

# Pancreas transplantation

Clinical Policy ID: CCP.1201

Recent review date: 3/2023

Next review date: 7/2024

Policy contains: Diabetes; islet cell; pancreas alone; pancreas–kidney.

AmeriHealth Caritas Louisiana has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Louisiana's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Louisiana when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Louisiana's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Louisiana's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Louisiana will update its clinical policies as necessary. AmeriHealth Caritas Louisiana's clinical policies are not guarantees of payment.

## Coverage policy

Pancreas transplantation is clinically proven and, therefore, medically necessary in members with type 1 diabetes mellitus when the following criteria are met (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009; Paty, 2013; Sung, 2015):

- For simultaneous pancreas–kidney transplantation using deceased donor pancreas and kidney or deceased donor pancreas and live donor kidney, members must meet all the criteria for kidney transplantation.
- For pancreas transplantation after a previous kidney transplantation (pancreas-after-kidney) in members with stable kidney graft function (creatinine clearance > 40 mL/min).
- For pancreas transplantation alone using deceased donor whole organ in members who meet all of the following criteria:
  - Diagnosis of type 1 diabetes mellitus and one of the following:
    - Be beta cell autoantibody-positive.
    - Demonstrate insulinopenia, defined as a fasting C-peptide level of  $\leq 110\%$  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 of  $\leq 225$  mg/dL.

- A history of severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and persistent labile diabetes despite optimal medical management.
- Optimally and intensively managed by an endocrinologist for at least 12 months with the most medically recognized advanced insulin formulations and delivery systems.
- Satisfactory kidney function (creatinine clearance  $> 40$  mL/min).
- Adequate cardiac status (e.g., no angiographic evidence of significant coronary artery disease, ejection fraction  $\geq 40$ , no myocardial infarction in the last six months or negative stress test).
- Documentation of compliance with medical management.
- An acceptable psychosocial risk for transplantation surgery and the lifelong need for immunosuppression.
- Otherwise a suitable candidate for transplantation.

Pancreas transplantation in members with type 2 diabetes mellitus is clinically proven and, therefore, medically necessary when all of the following criteria are met (Weems, 2014):

- Simultaneous pancreas–kidney transplantation using deceased donor pancreas and kidney or deceased donor pancreas and live donor kidney is performed.
- Body mass index less than  $30 \text{ kg/m}^2$ .
- Insulin dependence.
- Low total insulin requirements ( $< 1$  U/kg of ideal body weight per day).
- Imminent or established renal failure (dialysis dependent or pre-dialysis advanced diabetic nephropathy with glomerular filtration rate  $\leq 20 \text{ mL/min/1.73 m}^2$ ).
- Fasting C-peptide less than  $10 \text{ ng/mL}$ .
- Low cardiac and vascular disease risk.
- History of medical and dietary compliance.

Pancreas re-transplantation is clinically proven and, therefore, medically necessary upon individual case review.

Autologous islet cell transplantation is clinically proven and, therefore, medically necessary to prevent postsurgical diabetes in patients with medically refractory chronic pancreatitis who require total pancreatectomy (American Diabetes Association, 2020a).

The following procedures are investigational/not clinically proven and, therefore, not medically necessary:

- Allogeneic islet cell transplantation (Speight, 2010).
- Autologous islet cell transplantation in persons with type 1 diabetes mellitus.

### Limitations

Requests for pancreas transplantation in patients with the following conditions require secondary review:

- Chronic liver disease.
- Clinical evidence of severe cerebrovascular or peripheral vascular disease (e.g., ischemic ulcers, previous amputation secondary to vascular disease). Adequate peripheral arterial supply should

be determined by standard evaluation in the vascular laboratory, including Doppler examination and plethysmographic readings of systolic blood pressure.

- Past psychosocial abnormality.
- Body mass index  $\geq 30$  kg/m<sup>2</sup> but  $< 35$  kg/m<sup>2</sup>.
- Structural genitourinary abnormality or recurrent urinary tract infection.
- Substance use history (other than persistent substance use).
- Treated malignancy (simultaneous pancreas–kidney transplantation is considered medically necessary in persons with malignant neoplasm if the neoplasm has been adequately treated and the risk of recurrence is small).
- Uncontrolled hypertension.

