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.

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. Although the liver has been the traditional site for infusing the donor islets, researchers are investigating alternative sites, such as muscle tissue or another organ.

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
Wu et al. (2015) conducted a systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients. Twelve studies reporting the outcomes of 677 patients (mean age was 37.7 years, duration of pancreatitis 6.6 years) were included. Case reports and cohort studies with less than five patients or have a median length of follow-up less than 6 months were excluded. There were no RCT studies for analysis due to the ethical reasons of this procedure. The insulin independence rate at 1 year follow-up was 28.4% of 362 patients reported by five studies. The insulin independence rate at 2 year follow-up was 19.7% of 297 patients reported by three studies. The insulin independent rate for islet autotransplantation after total pancreatectomy at last follow-up was 3.72 per 100 person-years. The incidence density of mortality was 1.09 per 100 person-years. The 30-day mortality was 2.1%. The authors concluded islet autotransplantation can prevent brittle diabetes mellitus and improve patients’ quality of life.

Sutherland et al. (2012) reported results from the University of Minnesota >30-year-single-center-series. A total of 409 patients (53 children, 5–18 years) with chronic pancreatitis underwent total-pancreatectomy with intraportal islet autotransplantation (TP-IAT) from 1977-2011; (etiology idiopathic-41%; SOD/biliary-9%; genetic-14%; divisum-17%; alcohol-7%; other-12%); mean age-35.3 years). The efficacy of the TP-IAT in terms of islet function, pain relief, narcotic use and quality of life were assessed. Results demonstrated IAT function was achieved in 90% (C-peptide >0.6 ng/ml). At three years, 30% were insulin-independent (25% in adults, 55% in children) and 33% had partial function. After TP-IAT, 85% had pain improvement. By two years 59% had ceased narcotics. All children were on narcotics before, 39% at follow-up; pain improved in 94%; 67% became pain free. The authors stated that the capacity for TP to relieve pain, permit weaning of chronic narcotic therapy, and
restore quality of life, while IAT preserves some degree of islet function in the majority of recipients were demonstrated. The authors concluded that TPIAT should be considered as a first line surgical therapy for patient severely affected by chronic pancreatitis.

Bramis et al. (2012) performed a systematic review of five studies reporting outcomes for total pancreatectomy and islet autotransplantation for chronic pancreatitis. The techniques reported for pancreatectomy and islet cell isolation varied between studies. Total pancreatectomy/islet autotransplantation was successful in reducing pain in patients with chronic pancreatitis. The rate of insulin independence ranged from 46% at five-years to 10% at eight-year follow-up. The impact on quality of life was poorly reported. Data suggest that islet autotransplantation after total pancreatectomy results in a decrease in exogenous insulin requirements as evidenced by insulin independence at five to eight years.

Dong et al. (2011) reported results of a systematic review and meta-analysis of 15 observational studies examining the rate of insulin independence (II) and mortality after islet autotransplantation (IAT) post-total (TP) or partial pancreatectomy (PP). The II rates for IAT post-TP at last follow-up and transiently during the study were 4.62 per 100 person-years (95% CI: 1.53–7.72) and 8.34 per 100 person-years (95% CI: 3.32–13.37), respectively. The 30-day mortality for IAT post-TP and post-PP was 5% (95% CI: 2–10%) and 0, respectively. Long-term mortality was 1.38 per 100 person years (95% CI: 0.66–2.11) and 0.70 per 100 person-years (95% CI: 0.00–1.80) respectively. The data suggest that IAT post pancreatectomy offers insulin independence.

Although not robust, the data suggest effectiveness in preventing or reducing the impact of surgical diabetes by promoting a mechanism for internal insulin production in individuals who undergo islet cell autotransplantation after near total or total pancreatectomy. Autologous islet cell transplantation is considered a reasonable treatment option for these individuals.

**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 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.

The Clinical Islet Transplantation Consortium Protocol 07 (CIT-07) trial was a Phase III clinical trial of transplantation of a standardized, well-defined islet product (purified human pancreatic islets) in subjects with type 1 diabetes, impaired awareness of hypoglycemia, and intractable severe hypoglycemic events (SHEs). Four surveys, the Diabetes Distress Scale (DDS), the Hypoglycemic Fear Survey (HFS), the Short Form 36 Health Survey (SF-36), and the EuroQol 5 Dimensions (EQ-5D), were administered repeatedly before and after islet transplantation. 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 (Foster, et al., 2018).

Hering et al. (2016) reported results from a prospective Phase 3 study (Clinical Islet Transplantation [CIT] Consortium Protocol 07 [CIT-07] trial) of the investigational product purified human pancreatic islets (PHPI) that
was conducted at eight centers in North America. 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. A total of 48 adults with Type 1 diabetes (T1D) for >5 years, absent stimulated C-peptide, and documented Impaired awareness of hypoglycemia (IAH) and severe hypoglycemic events (SHEs) despite expert care, were enrolled. The primary end point was the achievement of HbA1c <7.0% at day 365 and freedom from SHEs from day 28 to day 365 after the first transplant. The primary end point was successfully met by 87.5% of subjects at 1 year and by 71% at 2 years. 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.

A number of small nonrandomized prospective and retrospective trials have demonstrated short-term insulin independence. Insulin independence ranging from 44%-60%, 33.3%, and 10-24%, at one-, two, and five-years, respectively, have been reported (Qi, et al., 2014; Fiorina and Secchi, 2007; Meloche, 2007; Shapiro, et al., 2006; Ryan, et al., 2005; Froud, et al., 2005).

Further data are needed to demonstrate the long-term safety and effectiveness of allogeneic islet cell transplantation. 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.

**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 (2019) states the following recommendation in section 4 on Comprehensive Medical Evaluation and Assessment of Comorbidities:

- Recommendation: Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Grade C (Supportive evidence from poorly controlled or uncontrolled studies/ Conflicting evidence with the weight of evidence supporting the recommendation)

**Organ Procurement and Transplant Network (OPTN):** The OPTN Policy on Allocation of Pancreas, Kidney-Pancreas, and Islets (Policy 11, effective 4/12/2019) 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%

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCDs): NCD for islet cell transplantation in the context of a clinical trial (260.3.10) states that Medicare will pay for the routine costs, as well as transplantation and appropriate related items and services, for Medicare beneficiaries participating in a National Institutes of Health (NIH)-sponsored clinical trial(s).
- Local Coverage Determinations (LCDs): None.

**Use Outside of the US**

**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.

Collaborative Islet Transplant Registry (CITR): The CITR mission is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on human-to-human islet/beta cell transplants performed in North America, and Juvenile Diabetes Research Institute-sponsored European and Australian sites. It is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with supplemental funding from the Juvenile Diabetes Research Foundation (JDRF).

As of September 30, 2015, the CITR Registry included data on 1,086 allogeneic islet transplant recipients, who received 2,150 allograft infusions from 2,619 allograft donors. The current report represents a 7% increase in the number of recipients, a 12% increase in the number of infusion procedures, and 8% increase in donors, compared to the 2013 report.

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:
<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
</tbody>
</table>

Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2102</td>
<td>Islet cell tissue transplant from pancreas; allogeneic</td>
</tr>
</tbody>
</table>


**References**


“Cigna Companies” refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2019 Cigna.