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.

Policy Guidelines

General Criteria
Potential contraindications for solid organ transplant 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 disease not attributed to kidney disease
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting 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:

- Documentation of severe hypoglycemia unawareness as evidenced by chart notes or emergency department visits
- Documentation of 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). According to International Pancreas Transplant Registry data, in 2010, 7% of pancreas transplant recipients had type 2 diabetes (Gruessner [2011]).

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**

- Artificial Pancreas Device Systems
- Islet Transplantation
- Kidney Transplant

**Benefit Application**

Benefit determinations should be based 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**

Small bowel/liver and multivisceral transplantation are surgical procedures and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

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

**Rationale**

**Background**

**Diabetes and Pancreatitis**

Insulin independence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. While pancreas transplantation is generally not considered a life-saving treatment, in a small subset of patients who experience life-threatening complications from diabetes, pancreas transplantation could be considered life-saving. Pancreas transplant alone (PTA) has also been investigated in patients following total pancreatectomy for chronic pancreatitis. In addition to the immune rejection issues common to all allotransplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.1
Treatment
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 transplants; (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 PTA. The total number of adult pancreas transplants (pancreas and pancreas plus kidney) in the United States peaked at 1484 in 2004 and has since steadily declined. In 2017, 213 PTAs and 789 simultaneous pancreas plus kidneys were performed in the United States.

Most patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where nonuremic type 1 diabetes patients have significant morbidity risks due to secondary complications of diabetes (e.g., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because virtually no published evidence addresses outcomes of medical management in this very small group of exceptional diabetic patients, it is not possible to generalize about which circumstances represent appropriate indications for PTA. Case-by-case consideration of each patient’s clinical situation may be the best option for determining the balance of risks and benefits.

According to the International Pancreas Transplant Registry data, the proportion of pancreas transplant recipients worldwide who have type 2 diabetes has increased over time, from 2% in 1995 to 7% in 2010. In 2010, approximately 8% of simultaneous pancreas plus kidney transplants, 5% of pancreas transplant after kidney transplant, and 1% of PTA were performed in patients with type 2 diabetes.

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.

Literature Review
This evidence review was informed in part by a Blue Cross Blue Shield Association Technology Evaluation Center (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. A TEC Assessment (2001) focused on pancreas retransplant. The assessments and subsequent evidence offer the following observations and conclusions.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to
assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

**Pancreas Transplant after Kidney Transplant**
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 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 PICOTS were 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 a pancreas transplant after a kidney 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, disease progression, graft failure, and adverse events.

**Timing**
In the short term postsurgery, follow-up monitors for graft failure. Long-term follow-up has extended over time out to 10 years as survival improves.

**Setting**
PAK transplant is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

**Case Series**
As reported by Gruessner and Gruessner (2016), according to United Network for Organ Sharing (UNOS) and International Pancreas Transplant Registry data, patient survival rates after PAK conducted from 2010 to 2014 was 97.9% after 1 year and 94.5% after 3 years. This compares with 1-year (96.4%) and 3-year (93.1%) patient survival rates for transplants conducted from 2005 to 2009, respectively.
Bazarbachi et al (2013) 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 = 0.93), all respectively. Patient survival rates (calculated from the time of pancreas transplantation) in the SPK and PAK groups were, respectively, 98% and 100% after 1 year, 96% and 100% after 3 years, and 94% and 100% after 5 years (p = 0.09), respectively.

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

Kleinclauss et al (2009) retrospectively reviewed data from 307 diabetic kidney transplant recipients from a single center and compared renal graft survival rates in those who subsequently received a pancreatic transplant with those who did not. The comparative group was analyzed separately based on whether patients were medically eligible for pancreas transplant, but chose not to proceed for financial or personal reasons, or were ineligible for medical reasons. The ineligible (n=57) group differed significantly at baseline from both the PAK group (n=175) and the eligible group (n=75) with respect to age, type of diabetes, and dialysis experience; kidney graft survival rates in the eligible group were lower (1-, 5-, and 10-year rates of 75%, 54%, and 22% respectively, p < 0.001) than in the other groups (1-, 5-, and 10-year rates: for the PAK group, 98%, 82%, and 67% vs for the eligible group, 100%, 84%, and 62%). The authors concluded that the subsequent transplant of a pancreas after a living donor kidney transplant does not adversely affect patient or kidney graft survival rates.

