100% and 89%, respectively (p=0.09). Death-censored pancreas graft failure rates for PAK and SPK at last follow-up were 13% and 25%, respectively (p=0.17). Patient survival at last follow-up was similar between groups (71% with PAK vs. 68% with SPK; p=0.79).

Bazarbachi et al (2013) reviewed a single center's experience with PAK and SPK.[9] Between 2002 and 2010, 172 pancreas transplants were performed in diabetic patients (123 SPK, 49 PAK). The median length of time between kidney transplant and pancreas transplant in the PAK group was 4.8 years. Graft and patient survival rates were similar for both 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 (p=0.93), all respectively. Patient survival rates (calculated from the time of pancreas transplantation) in the SPK and PAK groups were 98% and 100% after 1 year, 96% and 100% after 3 years, and 94% and 100% after 5 years (p=0.09), respectively.

Fridell et al (2009) reported on a retrospective review of a single center's experience with PAK and SPK since 2003, when current induction or tacrolimus immunosuppressive strategies became standard.[10] Of the 203 cases studied, 61 (30%) were PAK and 142 (70%) were SPK. One-year patient survival rates were 98% PAK and 95% SPK (p=0.44). Pancreas graft survival rates at 1 year were 95% and 90%, respectively (p=0.28). The authors concluded that using the modern immunosuppressive era, PAK should be considered as an acceptable alternative to SPK in candidates with an available living kidney donor.

Kleinclauss et al (2009) retrospectively reviewed data from 307 diabetic kidney transplant recipients from a single-center and compared renal graft survival rates in those who subsequently received a pancreatic transplant with those who did not.[11] The comparative group was analyzed separately based on whether patients were medically eligible for pancreas

transplant, but chose not to proceed for financial or personal reasons, or were ineligible for medical reasons. The ineligible (n=57) group differed significantly at baseline from both the PAK group (n=175) and the eligible group (n=75) with respect to age, type of diabetes, and dialysis experience; kidney graft survival rates in the eligible group were lower (1-, 5-, and 10-year rates of 75%, 54%, and 22%, respectively, p<0.001) than in the other groups (1-, 5-, and 10-year rates: for the PAK group, 98%, 82%, and 67% vs for the eligible group, 100%, 84%, and 62%). The authors concluded that the subsequent transplant of a pancreas after a living donor kidney transplant does not adversely affect patient or kidney graft survival rates.

Section Summary: PAK Transplant

Data from national and international registries have found relatively high patient survival rates after PAK (e.g., a 3-year survival rate of 94.5%). A 2013 analysis of data from a single-center found similar patient survival and death-censored pancreas graft survival rates after PAK (and SPK) transplants.

SIMULTANEOUS PANCREAS PLUS KIDNEY TRANSPLANTS WITH UREMIA

Clinical Context and Therapy Purpose

The purpose of a PAK transplant in individuals who have insulin-dependent diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with insulin-dependent diabetes with uremia.

Interventions

The therapy being considered is a pancreas transplant after a kidney transplant (SPK).

Comparators

The following therapy is currently being used to make decisions about insulin-dependent diabetes: insulin therapy.

Outcomes

The general outcomes of interest are overall survival, disease progression, graft failure, and adverse events.

Registry Studies and Retrospective Studies

The U.S.-based Organ Procurement and Transplant Network (OPTN) has reported a 1-year patient survival rate of 97.5% (95% confidence interval [CI], 96.9% to 98.0%) for SPK procedures performed between 2008 and 2015.[12] Three- and 5-year patient survival rates were 94.7% (95% CI, 93.9% to 95.5%) and 88.6% (95% CI, 87.5% to 89.7%), respectively.

A 2017 analysis of U.K. registry data by Barlow et al compared outcomes in patients with type 1 diabetes and end-stage renal disease who had SPK transplants (n=1739) with live donor kidney transplants (n=370).[13] In multivariate analysis, there was no significant association between type of transplant and patient survival (hazard ratio, 0.71; 95% CI, 0.47 to 1.06; p=0.095). SPK recipients with a functioning pancreas graft had significantly better overall survival than those with a living donor kidney transplant (p<0.001).

