7.03.12	Islet Transplantation		
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Section:	7.0 Surgery	**Page:**	Page 1 of 19

Policy Statement

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

Allogeneic islet transplantation is considered **investigational** for the treatment of type 1 diabetes.

Islet transplantation is considered **investigational** in all other situations.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

Coding
CPT code 48160 explicitly describes autologous pancreas islet cell transplantation at the time of pancreatectomy. CPT instructs the use of code 48999 (unlisted procedure, pancreas) for transplantation of islet cells as a stand-alone procedure.

Three HCPCS codes are specific to these procedures:

- **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

Description

Performed in conjunction with pancreatectomy for chronic pancreatitis, autologous islet transplantation is proposed to reduce the likelihood of insulin-dependent diabetes. Allogeneic islet cell transplantation is also being investigated as a treatment or cure for patients with type 1 diabetes.

Related Policies

- Allogeneic Pancreas Transplant
- Chronic Intermittent Intravenous Insulin Therapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the

contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The U.S. Food and Drug Administration 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.

Rationale

Background

Islet Transplantation

In autologous islet transplantation during the pancreatectomy procedure, 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.

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 3 donor pancreas transplants may be required to achieve insulin independence. However, a limitation of islet transplantation is that 2 or more donor organs are usually required for successful transplantation, although experimentation with single-donor transplantation is occurring. A pancreas that is rejected for whole-organ transplant is typically used for islet transplantation. Therefore, 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. Allogeneic transplantation may be performed in the radiology department.

In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen is known as the "Edmonton protocol."

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Chronic Pancreatitis

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.

Populations

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.

Comparators

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

Outcomes

The general outcomes of interest are overall survival (OS), insulin independence, change in disease status, medication use, resource utilization, and treatment-related morbidity.
Short-term follow-up (30 days) is required to monitor for transplant-related complications; long-term follow-up—1 to 3, 5, or even 10 years—is required to establish the durability of glucose control.[3]

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. Zhang et al (2020) 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.[4] 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^2=32.3%) at 1 year (8 studies). Mortality at 30 days was 1.32% (95% CI, 0.68 to 2.16; I^2=0.0%) and mortality at 1 year was 2.54% (95% CI, 1.32 to 4.16; I^2=17.6%).

Kempeneers et al (2019) published a systematic review of studies examining pain, endocrine function, or quality of life outcomes in patients with chronic pancreatitis undergoing total pancreatectomy with islet transplantation.[5] A total of 15 studies met the inclusion criteria. All included studies were retrospective and observational. The median age was 41 years. Pooled insulin free rate was 30% (95% CI, 20% to 43%) at 1 year (4 studies). The pooled mortality rate was 2% (95% CI, 1% to 4%) at 30 days (11 studies) and 4% at 1 year (6 studies). At 1 year, 63% (95% CI, 46% to 77%, I^2=89%) of patients were opioid free (6 studies, 657 patients). An analysis revealed a high risk for publication bias among the included studies, which could have led to an overestimation of the true effect.

Wu et al (2015) published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis.[6] Studies could use any design type but had to include at least 5 patients or have a median follow-up of at least 6 months. Twelve studies (N=677 patients) met reviewers' inclusion criteria. The mean age was 38 years and the mean duration of pancreatitis was 6.6 years. A meta-analysis of the insulin-independence rate at 1 year (5 studies, 362 patients) was 28.4% (95% CI, 15.7% to 46.0%). At 2 years, the pooled insulin-independence rate (3 studies, 297 patients) was 19.7% (95% CI, 5.1% to 52.6%). The pooled 30-day mortality rate (11 studies) was 2.1% (95% CI, 1.2% to 3.8%). Long-term mortality data were not pooled.

Dong et al (2011) published a systematic review that included studies irrespective of design or sample size.[7] 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 provides a crosswalk of studies included in the systematic reviews discussed. Tables 2 and 3 provide the characteristics and results of these systematic reviews.

