Pancreas Transplants* (Including Simultaneous Pancreas-Kidney, Pancreas alone, and Pancreas after Kidney)

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DESCRIPTION

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. 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 Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Achievement of insulin dependence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. Transplantation of the 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. 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 lifesaving.

Pancreas transplantation occurs in several different scenarios such as:

- A diabetic patient with renal failure who may receive a simultaneous cadaveric pancreas plus kidney transplant.
- A diabetic patient who may receive a cadaveric pancreas transplant after a cadaveric or living-related kidney transplantation.
- A nonuremic diabetic patient with severely disabling and potentially life-threatening diabetic problems who may receive a pancreas transplant alone.

Allogeneic Pancreas Transplant

In 2021, 41,355 transplants were performed in the United States procured from more than 13,800 deceased donors and 6,500 living donors. Pancreas-kidney transplants were the fifth most common procedure, with 820 transplants performed in 2021. Pancreas-alone transplants were the sixth most common procedure, with 143 transplants performed in 2021.

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 or living-related 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 2019, patients with type 2 diabetes accounted for 20.6% of all pancreas transplants, according to data from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Patients with type 2 diabetes accounted for 6.2%, 1%, and 22.4% of pancreas alone, pancreas after kidney, and simultaneous pancreas plus kidney transplants, respectively.

Pancreas Transplant Alone for Patients with Severe Complications

A pancreas transplant may involve either the whole pancreas or a pancreas segment. A whole organ transplantation is far more common, but a segmental transplant is possible. Segmental transplants are done if a living donor is involved (Organ Procurement and Transplantation Network 2018).

The overall number of pancreas transplants continued to increase to 1027 in 2018, after a nadir of 947 in 2015. New additions to waiting list remained stable, with 1485 candidates added in 2018. Proportions of patients with type II diabetes waiting for transplant (14.6%) and undergoing transplant (14.8%) have steadily increased since 2016. Pancreas graft survival data are being collected by the Organ Procurement and Transplantation Network and will be included in a future report once there are sufficient cohorts for analysis.

Clinical Context and Therapy Purpose

The purpose of pancreas transplant in patients who have insulin-dependent diabetes is to restore glucose control and is intended to prevent, halt, or reverse the secondary complications from diabetes such as retinopathy, neuropathy, or end-stage renal disease.

The question addressed in this evidence review is: Does a pancreas transplant improve the net health outcome in patients who have insulin-dependent diabetes with severe diabetic complications?

The following PICO was used to select literature to inform this review.

Patients

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. Pancreas transplant alone 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.

Most patients undergoing pancreas transplant alone (PTA) are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where nonuremic type I diabetes patients have significant morbidity risks due to secondary complications of diabetes 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 diabetic patients, 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 PTA. A PTA 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 (OS), disease progression (e.g., end-stage renal disease), graft failure, and adverse events (e.g., hypoglycemia, labile diabetes). In the short-term (post-surgery), follow-up monitors for graft failure. Long-term follow-up has extended to 5 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.

Review of Evidence

Registry Studies and Retrospective Studies
Pancreas transplant alone (PTA) graft survival has improved over time. According to International Pancreas Transplant Registry data, 1-year graft function increased from 51.5% for 1987 to 1993 to 77.8% for 2006 to 2010 ($p<0.001$). One-year immunologic graft loss remained higher (6.0%) after PTA than after 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. This compares with 1-year and 3-year patient survival rates of 97.5%

and 93.3% for 2005 to 2009, respectively. 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 pancreas transplant alone (PTA) were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression

Pancreas transplant is not typically used for the treatment of individuals with type II diabetes mellitus. However, according to the International Pancreas Transplant Registry data the proportion of pancreas transplant recipients worldwide who have type II diabetes has increased over time. Pancreas transplantation has been proposed to achieve insulin independence in persons with type II diabetes mellitus. Although the evidence in the peer reviewed medical literature is limited pancreas transplantation is an alternative treatment for insulin dependent individuals with type II diabetes mellitus.

(2021) Boggi et al. reported results of a single-center cohort study of 66 patients with type 1 diabetes who received PTA. 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, Scalea et al. (2008) reported on a single institutional review of 123 patients who received 131 PTA for the development of renal failure. Mean graft survival was 3.3 years (range, 0 to 11.3 years), and 21 patients were lost to follow-up. At a mean follow-up of 3.7 years, the mean eGFR was 88.9 mL/min/1.73 m^2 pretransplantation and 55.6 mL/min/1.73 m^2 posttransplantation. All but 16 patients had a decrease in eGFR. 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 should be offered PTA.