Simultaneous pancreas plus kidney transplant has been found to improve mortality in patients with type 1 diabetes. In 2014, van Dellen et al in the U.K. reported a retrospective analysis of data on 148 SPK patients and a wait-list control group of 120 patients.[14] All patients had uncomplicated type 1 (insulin dependent) diabetes. (The study also included 33 patients who had PAK and 11 PTA patients.) Overall mortality was 30% (30/120 patients) on the waiting list and patients who underwent transplantation had a mortality rate of 9% (20/193 patients); the difference between groups was statistically significant ($p<0.001$). One-year mortality was 13% (n=16) on the waiting list and 4% (n=8) in the transplant group ($p<0.001$).

In 2011, Sampaio and colleagues published an analysis of data from the United Network for Organ Sharing (UNOS) database.[15] 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.

Section Summary: Simultaneous Pancreas Plus Kidney Transplants
Data from national and international registries have found relatively high patient survival rates after SPK transplants (e.g., a 3-year survival rate of 95%). A retrospective analysis found a higher survival rate in patients with type 1 diabetes who had an SPK transplant than in those on a waiting list.

PANCREAS TRANSPLANT ALONE (PTA) FOR PATIENTS WITH SEVERE COMPLICATIONS

Clinical Context and Therapy Purpose
The purpose of a pancreas transplant in individuals who have insulin-dependent diabetes with severe diabetic complications is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOS** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have insulin-dependent diabetes with severe diabetic complications.

Although pancreas transplantation is generally not considered a life-saving treatment for individuals with insulin-dependent diabetes, in a small subset of patients who experience life-threatening complications from diabetes, pancreas transplantation could be considered lifesaving. 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]

Most patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where nonuremic type 1 diabetes patients have significant morbidity risks due to secondary complications of diabetes

(e.g., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because virtually no published evidence addresses 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 PTA. Case-by-case consideration of each patient's clinical situation may be the best option for determining the balance of risks and benefits.

Interventions
The therapy being considered is a pancreas transplant. A pancreas transplant is provided in a hospital setting with specialized staff and equipment to perform the surgical procedure and provide postsurgical intensive care.

Comparators
The following therapy is currently being used to make decisions about insulin-dependent diabetes with severe diabetic complications: insulin therapy.

Outcomes
The general outcomes of interest are overall survival, disease progression (e.g., end-stage renal disease), graft failure, and adverse events (e.g., hypoglycemia, labile diabetes).

Registry Studies and Case Series
PTA graft survival has improved over time. According to International Registry data 1-year graft function increased from 51.5% in 1987-1993 to 77.8% in 2006-2010 ($p<0.0001$).[17] One-year immunologic graft loss remains higher (6%) after PTA than PAK (3.7%) or SPK (1.8%). According to UNOS and the International Pancreas Transplant Registry data, for the period from 2010 to 2014, the patient survival rate for PTA was 96.3% after 1 year and 94.9% after 3 years.[5] This compares with 1-year and 3-year patient survival rates of 97.5% and 93.3% for 2005 to 2009, respectively. According to Gruessner (2011) in carefully selected patients with type 1 diabetes and severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and persistent labile diabetes despite optimal medical management, the benefits of PTA were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression.[17]

Boggi et al (2021) reported results of a single-center cohort study of 66 patients with type 1 diabetes who received PTA.[18,] After 10 years of follow-up, patient survival was 92.4%. Of these patients surviving to 10 years, 57.4% had optimal graft function (defined as normoglycemia and insulin independence) and 3.2% had good graft function (defined as HbA1c <7%, no severe hypoglycemia, >50% reduction in insulin requirements, and restoration of clinically significant C-peptide production). Four patients (6.0%) developed end-stage renal failure (stage 5, estimated glomerular filtration rate [eGFR] < 15 ml/min/1.73 m^2), and 2 additional patients (3.0%) showed stage 4 kidney failure (eGFR 15 to 30 ml/min/1.73 m^2) at the 10-year posttransplant assessment.

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.[19] 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.

Section Summary: PTA for Patients with Severe Complications
Data from international and national registries have found that graft and patient survival rates after PTA have improved over time. For the period of 2010 to 2014, 1- and 3-year survival rates had improved to 96.3% and 95%, respectively.

PANCREAS RETRANSPLANTATION

Clinical Context and Therapy Purpose
The purpose of a pancreas retransplant in individuals who have had a prior pancreas transplant and still meet criteria for a pancreas transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOS** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have had a prior pancreas transplant and still meet criteria for a pancreas transplant.

Interventions
The therapy being considered is a pancreas retransplant.