Absolute contraindications to pancreas transplantation include, but are not limited to:

- Acquired immune deficiency syndrome diagnosis with CD4 count  $< 200$  cells/mm<sup>3</sup> (Centers for Disease Control and Prevention, 2022) unless all of the following criteria are met:
  - CD4 count greater than 200 cells/mm<sup>3</sup> for more than six months.
  - Human immunodeficiency virus type 1 RNA undetectable.
  - Consistent anti-retroviral therapy for more than three months.
  - Absence of acquired immune deficiency syndrome complications (e.g., opportunistic infection, Kaposi's sarcoma, or other neoplasm).
  - Criteria met for pancreas or pancreas–kidney transplantation.
- Active drug use and alcohol dependence.
- Active hepatitis or cirrhosis.
- Active or recent malignancy.
- Active peptic ulcer.
- Body mass index  $\geq 35$  kg/m<sup>2</sup> (bariatric surgery should be considered).
- Demonstrated patient non-adherence to medical recommendations (e.g., failure to comply with prescribed drug regimens).
- Ongoing or recurring infections that are not effectively treated.
- Potential complications from immunosuppressive medications unacceptable to the patient.
- Psychiatric disease that may compromise patient compliance.
- Serious cardiac or other ongoing insufficiencies that create an inability to tolerate surgery.
- Serious conditions unlikely to be improved by transplantation as life expectancy can be finitely measured.

All other uses of pancreas transplantation are not medically necessary.

Alternative covered services

- Exogenous insulin therapy.
- Hemodialysis.
- Peritoneal dialysis.

## Background

The pancreas is an elongated organ located behind the stomach which possess digestive (exocrine) and hormonal (endocrine) functions and is made up of two types of glands. The digestive enzymes secreted by the exocrine (via ducts) portion helps to breakdown the protein, fats, carbohydrates, and acids we ingest in the duodenum. It also secretes bicarbonate to neutralize the stomach acid there. The endocrine

gland portion (via bloodstream) secretes glucagon, insulin and somatostatin to regulate the release of insulin and glucagon as needed for metabolism and other cellular functions in the body. Pancreatic islets containing beta cells that produce insulin are scattered throughout the pancreas and are responsible for the transport of glucose out of the bloodstream for the body to use it for energy. Diabetes develops as result of a poor functioning pancreas, or the body's cells to not effectively use insulin, or both scenerios (American Pancreatic Association, 2021).

The primary cause of pancreatic disease is type 1 diabetes mellitus, followed by type 2 diabetes mellitus, chronic pancreatitis, cancer, and cystic fibrosis (Kandaswamy, 2015). A pancreas transplantation is a means of providing an endogenous, self-regulated source to achieve physiologic insulin regulation without inducing adverse effects associated with administration of exogenous insulin (National Kidney Foundation, 2018). The goal of pancreas transplantation is to produce a lasting normoglycemic state that enhances quality of life. The procedure may involve the whole pancreas, a pancreas segment, or a large group of pancreatic islet cells, or be in combination with a kidney transplant.

The U.S. Food and Drug Administration (2019) does not regulate the transplantation of human organs containing blood vessels, such as kidney, liver, heart, lung or pancreas. However, they do regulate allogeneic islet cell transplantation as somatic cell therapy. Clinical studies to determine safety and effectiveness outcomes of allogeneic islet cell transplantation must be conducted under an investigational new drug regulation.

## **Findings**

We identified two systematic reviews (Bramis, 2012; Speight, 2010), one survival analysis (Sung, 2015), one economic analysis (Wilson, 2015), and two evidence-based guidelines (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009; Paty, 2013) for this policy. The majority of the evidence assessed pancreas transplantation in persons with difficult-to-control type 1 diabetes mellitus in whom a kidney transplantation had been performed or was imminent. Transplantation techniques examined were pancreas transplantation alone, simultaneous pancreas–kidney transplantation, pancreas-after-kidney transplantation, and allogeneic islet cell.

Pancreas transplantation using deceased or living donor organ, is associated with significant perioperative risks; as with other solid organ transplantations, contraindications are a large consideration that contribute to candidate selection and best outcomes. Increasing age has been a part of the exclusion criteria used when determining eligibility. While an upper age limit has not been established in the literature, a United Network for Organ Sharing database review of all adult pancreas alone and simultaneous pancreas–kidney transplantations between 1996 and 2012 found decreased patient and graft survival in patients of increasing age compared with patients younger than age 50 (Siskind, 2014).

