

7.03.02	Allogeneic Pancreas Transplant		
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Section:	11.0 Transplant	Page:	Page 1 of 19

Policy Statement

Pancreas transplant after a prior kidney transplant may be considered **medically necessary** in patients with insulin-dependent diabetes.

A combined pancreas and kidney transplant may be considered **medically necessary** in insulin-dependent diabetic patients with uremia.

Pancreas transplant alone may be considered **medically necessary** in patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile insulin-dependent diabetes that persists despite optimal medical management.

Pancreas retransplant after a failed primary pancreas transplant may be considered **medically necessary** in patients who meet criteria for pancreas transplantation.

Pancreas transplant is considered **investigational** in all other situations.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

General Criteria

Potential contraindications for solid organ transplant that are subject to the judgment of the transplant center, 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 diseases 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 the ability to adhere to therapy

Pancreas-Specific Criteria

Candidates for pancreas transplant alone should also meet one of the following severity of illness criteria:

- Documented severe hypoglycemia unawareness as evidenced by chart notes or emergency department visits
- Documented potentially life-threatening labile diabetes, as evidenced by chart notes or hospitalization for diabetic ketoacidosis

Additionally, most pancreas transplant patients will have type 1 diabetes. Those transplant candidates with type 2 diabetes, in addition to being insulin-dependent, should also not be obese (body mass index [BMI] should be 32 kg/m² or less). In 2018, patients with type 2 diabetes accounted for 14.8% of all pancreas transplants, according to data from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients.¹

Multiple Transplant Criteria

Although there are no standard guidelines for multiple pancreas transplants, 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 cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol

Description

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

Related Policies

- Kidney Transplant
- Islet Transplantation

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

Rationale

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

Allogeneic Pancreas Transplant

In 2019, 39,719 transplants were performed in the United States procured from almost 11,900 deceased donors and 7,400 living donors.³ Pancreas-kidney transplants were the fifth most common procedure, with 872 transplants performed in 2019. Pancreas-alone transplants were the sixth most common procedure, with 143 transplants performed in 2019.

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 2018, patients with type 2 diabetes accounted for 14.8% of all pancreas transplants, according to data from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients.¹ Patients with type 2 diabetes accounted for 1.1%, 10.3%, and 16.7% of pancreas alone, pancreas after kidney, and simultaneous pancreas plus kidney transplants, respectively.

Literature Review

This evidence review was informed in part by a TEC Assessment (1998), which focused on pancreas graft survival and health outcomes associated with both pancreas transplant alone (PTA) and pancreas after kidney (PAK) transplants.⁶ A TEC Assessment (2001) focused on pancreas retransplant also informed this evidence review.⁷ These 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 the 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 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 quality and credibility. To be relevant, studies must represent 1 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 (RCT) 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 retrospective data reported by single centers and registry data. The extant RCTs 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 pancreas 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.

Populations

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

Interventions

The therapy being considered is a PAK transplant.

Pancreas after kidney 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 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

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 were 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 ($p=.39$). During the entire study period, PAK patients were more likely to experience pancreas rejection (38% vs. 16%; $p=.005$). 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 ($p=.09$). Death-censored pancreas graft failure rates for PAK and SPK at last follow-up were 13% and 25%, respectively ($p=.17$). Patient survival at last follow-up was similar between groups (71% with PAK vs. 68% with SPK; $p=.79$).

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 ($p=.93$), 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. 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 ($p=.44$). 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.

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 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

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.

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.

Populations

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

Interventions

The therapy being considered is an SPK transplant.

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 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% 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, 87.6% to 89.8%), respectively.

An analysis of U.K. registry data by Barlow et al (2017) compared outcomes in patients with type 1 diabetes and end-stage renal disease who had SPK transplants (n=1739) versus 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=.095). Simultaneous pancreas plus kidney recipients with a functioning pancreas graft had significantly better OS than those with a living donor kidney transplant (p<.001).

Simultaneous pancreas plus kidney transplants have been found to reduce mortality in patients with type 1 diabetes. Van Dellen et al (2013) in the U.K. reported on a retrospective analysis of data for 148 SPK patients and a wait-list control group of 120 patients.¹⁴ All patients had type 1 (insulin-dependent) diabetes. (The study also included 33 patients who had PAK and 11 patients who had 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 ($p < .001$). The 1-year mortality rate was 13% ($n=16$) for the waiting list and 4% ($n=8$) for the transplant group ($p < .001$).

Sampaio et al (2011) published an analysis of data from the UNOS database.¹⁵ Outcomes for 6141 patients with type 1 diabetes and 582 patients with type 2 diabetes who underwent SPK were similar for both groups in adjusted analyses. After adjusting for other factors (e.g., body weight; dialysis time; cardiovascular comorbidities), type 2 diabetes was not associated with an increased risk of pancreas or kidney graft failure or mortality compared with type 1 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.

Pancreas Transplant Alone for Patients with Severe Complications

Clinical Context and Therapy Purpose

The purpose of a pancreas transplant in patients 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 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.

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 life-saving. 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.¹⁶

Most patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where patients with nonuremic type 1 diabetes 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 PTA.