The approach to retransplantation varies by cause of failure. Surgical and 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 transplant center has guidelines based on experience; some centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

Comparators
The following therapy is currently being used to make decisions about a failed pancreas transplant: insulin therapy.

Outcomes
The general outcomes of interest are overall survival, graft progression, transplant failure, and adverse events.

Registry Studies and Retrospective Studies
Parajuli et al (2019) compared outcomes among SPK patients who did or did not receive pancreas retransplantation after isolated pancreas graft failure.[20] Among 109 SPK patients with pancreas graft failure, 25 underwent pancreas retransplantation and 84 did not. Mean follow-up time after pancreas graft failure was longer among patients who underwent pancreas retransplantation (7.6 years vs. 4.6 years). Rates of death-censored kidney graft failure at last

follow-up were lower among patients who underwent pancreas retransplantation (24% vs. 48%; p=0.04). However, given the retrospective nature of the study, selection bias may have influenced the observed outcomes. Patient survival was not significantly different between groups. Among patients who underwent retransplantation, 1-year pancreas graft survival was 84%.

The retrospective observational study by Gasteiger et al (2018) assessed the outcomes of pancreas retransplantation for patients with pancreas graft failure (defined as a return to insulin dependence).[21] The study evaluated pancreas retransplantations performed between 1997 and 2013 at a single Austrian medical university. Fifty-two pancreas retransplantations were identified, and the median follow-up was 65.0 (range 0.8-174.3) months. At 5 years, the overall patient survival rate was 89%; the survival rate for patients who underwent simultaneous kidney-pancreas retransplantation was 90% (18/20), and the survival rate for those who received only a pancreas retransplantation was 88% (28/32). Graft survival rates were 79% at 1 year and 69% at 5 years. The 5-year graft survival rate was higher following simultaneous kidney-pancreas retransplantation than pancreas retransplantation alone: 80% for simultaneous kidney-pancreas (16/20) vs. 63% (20/32) for pancreas alone (P = 0.226). During the entire follow-up, 42% (22/52) of the grafts were lost. Two factors significantly associated with long-term graft survival were early surgical complications (odds ratio = 3.29; 95% CI, 1.09 to 9.99; P = 0.035) and acute rejection (odds ratio = 4.49; 95% CI, 1.59 to 12.68; P = 0.005). The authors note that because pancreas transplantation is not a life-saving operation, the risks and benefits of the procedure must be carefully considered.

The U.S.-based Organ Procurement Transfer Network (OPTN) reported data on transplants performed between 2008 and 2015.[12] Patient survival rates after repeat transplants were similar to survival rates after primary transplants. For example, the 1-year survival rate was 91.0% (95% confidence interval [CI]: 92.6 to 95.3%) after a primary pancreas transplant and 96.4% (95% CI: 92.1 to 98.4%) after a repeat pancreas transplant. The numbers of patients transplanted was not reported, but the OPTN data stated that 668 patients were alive 1 year after primary transplant and 157 after repeat transplants. Three-year patient survival rates were 87.5% (95% CI: 85.1 to 89.5%) after primary transplants and 83.7% (95% CI: 78.2 to 88.0%) 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 SPK transplants, but follow-up data are only available on a small number of patients who had repeat SPK transplants, so estimates of survival rates in this group are imprecise. Three-year patient survival rate was 94.8% (95% CI, 89% to 91%) after primary SPK transplant and87.9% (95% CI, 73.4% to 94.8%) after a repeat SPK transplant. The number of patients living 3 years after transplant was 2907 after a primary combined procedure and 36 after a repeat combined procedure.

Several centers have published outcomes after pancreas retransplantation and generally reported comparable graft and patient survival rates after initial transplants and retransplants.[22-25] For example, Fridell et al (2015) reported on 441 initial transplants and 20 late transplants.[23] One-year graft survival rates were 92% after initial transplant and 90% after retransplanting (p=0.48). Similarly, 1-year patient survival rates were 96% after initial transplants and 95% after retransplants (p=0.53). However, Rudolph et al (2015), who assessed the largest number of patients, reported higher graft survival rates, but not patient

survival rates, after primary transplant.[25] A total of 2145 pancreas transplants were performed, 415 (19%) of which were retransplants. The death-censored graft survival rate at 1 year was 88.2% in initial transplants and 75% in retransplants (p<0.001). Patient survival rates at 1 year were 91% after initial transplants and 88% after retransplants (p=0.06).

