Medical Coverage Policy

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Pancreatic Islet Cell Transplantation

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Related Coverage Resources

Kidney Transplantation, Pancreas-Kidney Transplantation, and Pancreas Transplantation Alone

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses pancreatic islet cell transplantation.

Coverage Policy

Pancreatic islet cell transplantation is considered a core medical service, not a service that falls under the transplant services benefit. As such, individuals receiving such services are NOT eligible for transplant travel benefits.

Autologous pancreatic islet cell transplantation is considered medically necessary for an individual undergoing total or near-total pancreatectomy for severe chronic pancreatitis.

Allogeneic (cadaver) pancreatic islet cell transplantation for the treatment of any condition (e.g., Type 1 diabetes) is considered experimental, investigational or unproven.

General Background

The islets of Langerhans containing alpha, beta, and delta cells are located throughout the glandular tissue of the pancreas. Beta cells, which secrete insulin are used in islet cell transplantation and make up only 1–2% of the cells. Transplantation of autologous (same individual) beta cells has been proposed for an individual who is undergoing total or near total pancreatectomy for severe, chronic pancreatitis that is refractory to standard therapy. Transplantation of allogeneic (cadaver) beta cells has been proposed for an individual with type I diabetes mellitus (DM) or for those with type I DM who are undergoing kidney transplantation.

Transplantation Process
The islet cell transplantation process involves the harvest of a single pancreas from the individual undergoing transplantation (i.e., autologous) or donor islet cells from a deceased donor or donors (i.e., allogeneic). Islet cells are separated from the pancreatic tissue by a series of enzymatic processes. The isolated islet cells are then infused into the liver by percutaneous catheter via the portal vein, or another venous tributary. Studies are evaluating other potential infusion sites such as the kidney capsule.

Autologous (same individual)
Pancreatic islet autologous transplantation (also known as autotransplantation or islet autotransplantation [IAT]) may be performed following total pancreatectomy—the surgical removal of the whole pancreas—in patients with severe and chronic pancreatitis that cannot be managed by other treatments. Total pancreatectomy with islet autotransplantation (TPIAT, TP-IAT) is a treatment option for patients with chronic pancreatitis that can provide pain relief and improvements in quality of life. The balance between the benefits and short and long-term risks of this operation require careful scrutiny. Best practice to select patients for surgical management with TPIAT is in evolution. Removal of the pancreas in individuals with chronic severe pancreatitis may eliminate the debilitating chronic pain; however, surgical removal of the pancreas results in a state of frank diabetes. The surgeon first removes the pancreas and then extracts and purifies islets from the pancreas. Within hours, the islets are infused through a catheter into the patient's liver. Pancreatic islets begin to release insulin soon after transplantation. However, full islet function and new blood vessel growth from the new islets take time. The goal of autologous islet cell transplantation is to promote insulin therapy independence and reduce potential complications of diabetes in patients who have undergone total or near-total pancreatectomy. This procedure is not considered experimental. Patients with type 1 diabetes cannot receive pancreatic islet auto-transplantation.

Allogeneic (cadaver)
Allogeneic transplantation is a procedure in which islets from the pancreas of a deceased organ donor(s) are purified, processed, and transferred into another person. It is proposed in the treatment of Type 1 diabetes mellitus. The goal is to give the body enough healthy islets to make insulin. Pancreatic islet allogeneic transplantation is currently considered an experimental procedure until the transplantation technology is considered successful enough to be labeled therapeutic.

Literature Review - Autologous Islet Cell Transplantation
In individuals who undergo islet cell autotransplantation after near total or total pancreatectomy, data supports the effectiveness of islet cells in preventing or reducing the impact of surgical diabetes by promoting a mechanism for internal insulin production. Autologous islet cell transplantation is considered a reasonable treatment option for these individuals (Sutherland, et al., 2012; Morgan, et al., 2018; Bellin, et al., 2019; Kempeneers, et al., 2019).

A systematic review included five observational studies in which 296 patients with chronic pancreatitis underwent total pancreatectomy followed by islet cell autotransplant. In the two studies that reported postoperative morphine requirements, there was a significant reduction in the frequency and severity of pain following surgery (Bramis, et al., 2012; Freedman, et al., 2021). In a meta-analysis including 12 studies and 677 patients, Wu et al. (2015) reported the insulin independence rate at 1 year follow-up was 28.4% of 362 patients in five studies. The insulin independence rate at 2 year follow-up was 19.7% of 297 patients reported by three studies.

Literature Review - Allogeneic Islet Cell Transplantation

Although pancreas transplantation requires major surgery and life-long immunosuppression, it remains the gold standard for a specific population of patients who suffer from type 1 diabetes and who do not respond to conventional therapy. Allogeneic islet transplantation is a proposed alternative to pancreas transplantation; however, patient outcomes remain less than optimal and significant progress is required in order for this procedure to be considered a reliable therapy. Although short-term improvement in metabolic control and hypoglycemic unawareness has been noted, sustainable insulin independence has not been achieved in a majority of study participants. Contributing factors may include autoimmune destruction of the transplanted cells, alloimmune rejection of the donor tissue, and toxicity of varying immunosuppressive drug regimens.