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 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 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 ($p < .001$).¹⁷ 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.⁴ 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 m²), and 2 additional patients (3.0%) showed stage 4 kidney failure (eGFR 15-30 ml/min/1.73 m²) 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.¹⁹ 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 m² pretransplantation and 55.6 mL/min/1.73 m² 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 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.

Pancreas Retransplantation

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

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. 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%.

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 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.^{22,23,24,25} The largest and most recent studies are further described here. 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 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.²⁵ 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.

Potential Contraindications

Pancreas Transplant in Human Immunodeficiency Virus-Positive Transplant Recipients

Current OPTN policy permits HIV-positive 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 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.²⁸ 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 18-29, %	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 transplants between 2003 and 2011.²⁹ 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.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) compared outcomes in 69 individuals at least 50 years old with 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 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,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 retrospective studies and registry studies. Relevant outcomes are OS, 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 94.5%). Single-center retrospective studies have 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 an improvement in the net health outcome.

For individuals who have insulin-dependent diabetes with uremia who receive SPK transplants, the evidence includes retrospective studies and registry studies. Relevant outcomes are OS, 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 versus those on a waiting list. The evidence is sufficient to determine that the technology results in an 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 OS, 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 94.9%). The evidence is sufficient to determine that the technology results in an 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 retrospective studies and registry studies. Relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. National data and specific transplant center data 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 an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.¹⁹ Key findings and recommendations are summarized in Table 2.

Table 2. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

Content Area	Key Point
1 Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2 Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3 Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4 OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5 Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Organ Procurement and Transplantation Network

The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in June 2020.²⁶

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 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.

Medicare National Coverage

An allogeneic pancreas transplant is covered under Medicare when performed in a facility approved by Medicare as meeting institutional coverage criteria.³³ The Centers for Medicare & Medicaid Services made the following national coverage decision on pancreas transplant for Medicare recipients.³⁴

"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 ... 1999, whole organ pancreas transplantation is nationally covered by Medicare when performed simultaneously 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 ... 2006, pancreas transplants alone (PA) are reasonable and necessary for Medicare beneficiaries in the following limited circumstances:

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

Nationally noncovered indications include "Transplantation of partial pancreatic tissue or islet cells (except in the context of a clinical trial)."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01047865	Type 1 Diabetes Recurrence in Pancreas Transplants	400	May 2022
NCT01957696	The Norwegian Pancreas Transplantation (PTx) Study (PTx)	80	Oct 2028
<i>Unpublished</i>			
NCT00238693	Transplant Patient Registry of Liver, Kidney and/or Pancreas	13,767	Aug 2018

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Nephrology consultation report and/or progress notes documenting:
 - Diagnosis (including disease staging) and prognosis
 - Synopsis of alternative treatments performed and results
 - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
 - Clinical history
 - Specific issues identified during the transplant evaluation
 - Consultation reports/letters (when applicable)
 - Correspondence from referring physicians (when applicable)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Chest x-ray (CXR) and other radiology reports (when applicable)
- Colonoscopy report if > 50 years of age
- Cardiology procedures and pulmonary function reports:
 - EKG
 - Cardiac echocardiogram, stress test, and cardiac catheterization (if needed)
 - Pulmonary function tests (PFTs)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
HCPCS	S2065	Simultaneous pancreas kidney transplantation

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/26/1988	Policy adopted
06/05/1991	Policy Revision
05/17/2001	Policy clarification
06/01/2001	Policy reviewed. Policy statement unchanged.
01/07/2011	Policy title change from Simultaneous Pancreas and Kidney Transplantation Policy revision with position change
04/01/2011	Policy revision with position change
07/14/2014	Policy revision with position change
05/29/2015	Policy revision with position change
10/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
10/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Policy guidelines and literature updated.
10/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Allogeneic Pancreas Transplant 7.03.02</p> <p>Policy Statement: Pancreas transplant after a prior kidney transplant may be considered medically necessary in patients with insulin-dependent diabetes.</p> <p>A combined pancreas and kidney transplant may be considered medically necessary in insulin-dependent diabetic patients with uremia.</p> <p>Pancreas transplant alone may be considered medically necessary in patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile insulin-dependent diabetes that persists despite optimal medical management.</p> <p>Pancreas retransplant after a failed primary pancreas transplant may be considered medically necessary in patients who meet criteria for pancreas transplantation.</p> <p>Pancreas transplant is considered investigational in all other situations.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>	<p>Allogeneic Pancreas Transplant 7.03.02</p> <p>Policy Statement: Pancreas transplant after a prior kidney transplant may be considered medically necessary in patients with insulin-dependent diabetes.</p> <p>A combined pancreas and kidney transplant may be considered medically necessary in insulin-dependent diabetic patients with uremia.</p> <p>Pancreas transplant alone may be considered medically necessary in patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile insulin-dependent diabetes that persists despite optimal medical management.</p> <p>Pancreas retransplant after a failed primary pancreas transplant may be considered medically necessary in patients who meet criteria for pancreas transplantation.</p> <p>Pancreas transplant is considered investigational in all other situations.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>