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

Study	Zhang et al (2020)[4]	Kempeneers et al (2019)[5]	Wu et al (2015)[6]	Dong et al (2011)[7]
Cameron et al (1981)[8]	●		●	●
Hinshaw et al (1981)[9]	●		●	●
Toledo-Pereyra et al (1983)[10]				●
Fontana et al (1994)[11]				●
Rastellini et al (1997)[12]	●		●	●
Jindal et al (1998)[13]				●
Rabkin et al (1999)[14]				●
Oberholzer et al (2000)[15]	●		●	●
Berney et al (2004)[16]				●
Ahmad et al (2005)[17]			●	●
Argo et al (2008)[18]	●	●	●	●
Dixon et al (2008)[19]	●	●	●	●
Sutherland et al (2008)[20]				●
Webb et al (2008)[21]				●
Jung et al (2009)[22]				●

Takita et al (2010)[23.]		●	●
Sutherland et al (2012)[24.]	●		●
Walsh et al (2012)[25.]	●	●	●
Dorlon et al (2013)[26.]			●
Garcea et al (2013)[27.]	●	●	●
Gruessner et al (2014)[28.]	●	●	
Wilson et al (2014)[29.]		●	
Chinnakotla et al (2015)[30.]		●	
Georgiev et al (2015)[31.]		●	
Takita et al (2015)[32.]		●	
Tai et al (2015)[33.]	●		
Wilson et al (2015)[34.]	●		
Mokadem et al (2016)[35.]	●	●	
Shahbazov et al (2016)[36.]		●	
Fan et al (2017)[37.]		●	
Quartuccio et al (2017)[38.]	●		
Shahbazov et al (2017)[36.]	●		
Solomina et al (2017)[39.]	●	●	
Morgan et al (2018)[40.]	●	●	

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

Study	Dates	Trials	Participants	N (Range)	Design	Duration, mo
Zhang et al (2020)[4.]	1977-2018	17	Individuals with chronic pancreatitis	1024 (5-409)	Observational	1-210
Kempeneers et al (2019)[5.]	1977-2017	15	Individuals with chronic pancreatitis	1255 (7-490)	Observational	6-138
Wu et al (2015)[6.]	1977-2014	12	Individuals with chronic pancreatitis	677 (5-409)	Case series	1-210
Dong et al (2011)[7.]	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)[4.]		
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)[5.]		
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)[6.]		
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

I^2, %	69	NR
n	297	NR
2-year follow-up (95% CI)	19.7 (5.1 to 52.6)	NR
I^2, %	87	NR
Dong et al (2011)[7.]		
n	NR	176
30-day follow-up (95% CI)	NR	5 (2 to 10)
I^2, %	NR	0
n	221	NR
1-year follow-up (95% CI)	27 (21 to 33)	NR
I^2, %	NR	NR
n	201	NR
2-year follow-up (95% CI)	21 (16 to 27)	NR
I^2, %	NR	NR

CI: confidence interval; NR: not reported

Nonrandomized Studies

Wilson et al (2014) reported on 166 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single-center.[29.] Actutimes 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 this improved to 73% at 5 years.

Chinnakotla et al (2014) included 484 patients with chronic pancreatitis who underwent total pancreatectomy and immediate islet autotransplantation.[3.] The 10-year survival rate was 84%. Patient survival at 5 years was 90.3% in the 80 patients with hereditary/genetic pancreatitis and 89.7% in the 404 patients with nonhereditary pancreatitis; the difference between groups was not statistically significant. Pancreatitis pain decreased significantly after the procedures, and there was no statistically significant difference in the rate of pancreatitis pain between the groups.

