Cigna Medical Coverage Policy

Subject **Pancreatic Islet Cell Transplantation**

Effective Date **6/15/2014**
Next Review Date **6/15/2015**
Coverage Policy Number **0107**

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Hyperlink to Related Coverage Policies

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

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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.

Cigna covers autologous pancreatic islet cell transplantation as medically necessary for an individual undergoing total or near-total pancreatectomy for severe chronic pancreatitis.

Cigna does not cover allogeneic pancreatic islet cell transplantation for the treatment of any condition because it 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 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 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 single or multiple donor pancreata from a deceased donor or donors (i.e., allogeneic). Subsequently the 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. Functioning as a free graft, the islet cells implant in the liver, with the goal of gradual normalization of basal hepatic glucose output and plasma concentrations of amino acids, improving insulin action (Fiorina, 2007).

Several infusions of islet cells may be necessary to increase the level of graft function. At least 9,000–10,000 islet equivalents (IE)/kilogram of body weight are required for a successful outcome (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2007). For allogeneic islet cell transplantation, multiple pancreata may be necessary to achieve adequate engraftment.

Autologous Islet Cell Transplantation
Chronic pancreatitis is a disease that progressively destroys pancreatic exocrine tissue, causes pain syndromes which frequently require hospitalization, and can severely compromise quality of life. The chronic inflammation associated with severe chronic pancreatitis is caused by autodigestion of the pancreas by pancreatic enzymes. It is also estimated that 30–50% of individuals with chronic pancreatitis develop diabetes.

There is sufficient evidence to suggest that 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 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.

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 metaanalysis 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.

Bellin et al. (2011) compared islet function between eight allogeneic and eight autologous islet transplantation recipients at a similar duration post transplant. The two groups differed significantly only in the transplanted islet mass (i.e., autologous: 4589 +/- 1233 IE/kg, allogeneic: 9929 +/-6246 IE/kg). Eleven healthy controls were matched to the allogeneic islet transplantation group for age, body mass index, and gender. The glycemic response to oral glucose tolerance testing, acute insulin response to glucose, and the acute insulin response to arginine did not differ significantly between islet allograft and autograft recipients, despite the autograft group receiving less than one-half the number of transplanted islets. The authors note “Better preservation of islet mass in the autograft setting is likely related to the lack of autoimmunity, alloimmunity, and immunosuppressive drug toxicity, highlighting the potential for better outcomes in islet allotransplant for type 1 diabetes mellitus with refinements in immunosuppression.”

Several retrospective reviews and case series have demonstrated the effectiveness of islet cell autotransplantation in preserving endocrine function in individuals undergoing total or near total pancreatectomy. In all patients, islet cell yield was high and 32%–70% of patients achieved complete insulin independence, with five-year insulin independence rates of 47% in the study by Sutherland (Garcea, 2009; Sutherland, 2008; Gruessner, 2004; Clayton, 2003; Rodriguez Rilo, 2003).

Summary of Autologous Islet Cell Transplantation: 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.

Allogeneic Islet Cell Transplantation
Type 1 diabetes mellitus (DM) is an autoimmune disorder that results in islet cell destruction and an inability to produce insulin, resulting in lifelong dependence on insulin replacement therapies. The goal of transplantation is to achieve glycemic control potentially reducing the long-term risks associated with complications of diabetes, and avoidance of lifelong dependence on external insulin therapy. Transplantation options for individuals with type I DM who have uncontrolled blood glucose may include pancreas transplantation alone (PTA): transplantation of a whole pancreas; pancreas-after-kidney transplantation (PAK): transplantation of a whole pancreas into an individual who has previously received kidney transplantation, and living-related donor segmental pancreas transplantation (LRD) which involves transplantation of the tail of the pancreas from a living relative. Transplantation of allogeneic islet cells has been proposed as an alternate method of achieving these goals for individuals with type I DM, including a subset of individuals who are receiving kidney transplantation. This option is also being explored for individuals for whom diet, exercise and aggressive insulin therapy are not sufficient to control blood glucose. While less invasive than other forms of pancreas transplantation, allogeneic islet cell transplantation also requires lifelong immunosuppression to prevent graft rejection. Associated comorbidities may include depression of bone marrow, nephrotoxicity, infection, gastrointestinal effects, and malignancy.

