

# Pancreatic Islet Cell Transplant



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## DESCRIPTION

Autologous islet cell transplantation performed in conjunction with pancreatectomy is proposed to reduce the likelihood of insulin-dependent diabetes. Allogeneic islet cell transplantation is also being investigated as a treatment or cure for individuals with type 1 diabetes. The islet cells originate from the patient (autologous transplant) or from a cadaveric donor (allogeneic transplant). Islet cell transplantation may benefit an individual who is without a functioning pancreas.

### Islet Transplantation

Autologous islet cell transplantation is generally performed during the pancreatectomy procedure, and the islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient's liver. Once implanted, the beta cells in these islets begin to make and release insulin. Because the body recognizes these islet cells as its own, there is no rejection of these cells by the patient's body.

Allogeneic islet transplantation potentially offers an alternative to whole-organ pancreas transplantation. In the case of allogeneic islet cell transplantation, cells are harvested from a deceased donor's pancreas, processed, and injected into the recipient's portal vein. Up to three donor pancreas transplants may be required to achieve insulin dependence. However, a limitation of islet transplantation is that two or more donor organs are usually required for a successful transplantation, although experimentation with single-donor transplantation is occurring. A pancreas that is rejected for whole organ transplant is typically used for allogeneic islet transplantation. Therefore, allogeneic islet transplantation has generally been reserved for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management. A modified immunosuppression regimen has increased the success of allogeneic islet transplantation, this regimen is known as the "Edmonton protocol" (sirolimus, tacrolimus and monoclonal antibody daclizumab).

### **Chronic Pancreatitis**

Chronic pancreatitis is inflammation of the pancreas that does not heal or improve, it gets worse over time and leads to permanent damage. Chronic pancreatitis eventually impairs an individual's ability to digest food and make pancreatic hormones. Individuals with chronic pancreatitis can experience intractable pain that can only be relieved with a total or near total pancreatectomy. However, the pain relief must be balanced against the certainty that the individual will be rendered an insulin-dependent diabetic.

### **Clinical Context and Therapy Purpose**

The purpose of autologous pancreas islet transplantation for patients with chronic pancreatitis who are undergoing total or near total pancreatectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous pancreas islet transplantation improve the net health outcome in individuals who have chronic pancreatitis who are undergoing total or near-total pancreatectomy?

The following PICO was used to select literature to inform this review.

### **Patients**

The relevant population of interest is individuals who have chronic pancreatitis who are undergoing total or near-total pancreatectomy. Primary risk factors for chronic pancreatitis may be categorized as the following: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and severe acute, or obstructive (TIGAR-O classification system). Patients with chronic pancreatitis may experience intractable pain that can only be relieved with a total or near-total pancreatectomy. However, the pain relief must be balanced against the certainty that the patient will be rendered an insulin-dependent diabetic.

## **Interventions**

The therapy being considered is autologous pancreas islet transplantation. Islet transplantation is provided in a hospital setting with specialized staff who are equipped to perform the cell isolation and re-infusion procedures and manage post-transplant care.

## **Comparators**

The following practice is currently being used to make decisions about managing chronic pancreatitis: medical management, which may include medications or endoscopy.

## **Outcomes**

Outcomes of interest include overall survival, insulin independence, change in disease status, medication use, resource utilization and treatment-related morbidity.

Short-term follow-up is required to monitor for treatment related complications and long-term follow-up 1 to 3, 5 or even 10 years is required to establish durability of glucose control.

## **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

## **Review of Evidence**

### **Systematic Reviews**

There are several systematic reviews of the literature on chronic pancreatitis patients.

(2020) Zhang et al. published a systematic review and meta-analysis of 17 studies that reported clinical outcomes following total pancreatectomy with islet transplant in patients with chronic pancreatitis. Most studies were single-center, small case series from the United States. The median age was 53 years. Insulin independence was 33.29% (95% CI, 27.77% to 39.05%; I<sup>2</sup>=32.3%) at 1 year (8 studies). Mortality at 30 days was 1.32% (95% CI, 0.68% to 2.16%; I<sup>2</sup>=0.0%) and mortality at 1 year was 2.54% (95% CI, 1.32% to 4.16%; I<sup>2</sup>=17.6%).

(2019) Kempeneers et al. published a systematic review of studies examining pain, endocrine function, or quality of life (QOL) outcomes in patients with chronic pancreatitis undergoing total pancreatectomy with islet transplantation. The review included 15 observational studies evaluating 1,255 patients, of whom 28% had had endoscopic and 23% operative therapy. One year after total pancreatectomy with islet cell auto-transplantation, the opioid-free rate had improved from between 0% and 15% to 63% (95% CI 46-77), and the insulin-free rate had decreased from between 89.5% and 100% to 30% (95% CI 20-43). An alcoholic etiology was associated with a lesser insulin-free rate after total pancreatectomy with islet cell auto-transplantation. Quality of life improved statistically after total pancreatectomy with islet cell auto-transplantation. Publication bias was present for both opioid and insulin outcomes. The authors concluded in selected patients with painful, treatment refractory, chronic pancreatitis, evidence shows that total pancreatectomy with islet cell auto-transplantation is effective for pain control in almost two-thirds of patients, whereas the insulin-free rate is relatively low.

