Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for allogeneic pancreas transplants when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
A combined pancreas-kidney transplant may be considered medically necessary in insulin dependent diabetic patients with uremia.

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

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 of optimal medical management.

Pancreas retransplantation after a failed primary pancreas transplant may be considered medically necessary in patients who meet criteria for pancreas transplantation.
When Policy Topic is not covered
Pancreas transplant is considered investigational in all other situations.

Considerations

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

Pancreas Specific
Candidates for pancreas transplant alone should additionally meet 1 of the following severity of illness criteria:
- Documentation of severe hypoglycemia unawareness as evidenced by chart notes or emergency room visits; OR
- 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 should be ≤32 kg/m²). According to International Pancreas Transplant Registry data, in 2010, 7% of pancreas transplant recipients had type 2 diabetes (Gruessner [2011]).

Multiple Transplants
Although there are no standard guidelines regarding 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.

Transplant Benefit
Transplant requests should be reviewed by the Plan medical director or his or her designee. Only patients accepted for transplantation by an approved
transplantation center and actively listed for transplant should be considered for precertification or prior approval. Guidelines should be followed for transplant network or consortiums, if applicable.

Pancreas transplants should be considered for coverage under the transplant benefit.

What is covered under the scope of the human organ transplant (HOT) benefit needs to be considered. Typically, the following are covered under the HOT benefit:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis;
- hospital room, board, and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians’ services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ;
- diagnostic services;
- drugs that require a prescription by federal law.

Expenses incurred in the evaluation and procurement of organs and tissues are benefits when billed by the hospital. Included in these expenses may be specific charges for participation with registries for organ procurement, operating rooms, supplies, use of hospital equipment, and transportation of the tissue or organ to be evaluated.

Administration of products with a specific transplant benefit needs to be defined as to:
- when the benefit begins (at the time of admission for the transplant or once the patient is determined eligible for a transplant, which may include tests or office visits prior to transplant);
- when the benefit ends (at the time of discharge from the hospital or at the end of required follow-up, including the immunosuppressive drugs administered on an outpatient basis).

Coverage usually is not provided for:
- HOT services, for which the cost is covered/funded by governmental, foundational, or charitable grants;
- organs sold rather than donated to the recipient;
- an artificial organ.
### Description of Procedure or Service

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

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

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

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

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

**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 allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.1

**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.2 In 2017, 213 PTAs and 789 simultaneous pancreas plus kidneys were performed in the United States.2
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 (eg, 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 a pancreas transplant alone 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.

**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**

**Literature Review**

This evidence review was created in December 1996 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 10, 2019.

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

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

Pancreas Transplant After Kidney Transplant

Clinical Context and Therapy Purpose
The purpose of a PAK transplant in 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 PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with insulin-dependent diabetes.
Interventions
The therapy being considered is a PAK transplant.

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

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

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

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

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.

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 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: PAK Transplant**
Data from national and international registries have found relatively high patient survival rates after PAK (eg, 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 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(s) were used to select literature to inform this review.

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

**Interventions**
The therapy being considered is an SPK transplant.

SPK transplant is provided in a hospital setting with specialized staff and equipment to perform the surgical procedure and provide postsurgical intensive care.
Comparators
The following therapy is currently being used to make decisions about insulin-dependent diabetes with uremia: insulin therapy.

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

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. 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). 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 OS 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. 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. 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 (eg, bodyweight; 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: SPK Transplants for Patients with Uremia
Data from national and international registries have found relatively high patient survival rates after SPK transplants (eg, 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 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 PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are 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. PTA has also been investigated in patients following total pancreatectomy for chronic pancreatitis. In addition to the immune rejection issues common to all allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.[1]

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

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

Comparators
The following therapy is currently being used to make decisions about insulin-dependent diabetes with severe diabetic complications: insulin therapy.
**Outcomes**
The general outcomes of interest are 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 five years as survival improves.

**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, the 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 diseases, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA.

**Section Summary: PTA for Patients with Severe Complications**
Data from international and national registries have found that graft and patient survival rates after PTA have improved over time. For the period of 2010 to 2014, 1- and 3-year survival rates had improved to 96% 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 PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are 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.

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

**Comparators**
The following therapy is currently being used to make decisions about 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 five years as survival improves.