Data from the Collaborative Islet Transplant Registry annual report ([CITR], 2011) notes that between 1999 and 2009, 571 allogeneic transplantation recipients received 1072 infusion procedures. Four hundred eighty-one were islet transplants alone [ITA] and 90 occurred after, or simultaneous with kidney transplantation [IAK/SIK]) from 1187 donors. Combining the data from both groups, 31% received a single islet infusion, 47% received two, 20% received three, and 2% received four-six infusions. Overall, non-stratified achievement of insulin independence was 65% in the first-year post initial infusion (with or without reinfusion); this increased to 75% by the second year. According to a proportional hazards analysis, five-year graft survival (i.e., fasting c-peptide ≥0.3 ng/mL) ranges from 40% to 80%, respectively, for individuals with unfavorable (e.g., recipient age <3 years, $p< 0.001$; islets not cultured, $p<0.001$) and favorable factors (e.g., T-cell depletion plus tumor necrosis factor-a inhibition, $p=0.04$). The CITR also notes that islet cell transplantation is experimental in the U.S. and is only available at sites that have received exemption from the U.S. Food and Drug Administration (FDA) for clinical research of islet transplantation in type I diabetes mellitus.

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 (Fiorina, 2007; Meloche, 2007; Bromberg, 2006; Shapiro, 2006; Ryan, 2005, Froud, 2005).

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 promising 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 (Vardanyan, 2010). 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 (Bellin, 2011). There remain unresolved concerns including the duration of islet cell function, limited islet supply, 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.

U.S. Food and Drug Administration (FDA)
The clinical use of allogeneic pancreatic islet cells to treat Type 1 diabetes mellitus (DM) meets the criteria for the U.S. Food and Drug Administration (FDA) regulation as both a biologic product and a drug product (Wonnacott, 2005). Investigational New Drug (IND) regulations set by the FDA require clinical studies to gather safety and effectiveness data and to ensure the safety and rights of patients in all phases of the investigation.

Professional Societies/Organizations
American Diabetes Association: Based on their review of the scientific literature, the American Diabetes Association (2006) notes allogeneic pancreatic islet cell transplantation holds significant, potential advantages over whole pancreas transplant. At this time, however, islet cell transplantation is a rapidly evolving technology that requires systemic immunosuppression, and should be performed only within the setting of controlled research studies.

Summary of Allogeneic Islet Cell Transplantation: 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.

Use Outside of the US
National Institute for Health and Care Excellence ([NICE], 2008): NICE (United Kingdom) published a Guidance document regarding allogeneic pancreatic islet cells that notes "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. In units with established experience in allogeneic pancreatic islet cell transplantation, the procedure may be used with normal arrangements for clinical governance." NICE also published a Guidance document regarding autologous pancreatic islet cell transplantation that notes "The current evidence on autologous pancreatic islet cell transplantation for improved glycaemic 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). The procedure may be used with normal arrangements for clinical governance in units with facilities for islet cell isolation.'

Summary
Transplantation of autologous beta cells of the islets of Langerhans in the pancreas has been proposed for the treatment of individuals undergoing total or near-total pancreatectomy for chronic severe pancreatitis. Although evidence is not robust, the published peer-reviewed scientific literature supports improved health benefits related to promotion of insulin therapy independence and reduction of potential complications of diabetes for this indication.

However, there is insufficient evidence to support the effectiveness of allogeneic islet cell transplantation for the treatment of any condition. Study limitations include a lack of randomization, and small patient numbers. Outcomes reflect variable long-term rates of insulin independence. Although results are promising, the role of allogeneic islet cell transplantation has not been yet been established in routine clinical practice for any indication.

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

Covered when medically necessary:

CPT®* Codes	**Description**
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells

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

Experimental/Investigational/Unproven/Not Covered:

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

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