(2015) Wu et al. published a systematic review and meta-analysis of studies on islet transplantation after total pancreatectomy (TP) for chronic pancreatitis (CP). Twelve studies reporting the outcomes of 677 patients were included in this review. The insulin independent rate for islet autologous transplant (IAT) after total pancreatectomy (TP) at last follow-up was 3.72 per 100 person-years (95% CI: 1.00-6.44). The 30-day mortality was 2.1% (95% CI: 1.2-3.8%). The mortality at last follow-up was 1.09 per 100 person-years (95% CI: 0.21-1.97). Factors associated with incidence density of insulin independence in univariate meta-regression analyses included islet equivalents per kg body weight (IEQ/kgBW) (P=0.026). Our systematic review suggests that IAT is a safe modality for patients with CP need to undergo TP. A significant number of patients will achieve insulin independence for a long time after receiving enough IEQ/kgBW.

(2011) Dong et al. published a systematic review that included studies irrespective of design or sample size. After reviewing 84 studies, 15 observational studies met eligibility criteria. Eleven studies assessed total pancreatectomy, 2 studies evaluated partial pancreatectomy, and 2 studies included both types of surgery. Sample sizes in individual studies ranged from 3 to 173 patients. Thirteen studies included patients with chronic pancreatitis and 2 included patients with benign pancreatic tumors. The pooled 30-day mortality rate was 5% (95% CI, 2% to 10%), and the cumulative mortality at 1 year (reported by 10 studies) was 4.9% (95% CI, 2.6% to 7.3%). In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100 person-years (95% CI, 1.53 to 7.62). The pooled rate of insulin independence was 27% (95% CI, 21% to 33%) at 1 year (5 studies) and 21% (95% CI, 16% to 27%) at 2 years (3 studies).

**Table 1. Comparison of Studies Included in Systematic Reviews Assessing Autologous Pancreas Islet Transplants**

Study	Zhang et al (2020)	Kempeneers et al (2019)	Wu et al (2015)	Dong et al (2011)
Cameron et al (1981)	●		●	●
Hinshaw et al (1981)	●		●	●

Toledo-Pereyra et al (1983)				●
Fontana et al (1994)				●
Rastellini et al (1997)	●		●	●
Jindal et al (1998)				●
Rabkin et al (1999)				●
Oberholzer et al (2000)	●		●	●
Berney et al (2004)				●
Ahmad et al (2005)			●	●
Argo et al (2008)	●	●	●	●
Dixon et al (2008)	●	●	●	●
Sutherland et al (2008)				●
Webb et al (2008)				●
Jung et al (2009)				●
Takita et al (2010)		●	●	
Sutherland et al (2012)	●		●	
Walsh et al (2012)	●	●	●	
Dorlon et al (2013)			●	
Garcea et al (2013)	●	●	●	
Gruessner et al (2014)	●	●		
Wilson et al (2014)		●		
Chinnakotla et al (2015)		●		
Georgiev et al (2015)		●		
Takita et al (2015)		●		
Tai et al (2015)	●			
Wilson et al (2015)	●			
Mokadem et al (2016)	●	●		
Shahbazov et al (2016)		●		
Fan et al (2017)		●		
Quartuccio et al (2017)	●			
Shahbazov et al (2017)	●			
Solomina et al (2017)	●	●		
Morgan et al (2018)	●	●		

**Table 2. Characteristics of Systematic Reviews Assessing Autologous Pancreas Islet Transplants**

Study	Dates	Trials	Participants	N (Range)	Design	Duration, mo
Zhang et al (2020)	1977-2018	17	Individuals with chronic pancreatitis	1024 (5-409)	Observational	1-210
Kempeneers et al (2019)	1977-2017	15	Individuals with chronic pancreatitis	1255 (7-490)	Observational	6-138
Wu et al (2015)	1977-2014	12	Individuals with chronic pancreatitis	677 (5-409)	Case series	1-210
Dong et al (2011)	1977-2007	15	Individuals with chronic pancreatitis or benign pancreatic disease	384 (3-173)	Case series	3-100

**Table 3. Results of Systematic Reviews Assessing Autologous Pancreas Islet Transplants**

Study	Insulin-Independence Rate	Mortality Rate
Zhang et al (2020)		
n	NR	NR
30-day follow-up (95% CI)	NR	1.32 (0.68 to 2.16)
$I^2$ , %	NR	0.0
n	603	NR
1-year follow-up (95% CI)	33.29 (27.77 to 39.05)	2.54 (1.32 to 4.16)
$I^2$ , %	32.3	17.6
Kempeneers et al (2019)		
n	NR	1036
30-day follow-up (95% CI)	NR	2 (1 to 4)
$I^2$ , %	NR	35
n	653	669
1-year follow-up (95% CI)	30 (20 to 43)	4 (2 to 6)
$I^2$ , %	82	0
n	NR	NR
2-year follow-up (95% CI)	NR	NR
$I^2$ , %	NR	NR
Wu et al (2015)		
n	NR	672
30-day follow-up (95% CI)	NR	2.1 (1.2 to 3.8)
$I^2$ , %	NR	0
n	362	NR
1-year follow-up (95% CI)	28.4 (15.7 to 46.0)	NR