Sutherland et al (2012) reported on 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single-center.[24.] Fifty-three (13%) of the 409 patients were children between the ages of 5 and 18 years. Actutimes survival postsurgery was 96% in adults and 98% in children after 1 year and 89% in adults and 98% in children after 5 years. A total of 15.9% of patients experienced surgical complications requiring reoperation during the initial admission. The most common reason for reoperation was bleeding, occurring in 9.5% of patients. At 3 years, 30% of patients were insulin-independent (25% of adults, 55% of children). A survey of quality of life outcomes was initiated in 2008; responses were available for 102 patients. At baseline, all 102 patients reported using opioid analgesia for pain control. At 12 months, the proportion of patients on narcotics decreased to 56% (n=32), and at 24 months, 41% of respondents (n=21) reported using narcotics.

Tables 4 and 5 provide the characteristics and results of the nonrandomized studies assessed.

Table 4. Summary of Key Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	FU, y
Wilson et al (2014)[29.]	Cohort	U.S.	2000-2013	Individuals with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=166)	≥5
Chinnakotla et al (2014)[3.]	Cohort	U.S.	1977-2012	Individuals with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=484)	NR
Sutherland et al (2012)[24.]	Cohort	U.S.	1977-2011	Individuals with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=409)	NR

FU: follow-up; NR: not reported.

Table 5. Summary of Key Nonrandomized Study Results

Study	Survival Rate, %		Insulin-Independence Rate, %		
	1-Year	5-Year	1-Year	3-Year	5-Year
Wilson et al (2014)[29.]	98.2	94.6	38	NR	27
Chinnakotla et al (2014)[3.]					
Hereditary/genetic pancreatitis		90.27	20.0	NR	NR
Nonhereditary pancreatitis		89.72	32.9	NR	NR
p		.166	.022		
Sutherland et al (2012)[24.]	97	90	26	30	NR

NR: not reported.

Section Summary: Chronic Pancreatitis
Autologous islet transplantation is frequently performed as an adjunct to a total or near-total pancreatectomy 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 1 Diabetes
Clinical Context and Therapy Purpose
The purpose of allogeneic pancreas islet transplantation for patients who have type 1 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.

Populations
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.[41.]

Interventions
The therapy being considered is allogeneic pancreas islet transplantation.

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
The general outcomes of interest are 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 RCTs for evaluating the safety and efficacy of islet cell products in patients with metabolically unstable type 1 diabetes.[42.] Attainment of a normal hemoglobin A_{1c} (HbA_{1c}) range (i.e., ≤6.5%) and elimination of hypoglycemia are acceptable primary endpoints. To assess the durability of the islet cell procedure, primary endpoints should be measured at least 12 months after the final infusion. Other key clinical outcomes include insulin independence, measures of glucose metabolic control such as fasting plasma glucose level, 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

A systematic review by Health Quality Ontario (2015) reported on islet transplantation for patients with type 1 diabetes.[43] Case series derived from single-centers constitutes most of the evidence. For nonuremic patients, rates of insulin independence ranged from 30% to 70% from observational case series at 1 year after islet transplantation. For uremic patients, reported insulin-independence rates ranged from 20% to 67%. Evidence of changes in secondary complications such as diabetic retinopathy and nephropathy were conflicting across different studies.

A TEC Assessment (2004) evaluated the evidence on islet cell transplantation in type 1 diabetes.[44] The Assessment found that published data on clinical outcomes of islet-alone transplantation were limited by small sample sizes (i.e., ≤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 posttransplantation lymphoproliferative disease have been reported for islet-alone transplantation.