Section Summary: Pancreas Transplant Alone (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 94.9%, respectively.

Summary of Evidence: Pancreas Transplant Alone (PTA) for Patients with Severe Complications
For individuals who have insulin dependent diabetes and severe complications who receive pancreas transplant alone (PTA), the evidence includes registry studies. 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 rate of 95%). 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 pancreas transplant alone (PTA) were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression. The evidence is sufficient to determine that pancreas transplant alone (PTA) results in meaningful improvement in net health outcomes.

Pancreas Transplant after Kidney Transplant (PAK)
Pancreas transplant after kidney (PAK) transplantation permits uremic patients 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. 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.

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

The question addressed in this evidence review is: Does a PAK transplant improve the net health outcome in patients with insulin-dependent diabetes?

The following PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is pancreas transplant after kidney (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.

PAK 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: 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 10 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.

Review of Evidence

Registry Studies and Retrospective Studies
(2019) Parajuli et al. described a single center's experience with 635 pancreas and kidney transplant patients (611 SPK, 24 PAK). 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).

(2016) As reported by Gruessner and Gruessner 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. This compares with 1-year (96.4%) and 3-year (93.1%) patient survival rates for transplants conducted from 2005 to 2009.

(2013) Bazarbachi et al. reviewed a single center's experience with PAK and SPK. 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=.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=.09), respectively.

(2009) Fridell et al. 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. 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=.44). Pancreas graft survival rates at 1 year were 95% and 90%, respectively (p=.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.

(2009) Kleinclauss et al. 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. 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 at 1, 5, and 10 years were lower in the ineligible group (75%, 54%, and 22%, respectively; p<.001) than in the other groups (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: Pancreas Transplant After Kidney Transplant (PAK)
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%). Single-center retrospective analyses have found similar patient survival and death-censored pancreas graft survival rates after PAK and SPK transplants.

Summary of Evidence: Pancreas Transplant after Kidney Transplant (PAK)
For individuals who have insulin dependent diabetes who receive a pancreas transplant after a kidney (PAK) transplant, the evidence includes case series and registry studies. Data from national and international registries have found relatively high patient survival rates after pancreas transplant after kidney (PAK), a 3-year survival rate of 93%. 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. The evidence is sufficient to determine the technology results in a meaningful improvement in the net health outcomes.

Simultaneous Pancreas Plus Kidney Transplants for Patients with Uremia

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

The question addressed in this evidence review is: Does an SPK transplant improve the net health outcome in patients who have insulin-dependent diabetes with uremia?

The following PICO was used to select literature to inform this review.

Simultaneous Pancreas Plus Kidney Transplants for Patients with Uremia
The kidney is frequently transplanted with the pancreas and individuals who have insulin-dependent diabetes with uremia. Many people suffering from pancreas failure also have renal failure. In most cases a kidney-pancreas transplant is performed from a cadaveric donor.

Clinical Context and Therapy Purpose
The purpose of simultaneous pancreas-kidney (SPK) transplant in patients who have insulin dependent diabetes with uremia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Interventions
The therapy being considered is a simultaneous pancreas-kidney (SPK) transplant.

SPK 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 uremia: 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 10 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.

Review of Evidence

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. Three- and 5-year patient survival rates were 94.7% (95% CI, 93.9% to 95.5%) and 88.6% (95% CI, 87. 6% to 89. 8%), respectively.

(2017) An analysis of a U.K. registry data by Barlow et al. compared outcomes in patients with type I diabetes and end stage renal disease who had simultaneous pancreas-kidney (SPK) transplants (n=1739) with live donor transplants (n=370). 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). Simultaneous pancreas-kidney recipients with a functioning pancreas graft and significantly better overall survival than those with a living donor kidney transplant (p<0.001).

(2013) Simultaneous pancreas-kidney (SPK) transplants have been found to reduce mortality in patients with type I diabetes. Van Dellen et al. reported on a retrospective analysis of data for 148 SPK patients and a wait-list control group of 120 patients. All patients had type I insulin dependent diabetes. The study also included 33 patients who had pancreas after kidney (PAK) transplant and 11 patients who had pancreas transplant alone (PTA). Overall mortality (mortality at any time point) was 30% (30/120) for the waiting list and 9% (20/193) for transplanted patients; the difference between groups was statistically significant (p<0.001). The 1-year mortality rate was 13% (n=16) for the waiting list and 4% (n=8) for the transplant group (p<0.001).