$\rho$ , %	69	NR
n	297	NR
2-year follow-up (95% CI)	19.7 (5.1 to 52.6)	NR
$\rho$ , %	87	NR
Dong et al (2011)		
n	NR	176
30-day follow-up (95% CI)	NR	5 (2 to 10)
$\rho$ , %	NR	0
n	221	NR
1-year follow-up (95% CI)	27 (21 to 33)	NR
$\rho$ , %	NR	NR
n	201	NR
2-year follow-up (95% CI)	21 (16 to 27)	NR
$\rho$ , %	NR	NR

CI: confidence interval; NR: not reported

### Nonrandomized Studies

(2018) Morgan et al. studied patient selection for total pancreatectomy with islet auto-transplantation (TPIAT) in the surgical management of chronic pancreatitis. A prospectively maintained database of patients undergoing TPIAT was reviewed. Islet function was inferred from daily insulin requirement. Pain relief was evaluated by healthcare use and narcotic use. Quality of life (QOL) was measured with the RAND 12-Item Short Form Survey. One hundred and ninety-five patients (141 women, aged 40.3 years, BMI 26.5 kg/m<sup>2</sup>) underwent TPIAT. Mean duration of disease before operation was 8.1 years. Fifty-six (29%) patients had pancreatic operations before TPIAT, 37 (19%) patients were diabetic preoperatively, and 52 (27%) patients were smokers. A mean of 3,253 islet equivalents transplanted/kg were harvested. Insulin independence was achieved in 29%, 28%, and 23% of patients at 1, 2, and 5 years postoperative. Nonsmokers with a shorter duration of chronic pancreatitis and no earlier pancreas operation were more likely to be insulin free. Median number of preoperative emergency department visits and hospitalizations were 6.6 and 4.3 annually, respectively, compared with 0 at 1, 2, and 5 years postoperative. Median oral morphine equivalents were 214 mg/kg preoperation and 60, 64, 69, at 1, 2, 5 years postoperative. Preoperative, 1, 2, 5 years postoperative QOL scores were 29, 36, 34, and 33 (physical;  $p < 0.01$ ) and 39, 44, 42, and 42 (mental health;  $p < 0.02$ ). Genetic pancreatitis patients were more often narcotic free and had better QOL than patients with pancreatitis of other causes. At 5 years, overall survival was 92.3%. The authors concluded total pancreatectomy with islet auto-transplantation is a durable operation, with islet function, pain relief, and QOL improvements persisting to 5 years postoperative. Patients with genetic pancreatitis, short duration of disease, and nonsmokers have superior outcomes.

(2017) Solomina et al. analyzed results in 20 patients who underwent TP-IAT at The University of Chicago. The median observation period was 28 months. Data were

collected prospectively then analyzed retrospectively. The number of patients requiring opioids daily for pain control decreased from 16 (80%) prior to surgery to 2 (13%) 1 year after, with only 1 (6.5%) patient experiencing persistent phantom pancreatic pain. Opioid requirements decreased from a median 56.3 (0-240) morphine equivalent dose to 5 (0-130) on day 75 and to 0 (0-30) at 1-year follow up. Five patients (25%) completely stopped insulin support prior to day 75 while maintaining hemoglobin A1c of 5.9% (5-6.3). Eight (53%) patients were insulin free at 1 year with A1c of 6% (5.5-6.8) and a similar rate persisted in next 2 years. For the remaining patients, the more islet function that was preserved, the less insulin they required and A1c was closer to optimal. Quality of Life (QoL) measured by SF36 Physical (PCS) and Mental (MCS) Component Score improved on day 75 ( $P < .001$ ) and maintained improvement later on. Both PCS and MCS improved regardless of whether patient requires insulin support or not. The authors concluded improvements of QoL with pain resolution and good glucose control can be achieved after TP-IAT in properly selected patients with chronic pancreatitis (CP) and intractable pain, regardless of patient insulin support status.

(2014) Wilson et al. reported on 166 patients with chronic pancreatitis (CP) who underwent total pancreatectomy and islet autologous transplantation at a single center. Actuarial survival rate at 5 years was 94.6%. Five or more years of data were available for 112 (67%) patients. At 1 year, 38% of patients were insulin independent and that declined to 27% at the 5-year follow-up. Daily insulin requirement, however, remained stable over the 5 years. Fifty-five percent of patients were independent of opioid analgesics at 1 year and improved to 73% at 5 years.