Section Summary: Pancreas Retransplantation
National and international data reported from specific transplant centers have generally reported similar graft and patient survival rates after pancreas retransplantation compared with initial transplantation.

POTENTIAL CONTRAINDICATIONS

Pancreas Transplant in HIV + Transplant Recipients
The current OPTN policy permits HIV+ transplant candidates.[26]

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[27] For kidney-pancreas transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 count >200 cells/mL for at least 3 months (insufficient data to recommend for or against transplantation in patients with counts >100 cells/mL and no history of opportunistic infection)
- Undetectable HIV viral load while receiving antiretroviral therapy
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring

The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled hepatitis B infection may be considered for transplant. Caution is recommended in hepatitis C-coinfected patients who have not been initiated on direct acting antiviral therapy.

Age
Recipient age older than 50 years has in the past been considered a relative contraindication for pancreas transplant. In the past 5 to 10 years, several analyses of outcomes by patient age group have been published and there is now general agreement among experts that age should not be a contraindication; however, age-related comorbidities are important to consider when selecting patients for transplantation.

In the largest study of pancreas outcomes by recipient age, Siskind et al (2014) used data from the UNOS database.[28] Investigators included all adult patients who received SPK or PTA between 1996 and 2012 (N=20,854). This included 3160 patients between the ages of 50 and 59 years, and 280 patients, 60 years or older. Overall, Kaplan-Meier survival analysis found statistically significant differences in patient survival (p<0.001) and graft survival (p<0.001) among age categories. Graft survival was lowest in the 18-to-29 age group at 1, 5, and 10 years, which the authors noted might be due to early immunologic graft rejection as a result of

more robust immune responses. However, 10- and 15-year graft survival was lowest in the 60 and older age group. Patient survival rates decreased with increasing age, and the differential between survival in older and younger ages increased with longer follow-up intervals. Lower survival rates in patients 50 and older could be due in part to comorbidities at the time of transplantation. Also, as patients' age, they are more likely to die from other causes. Still, patient survival at 5 and 10 years was relatively high, as shown in Table 1.

Table 1. Patient Survival by Age Group

Years after Transplant	Age 18-29, %	Age 30-39, %	Age 40-49, %	Age 50-59, %	Age 60+, %
1 year	95.4	96.0	94.9	93.3	91.0
5 years	86.3	87.8	85.7	81.6	71.4
10 years	73.5	76.8	71.8	61.5	42.5

Adapted from Siskind et al (2014).[28]

Among previous studies on pancreas outcomes in older patients, Shah et al (2013) reviewed data on 405 patients who underwent PTA between 2003 and 2011.[29] One-year patient survival was 100% for patients younger than age 30 years, 98% for patients age 30 to 39 years, 94% for patients 40 to 49 years, 95% for patients 50 to 59 years, and 93% for patients age 60 or older. There was not a statistically significant difference in patient survival by age (p=0.38). Findings were similar for 1-year graft survival; there was not a statistically significant difference in outcomes by age of transplant recipients (p=0.10).

A 2011 study by Afaneh et al 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 United States.[30] The 2 groups had similar rates of surgical complications, acute rejection, and nonsurgical infections. Overall patient survival was similar. Three- and 5-year survival rates were 93% and 90%, respectively, in the younger group, and 92% and 82%, respectively, in the older group. Schenker et al (2011) in Germany compared outcomes in 69 individuals at least 50 years old and 329 individuals younger than 50 years who had received pancreas transplants.[31] 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, 5-year patient survival was 89% in both groups. Five-year pancreas graft survival 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,[32] agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

SUMMARY OF EVIDENCE

For individuals who have insulin-dependent diabetes who receive a pancreas transplant after a kidney transplant, the evidence includes case series and registry studies. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Data from national and international registries have found relatively high patient survival rates with a pancreas transplant after a kidney transplant (e.g., a 3-year survival rate of 93%). A 2012 analysis of data from a single center found similar patient survival and death-censored pancreas graft survival rates with a pancreas transplant after a kidney transplant or a SPK transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have insulin-dependent diabetes with uremia who receive SPK transplant, the evidence includes registry studies. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Data from national and international registries have found relatively high patient survival rates after SPK transplant. A retrospective analysis found a higher survival rate in patients with type 1 diabetes who had an SPK transplant vs. those on a waiting list. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have insulin-dependent diabetes and severe complications who receive pancreas transplant alone, the evidence includes registry studies. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Data from International and national registries have found that graft and patient survival rates after pancreas transplant alone have improved over time (e.g., 3-year survival of 95%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had a prior pancreas transplant who still meet criteria for a pancreas transplant who receive pancreas retransplantation, the evidence includes case series and registry studies. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. National data and data reported from specific transplant centers have generally found similar graft and patient survival rates after pancreas retransplantation compared with initial transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Organ Procurement and Transplantation Network

The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in May 2024.[26]

“Each candidate registered on the pancreas waiting list must meet one of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency
- Require the procurement or transplantation of a pancreas as part of a multiple organ transplant for technical reasons.”