There remain unresolved concerns including the duration of islet cell function, limited islet supply, and effect of islet cell transplantation on the incidence and progression of diabetic complications in recipients, and the risk of transmission of adventitious disease if multiple donors are used. Additionally, long-term effects of immunosuppressant therapy, variance in study protocols, including participant eligibility criteria and differing immunosuppressive regimens, and inconsistency in islet isolation and infusion techniques are issues that require resolution. At this time the role of allogeneic islet cell transplantation has not been established for any indication, including the treatment of type I diabetes mellitus.

The Clinical Islet Transplantation Consortium Protocol 07 (CIT-07) trial was a multicenter prospective clinical trial of transplantation of a standardized, well-defined allogeneic islet product (purified human pancreatic islets, PHPI) in subjects with type 1 diabetes (T1D), impaired awareness of hypoglycemia, and intractable severe hypoglycemic events (SHEs). Pancreata from deceased donors 15–65 years of age were processed within 12 hours of procurement. Donor exclusion criteria included history of diabetes. The authors stated the study was performed in accordance with U.S. FDA regulations and Good Clinical Practice Guidelines under a U.S. Investigational New Drug application for PHPI. The primary end point was the composite of achieving an HbA1c level of <7.0% (53 mmol/mol) at day 365 after the initial islet transplantation and freedom from SHEs from day 28 to day 365 after the initial islet transplantation. Results demonstrated the primary end point was met by 42 of the 48 subjects; 87.5% of the subjects achieved the primary end point of freedom from SHE along with glycemic control (HbA1C <7%) at 1 year post-initial islet transplantation. The same subjects reported consistent, statistically significant, and clinically meaningful improvements in condition-specific health-related quality of life as well as self-assessments of overall health. Safety events occurred related to the infusion procedure and immunosuppression, including bleeding and decreased renal function. The authors stated that transplantation of human islets is an effective treatment for T1D complicated by IAH and SHEs, resulting in the restoration of hypoglycemia awareness, elimination of SHEs, and normal or near-normal glycemic control in 87.5% of participants. The authors concluded that islet transplantation should be considered for patients with T1D and IAH in whom other, less invasive current treatments have been ineffective in preventing SHEs (Hering, et al., 2016; Foster, et al., 2018).

In a parallel trial of allogeneic islet product (purified human pancreatic islets, PHPI) transplant conducted by the CIT Consortium in patients with Type 1 diabetes (T1D) after kidney transplant (Protocol CIT06), Markmann et al. (2020) prospectively reported on 24 subjects with T1D who had previously received a kidney transplant. The primary endpoint of achieving an HbA1c ≤ 6.5% or a reduction in HbA1c of ≥1 point in the absence of experiencing severe hypoglycemic event (SHE) at day 365 was achieved by 15 subjects (62.5%; $p < .001$). Fourteen (58.3%; $p = .0012$) and 11 (45.8%; $p = .0369$) subjects also achieved the primary endpoint criteria evaluated at day 730 and day 1095, respectively. No patients experienced renal allograft rejection. The 24 subject recipients in CIT06 experienced 22 serious adverse events (SAE) from induction immunosuppression initiation through day 365 post-transplant and 24 additional SAEs through day 1095 after final transplant. The authors noted that the results of CIT06, like those of CIT07, find PHPI to be safe and effective at achieving on-target glycemic control in the absence of SHEs and better disease-specific QOL scores.

TRIMECO was a randomized controlled trial involving 15 university hospitals in France (Lablanche, et al., 2020). Patients (total participants = 50) were aged 18–65 years with type 1 diabetes diagnosed at least 5 years previously. To be eligible for allogeneic islet transplantation, patients had to have severe glycemic lability, associated with at least two severe hypoglycemic events per year, severe impairment of quality of life related to hypoglycemia, or hypoglycemia unawareness. Patients with type 1 diabetes who had received a kidney graft were eligible for islet transplantation if they had a functional kidney graft and poor glycemic control or substantial deterioration in quality of life related to diabetes. Patients were randomly assigned to immediate islet

transplantation (n=26) or to insulin therapy for 6 months followed by islet transplantation (insulin group, n=24). Median follow-up was 184-185 days. At 6 months, 16 (64%) of 25 patients in the immediate islet transplantation group had a modified β-score of 6 or higher versus none (0%) of the 22 patients in the insulin group (p<0·0001). At 12 months after first islet infusion, 29 (63%) of the 46 transplantation recipients in the overall study cohort had a modified β-score of 6 or higher. Insulin independence was achieved in 27 (59%) of these patient. The authors noted immunosuppression can affect kidney function, necessitating careful selection of patients. They concluded that although studies with longer-term follow-up are needed, their findings suggest that islet transplantation is a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments.