There is some data on outcomes in patients with type II compared with type I diabetes. In 2011, Sampaio et. al. published an analysis of date from the United Network for Organ Sharing (UNOS) database. The investigators compared outcomes in 6141 patients with

type 1 diabetes and 582 patients with type II diabetes who underwent SPK between 2000 and 2007. In adjusted analyses, outcomes were similar between the two groups. After adjusting for other factors such as body weight, dialysis time, and cardiovascular comorbidities, type II diabetes was not associated with an increased risk of pancreas or kidney graft failure or mortality compared with type I diabetes.

Section Summary: Simultaneous Pancreas Plus Kidney Transplants for Patients with Uremia
Data from national and international registries have found relatively high patient survival rates after SPK transplants (e.g., a 3-year survival rate of 94.7% and a 5-year survival rate of 88.6%). 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.

Summary of Evidence: Simultaneous Pancreas Plus Kidney Transplants for Patients with Uremia
For individuals who have insulin-dependent diabetes with uremia who receive simultaneous pancreas-kidney (SPK) transplant, the evidence includes registry studies. Data from national and international registries have found relatively high patient survival rates with simultaneous pancreas-kidney (SPK) transplants, a 3- year survival rate of 95%. A retrospective analysis found a higher survival rate in patients with type I diabetes who had an SPK transplant than in those on a waiting list. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

Pancreas Retransplantation
The last four decades have seen a significant and progressive improvement in outcomes for pancreas transplantation. Improvements in immunosuppression, surgical technique and post-transplant management have all contributed to better graft survival. However, despite refinements in surgical technique, technical failure is defined by the International Pancreas Transplant Registry as graft loss secondary to vascular thrombosis, bleeding, anastomotic leaks, or infection/pancreatitis and is responsible for more than 50% of all pancreas grafts lost in the first 6 months following transplantation. Thrombosis accounts for more than one-half of these technical failures, and may be influenced by donor and recipient factors, preservation and ischemic injury, immunological issues and surgical technique.

The decision to retransplant the pancreas after an early graft failure is complex. Prior to proceeding with retransplantation, a careful analysis of the factors contributing to the technical failure must be undertaken and reversible risk factors must be addressed. Surgical issues leading to thrombosis such as improper suturing of the vascular anastomosis, poor positioning of the allograft or inadequate hemostasis may be the primary cause of graft thrombosis. However, there may be no obvious surgical cause for graft loss identified. Reconfirming the tissue typing with the original donor and evaluating the patient for hypercoagulable state should be considered prior to attempting

retransplantation in order to guide anticoagulation and immunosuppression management for the second graft.

Following appropriate evaluation for the causes of graft failure, repeat pancreas transplantation may be considered, although the optimal timing for retransplantation remains somewhat controversial. From a surgical perspective, retransplanting in the early post-pancreatectomy period may be preferable because extensive adhesions have not yet formed, this facilitates placing the new graft in the same anatomic site as the prior transplant. Some previous studies suggest that immediate retransplantation is associated with similar graft and patient survival as primary transplants, others indicate that this approach is associated with higher incidence of post-operative complications and rejection leading to premature loss of the second graft.

Clinical Context and Therapy Purpose
The purpose of a pancreas retransplant in patients 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 question addressed in this evidence review is: Does a pancreas retransplant improve the net health outcome in patients who have had a prior pancreas transplant and still meet criteria for a pancreas transplant?

The following PICO was 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 OS, graft progression, transplant failure, and adverse events. In the short-term (post-surgery), follow-up monitors for graft failure. Long-term follow-up has extended over time to 5 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.

Review of Evidence
Registry Studies and Retrospective Studies
(2019) Parajuli et al. compared outcomes among SPK patients who did or did not receive pancreas retransplantation after isolated pancreas graft failure. Among 109 SPK patients with pancreas graft failure, 25 underwent pancreas retransplantation and 84 did not. The 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=.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%.

