Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First	**Submission Date**: 4/1/2024
Policy Number: ccp.1201	**Effective Date:** 4/2016 **Revision Date:** March 1, 2024
Policy Name: Pancreas transplantation	

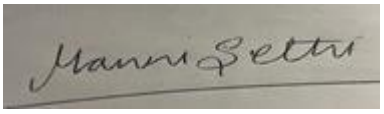
Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Manni Sethi, MD, MBA, CHCQM	

Pancreas transplantation

Clinical Policy ID: CCP.1201

Recent review date: 3/2024

Next review date: 7/2025

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

Keystone First- CHIP has developed clinical policies to assist with making coverage determinations. Keystone First- CHIP'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 Keystone First- CHIP, on a case by case basis, 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. Keystone First- CHIP'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. Keystone First- CHIP's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First- CHIP will update its clinical policies as necessary. Keystone First- CHIP's clinical policies are not guarantees of payment.

Coverage policy

Pancreas transplantation is clinically proven and, therefore, may be 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 ≤ 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 ≤ 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 ≥ 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, may be 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 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 ≤ 20 mL/min/1.73 m^2).
- Fasting C-peptide less than 10 ng/mL.
- Low cardiac and vascular disease risk.
- History of medical and dietary compliance.

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

Autologous islet cell transplantation is clinically proven and, therefore, may be 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 members 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 ≥ 30 kg/m^2 but < 35 kg/m^2.
- 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^3 (Centers for Disease Control and Prevention, 2022) **unless** all of the following criteria are met:

- CD4 count greater than 200 cells/mm^3 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 ≥ 35 kg/m^2 (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 organ behind the stomach with digestive (exocrine) and hormonal (endocrine) functions. The digestive enzymes secreted by the exocrine (via ducts) portion help break down protein, fats, carbohydrates, and acids ingested in the duodenum, and secretes bicarbonate to neutralize stomach acid. The endocrine gland portion (via bloodstream) secretes glucagon, insulin and somatostatin to regulate release of insulin and glucagon needed for metabolism and other cellular functions. Diabetes develops as a result of a poorly functioning pancreas, or cells not effectively using insulin, or both (Longnecker, 2021).

Every year about 80,000 people are diagnosed with chronic pancreatitis 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 extracting islet cells from the pancreas and reintroducing them 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).

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 provides an endogenous, self-regulated source to achieve physiologic insulin regulation without inducing adverse effects associated with administration of exogenous insulin. 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, a large group of pancreatic islet cells, or be in combination with a kidney transplant.

The U.S. Food and Drug Administration (2009) does not regulate the transplantation of human organs containing blood vessels, such as kidney, liver, heart, lung or pancreas. However, it does 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).

Pancreas alone and pancreas/kidney transplants have one year and five year survival rates of 96% and 89% (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.

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).

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, 2020).

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.

The rate of pancreas transplantation among individuals with type 2 diabetes mellitus has increased significantly. Currently 18.6% of persons with simultaneous transplants, 4.8% with kidney transplant after pancreas transplant, and 15.3% with pancreas transplant after kidney transplant have type 2 diabetes (Amara, 2022).

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^2.
- 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 ≤ 20 mL/min/1.73 m^2).
- 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). 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.

In 2024, we added a systematic review of 39 studies of pancreas transplantation in patients with type 2 diabetes. Studies found favorable outcomes in patient survival, graft survival, and glycemic control. Authors suggest better characterization of these patients would help predict who would benefit most from the procedure (Amara, 2022). No policy changes are warranted.

References

On December 6, 2023, 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.

Amara D, Hansen KS, Kupiec-Weglinski SA, et al. Pancreas transplantation for type 2 diabetes: A systematic review, critical gaps in the literature, and a path forward. *Transplantation*. 2022;106(10):1916-1934. Doi: 10.1097/TP.0000000000004113.

American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S37-s47. Doi: 10.2337/dc20-S004.(a)

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S98-s110. Doi: 10.2337/dc20-S009.(b)

Andacoglu OM, Himmler A, Geng X, Ahn J, Ghasemian S, Cooper M, Abrams P. Comparison of glycemic control after pancreas transplantation for type 1 and type 2 diabetic recipients at a high volume center. *Clin Transplant.* 2019;33(8):e13656. Doi: 10.1111/ctr.13656.

Bramis K, Gordon-Weeks AN, Friend PJ, et al. Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Br J Surg.* 2012;99(6):761-766. Doi: 10.1002/bjs.8713.

Centers for Disease Control and Prevention. About HIV/AIDS. https://www.cdc.gov/hiv/basics/whatishiv.html. Reviewed June 30, 2022.

Esmeijer K, Hoogeveen EK, van den Boog PJM, et al. Superior long-term survival for simultaneous pancreas-kidney transplantation as renal replacement therapy: 30-year follow-up of a nationwide cohort. *Diabetes Care.* 2020;43(2):321-328. Doi: 10.2337/dc19-1580.

Hau HM, Jahn N, Brunotte M,et al. Short and long- term metabolic outcomes in patients with type 1 and type 2 diabetes receiving a simultaneous pancreas kidney allograft. *BMC Endocr Disord*. 2020;20(1):30. Doi: 10.1186/s12902-020-0506-9.