Section Summary: Pancreas 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 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.

Simultaneous Pancreas plus Kidney Transplants
Clinical Context and Therapy Purpose
The purpose of an 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 PICOTS were used to select literature to inform this review.

**Patients**
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 overall survival, disease progression, graft failure, and adverse events.

Timing
In the short term postsurgery, follow-up monitors for graft failure. Long-term follow-up has extended over time out to 10 years as survival improves.

Setting
SPK transplant is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

Case Series
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 2015.2 Three- and 5-year patient survival rates were 94.7% (95% CI, 93.9% to 95.5%) and 88.6% (95% CI, 87.5% to 89.7%), respectively.

Analysis of a 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) with live donor kidney transplants (n=370).10 In multivariate analysis, there was no significant association between type of transplant and patient survival (hazard ratio, 0.71; 95% CI, 0.47 to 1.06; p=0.095). SPK recipients with a functioning pancreas graft had significantly better overall survival than those with a living donor kidney transplant (p<0.001).

SPK 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.11 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<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).

Sampaio et al (2011) published an analysis of data from the UNOS database.12 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
Data from national and international registries have found relatively high patient survival rates after SPK transplants (e.g., a 3-year survival rate of 95%). A retrospective analysis found a higher survival rate in patients with type 1 diabetes who had an SPK transplant than in those on a waiting list.

Pancreas Transplant Alone
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 PICOTS were 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.

**Interventions**
The therapy being considered is a pancreas transplant.

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

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

**Timing**
In the short term postsurgery, follow-up monitors for graft failure. Long-term follow-up has extended over time out to 5 years as survival improves.

**Setting**
A pancreas transplant is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

**Registry Studies and Case Series**
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%) 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. 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.

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, 0-11.3 years), and 21 patients were lost to follow-up. At a mean follow-up of 3.7 years, mean estimated glomerular filtration rate 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 estimated glomerular filtration rate. Thirteen developed end-stage renal disease, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA.

**Section Summary: Pancreas Transplant Alone**
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% and 95%, 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 PICOTS were used to select literature to inform this review.

Patients
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.

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

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

Timing
In the short term postsurgery, follow-up monitors for graft failure. Long-term follow-up has extended over time out to 5 years as survival improves.

Setting
Pancreas retransplant is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

Case Series
OPTN has reported data on transplants performed between 1997 and 2004.2 Patient survival rates after repeat transplants were similar to survival rates after primary transplants. For example, the 1-year survival rate was 94% (95% CI, 93% to 95%) after a primary pancreas transplant and 96% (95% CI, 93% to 99%) after a repeat pancreas transplant. The numbers of patients transplanted were not reported, but OPTN data stated that 1217 patients were alive 1 year after primary transplant and 256 after repeat transplants. The 3-year patient survival rate was 90% (95% CI, 88% to 91%) after primary transplants and 90% (95% CI, 86% to 94%) after repeat transplants. The 1-year graft survival rate was 78% (95% CI, 76% to 81%) after primary pancreas transplant and 70% (95% CI, 65% to 76%) 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 90% (95% CI, 89% to 91%) after primary SPK transplant and 80% (95% CI, 64% to 96%) after a repeat SPK transplant. The number of patients living 3 years after transplant was 2907 after a primary combined procedure and 26 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.14-17
For example, 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=0.48). Similarly, 1-year patient survival rates were 96% after initial transplants and 95% after retransplants (p=0.53). However, Rudolph et al (2015), who assessed the largest number of patients, reported higher graft survival rates, but not patient survival rates, after primary transplant. A total of 2145 pancreas transplants were performed, 415 (19%) of which were retransplants. The death-censored graft survival rate at 1 year was 88.2% in initial transplants and 75% in retransplants (p<0.001). Patient survival rates at 1 year were 91% after initial transplants and 88% after retransplants (p=0.06).