(2014) Chinnakotla et al. reviewed a prospectively maintained database of 484 patients with chronic pancreatitis who underwent a total pancreatectomy (TP) and immediate islet autologous transplantation (IAT) at a single center. The outcomes (e.g., pain relief, narcotic use,  $\beta$ -cell function, health-related quality of life measures) of patients who received TP-IAT for hereditary/genetic pancreatitis (HGP) (protease trypsin 1,  $n = 38$ ; serine protease inhibitor Kazal type 1,  $n = 9$ ; cystic fibrosis transmembrane conductance regulator,  $n = 14$ ; and familial,  $n = 19$ ) were evaluated and compared with those with non-hereditary/nongenetic causes. All 80 patients with HGP were narcotic dependent and failed endoscopic management or direct pancreatic surgery. Post TP-IAT, 90% of the patients were pancreatitis pain free with sustained pain relief; >65% had partial or full  $\beta$ -cell function. Compared with nonhereditary causes, HGP patients were younger (22 years old vs 38 years old;  $p \leq 0.001$ ), had pancreatitis pain of longer duration ( $11.6 \pm 1.1$  years vs  $9.0 \pm 0.4$  years;  $p = 0.016$ ), had a higher pancreas fibrosis score ( $7 \pm 0.2$  vs  $4.8 \pm 0.1$ ;  $p \leq 0.001$ ), and trended toward lower islet yield ( $3,435 \pm 361$  islet cell equivalent vs  $3,850 \pm 128$  islet cell equivalent;  $p = 0.28$ ). Using multivariate logistic regression, patients with non-HGP causes ( $p = 0.019$ ); lower severity of pancreas fibrosis ( $p < 0.001$ ); shorter duration of years with pancreatitis ( $p = 0.008$ ); and higher transplant islet cell equivalent per kilogram body weight ( $p \leq 0.001$ ) were more likely to achieve insulin independence ( $p < 0.001$ ). There was a significant improvement in health-related quality of life from baseline by RAND 36-Item Short Form Health Survey and in physical and mental component health-related quality of life scores ( $p < 0.001$ ). None of the patients in the



entire cohort had cancer of pancreatic origin in the liver or elsewhere develop during 2,936 person-years of follow-up. The authors concluded, total pancreatectomy and islet autologous transplantation in patients with chronic pancreatitis due to hereditary/genetic pancreatitis (HGP) cause provide long-term pain relief (90%) and preservation of  $\beta$ -cell function. Patients with chronic painful pancreatitis due to HGP with a high lifetime risk of pancreatic cancer should be considered earlier for total pancreatectomy (TP) and islet autologous transplantation (IAT) before pancreatic inflammation results in a higher degree of pancreatic fibrosis and islet function loss.

### **Section Summary: Chronic Pancreatitis**

Autologous islet transplantation is frequently performed as an adjunct to total or near total pancreatectomies for chronic pancreatitis. Evidence from nonrandomized studies and systematic reviews has demonstrated that autologous islet transplantation decreases the incidence of diabetes in the setting of pancreatectomies for the treatment of chronic pancreatitis.

### **Type I Diabetes**

Glucose control is a challenge for individual with type I diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease.

### **Clinical Context and Therapy Purpose**

The purpose of allogeneic pancreas islet transplantation for patient who have type I diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does allogeneic pancreas islet transplantation improve the net health outcome in individuals with type 1 diabetes?

The following PICO was used to select literature to inform this review.

### **Patients**

The relevant population of interest is individuals with type 1 diabetes.

Glucose control is a challenge for individuals with type 1 diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease

### **Interventions**

The therapy being considered is allogeneic pancreas islet transplantation. Islet transplantation is provided in a hospital setting with specialized staff who are equipped to perform the cell isolation and re-infusion procedures and manage post-transplant care.

## **Comparators**

The following practice is currently being used to make decisions about managing type 1 diabetes: medical management, which generally includes daily insulin injections as well as diet and lifestyle changes.

## **Outcomes**

General outcomes of interest are overall survival (OS), insulin independence, change in disease status, medication use, resource utilization, and treatment-related morbidity.

According to U.S. Food and Drug Administration (2009) industry guidance on evaluating allogeneic pancreatic islet cell products, single-arm trials with historical controls may be acceptable alternatives to randomized controlled trials (RCTs) for evaluating the safety and efficacy of islet cell products in patients with metabolically unstable type I diabetes. Attainment of a normal hemoglobin A1C (HbA1C) range (i.e.,  $\leq 6.5\%$ ) and elimination of hypoglycemia are acceptable primary end points. To assess the durability of the islet cell procedure, primary end points should be measured at 12 months after the final infusion. Other key clinical outcomes include insulin independence, measures of glucose metabolic control such as fasting plasma glucose levels and loss of hypoglycemia unawareness.

Short-term (30 days) follow-up is required to monitor for transplant related complications; the long-term follow-up to assess the durability of glucose control and monitor immunosuppression is lifelong.

## **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

## **Review of Evidence**

### **Systematic Reviews**

(2015) A systematic review by Health Quality Ontario reported on allogeneic islet transplantation for patients with type I diabetes. The search yielded 1,354 citations. One health technology assessment, 11 additional observational studies to update the health technology assessment, one registry report, and four guidelines were included; the

observational studies examined islet transplantation alone, islet-after-kidney transplantation, and simultaneous islet-kidney transplantation. 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. 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. The authors concluded, for patients with type 1 diabetes with difficult-to-control blood glucose levels, islet transplantation may be a beneficial  $\beta$ -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 to very low quality of evidence for all outcomes of interest. Additional long-term comparative studies are required for better understanding of continuing effects of transplanted islets and the immunosuppression protocols used.