Every year about 80,000 people are diagnosed with chronic pancreatitis according to the National Pancreas foundation that can occur over several years and become life threatening. The debilitation from the disease results in frequent hospitalizations, increasing narcotic use for pain control, and a resultant decrease in quality of life. Islet cell transplant is critical for patients with immense pain who have failed other treatments. The autologous islet cell transplant procedure consists of having the islet cells extracted from the pancreas and reintroduced into the patients liver via the portal vein where the cells continue to produce insulin to regulate glucose. This process removes the diseased organ's debilitating symptoms and creates a new pathway for the production of insulin, thus eliminating the risk of becoming a diabetic (PRWeb 2021).

According to NHS data, pancreas alone transplant has a survival rate at one year of 96/100, and 89/100 in five years. Pancreas/kidney transplant has a survival rate of 96/100 at one year and 89/100 at five years (NHS, 2020). There is sufficient evidence to support pancreas transplantation alone (deceased or living-donor segmental) in patients with type 1 diabetes mellitus and preserved renal function to correct severe metabolic complications. It has been performed mostly in patients with hypoglycemic unawareness or labile diabetes (including patients with frequent episodes of ketoacidosis) who have failed insulin-based management and may have incapacitating clinical or emotional problems with exogenous insulin therapy. Procedural success can eliminate the acute complications commonly experienced by individuals with type 1 diabetes mellitus, stabilize neuropathy, and improve quality of life primarily by eliminating the need for exogenous insulin, frequent daily blood glucose measurements, and many of the dietary restrictions imposed by the disorder. Patient survival rates of pancreas transplantation alone and pancreas–kidney transplantations are similar, and graft survival rates of pancreas transplantation alone and pancreas-after-kidney are similar (NHS, 2021).

Two Organ Procurement and Transplantation Network/United Network for Organ Sharing database analyses underscore the importance of monitoring kidney function before and after pancreas transplantation alone. Kidney failure developed in approximately 10% of patients at five years' follow-up, and kidney transplantations were required (Nata, 2013). Kidney function before pancreas transplantation alone is a strong, independent predictor of end-stage renal disease (Kim, 2014). End-stage renal disease was 7.74 (95% confidence interval 4.37 to 13.74) and 3.25 (95% confidence interval 1.77 to 5.97) times more likely to develop in patients with an estimated glomerular filtration rate of < 60 mL/min/1.73 m<sup>2</sup> and 60 to 89.9 mL/min/1.73 m<sup>2</sup>, respectively, than in those with an estimated glomerular filtration rate of ≥ 90 mL/min/1.73 m<sup>2</sup>. The ideal management of candidates for pancreas transplantation alone with an estimated glomerular filtration rate of < 60 mL/min/1.73 m<sup>2</sup> remains to be determined. These results may inform patient selection and the use of targeted interventions to reduce the risk of progressive kidney impairment in this patient population.

A glycemic control comparison post pancreas transplant was performed by Andacoglu and colleagues (2019) in which both the type 1 and type 2 diabetic recipients at a high volume center were reviewed. Increased complication rates such as increased Basal metabolic index, higher short term insulin requirements, and transplant rejection occurred more frequently in the type 2 diabetic recipients than in the type 1. Graft survival was 95% and 82% for the type 1 and type 2 diabetics at the two year time frame although both remained statistically insignificant.

There is sufficient evidence to support the use of pancreas–kidney transplantation either simultaneously or sequentially in patients with uremia and type 1 diabetes mellitus who have been carefully selected. Successful transplantation does not jeopardize patient survival, may improve kidney survival, will restore normoglycemia and improves quality of life. As a single procedure, simultaneous pancreas–kidney transplantation offers the potential benefits of shorter waiting time, an expanded organ donor pool and improved short-term and long-term renal graft function. Regarding metabolic function, a selected group of type 2 diabetic recipients benefit from the simultaneous pancreatic-kidney transplant. For those who have a living kidney donor, pancreas-after-kidney is preferable to waiting years for a cadaver donor for a simultaneous procedure (Hau).

There is insufficient evidence to support the use of islet cell transplantation for treating type 1 diabetes mellitus. It holds significant potential advantages over whole-gland transplantation and for patients with benign prostatic disease (e.g., chronic pancreatitis), but its long-term survival has yet to be achieved. At this time, it is a rapidly evolving technology that also requires systemic immunosuppression and should be performed only within the setting of controlled research studies.

