Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/23**
(See policy history boxes for previous effective dates)

Title: Islet Transplantation

Description/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 was developed in Edmonton, Canada and is known as the "Edmonton protocol." Nevertheless, allogenic islet transplantation has not gained wide acceptance and has generally been limited to patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin based management.

Regulatory Status:

Islet cells are subject to regulation by the U.S. Food and Drug Administration (FDA), which classifies allogeneic islet cell transplantation as somatic cell therapy, requiring premarket approval. Islet cells also meet the definition of a drug under the federal Food, Drug, and Cosmetic Act. Clinical studies to determine safety and effectiveness outcomes of allogeneic islet transplantation must be conducted under FDA investigational new drug regulation. While at least 35 investigational new drug applications have been submitted to the FDA, no center has submitted a biologics license application.

Medical Policy Statement

The safety and effectiveness of *autologous* islet cell transplantation have been established. It may be considered a useful therapeutic option when indicated.

Allogeneic islet cell transplantation for the treatment of type 1 diabetes is experimental/ investigational. Its safety and effectiveness for this indication have not been established.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Autologous islet cell transplantation as an adjunct to a total or near total pancreatectomy or partial pancreatectomy in individuals with chronic pancreatitis.

Exclusions:
- *Autologous* or *allogeneic* islet cell transplantation in individuals in all other situations.
- *Allogeneic* islet cell transplantation for the treatment of type I diabetes.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

48160 G0341 G0342 G0343 0584T 0585T 0586T

Other codes (investigational, not medically necessary, etc.):

S2102

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs 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** were 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, 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 durability of glucose control.[5]

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 longer 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; I2=32.3%) at 1 year (8 studies). Mortality at 30 days was 1.32% (95% CI, 0.68 to 2.16; I2=0.0%) and mortality at 1 year was 2.54% (95% CI, 1.32 to 4.16; I2=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% confidence interval [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 affect.

In 2015, Wu et al published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis.[6] Studies could use any type of design but needed to include at least 5 patients or have a median follow-up of at least 6 months. Twelve studies with a total of 677 patients met the review's inclusion criteria. The mean age of the patients was 38 years and 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% confidence interval

[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.

In 2011, Dong et al published a systematic review that included meta-analyses.[7] Studies were included regardless of design or sample size. After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, 2 studies of partial pancreatectomy, and 2 studies that 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 was 5% (95% confidence interval [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 at 1 year (5 studies) was 27% (95% CI: 21-33%) and at 2 years (3 studies) was 21% (95% CI: 16-27%).

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 the Systematic Reviews

Study	Zhang et al (2020)[4]	Wu et al (2015)[3]	Dong et al (2011)[4]	Kempeneers et al (2019)[2]
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)[33]	•			•
Wilson et al (2015)[34]	•			•
Mokadem et al (2016)	•			•
Shahbazov et al (2016)				

Fan et al (2017)			
Quartuccio et al (2017)[38]	•		
Shahbazov et al (2017)[39]	•		
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
Zhange 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)
I2, %	32.3	17.6
Kempeneers et al (2019)[5]		
n	NR	1036
I^2, %	NR	2 (1 to 4)
n	NR	35
1-year follow-up (95% confidence interval)	30 (20 to 43)	4 (2 to 6)
I^2, %	82	0
n	NR	NR
2-year follow-up (95% confidence interval)	NR	NR
I^2, %	NR	NR
Wu et al (2015)[6]		
n		672
30-day follow-up (95% confidence interval)		2.1 (1.2 to 3.8)
I^2, %		0
n	362	
1-year follow-up (95% confidence interval)	28.4 (15.7 to 46.0)	
I^2, %	69	
n	297	
2-year follow-up (95% confidence interval)	19.7 (5.1 to 52.6)	
I^2, %	87	
Dong et al (2011)[7]		

n		176
30-day follow-up (95% confidence interval)		5 (2 to 10)
I^2, %		0
n	221	
1-year follow-up (95% confidence interval)	27 (21 to 33)	
I^2, %	NR	
n	201	
2-year follow-up (95% confidence interval)	21 (16 to 27)	
I^2, %	NR	

CI=confidence interval; NR=not reported

Nonrandomized Studies

In 2014, Wilson et al reported on 166 patients age 14 or older with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center.[29] Actuarial survival at 5 years was 94.6%. Five year or longer data were available for 112 patients (67%). At 1 year, 38% of patients were insulin dependent 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 narcotic independent at 1 year, and this increased to 73% at 5 years.

A 2014 study by Chinnakotla et al included 484 patients with chronic pancreatitis.[3] Patients underwent total pancreatectomy and immediate islet auto transplantation. Actuarial 10-year survival 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 with and without genetic/hereditary disease.

In 2012, Sutherland et al reported on 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center.[24] Fifty-three of 409 patients (13%) were children between the ages of 5 and 18 years. Actuarial survival post-surgery 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 and 55% of children). A survey of quality-of-life outcomes was initiated in October 2008; responses were available for 102 patients. At baseline, all 102 patients reported using narcotics for pain. 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	F/U, 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

F/U: 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		0.166	0.022		
Sutherland et al (2012)[24]	97	90	26	30	NR

NR: Not reported

Section Summary: Chronic Pancreatitis

Autologous islet transplantation is frequently performed in cases of 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 total or near total 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** were 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.[35]

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 overall survival, 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 end points. To assess the durability of the islet cell procedure, primary end points 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 longer 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.