Randomized Controlled Trials

Lablanche et al (2018) published a multicenter, open-label, RCT (TRIMECO trial) evaluating patients who had type 1 diabetes with severe hypoglycemia or after kidney transplantation.[45] Patients received immediate islet transplantation (n=25) or intensive insulin therapy followed by delayed islet transplantation (n=22). Median follow-up was 6 months for both groups. The primary endpoint was a composite score (β score), which has not been validated and which reflected fasting glucose, HbA_{1c} level, C-peptide, and insulin independence. At 6 months, 16 of 25 patients in the immediate transplantation group and none of 22 patients in the control group had a modified β score of 6 or higher (p<.001). Of note, few patients in the insulin group used continuous glucose monitoring or other technologies to monitor for hypoglycemia. At 6 months, insulin independence was achieved in 44% of patients in the immediate transplantation group (n=25; p<.001). After the entire cohort received islet transplantation, the 1-year insulin independence rate was 59% (n=46; p<.001). Subsequent to islet transplantation, 6% of patients had bleeding complications. Trial limitations included possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability.

Registry Studies

LaBlanche et al (2021) 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.[46] Thirty one patients were still being followed at 10 years; 6 patients died between years 1 and 10 posttransplant. Median HbA_{1c} 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.[47] Three years after the first cell infusions, 23% of islet-alone recipients were insulin-independent (defined as insulin-independent ≥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 HbA_{1c} levels, processing centers related to the transplant center, and larger islet size.

Barton et al (2012) updated the Collaborative Islet Transplant Registry report, which focused on changes in outcomes over time.[48] The number of patients receiving islet transplants was 214 from 1999 to 2002, 255 between mid-2003 and 2006, and 208 from 2007 to 2010. A total of 575 (85%) of the 677 islet transplant recipients received islets only; the remainder underwent simultaneous kidney and islet transplants. In the 1999 to 2002 group, rates of insulin independence were 51% after 1 year, 36% after 2 years, and 27% after 3 years. Rates for the 2007 to 2010 group were 66%, 55%, and 44%, respectively. The incidence of clinically reportable adverse events in the first year after infusion decreased from a range of 50% to 53% in 1999 to 2006 to 38% in 2007 to 2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999 to 2003 and 3.1% in 2007 to 2010. The authors did not report findings separately for the subset of patients who underwent islet-only transplants.

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.[49,50] Hering et al (2016) studied 48 patients with type 1 diabetes, hypoglycemic unawareness, and a history of experiencing severe hypoglycemic events (Protocol CIT07).[49] The primary outcome (HbA_{1c} level ≤7% and freedom from severe hypoglycemia after 1 year) was achieved in 87.5% and 71% of patients at 1 and 2 years. Median HbA_{1c} 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.

Markmann et al (2021) conducted a similar trial in 24 patients with type 1 diabetes and hypoglycemic unawareness who had previously received a kidney transplant (Protocol CIT06).[50] The primary outcome (HbA_{1c} level ≤6.5% or a reduction in HbA_{1c} 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.

Thompson et al (2011) in Canada published findings from a prospective crossover study of intensive medical therapy (pretransplant) versus islet cell transplantation in patients with type 1 diabetes.[41] 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 HbA_{1c} 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 mL/min/1.73 m^2/year pretransplant and -1.3

mL/min/1.73 m^2/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.[51,52,53,54.] 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.54, 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.[52.] Fourteen (82%) patients attained the primary endpoint, which was an HbA_{1c} 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 1 Diabetes
Allogeneic islet transplantation has been investigated in the treatment of type 1 diabetes. One RCT found that quality of life was significantly improved after islet transplantation; however, the short length of follow-up limits these conclusions. Evidence from registry studies, single-arm prospective studies, and systematic reviews has demonstrated varying ranges of insulin independence posttransplantation. There is conflicting evidence that allogeneic islet transplantation reduces long-term diabetic complications. Long-term comparative studies are required to determine the effects of allogeneic islet transplantation in type 1 diabetics and posttransplant 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 decrease significantly the incidence of diabetes after total or near-total pancreatectomy in patients with chronic pancreatitis. Also, this islet procedure is not associated with serious complications and is performed in patients who are already undergoing a pancreatectomy procedure. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with type 1 diabetes who receive allogeneic pancreas islet transplantation, the evidence includes an RCT , single-arm prospective studies, registry studies, and systematic reviews. Relevant outcomes are OS, change in disease status, medication use, resource utilization, and treatment-related morbidity. Results of a 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 independence has been reported in single-arm prospective studies and case series. There is conflicting evidence on whether allogeneic islet transplantation reduces long-term diabetic complications. Long-term comparative studies are required to determine the effects of allogeneic islet transplantation in patients with type 1 diabetes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.[50] Key findings and recommendations are summarized in Table 6.