Professional Societies/Organizations
The Endocrine Society, the American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA) do not address islet cell transplantation in their guidelines.

American Diabetes Association (ADA): The ADA Standards of Medical Care in Diabetes (2021) states the following:

- Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of patients undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a decade after the surgery in some patients.
  Both patient and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.
  (4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes – 2021).

- For patients with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental.
  (6. Glycemic Targets: Standards of Medical Care in Diabetes – 2021).

Organ Procurement and Transplant Network (OPTN): The OPTN Policy on Allocation of Pancreas, Kidney-Pancreas, and Islets (Policy 11.3.C, effective 3/15/2021) addresses Islet Registration Status as follows:

A transplant hospital may register an islet candidate on the waiting list with an active status if the candidate meets either of the following requirements:

1. Is insulin dependent
2. Has a hemoglobin A1c (HbA1c) value greater than 6.5%

Use Outside of the US
National Institute for Health and Care Excellence (NICE): Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy Interventional procedures guidance (IPG274, September 2008):

- The current evidence on autologous pancreatic islet cell transplantation for improved glycemic control after pancreatectomy shows some short term efficacy, although most patients require insulin therapy in the long term. The reported complications result mainly from the major surgery involved in pancreatectomy (rather than from the islet cell transplantation).
- During consent, clinicians should ensure that patients understand that they may require insulin therapy in the long term.
- Patient selection for this procedure should involve a multidisciplinary team with experience in the management of benign complex chronic pancreatic disease. The procedure should be carried out by surgeons with experience in complex pancreatic surgery and clinicians with experience in islet cell isolation and transplantation.

Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus Interventional procedures guidance (IPG257, April 2008):

- The evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. The evidence on safety shows that serious complications may occur as a result of the procedure. The long-term immunosuppression required is also associated with a risk of adverse events.
- During consent, clinicians should ensure that patients understand the potential complications of the procedure and the uncertainty about its efficacy in the long term.
- Patient selection for this procedure should involve a multidisciplinary team. Selection criteria should take into account that the procedure is particularly indicated for patients with hypoglycaemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation.

Diabetes Canada (previously Canadian Diabetes Association): Diabetes Canada published their 2018 Clinical Practice Guidelines. Diabetes and Transplantation (Chapter 20) recommendations specific to islet cell transplant include:

- Individuals with type 1 diabetes with inadequate glycemic control characterized by marked glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control and who have a) preserved renal function or b) who have had a successful kidney transplant may be considered for
  - islet allotransplantation (Grade C, Level 3*) or
  - pancreas transplantation (Grade C, Level 3 for pancreas after kidney; Grade D, Level 4 for pancreas transplant alone).
- Individuals undergoing total pancreatectomy for benign pancreatic disease may be considered for islet autotransplantation to prevent the development of diabetes where suitable facilities are accessible (Grade D, Level 4).

*Grade C: The best evidence was at Level 3
Level 3: Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Grade D: The best evidence was at Level 4 or consensus
Level 4: Other

Health Quality Ontario: The Ontario Health Technology Assessment on Pancreas Islet Transplantation for Patients With Type 1 Diabetes Mellitus (Health Quality Ontario, September 2015) found that in general, low to very low quality of evidence exists for islet transplantation in patients with type 1 diabetes with difficult-to-control blood glucose levels, with or without kidney disease, for these outcomes: health-related quality of life, secondary complications of diabetes, glycemic control, and adverse events. However, high quality of evidence exists for the specific glycemic control outcome of insulin independence compared with intensive insulin therapy. Health Quality Ontario found that for patients without kidney disease, islet transplantation improves glycemic control and diabetic complications for patients with type 1 diabetes when compared with intensive insulin therapy. However, results for health-related quality of life outcomes were mixed, and adverse events were increased compared with intensive insulin therapy. For patients with type 1 diabetes with kidney disease, islet-after-kidney transplantation or simultaneous islet-kidney transplantation also improved glycemic control and secondary diabetic complications, although the evidence was more limited for this patient group. Compared with intensive insulin therapy, adverse events for islet-after-kidney transplantation or simultaneous islet-kidney transplantation were increased, but were in general less severe than with whole pancreas transplantation. Health Quality Ontario concluded that for patients with type 1 diabetes with difficult-to-control blood glucose levels, islet transplantation may be a beneficial β-cell replacement therapy to improve glycemic control and secondary complications of diabetes. However, there is uncertainty in the estimates of effectiveness because of the generally low quality of evidence.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Islet Cell Transplantation in the Context of a Clinical Trial (260.3.1)	10/1/2004
LCD		No Local Coverage Determination found.	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	**Description**
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open

HCPCS Codes	**Description**
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion

Considered Experimental/Investigational/Unproven:

CPT®* Codes	**Description**
S2102	Islet cell tissue transplant from pancreas; allogeneic

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