(2018) The retrospective observational study by Gasteiger et al. assessed the outcomes of pancreas retransplantation for patients with pancreas graft failure (defined as a return to insulin dependence). 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 to 174.3) months. At 5 years, the overall patient survival rate was 89%; the survival rate for patients who underwent SPK 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 SPK retransplantation than pancreas retransplantation alone: 80% for SPK

(16/20) versus 63% (20/32) for pancreas alone (p=.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=.035) and acute rejection (odds ratio, 4.49; 95% CI, 1.59 to 12.68; p=.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 OPTN has 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 90.9% (95% CI, 88.7% to 92.8%) after a primary pancreas transplant and 96.3% (95% CI, 92.0% to 98.3%) after a repeat pancreas transplant. The numbers of patients transplanted were not reported, but OPTN data stated that 663 patients were alive 1 year after primary transplant and 154 after repeat transplants. The 3-year patient survival rate was 87.5% (95% CI, 85.0% to 89.5%) after primary transplants and 90.8% (95% CI, 85.6% to 94.2%) after repeat transplants. The 5-year patient survival rate was 79.6% (95% CI, 77.0% to 81.9%) after primary transplants and 82.5% (95% CI, 76.6% to 87.0%) after repeat transplants. The 1-year graft survival rate was 81.8% (95% CI, 78.9% to 84.3%) after primary pancreas transplant and 77.7% (95% CI, 70.8% to 83.1%) after repeat transplant.

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 94.7% (95% CI, 93.9% to 95.5%) after primary SPK transplant and 87.7% (95% CI, 72.9% to 94.7%) after a repeat SPK transplant. The number of patients living 3 years after transplant was 2837 after a primary combined procedure and 35 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. The largest and most recent studies are further described here. Fridell et al (2015) reported on 441 initial transplants and 20 late transplants. One-year graft survival rates were 92% after initial transplant and 90% after retransplant (p=.48). Similarly, 1-year patient survival rates were 96% after initial transplants and 95% after retransplants (p=.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. A total of 2145 pancreas transplants were performed, 415 (19.3%) of which were retransplants. The death-censored graft survival rate at 1 year was 88.2% in initial transplants and 75.0% in retransplants (p<.001). Patient survival rates at 1 year were 91.3% after initial transplants and 88.2% after retransplants (p=.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.

Summary of Evidence: Pancreas Retransplantation
For individuals who have had a prior pancreas transplant and still meet criteria for a pancreas transplant and receive pancreas retransplantation, the evidence includes national and international data reported form specific transplant centers that have generally reported similar graft and patient survival rates after pancreas retransplantation compared with initial transplantation. Although there are no standard guidelines regarding multiple pancreas transplants, each transplant center has its own guidelines based on experience. The evidence is sufficient to determine that pancreas retransplantation in patients who still meet criteria for transplant results in meaningful improvement in net health outcomes.

Potential Contraindications

Pancreas Transplant in Human Immunodeficiency Virus-Positive Transplant Recipients
Current OPTN policy permits human immunodeficiency virus (HIV) -positive transplant candidates.

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients. 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 been considered a relative contraindication for a pancreas transplant. Several analyses of outcomes by patient age group have prompted general agreement among experts that age should not be a contraindication; however, age-related comorbidities must be considered when selecting patients for transplantation.

In the largest study of pancreas outcomes by recipient age, Siskind et al. (2014) assessed data from the UNOS database. Investigators included all adults who received SPK or PTA transplants between 1996 and 2012 (N=20,854). This included 3160 patients between the ages of 50 and 59 years, and 280 patients aged 60 years or older. Overall, Kaplan-Meier survival analysis found statistically significant differences in patient survival ($p<.001$) and graft survival ($p<.001$) by age category. 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 rates at 5 and 10 years are relatively high, as shown in Table 1.

Table 1. Patient Survival by Age Group

Years After Transplant	Age 18 to 29, %	Age 30 to 39, %	Age 40 to 49, %	Age 50 to 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).

Among previous studies on pancreas outcomes in older patients, Shah et al. (2013) reviewed data on 405 patients who underwent PTA transplants between 2003 and 2011. One-year patient survival was 100% for patients younger than age 30 years, 98% for patients aged 30 to 39 years, 94% for patients aged 40 to 49 years, 95% for patients aged 50 to 59 years, and 93% for patients aged 60 years or older. There was no statistically significant difference in patient survival by age group ($p=.38$). Findings were similar for 1-year graft survival; there was no statistically significant difference in outcomes by age of transplant recipients ($p=.10$).

A study by Afaneh et al. (2011) 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. 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) compared outcomes in 69 individuals at least 50 years old with 329 individuals younger than 50 years who had received pancreas transplants. Mean duration of follow-up was 7.7 years. One-, 5-, and 10-year patient and graft survival rates were similar for the groups. For example, the 5-year patient survival rate was 89% in both groups. The 5-year pancreas graft 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 et al. (2011) article, agreed that individuals aged 50 years and older are suitable candidates for pancreas transplantation.