For combined kidney plus pancreas registration: “Each candidate registered on the kidney-pancreas waiting list must be diagnosed with diabetes or have pancreatic exocrine insufficiency with renal insufficiency.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01047865	Recurrence of T1D in pancreas transplantation	400	May 2025
NCT01957696	A prospective, observational study in pancreatic allograft recipients: the effect of risk factors, immunosuppressive level and the benefits of scheduled biopsies-on surgical complications, rejections and graft survival	80	Oct 2028
Unpublished			
NCT00238693	Transplant patient registry of liver, kidney, and/or pancreas	13,767	Jan 2018
NCT03921593	Prospective longitudinal observational study on insulin dependent diabetic patients undergoing any form of solid organ pancreas transplantation aimed to clarify quality of life changes after pancreas transplant	110	Mar 2022

NCT: national clinical trial

Government Regulations

National: NCD for Pancreas Transplants (260.3), effective date 4/26/2006.

Allogeneic pancreas transplant is covered under Medicare when performed in a facility that is approved by Medicare as meeting institutional coverage criteria.[33] 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 :
1. PA (prior auth) 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
Nationally noncovered indications include "Transplantation of partial pancreatic tissue or islet cells (except in the context of a clinical trial)."

Local:

There is no local WPS coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Transplant-Heart
- Transplant-Heart and Lung (Combined)
- Bone Marrow Transplant(s)
- Transplant-Liver
- Transplant-Liver and Kidney (Combined)
- Transplant-Lung and Lobar Lung
- Transplant-Small Bowel Transplant (Isolated)
- Transplant-Small Bowel/Liver and Multivisceral
- Transplant-Kidney
- Transplant-Kidney and Liver (Combined)
- Transplant-Lung/Double Lung and Liver (Combined)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/8/02	7/8/02	7/8/02	Joint policy established
9/10/03	9/10/03	10/14/03	Routine maintenance
2/28/05	2/28/05	2/25/03	Routine maintenance
9/1/06	9/01/06	9/20/06	Routine maintenance
9/1/07	7/3/07	8/25/07	Routine maintenance
9/1/08	7/3/08	7/3/08	Routine maintenance
9/1/09	6/16/09	6/16/09	Routine maintenance
9/1/13	6/18/13	6/26/13	Routine maintenance; policy reformatted to mirror BCBSA policy. References updated. Deleted references to type 1 and type 2 diabetes, replaced with insulin-requiring diabetes.
1/1/15	10/21/14	11/3/14	Routine maintenance. Policy title updated, inclusionary criteria enhanced to reflect pancreas retransplants.
3/1/16	12/10/15	12/10/15	Routine maintenance
3/1/17	12/13/16	12/13/16	Routine policy maintenance. Added reference #26.
3/1/18	12/12/17	12/12/17	Updated rationale section, added references 6, 10, 15, and 17. No change in policy status.
3/1/18	12/11/18		Reformatting of rationale sections. Reference #20 added. Policy status unchanged.
3/1/20	12/10/19		Routine policy update. Removed 3 outdated references, added reference #10. No change in policy status.
3/1/21	12/15/20		Rationale updated, references 1, 2,10 and 21 added. No change in policy status.
3/1/22	12/14/21		Rationale updated, references #5 and 18 added. No change in policy status.

3/1/23	12/20/22		Substituted “individuals” in stead of “patients” in MPS. Routine policy maintenance, no change in policy status.
3/1/24	12/19/23		Routine policy maintenance, added statement to inclusion section and bullet to exclusion section. Title change to “Transplant-Pancreas (allogeniec). Vendor managed: N/A (ds)
3/1/25	12/17/24		Changes made to inclusion/exclusion sections. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSPLANT-PANCREAS (ALLOGENEIC)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. Transportation, meals and lodging expenses related to the transplant are not covered unless specifically noted in the member's certificate/rider.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.