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

Potential Contraindications (Applies to all Indications above)

Pancreas Transplant in HIV-Positive Transplant Recipients
Current OPTN policy permits HIV-positive transplant candidates. The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease. These criteria may be extrapolated to other organs:
- Adherent with treatment, particularly antiretroviral therapy
- Cluster of differentiation 4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

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, 60 years or older. Overall, Kaplan-Meier survival analysis found statistically significant differences in patient survival (p<0.001) and graft survival (p<0.001) 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>
<thead>
<tr>
<th>Table 1. Patient Survival by Age Group</th>
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<tr>
<td><strong>Years After Transplant</strong></td>
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<tr>
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<tr>
<td>1 year</td>
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<td>5 years</td>
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<td>10 years</td>
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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.\textsuperscript{1} One-year patient survival was 100% for patients younger than age 30 years, 98% for patients age 30 to 39 years, 94% for patients 40 to 49 years, 95% for patients 50 to 59 years, and 93% for patients age 60 or older. There was no statistically significant difference in patient survival by age group (p=0.38). Findings were similar for 1-year graft survival; there was no statistically significant difference in outcomes by age of transplant recipients (p=0.10).

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 United States.\textsuperscript{2} 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.\textsuperscript{3} 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 article,\textsuperscript{4} agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

Summary of Evidence

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

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

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

For individuals who have had a prior pancreas transplant who still meet criteria for a pancreas transplant who receive pancreas retransplantation, the evidence includes case series and registry studies. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. National data and 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 a meaningful improvement in the net health outcome.
Supplemental Information
Practice Guidelines and Position Statements
The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in June 2018.25
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.26 The Centers for Medicare & Medicaid Services made the following national coverage decision on pancreas transplant for Medicare recipients.27
“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 simultaneous with or after a kidney transplant. If the pancreas transplant occurs after the kidney transplant, immunosuppressive therapy begins with the date of discharge from the inpatient stay for the pancreas transplant.
Effective ... 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.
   • Patients must have a diagnosis of type I diabetes
   • Patient with diabetes must be beta cell autoantibody positive; or
2. 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 unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NC01047865</td>
<td>Type 1 Diabetes Recurrence in Pancreas Transplants</td>
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<td>May 2019</td>
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<tr>
<td>NC01957696</td>
<td>The Norwegian Pancreas Transplantation (PTx) Study</td>
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<td>Oct 2020</td>
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<tr>
<td>NC00238693</td>
<td>Transplant Patient Registry of Liver, Kidney and/or Pancreas</td>
<td>15,000</td>
<td>Jan 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**


Documentation for Clinical Review

Please provide the following documentation (if/when requested):
- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>48550</td>
<td>Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation</td>
</tr>
<tr>
<td>CPT</td>
<td>48551</td>
<td>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</td>
</tr>
<tr>
<td>CPT</td>
<td>48552</td>
<td>Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each</td>
</tr>
<tr>
<td>CPT</td>
<td>48554</td>
<td>Transplantation of pancreatic allograft</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2065</td>
<td>Simultaneous pancreas kidney transplantation</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>0FSG0ZZ</td>
<td>Reposition Pancreas, Open Approach</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>0FSG4ZZ</td>
<td>Reposition Pancreas, Percutaneous Endoscopic Approach</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>0FYG0Z0</td>
<td>Transplantation of Pancreas, Allogeneic, Open Approach</td>
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<tr>
<td>ICD-10 Procedure</td>
<td>0FYG0Z1</td>
<td>Transplantation of Pancreas, Syngeneic, Open Approach</td>
</tr>
</tbody>
</table>

**Policy History**

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/26/1988</td>
<td>Policy adopted</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/05/1991</td>
<td>Policy Revision</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/17/2001</td>
<td>Policy clarification</td>
<td>Transplant Team Review</td>
</tr>
<tr>
<td>06/01/2001</td>
<td>Policy reviewed. Policy statement unchanged.</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal 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.