Practice Guidelines and Position Statements

American Diabetes Association (ADA)
(2014) The American Diabetes Association issued a position statement regarding type I diabetes through the life span, which included recommendations regarding pancreas transplants.

Successful pancreas transplantation has been demonstrated to be efficacious in significantly improving the quality of life of people with diabetes, primarily by eliminating the need for exogenous insulin, frequent daily blood glucose measurements, and many of the dietary restrictions improved by the disorder. Transplantation can also eliminate the acute complications of diabetes. (Accessed October 2021)

Recommendations
Consider solid organ pancreas transplantation simultaneously with kidney transplantation in patients with type I diabetes who have an indication for kidney transplantation and are poorly controlled with large glycemic excursions.

Consider solid organ pancreas transplantation after kidney transplantation in adult patients with type I diabetes who have already received a kidney transplant.
Judiciously consider solid organ pancreas transplantation alone in adults with type I diabetes, unstable glucose control, hypoglycemia unawareness, and an increased risk of diabetes-related mortality, who have attempted all of the more traditional approaches to glycemic control and have remained unsuccessful yet are judged responsible enough to manage the anti-rejection medication regimen, risk, and follow-up required with an organ transplant.

Organ Procurement and Transplantation Network
The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in April 2022.

- **For pancreas registration**: 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 of transplantation of a pancreas as part of a multiple organ transplant for technical reasons
- **Combined Kidney-Pancreas Registration**
  - Each candidate registered on the kidney-pancreas waiting list must be diagnosed with diabetes or have pancreatic exocrine insufficiency with renal insufficiency.

Regulatory Status

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA 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. Solid organs used for transplantation are subject to these regulations.

PRIOR APPROVAL

Prior approval is required.

POLICY

See Related Medical Policy

- 07.03.01 Pancreatic Islet Cell Transplant

Pancreas Transplant Alone (PTA)

Pancreas transplant alone (PTA) may be considered **medically necessary** in patients who have insulin-dependent diabetes mellitus with severe diabetes despite optimal medical management including **one of** the following:

- Documentation of severe hypoglycemia unawareness as evidenced by chart notes or emergency department visits; **or**
- Documentation of potentially life-threatening, difficult to manage (e.g., labile) diabetes, as evidenced by chart notes or hospitalization for diabetic ketoacidosis.

*Note: In addition, most pancreas transplant patients will have type I diabetes mellitus. The transplant candidates with type II diabetes mellitus should also meet **all of the following** criteria:*

- *Be insulin dependent*
- *Their body mass index (BMI) should be 32 kg/m2 or less*

Pancreas-after-Kidney (PAK) Transplant

Pancreas transplant after a prior kidney (PAK) transplant may be considered **medically necessary** in individuals with insulin-dependent diabetes.

Simultaneous Pancreas-Kidney (SPK) Transplant

Simultaneous pancreas-kidney (SPK) transplant may be considered **medically necessary** in insulin-dependent diabetics with impending or established renal failure.

Retransplantation

Retransplantation after a failure of the primary graft may be considered **medically necessary** provided the individual meets the transplant criteria above.

Investigational
Pancreas transplant alone (PTA), pancreas transplant after prior kidney transplant (PAK), simultaneous pancreas-kidney (SPK) transplant performed, and/or retransplantation is considered **investigational** when the above criteria is not met and for all other situations**,** because the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Policy Guidelines

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

- If there is early graft loss resulting from technical factors (e.g., venous thrombosis), a retransplant may generally be performed without substantial additional risk.
- 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 crossmatch. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

Potential Contraindications
*Contraindications are subjection are subject to the judgement of the transplant center to include the following***:**

- 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 moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 48554 Transplantation of pancreatic allograft
- S2065 Simultaneous pancreas kidney transplantation

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POLICY HISTORY		
Date	**Reason**	**Action**
October 2022	Annual Review	Policy Revised
October 2021	Annual Review	Policy Renewed
October 2020	Annual Review	Policy Revised
October 2019	Annual Review	Policy Renewed
October 2018	Annual Review	Policy Revised
October 2017	Annual Review	Policy Renewed
October 2016	Annual Review	Policy Revised
November 2015	Annual Review	Policy Revised
March 2015	Interim Review	Policy Revised
December 2014	Annual Review	Policy Revised
January 2014	Annual Review	Policy Renewed
March 2013	Annual Review	Policy Renewed
March 2012	Annual Review	Policy Renewed
April 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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