



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Pancreatic Islet Cell Transplantation

Effective Date 6/15/2011
Next Review Date 6/15/2012
Coverage Policy Number 0107

Table of Contents

Coverage Policy	1
General Background	1
Coding/Billing Information	4
References	5
Policy History	8

Hyperlink to Related Coverage Policies

Kidney Transplantation
 Pancreas-Kidney Transplantation and
 Pancreas Transplantation Alone

INSTRUCTIONS FOR USE

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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

Scattered throughout the glandular tissue of the pancreas are masses of cells called the islets of Langerhans. Alpha, beta and delta cells are within the islets. Beta cells, used in islet cell transplantation, make up only 1–2% of the cells. Transplantation of autologous beta cells, which secrete insulin, has been proposed for individuals who are 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 individuals with type I diabetes mellitus (DM) and for those with type I DM who are undergoing kidney transplantation.

Transplantation Process

The islet cell transplantation process involves the harvest of a donor pancreas, either from the individual undergoing transplantation (i.e., autologous) or from a deceased donor (i.e., allogeneic). Subsequently the islet cells are separated from the pancreatic tissue by a series of enzymatic processes. The isolated islet cells are 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, and gradually begin to normalize basal hepatic glucose output and plasma concentrations of amino acids, and improve insulin action (Fiorina, 2008). 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. Several infusions of islet cells may be necessary to increase the level of graft function.

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 gland by pancreatic enzymes. There is sufficient evidence to suggest that removal of the pancreas in these individuals may eliminate the debilitating chronic pain, however, surgical removal of the pancreas results in a state of frank diabetes. It is estimated that 30–50% of individuals with chronic pancreatitis develop 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.

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).

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.

According to data from the Collaborative Islet Transplant Registry annual report ([CITR], 2009), between 1999 and 2008, 412 recipients received 828 infusion procedures from 905 donors; 84% (n=347) received islet cell transplantation alone (IA) (i.e., no prior kidney transplantation). The percentage of all IA recipients who are insulin independent declines steadily from 55% at six months post transplantation to 16% at four years post transplantation. At three-year follow-up post first infusion, 27% are insulin independent, 30% are insulin dependent with detectable C-peptide (as a measure of islet cell function), and 27% have no detectable C-peptide.

A number of nonrandomized prospective and retrospective trials have demonstrated short-term insulin independence. Shapiro et al. (2006) reported outcomes of an international prospective study involving 36 individuals who received allogeneic islet cell transplantation utilizing glucocorticoid-free immunosuppressive therapy combined with infusion of islet cells without culture from two or more pancreata from deceased donors (i.e., the Edmonton protocol). Thirty-one percent of participants received a single infusion of islet cells, other participants received two or greater infusions. Insulin independence was achieved by 44% of patients at one year; additionally, 28% had partial function. Twenty-eight percent had complete graft loss at one year after final transplantation. A total of 21 patients (58%) attained insulin independence with good glycemic control at some point throughout the trial. Other studies have reported insulin independence rates of 46.6%-60% and 33.3% at one-, and two-years, respectively. These results have not been shown to be durable in the long-term with insulin independence rates of 10%-24% at five years (Fiorina, 2008; Meloche, 2007; Bromberg, 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, effects 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.

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.

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 pancreatic islet cell transplants hold 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.

Juvenile Diabetes Research Foundation: The Juvenile Diabetes Research Foundation International (2009) notes that currently islet cell transplants are experimental and should be performed only as part of closely controlled and monitored clinical research studies.

National Institute for Health and Clinical Excellence (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. In units with established experience in allogeneic pancreatic islet cell transplantation, the procedure may be used with normal arrangements for clinical governance.”

Summary

Although evidence in the published, peer-reviewed scientific literature is not robust, autologous pancreatic islet cell transplantation is considered a reasonable treatment option for individuals undergoing total or near-total pancreatectomy for chronic pancreatitis.

There is insufficient evidence in the peer-reviewed, published scientific literature to support the effectiveness of allogeneic islet cell transplantation for the treatment of any condition. Although promising, the role of allogeneic islet cell transplantation has not been yet been established for any indication.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary when used to report autologous pancreatic islet cell transplantation:

CPT[®]* Codes	Description
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells
0141T	Pancreatic islet cell transplantation through portal vein, percutaneous
0142T	Pancreatic islet cell transplantation through portal vein, open
0143T	Laparoscopy, surgical, pancreatic islet cell transplantation through portal vein

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

ICD-9-CM Diagnosis Codes	Description
577.1	Chronic pancreatitis

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
S2102	Islet cell tissue transplant from pancreas; allogeneic

ICD-9-CM Diagnosis Codes	Description
	All codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2008	0107	Pancreatic Islet Cell Transplantation
Great-West Healthcare	5/16/2006	06.342.01	Transplantation, Pancreatic Islet Cells

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