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.

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 post-transplantation 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 end point 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 ($p<0.001$). 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; $p<0.001$). After the entire cohort received islet transplantation, the 1-year insulin independence rate was 59% (n=46; $p<0.001$). 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 $\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 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 1999-2002 group, rates of insulin independence were 51% after 1 year, 36% after 2 years, and 27% after 3 years. Rates for the 2007-2010 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 1999-2006 to 38% in 2007-2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999-2003 and 3.1% in 2007-2010. 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 (HbA1c 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 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.

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) vs. 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 post-transplant. The overall mean HbA_{1c} level was 7.8% pretransplant and 6.7% post-transplant (p<0.001). 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/y pretransplant and -1.3 mL/min/1.73 m^2/y post-transplant (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 vs. 0 of 51 post-transplant (p<0.01). (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.[51-54] 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 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 one required a blood transfusion. Procedure-related complications included 1 partial portal vein thrombosis and 3 post-operative 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 case series 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 required to determine the effects of allogeneic islet transplantation in type 1 diabetics 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 overall survival, 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 for chronic pancreatitis. The procedure appears to significantly decrease the incidence of diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. Also, this procedure itself 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 a meaningful improvement in the net health outcome.

For individuals with type 1 diabetes who receive allogeneic pancreas islet transplantation, the evidence includes an RCT, registry studies, and systematic reviews. Relevant outcomes are overall survival, 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 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 1 diabetics. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

Guidance from the National Institute for Health and Care Excellence (2008) indicated 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 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.[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 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.

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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05287737	Clinical Outcome After Total Pancreatectomy with islet Autotransplantation	100	Mar 2047
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	6	Jun 2026
NCT00679042	Islet transplantation in type 1 diabetic patients using the University of Illinois at Chicago (UIC) protocol	50	Dec 2023
NCT01897688	A phase 3 single center study of islet transplantation in non-uremic diabetic patients	40	Mar 2027
NCT00306098	Islet cell transplantation alone in patients with type 1 diabetes mellitus: steroid-free immunosuppression	40	May 2023
NCT00706420	Islet transplantation alone (ITA) in patients with difficult to control Type I Diabetes Mellitus using a glucocorticoid-free immunosuppressive regimen	20	Dec 2021
NCT03698396	A phase I/II, open-arm study evaluating the safety of islet transplant in patient with type I diabetes	10	Dec 2023

NCT: national clinical trial.

Government Regulations
National/Local:

National Coverage Determination for pancreas Transplants (260.3). Effective 07/03/2006. Medicare will cover pancreatic islet transplantation in patients with type 1 diabetes participating in the context of a clinical trial sponsored by the National Institutes of Health.[60] Partial pancreatic tissue transplantation or islet transplantation performed outside the context of a clinical trial will continue to not be covered.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

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Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/13	6/19/13	6/26/13	Policy updated to mirror BCBSA; this policy replaces the JUMP policies: Allogeneic Islet Cell Transplant for Type 1 Diabetes and Autologous Islet Cell Transplant for Pancreatitis (Retired)
11/1/14	8/19/14	8/25/14	Routine update. Additional references added, rationale updated. No change in policy status.
11/1/15	8/24/15	9/14/15	Routine maintenance. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance. No change in policy status.
9/1/18	6/19/18	6/19/18	Routine policy update. Added reference #14. No change in policy status.
9/1/19	6/18/19		Routine policy update, added references 8 and 10. No change in policy status.
1/1/20	10/15/19		Added codes 0584T-0586T as established. Routine policy update. No change in policy status.
1/1/21	10/20/20		Routine policy update, added references 2, 45 and 46. No change in policy status.
1/1/22	10/19/21		Updated rationale, added references 1,2,4, 33, 34, 38, 39, 46, 49, and 50. No change in policy status.
1/1/23	10/18/22		Routine policy maintenance, no change in policy status.

Next Review Date: 4th Qtr. 2023

Joint BCBSM/BCN Medical Policy History
Allogeneic Islet Cell Transplant for Type 1 Diabetes

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/26/05	N/A	N/A	Joint policy established
11/1/06	8/28/06	10/29/06	Routine maintenance
11/1/07	8/21/07	10/22/07	Routine maintenance
11/1/08	8/19/08	10/28/08	Routine maintenance
1/1/10	10/13/09	10/13/09	Routine maintenance of non-established service.
7/1/12	4/10/12	5/18/12	Routine maintenance of non-established service. Policy reformatted to mirror BCBSA policy. References added. No change in policy statement.

Joint BCBSM/BCN Medical Policy History
Autologous Islet Cell Transplantation for Pancreatitis

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
2/11/03	2/11/03	2/11/03	Joint medical policy established
3/19/04	3/19/04	3/26/04	Routine maintenance
6/25/05	6/25/05	6/30/05	Maintenance with policy statement change
11/1/06	8/28/06	10/29/06	Routine maintenance
11/1/07	8/21/07	10/22/07	Routine maintenance
11/1/08	8/19/08	10/28/08	Routine maintenance; policy retired.

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: ISLET TRANSPLANTATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	**Autologous** islet transplantation is covered when done as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis. **Autologous** islet transplantation is experimental/investigational for all other conditions. **Allogeneic** islet transplantation is experimental/investigational for all indications.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.