Table 6. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

	Content Area	Key Point
1	Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2	Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV "positive" organs
3	Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4	OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5	Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2008, NICE published guidance indicating the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes has shown that serious procedure-related complications may occur, and the long-term immunosuppression required is associated with risk of adverse events.[55.] A related 2008 guidance addressed autologous islet cell transplantation for improved glycemic control after pancreatectomy and stated that studies have shown "some short-term efficacy, although most patients require insulin therapy in the long term... complications result mainly from the major surgery involved in pancreatectomy (rather than from the islet cell transplantation)."[56.]

American Diabetes Association

In 202 1, 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.[57.] 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.[58.] Because of the need for immunosuppressive agents posttransplantation, 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.

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.[59] 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.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Medicare covers pancreatic islet transplantation in patients with type 1 diabetes participating in a clinical trial sponsored by the National Institutes of Health.[60] Partial pancreatic tissue transplantation or islet transplantation performed outside a clinical trial are not covered.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 7

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04711226	An Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of Immunomodulation With AT-1501 in Adults With Type 1 Diabetes Undergoing Islet Cell Transplant	12	June 2026
NCT00160732	Allogenic Islet Cell Transplantation	50	Oct 2025
NCT00706420	Islet Transplantation Alone (ITA) in Patients With Difficult to Control Type I Diabetes Mellitus Using a Glucocorticoid-free Immunosuppressive Regimen	20	Dec 202 1
NCT00306098	Islet Cell Transplantation Alone in Patients With Type 1 Diabetes Mellitus: Steroid-Free Immunosuppression	40	May 202 3
NCT01909245	Islet Cell Transplant for Type 1 Diabetes (TCD)	20	Jul 202 6
NCT01974674	Allogeneic Islet Transplantation for the Treatment of Type 1 Diabetes (GRIIF)	19	Jan 2022
NCT03698396	Islet Transplant in Patients with Type 1 Diabetes	10	Dec 2023
NCT01897688	A Phase 3 Single Center Study of Islet Transplantation in Non-uremic Diabetic Patients	40	Mar 2027
NCT00679042	Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol	50	Dec 2023

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Nephrology consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Chest x-ray (CXR) and other radiology reports (when applicable)
- Colonoscopy report if > 50 years of age
- Cardiology procedures and pulmonary function reports:
  - EKG
  - Cardiac echocardiogram, stress test, and cardiac catheterization (if needed)
  - Pulmonary function tests (PFTs)

- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
	48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells
	48999	Unlisted procedure, pancreas
HCPCS	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	Islet cell tissue transplant from pancreas; allogeneic

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2017	BCBSA Medical Policy Adoption
10/01/2018	Policy revision without position change
10/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Literature review updated. Coding update.
10/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional

standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Islet Transplantation 7.03.12 **Policy Statement:** Autologous pancreas islet transplantation may be considered **medically necessary** as an adjunct to a total or near-total pancreatectomy in patients with chronic pancreatitis. Allogeneic islet transplantation is considered **investigational** for the treatment of type 1 diabetes. Islet transplantation is considered **investigational** in all other situations. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.	**Islet Transplantation 7.03.12** **Policy Statement:** Autologous pancreas islet transplantation may be considered **medically necessary** as an adjunct to a total or near-total pancreatectomy in patients with chronic pancreatitis. Allogeneic islet transplantation is considered **investigational** for the treatment of type 1 diabetes. Islet transplantation is considered **investigational** in all other situations. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.