(2004) A TEC Assessment evaluated the evidence on islet cell transplantation in type 1 diabetes. The Assessment found that published data on clinical outcomes of islet-alone transplantation were limited by small sample sizes (i.e.,  $\leq 35$  enrolled patients), few transplant centers, short duration of follow-up, and lack of standardized methods of reporting clinical outcomes. Also, rare, serious adverse events have occurred in patients given islet transplants, although recent procedure modifications reportedly minimized risks of these adverse events. No procedure-related deaths, cytomegalovirus infection, or post transplantation lymphoproliferative disease have been reported for islet-alone transplantation.

### **Randomized Controlled Trials**

(2018) Leblanche et al. published a multicenter, open label, randomized controlled trial (TRIMECO trial) evaluating patients with type I diabetes with severe hypoglycemia or poorly controlled glycaemia after kidney transplantation. Patients with type I diabetes were randomly assigned (1:1) at 15 university hospital to receive immediate allogeneic islet transplantation or intensive insulin therapy (followed by delayed islet transplantation). Eligible patients were aged 18-65 years and had severe hypoglycemia or hypoglycemia unawareness, or kidney grafts with poor glycemic control. We used computer-generated randomization, stratified by center and type of patient. Islet recipients were scheduled to receive 11,000 islet equivalents per kg bodyweight in one to

three infusions. The primary outcome was proportion of patients with a modified  $\beta$ -score (in which an overall score of 0 was not allocated when stimulated C-peptide was negative) of 6 or higher at 6 months after first islet infusion in the immediate transplantation group or 6 months after randomization in the insulin group. The primary analysis included all patients who received the allocated intervention; safety was assessed in all patients who received islet infusions. This trial is registered with ClinicalTrials.gov, number NCT01148680, and is completed. Between July 8, 2010, and July 29, 2013, 50 patients were randomly assigned to immediate islet transplantation (n=26) or insulin treatment (n=24), of whom three (one in the immediate islet transplantation group and two in the insulin therapy group) did not receive the allocated intervention. Median follow-up was 184 days (IQR 181-186) in the immediate transplantation group and 185 days (172-201) in the insulin therapy group. At 6 months, 16 (64% [95% CI 43-82]) of 25 patients in the immediate islet transplantation group had a modified  $\beta$ -score of 6 or higher versus none (0% [0-15]) of the 22 patients in the insulin group ( $p < 0.0001$ ). At 12 months after first infusion, bleeding complications had occurred in four (7% [2-18]) of 55 infusions, and a decrease in median glomerular filtration rate from 90.5 mL/min (IQR 76.6-94.0) to 71.8 mL/min (59.0-89.0) was observed in islet recipients who had not previously received a kidney graft and from 63.0 mL/min (55.0-71.0) to 57.0 mL/min (45.5-65.1) in islet recipients who had previously received a kidney graft. Trial limitations include possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability. The authors concluded for the indications assessed in this study, islet transplantation effectively improves metabolic outcomes. Although studies with longer-term follow-up are needed, islet transplantation seems to be a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments. However, immunosuppression can affect kidney function, necessitating careful selection of patients.

### Registry Studies

(2021) LaBlanche et al. reported 10-year outcomes from the Swiss-French GRAIL Network of 44 patients who received islet transplant for type 1 diabetes between 2003 and 2010.<sup>46</sup> Thirty one patients were still being followed at 10 years; 6 patients died between years 1 and 10 posttransplant. Median HbA1c levels were 7.2% (range, 6.2% to 8.0%) after 10 years compared to 8.0% pretransplant ( $p < .001$ ). One patient was insulin independent at 10 years and 73.9% were free of severe hypoglycemia. Insulin requirements were significantly lower posttransplant (0.3 units/kg/day vs. 0.5 units/kg/day;  $p < .001$ ). Islet graft survival was 51.9% at 10 years.

In a report from the Collaborative Islet Transplant Registry, which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, Alejandro et al. (2008) assessed data on 325 adult recipients. Three years after the first cell infusions, 23% of islet-alone recipients were insulin-independent (defined as insulin-independent  $\geq 2$  weeks), 29% were insulin-dependent with detectable C-peptide, 26% had lost function, and 22% had missing data. Seventy percent achieved insulin independence at least once, 71% of whom were still insulin-independent 1 year later and 52% at 2 years. Factors that favored primary outcomes were a higher number of islet

infusions, a greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size.