Kandaswamy R, Skeans MA, Gustafson SK, et al. OPTN/SRTR 2013 Annual Data Report: Pancreas. *Am J Transplant.* 2015;15 Suppl 2:1-20. Doi: 10.1111/ajt.13196.

Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9 Suppl 3:S1-155. Doi: 10.1111/j.1600-6143.2009.02834.x.

Kim SJ, Smail N, Paraskevas S, et al. Kidney function before pancreas transplant alone predicts subsequent risk of end-stage renal disease. *Transplantation.* 2014;97(6):675-680. Doi: 10.1097/01.TP.0000437556.87109.45.

Longnecker DS. American Pancreatic Association. Anatomy and histology of the pancreas. *Pancreapedia: Exocrine pancreas knowledge base.* 2021. https://www.pancreapedia.org/reviews/anatomy-and-histology-of-pancreas. Doi: 10.3998/panc.2021.01.

Nata N, Huang E, Kamgar M, et al. Kidney failure requiring kidney transplantation after pancreas transplant alone. *Clin Transpl.* 2013:45-52. http://www.ncbi.nlm.nih.gov/pubmed/25095491. Published 2013.

NHS Blood and Transplant. Annual report on pancreas and islet transplantation: Report for 2019/2020 (1 April 2010-31 March 2020). https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19868/nhsbt-pancreas-and-islet-transplantation-annual-report-2019-2020.pdf. Published September 2020.

Parajuli S, Bath NM, Aziz F, et al. More than 25 years of pancreas graft survival after simultaneous pancreas and kidney transplantation: Experience from the world's largest series of long-term survivors. *Transplantation.* 2020;104(6):1287-1293. Doi: 10.1097/tp.0000000000002960.

Paty BW, Koh A, Senior P. Pancreas and islet transplantation. *Can J Diabetes.* 2013;37 Suppl 1:S94-96. Doi: 10.1016/j.jcjd.2013.01.028.

PRWeb. AHN performs its first islet cell transplants to treat chronic pancreatitis: Advanced capability compliments network’s unique islet cell isolation lab at AGH, making organization one of a select group across the country offering comprehensive care for debilitating condition. https://www.prweb.com/releases/ahn-performs-its-first-islet-cell-transplants-to-treat-chronic-pancreatitis-844118706.html. Published October 5, 2021.

Scalea JR, Redfield RR, 3rd, Arpali E, et al. Pancreas transplantation in older patients is safe, but patient selection is paramount. *Transpl Int.* 2016;29(7):810-818. Doi: 10.1111/tri.12754.

Siskind E, Maloney C, Akerman M, et al. An analysis of pancreas transplantation outcomes based on age groupings--an update of the UNOS database. *Clin transplant.* 2014;28(9):990-994. Doi: 10.1111/ctr.12407.

Speight J, Reaney MD, Woodcock AJ, Smith RM, Shaw JA. Patient-reported outcomes following islet cell or pancreas transplantation (alone or after kidney) in Type 1 diabetes: A systematic review. *Diabet Med.* 2010;27(7):812-822. Doi: 10.1111/j.1464-5491.2010.03029.x.

Sucher R, Rademacher S, Jahn N, et al. Effects of simultaneous pancreas-kidney transplantation and kidney transplantation alone on the outcome of peripheral vascular diseases. *BMC Nephrol.* 2019;20(1):453. Doi: 10.1186/s12882-019-1649-7.

Sung RS, Zhang M, Schaubel DE, et al. A Reassessment of the survival advantage of simultaneous kidney-pancreas versus kidney-alone transplantation. *Transplantation.* 2015;99(9):1900-1906. Doi: 10.1097/tp.0000000000000663.

U.S. Food and Drug Administration. Guidance for industry. Considerations for allogeneic pancreatic islet cell products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-allogeneic-pancreatic-islet-cell-products. Published September 2009.

Vantyghem MC, Chetboun M, Gmyr V, et al. Ten-year outcome of islet alone or islet after kidney transplantation in type 1 diabetes: A prospective parallel-arm cohort study. *Diabetes Care.* 2019;42(11):2042-2049. Doi: 10.2337/dc19-0401.

Vantyghem MC, de Koning EJP, Pattou F, Rickels MR. Advances in beta-cell replacement therapy for the treatment of type 1 diabetes. *Lancet.* 2019;394(10205):1274-1285. Doi: 10.1016/s0140-6736(19)31334-0.

Weems P, Cooper M. Pancreas transplantation in type II diabetes mellitus. *World Journal of Transplantation.* 2014;4(4):216-221. Doi: 10.5500/wjt.v4.i4.216.

Wilson GC, Ahmad SA, Schauer DP, Eckman MH, Abbott DE. Cost-effectiveness of total pancreatectomy and cell autotransplantation for the treatment of minimal change chronic pancreatitis. *J Gastrointestl Surg.* 2015;19(1):4654; discussion 54-45. Doi: 10.1007/s11605-014-2612-3.

Policy updates

10/2015: initial review date and clinical policy effective date: 4/2016

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.

3/2024: Policy references updated.