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

The OPTN has reported data on transplants performed between 1997 and 2004.\(^1\) 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.\(^{13,14,15,16}\) For example, Fridell et al (2015) reported on 441 initial transplants and 20 late transplants.\(^{14}\) 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.\(^{16}\) 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 Human Immunodeficiency Virus-Positive Transplant Recipients
Current OPTN policy permits HIV-positive transplant candidates.17, The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.18, 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 six 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.19, Investigators included all adults who received SPK or PTA transplants between 1996 and 2012 (n=20854). 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 five and ten years are relatively high, as shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Patient Survival by Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years After Transplant</strong></td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>1 year</td>
</tr>
<tr>
<td>5 years</td>
</tr>
<tr>
<td>10 years</td>
</tr>
</tbody>
</table>

Adapted from Siskind et al (2014).19,
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 2011.21 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 age 60 or older. There was no statistically significant difference in patient survival by age group (p=0.38). Findings were similar for one-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 U. S.20, The two 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.21 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,22 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 PAK transplant, the evidence includes case series and registry studies. The 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 PAK transplant (eg, 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 PAK 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. The 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 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 PTA, the evidence includes registry studies. The 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 PTA have improved over time (eg, 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. The 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 a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements

Organ Procurement and Transplantation Network
The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in May 2019.23.

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.24. The Centers for Medicare & Medicaid Services made the following national coverage decision on pancreas transplant for Medicare recipients.25.
"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.
   - 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 ongoing and unpublished trials that might influence this review are listed in Table 2.
<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01047865</td>
<td>Type 1 Diabetes Recurrence in Pancreas Transplants</td>
<td>400</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT01957696</td>
<td>A Prospective, Observational Study in Pancreatic Allograft Recipients: The Effect of Risk Factors, Immunosuppressive Level and the Benefits of Scheduled Biopsies - on Surgical Complications, Rejections, and Graft Survival</td>
<td>80</td>
<td>Oct 2028</td>
</tr>
<tr>
<td>NCT00238693</td>
<td>Transplant Registry: Patients Who May Require Transplantation and Those Who Have Undergone Transplantation of Liver, Kidney and/or Pancreas</td>
<td>13,767</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES

**Billing Coding/Physician Documentation Information**

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
48556 Removal of transplanted pancreatic allograft
50300 Donor nephrectomy, with preparation and maintenance of allograft, from cadaver donor, unilateral or bilateral
50320 Donor nephrectomy, open from living donor (excluding preparation and maintenance of allograft)
50340 Recipient nephrectomy (separate procedure)
50360 Renal allotransplantation, implantation of graft; excluding donor and recipient nephrectomy
Allogeneic Pancreas Transplant 7.03.02

50365  Renal allotransplantation, implantation of graft; with recipient nephrectomy
S2065  Simultaneous pancreas kidney transplant

ICD-10 Codes
E10.10-  Type I diabetes mellitus with ketoacidosis, code range
E10.11
E10.21-  Type I diabetes mellitus with kidney complications, code range
E10.29
E10.641- Type I diabetes mellitus with hypoglycemia, code range
E10.649
E10.69  Type I diabetes mellitus other specified complications
E10.8   Type I diabetes mellitus with unspecified complications
T86.890- Complications of other transplanted tissue, code range
T86.899
Z90.5   Acquired absence of kidney

Additional Policy Key Words
N/A

Policy Implementation/Update Information
8/1/01  New policy added to the Surgery section.
8/1/02  No policy statement changes. Added to the Transplant section.
8/1/03  No policy statement changes.
8/1/04  Policy statement revised to include HIV+ status as investigational. Also added the “severity of illness criteria” to the policy statement.
8/1/05  Policy statement revised to remove HIV+ status as investigational.
4/1/06  No policy statement changes. General criteria added to the Considerations section.
8/1/06  No policy statement changes.
8/1/07  No policy statement changes.
8/1/08  Policy statement revised, removed statement regarding “two or more failed pancreas transplants.”
8/1/09  No policy statement changes.
8/1/10  No policy statement changes.
8/1/11  Not medically necessary indications regarding malignancy, infection and terminal conditions added to policy statement; relative contraindications clarified in Considerations section.
8/1/12  “Not medically necessary” statement removed. Contraindications combined (absolute and relative) and moved to Considerations section. Wording of contraindications changed to be consistent with other solid organ transplant policies.
8/1/13  No policy statement changes.
8/1/14  Statement on retransplantation modified to state that it applies to patients who meet criteria for pancreas transplant.
8/1/15  Not covered statement revised from not medically necessary to investigational when criteria are not met.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.