(2012) Barton et al. updated the Collaborative Islet Transplantation Registry (CITR) report, which focused on changes in outcomes over time. A total of 677 allogeneic islet transplant-alone or islet-after-kidney recipients with type I diabetes in the CITR were analyzed for five primary efficacy outcomes and overall safety to identify any differences by early (1999-2002), mid (2003-2006), or recent (2007-2010) transplant era based on annual follow-up to 5 years. Insulin independence at 3 years after transplant improved from 27% in the early era (1999-2002, n = 214) to 37% in the mid (2003-2006, n = 255) and to 44% in the most recent era (2007-2010, n = 208; P = 0.006 for years-by-era; P = 0.01 for era alone). C-peptide  $\geq 0.3$  ng/mL, indicative of islet graft function, was retained longer in the most recent era (P < 0.001). Reduction of HbA(1c) and resolution of severe hypoglycemia exhibited enduring long-term effects. Fasting blood glucose stabilization also showed improvements in the most recent era. There were also modest reductions in the occurrence of adverse events. The islet reinfusion rate was lower: 48% by 1 year in 2007-2010 vs. 60-65% in 1999-2006 (P < 0.01). Recipients that ever-achieved insulin-independence experienced longer duration of islet graft function (P < 0.001). The authors concluded the CITR shows improvement in primary efficacy and safety outcomes of islet transplantation in recipients who received transplants in 2007-2010 compared with those in 1999-2006, with fewer islet infusions and adverse events per recipient.

Other small case series have reported some success and also adverse events. For example, O'Connell et al. (2013) reported on 17 patients with type I diabetes with severe hypoglycemia who underwent allogeneic islet transplantation. The aim of this single-arm, multicenter study was to evaluate an immunosuppressive protocol of initial antithymocyte globulin (ATG), tacrolimus and mycophenolate mofetil (MMF) followed by switching to sirolimus and MMF. Islets were cultured for 24 h prior to transplantation. The primary endpoint was an HbA1c of <7% and cessation of severe hypoglycemia. Seventeen recipients were followed for  $\geq 12$  months. Nine islet preparations were transported interstate for transplantation. Similar outcomes were achieved at all three centers. Fourteen of the 17 (82%) recipients achieved the primary endpoint. Nine (53%) recipients achieved insulin independence for a median of 26 months (range 7-39 months) and 6 (35%) remain insulin independent. All recipients were C-peptide positive for at least 3 months. All subjects with unstimulated C-peptide >0.2 nmol/L had cessation of severe hypoglycemia. Nine of the 17 recipients tolerated switching from tacrolimus to sirolimus with similar graft outcomes. There was a small but significant reduction in renal function in the first 12 months. The combination of islet culture, ATG, tacrolimus and MMF is a viable alternative for islet transplantation. Most adverse events were related to immunosuppression. Seven (41%) of the 17 patients developed mild lymphopenia and 1 developed clostridium difficile colitis; all responded to treatment. Eight patient developed anemia shortly after transplant and one required a blood transfusion. Procedure-related complications included 1 portal vein thrombosis and 3 postoperative bleeds; 2 of the bleeds required transfusion.

(2011) Thompson et al. published findings from a prospective, crossover, cohort study comparing allogeneic islet cell transplantation (ICT) with intensive medical therapy on the progression of diabetic neuropathy, retinopathy, and neuropathy. The study included 45 patients; at the time of data analysis, 32 had received islet cell transplants. Median follow-up was 47 months pretransplant and 66 months post-transplant. The overall HbA1C level was 7.8% pretransplant and 6.7% post-transplant ( $p < 0.001$ ). In the 16 patients for whom sufficient pre and post-transplant data were available on renal outcomes, the median decline in glomerular filtration rate was  $-6.7 \text{ mL/min/1.73 m}^2/\text{y}$  pretransplant and  $-1.3 \text{ mL/min/1.73 m}^2/\text{y}$  posttransplant ( $p = 0.01$ ). Retinopathy was assessed using a scale that categorized nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 (12%) of 82 eyes pretransplant versus 0 of 51 post-transplant ( $p < 0.01$ ). The authors concluded, the rate of decline in glomerular filtration rate is slower after ICT than on medical therapy. There was significantly more progression of retinopathy in medically treated patients than post ICT. There was a nonsignificant trend for improved nerve conduction velocity post ICT. Islet cell transplantation is associated with less progression of microvascular complications than intensive medical therapy which might have been due in part to the choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil. Multicenter randomized trials are needed to further study the role of ICT in slowing the progression of diabetic complications.

### **Prospective Trials**

Two prospective, Phase 3, single-arm, open-label, multicenter trials of purified human pancreatic islet cell transplant have been conducted in North America under the guidance of the National Institutes of Health-sponsored Clinical Islet Transplantation (CIT) Consortium. Hering et al. (2016) studied 48 patients with type 1 diabetes, hypoglycemic unawareness, and a history of experiencing severe hypoglycemic events (Protocol CIT07). The primary outcome (HbA1c level  $\leq 7\%$  and freedom from severe hypoglycemia after 1 year) was achieved in 87.5% and 71% of patients at 1 and 2 years. Median HbA1c level decreased from 7.2% at baseline to 5.6% at 1 and 2 years (both  $p < .001$ ). Only 2 patients experienced severe hypoglycemia in the first year posttransplant. Insulin independence was achieved in 52.1% of patients at 1 year, and median insulin use decreased from 0.49 units/kg/day at baseline to 0 units/kg/day at 1 year ( $p < .0003$ ). Glomerular filtration rate decreased posttransplant ( $p < .0008$  vs. baseline) due to adverse effects of immunosuppression. Twenty-two serious adverse events during the first year were attributed to the procedure or subsequent immunosuppression.