Since 1995, the rate of pancreas transplantation among individuals with type 2 diabetes mellitus has increased significantly (Gruessner, 2011). Yet, there remains an absence of unified and defined criteria for candidacy. Results from a small number of case series suggest five-year patient and graft survival after simultaneous pancreas–kidney transplantation is comparable between patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus, but long-term outcomes are lacking. Simultaneous pancreas-kidney transplantation candidates with type 2 diabetes mellitus tend to be younger with a relatively lean body habitus and limited advanced diabetic cardiovascular disease. For potential candidates with type 2 diabetes mellitus, Weems (2014) proposed the following selection criteria for simultaneous pancreas–kidney transplantation:

- Younger than age 55 years.
- Body mass index less than 30 kg/m<sup>2</sup>.
- Insulin dependence.
- Low total insulin requirements (< 1 U/kg of ideal body weight per day).
- Presence of renal failure (dialysis-dependent or pre-dialysis advanced diabetic nephropathy with glomerular filtration rate  $\leq$  20 mL/min/1.73 m<sup>2</sup>).
- Fasting C-peptide less than 10 ng/mL.
- Low cardiac and vascular disease risk.
- History of medical and dietary compliance.

Growing evidence suggests chronologic age alone should not exclude a patient for candidacy. One large case series found that while complications may occur, older recipients (age 55 and older) of pancreas transplantation had comparable long-term patient and graft survival rates to those of younger recipients; additionally, type of organ transplantation did not correlate with patient survival in older patients (Scalea, 2016). Patient selection should be based on clinical criteria other than absolute age.

In 2018, we added an evidence-based guideline from the American Diabetes Association (2018) supporting autologous islet cell transplantation for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical complete insulin and glucagon deficiency. This indication was added to the policy.

In 2019, we added no new information to the policy, removed three older systematic reviews, and made no policy changes. The policy ID was changed from CP# 08.02.06 to CCP.1201.

In 2020, we updated the American Diabetes Association Standards of Diabetes Care (2019). There continues to be interest in both allogenic and autologous islet cell transplantation as potential alternatives to whole-organ pancreas transplantation for restoring normoglycemia and reducing or eliminating long-term complications in people with type 1 diabetes. As both techniques continue to evolve, the impact on net health outcomes remains uncertain, although longer term data are beginning to emerge (Vantyghem, 2019a, 2019b). In one prospective parallel-arm cohort study (Vantyghem, 2019a), 28 participants with type 1 diabetes received allogenic islet cell transplantation alone or after a kidney graft. At five and 10 years after islet transplantation, 39% (95% confidence interval 22% to 57%) and 28% (95% confidence interval 13% to 45%) achieved insulin independence (defined as A1C  $\leq$  6.5% [48 mmol/mol]), and graft function persisted in 82% (95% confidence interval 62% to 92%) and 78% (95% confidence interval 57% to 89%) of participants, respectively. Allogenic islet transplantation was associated with improvements in glucose control, need for exogenous insulin, and rate of severe hypoglycemic events. No policy changes are warranted at this time.

In 2021, we updated the references to the American Diabetes Association Standards of Diabetes Care (2020a, 2020b, updates of 2019a, 2019b) and deleted two older references. We added three large cohort studies that confirm earlier findings of a long-term graft and individual survival benefit and improved

metabolic outcomes after simultaneous pancreas-kidney transplantation among diabetic recipients (Esmeijer, 2020; Parajuli, 2020; Sucher, 2019). No policy changes are warranted.

In 2022, we included additional definition to the background, post-transplant data and updated the references. No policy changes are warranted.

In 2023, we included additional data, updated the references, confirmed the information contained is current and unchanged. No policy changes are warranted.

## References

On December 18, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “pancreas transplantation” “pancreas-kidney transplant” (MeSH) and “islets of Langerhans transplantation” “end stage renal disease” (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## **Policy updates**

10/2015: initial review date and clinical policy effective date: 3/2016

2/2017: Policy references updated.

2/2018: Policy references updated. Coverage expanded per American Diabetes Association (2018) guideline.

2/2019: Policy references updated. Policy ID changed.

2/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated.

3/2023: Policy references updated.