(2021) Markmann et al. conducted a similar trial in 24 patients with type 1 diabetes and hypoglycemic unawareness who had previously received a kidney transplant (Protocol CIT06). The primary outcome (HbA1c level  $\leq 6.5\%$  or a reduction in HbA1c level of at least 1% and freedom from severe hypoglycemia after 1 year) was achieved by 62.5% of patients. At 2 and 3 years, 58.3% and 45.8% had achieved these glycemic targets. Severe hypoglycemia was eliminated in 79.2% of patients at 1 year, 75% at 2 years, and 62.5% at 3 years. Median insulin requirements decreased from 0.5 units/kg/day at baseline to 0 units/kg/day at 1, 2, and 3 years ( $p < .001$ ,  $p < .001$ , and  $p = .002$ , respectively). Kidney

function remained stable throughout follow-up. Thirteen serious adverse events were considered related or possibly related to islet transplant or immunosuppression.

(2011) Thompson et al. in Canada published findings from a prospective crossover study of intensive medical therapy (pretransplant) versus islet cell transplantation in patients with type 1 diabetes. The article reported on 45 patients; at the time of data analysis, 32 had received islet cell transplants. Median follow-up was 47 months pretransplant and 66 months posttransplant. The overall mean HbA1c level was 7.8% pretransplant and 6.7% posttransplant ( $p < .001$ ). In the 16 patients for whom sufficient pre- and posttransplant data were available on renal outcomes, the median decline in glomerular filtration rate was  $-6.7 \text{ mL/min/1.73 m}^2/\text{year}$  pretransplant and  $-1.3 \text{ mL/min/1.73 m}^2/\text{year}$  posttransplant ( $p = .01$ ). Retinopathy was assessed using a scale that categorized nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 (12%) of 82 eyes pretransplant versus 0 of 51 posttransplant ( $p < .01$ ). (The numbers of patients in the retinopathy analyses were not reported.) The authors noted that their finding of reduced microvascular complications after islet transplantation might have been due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil.

### **Case Series**

Other small case series have reported some success and also adverse events. Lemos et al. (2021) reported 20-year results for a retrospective series of 49 patients with type 1 diabetes, hypoglycemic unawareness, and severe hypoglycemia who underwent islet transplant. Median follow-up time after transplant was 13.8 years. Median duration of graft function while on immunosuppression was 4.4 years (interquartile range, 1.3 to 12.2 years). Kaplan-Meier survival analysis showed cumulative survival of  $>80\%$  at 20 years; 2 patients died during follow-up, 1 from myocardial infarction and 1 from suspected hypoglycemia.

In another case series, O'Connell et al. (2013) reported on 17 patients with type 1 diabetes and severe hypoglycemia who underwent islet transplantation in Australia. Fourteen (82%) patients attained the primary endpoint, which was an HbA1c level of less than 7% and no severe hypoglycemic events 2 months after the initial transplant. Nine (53%) patients attained insulin independence for a median of 26 months. Most adverse events were related to immunosuppression. Seven (41%) of the 17 patients developed mild lymphopenia and 1 developed *Clostridium difficile* colitis; all responded to treatment. Eight patients developed anemia shortly after transplant and 1 required a blood transfusion. Procedure-related complications included 1 partial portal vein thrombosis and 3 postoperative bleeds; 2 of the bleeds required transfusion.

### **Section Summary: Type I Diabetes**

Allogeneic islet transplantation has been investigated in the treatment of type I diabetes. One randomized controlled trial (RCT) found the quality of life (QOL) was significantly improved after islet transplantation; however, the short length of follow-up limits these conclusions. Evidence from registry studies and systematic reviews has demonstrated

varying ranges of insulin independence post-transplantation. There is conflicting evidence that allogeneic islet transplantation reduces long-term diabetic complications. Long term comparative studies are needed to determine the effects of allogeneic islet transplantation in type 1 diabetic and post-transplant immunosuppression.

### **Summary of Evidence**

For individuals with chronic pancreatitis undergoing total or near-total pancreatectomy who receive autologous pancreas islet transplantation, the evidence includes nonrandomized studies and systematic reviews. Relevant outcomes are OS, change in disease status, medication use, resource utilization, and treatment-related morbidity. Autologous islet transplants are performed in the context of total or near-total pancreatectomies to treat intractable pain from chronic pancreatitis. The procedure appears to significantly decrease the incidence of diabetes after total or near-total pancreatectomy in patients with chronic pancreatitis. Also, the autologous islet cell transplant procedure is not associated with serious complications itself and is performed in patients who are already undergoing a pancreatectomy procedure. The evidence is sufficient to determine autologous islet cell transplantation results in a meaningful improvement in net health outcomes.

For individuals with type I diabetes who receive allogeneic pancreas islet transplantation, the evidence includes a randomized controlled trial (RCT), single-arm prospective studies, registry studies, and systematic reviews. Results of the 2018 randomized trial have suggested some reduction in the number of severe hypoglycemic incidence annually, but limited follow-up and other trial limitations reduce the certainty in conclusions drawn. A wide range of insulin dependence has been reported in single-arm prospective studies and case series. There is conflicting evidence whether allogeneic islet transplantation reduces long-term diabetic complications. Long-term comparative studies are required to determine the effects of allogeneic islet transplantation in type I diabetics. The evidence is insufficient to determine the effects of allogeneic pancreatic islet transplantation on net health outcomes.

### **Practice Guidelines and Position Statements**

#### **American Diabetes Association (ADA)**

(2022) The American Diabetes Association standards of medical care recommended autologous islet cell transplantation be considered in patients undergoing total pancreatectomy for chronic pancreatitis to prevent postsurgical diabetes. The standards of care note that islet cell transplantation may have a role in type 1 diabetes; however, it is considered experimental and improved blood glucose monitoring technology may be a better alternative. Because of the need for immunosuppressive agents post transplantation, the guideline notes that transplantation in type 1 diabetes should be reserved for patients also undergoing renal transplantation or experiencing recurrent ketoacidosis with severe hypoglycemia despite intensive management. (*Accessed September 2022*)



## **International Consensus Guidelines for Chronic Pancreatitis**

In 2020, the International Consensus Guidelines for Chronic Pancreatitis panel released a statement on the role of total pancreatectomy and islet transplant in patients with chronic pancreatitis. The panel stated that islet transplant should be considered for patients undergoing total pancreatectomy due to the potential for insulin independence and better long-term glycemic outcomes compared to pancreatectomy alone (weak recommendation based on low quality evidence). However, there is not enough information to definitively conclude when transplant should be performed relative to other interventions. Major indications for pancreatectomy with islet transplant include debilitating pain or recurrent pancreatitis episodes that diminish quality of life (strong recommendation based on low quality evidence). Contraindications to pancreatectomy with islet transplant include active alcoholism, pancreatic cancer, end-stage systemic illness, or psychiatric illness or socioeconomic status that would hinder either the procedure itself or posttransplant care (strong recommendation based on low quality evidence). Pancreatectomy with islet transplant improves quality of life, opioid use, and pancreatic pain in this population, but evidence about the effect on healthcare utilization is limited. (*Accessed September 2022*)

## **Organ Procurement and Transplantation Network (OPTN)**

### **Islet Registration Status**

(2022) The following is the allocation policy of the Organ Procurement and Transplantation Network (OPTN) for the allocation of islet cells.

### **Islet Registration Status**

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:

- Is insulin dependent
- Has a hemoglobin A1c (HcA1c) value greater than 6.5%

An islet candidate that does not meet either of these requirements above must have an inactive status on the waiting list. If the transplant hospital changes a candidate's status from inactive to active, the transplant hospital must document that the candidate met one of the above requirements.

If a candidate's clinical condition changes and the candidate becomes inactive, the transplant hospital must report this to the OPTN Contractor within 72 hours of the transplant hospital's knowledge of this change. The transplant hospital must document in the candidate's medical record when the transplant hospital learned of this change.

If the candidate is active and is insulin independent, then the transplant hospital must document in the candidate's medical record the candidate's insulin status and HbA1c value. The transplant hospital must use the most recent HbA1c test performed within the last six months when determining whether the candidate meets the criteria for active status. (*Accessed September 2022*)

## Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Allogeneic islet cells are included in these regulations. (*Accessed October 2021*)

## PRIOR APPROVAL

Not applicable.

## POLICY

See Related Medical Policy:

- [07.03.09 Pancreas Transplants \(Including Simultaneous Pancreas-Kidney, Pancreas alone, and Pancreas after Kidney\)](#)

### Autologous Pancreas Islet Cell Transplantation

Autologous pancreas islet cell transplantation may be considered **medically necessary** as an adjunct to a total or near-total pancreatectomy in patients with chronic pancreatitis.

Autologous pancreas islet cell transplantation is considered **investigational** when the above criteria is not met and for all other indications as the evidence is insufficient to determine the effects on net health outcomes.

### Allogeneic Pancreas Islet Cell Transplantation

Allogeneic pancreas islet cell transplantation is considered **investigational** for all indications including the treatment of type 1 diabetes as the evidence is insufficient to determine the effects on net health outcomes.

## PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT\* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 48160 Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells.
- 48999 unlisted procedure, pancreas (when specified as pancreatic islet cell transplantation)
- 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
- 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
- S2102 Transplant, islet cell tissue, allogeneic

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<b>POLICY HISTORY</b>		
<b>Date</b>	<b>Reason</b>	<b>Action</b>
October 2022	Annual Review	Policy Renewed
October 2021	Annual Review	Policy Renewed
October 2020	Annual Review	Policy Renewed
October 2019	Annual Review	Policy Renewed
October 2018	Annual Review	Policy Revised
October 2017	Annual Review	Policy Renewed
October 2016	Annual Review	Policy Renewed
November 2015	Annual Review	Policy Renewed
December 2014	Annual Review	Policy Revised
February 2014	Annual Review	Policy Revised
March 2013	Annual Review	Policy Renewed
July 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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