Policy Number	**SUR703.057**
Policy Effective Date	**01/01/2025**

Islet Transplantation

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
SUR703.13 Allogeneic Pancreas Transplant

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

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

Allogeneic islet transplantation using an FDA-approved cellular therapy product (donislecel-jujn [i.e., Lantidra]) **is considered not medically necessary** for the treatment of type 1 diabetes.

Islet transplantation **is considered experimental, investigational and/or unproven** in all other situations.

Policy Guidelines

None.

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 with donislecel-jujn is also being investigated as a treatment or cure for patients with type 1 diabetes.

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. (1) 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 patients with type 1 diabetes. (2) 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. 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."

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. Donislecel- jujn (Lantidra™), a first-in-class deceased donor-derived allogeneic pancreatic islet cellular therapy product, was approved by the FDA in June 2023 for the treatment of type 1 diabetes in adults who are unable to approach target hemoglobin A1c due to repeated episodes of severe hypoglycemia despite intensive diabetes management and education. (3)

<u>Additional Information Specific to Donislecel- jujn (Lantidra™)</u>
Only adult subjects were enrolled in donislecel-jujn (Lantidra) clinical studies, although clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Risks of donislecel-jujn infusion in pregnancy have not been assessed.

There are risks associated with the infusion procedure and long-term immunosuppression. There is no evidence of donislecel-jujn benefit for individuals whose diabetes is well-controlled with insulin therapy or for those with hypoglycemic unawareness who are able to prevent current repeated severe hypoglycemic events (neuroglycopenia requiring active intervention from a third party) using intensive diabetes management (including insulin, devices, and education).

Repeated intraportal islet infusions are not recommended in patients who have experienced prior portal thrombosis unless the thrombosis was limited to second- or third-order portal vein branches. There is no evidence to support donislecel-jujn for individuals with liver disease, renal failure, or who have received a renal transplant.

Islet transplantation does not supplant future whole pancreatic transplantation (see policy SUR703.013).

A specific target of HbA1c cannot be provided for all patients, as the target can be different based on age, duration of diabetes, and diabetic complications.

Current repeated episodes" indicates risk within 1 year of the intended transplantation and is not related to events more than 1 year prior to the intended transplantation.

Rationale

This medical policy was created in October 2023 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 2023.

Medical policies 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. 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 individuals 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 following PICO was used to select literature to inform this policy.

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. (4)

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

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. (5) 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. (6) 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.

Wu et al. (2015) published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis. (7) 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 the reviews' 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. (8) 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 the Systematic Reviews Assessing Autologous Pancreas Islet Transplants

Study	Zhang et al. (2020) (5)	Kempeneers et al. (2019) (6)	Wu et al. (2015) (7)	Dong et al. (2011) (8)
Cameron et al. (1981) (9)	●		●	●
Hinshaw et al. (1981) (10)	●		●	●
Toledo-Pereyra et al. (1983) (11)				●
Fontana et al. (1994) (12)				●
Rastellini et al. (1997) (13)	●		●	●
Jindal et al. (1998) (14)				●
Rabkin et al. (1999) (15)				●
Oberholzer et al. (2000) (16)	●		●	●
Berney et al. (2004) (17)				●
Ahmad et al. (2005) (18)			●	●
Argo et al. (2008) (19)	●	●	●	●
Dixon et al. (2008) (20)	●	●	●	●
Sutherland et al. (2008) (21)				●
Webb et al. (2008) (22)				●
Jung et al. (2009) (23)				●
Takita et al. (2010) (24)		●	●	
Sutherland et al. (2012) (25)	●		●	
Walsh et al. (2012) (26)	●	●	●	
Dorlon et al. (2013) (27)			●	

Garcea et al. (2013) (28)	●	●	●	
Gruessner et al. (2014) (29)	●	●		
Wilson et al. (2014) (30)		●		
Chinnakotla et al. (2015) (31)		●		
Georgiev et al. (2015) (32)		●		
Takita et al. (2015) (33)		●		
Tai et al. (2015) (34)	●			
Wilson et al. (2015) (35)	●			
Mokadem et al. (2016) (36)	●	●		
Shahbazov et al. (2017) (37)		●		
Fan et al. (2017) (38)		●		
Quartuccio et al. (2017) (39)	●			
Solomina et al. (2017) (40)	●	●		
Morgan et al. (2018) (41)	●	●		

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

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

Dong et al. (2011) (8)	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) (5)		
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) (6)		
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) (7)		
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) (8)		
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. (30) Actuarial survival 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 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 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 transplantation at a single center. (4) 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. (25) 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 October 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, year
Wilson et al. (2014) (30)	Cohort	U.S.	2000-2013	Individual with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=166)	≥ 5

Chinnakotla et al. (2014) (4)	Cohort	U.S.	1977-2012	Individual with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=484)	NR
Sutherland et al. (2014) (25)	Cohort	U.S.	1977-2011	Individual with chronic pancreatitis	Total pancreatectomy and islet auto-transplantation (n=409)	NR

FU: follow-up; NR: not reported; U.S.: United States

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) (30)	98.2	94.6	38	NR	27
Chinnakotla et al. (2014) (4)					
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) (25)	97	90	26	30	NR

NR: Not reported.

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.

Donislecel-jujn for Pancreatic Islet Cell Transplantation in Type 1 Diabetes

Clinical Context and Therapy Purpose

The purpose of donislecel-jujn in allogeneic pancreas islet transplantation for individuals who have type 1 diabetes mellitus is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Population

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. (42)

Interventions
The therapy being considered is donislecel-jujn for 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; and whole pancreatic transplant.

Outcomes
The general outcomes of interest are OS, insulin independence, change in disease status, medication use, resource utilization, and treatment-related morbidity.

According to the U.S. Food and Drug Administration (FDA; 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, or "brittle" type 1 diabetes. (43) Attainment of normal Hemoglobin A_{1c} (HbA1c) range (i.e., ≤6.5%) and elimination of hypoglycemia are acceptable 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 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.

Review of Evidence
In June 2023, the FDA approved donislecel-jujn for the treatment of adults with type 1 diabetes who are unable to approach target HbA1c because of repeated episodes of severe hypoglycemia despite intensive diabetes management and education. (3) The approval was based on a phase 1/2 trial in patients with brittle type 1diabetes complicated by hypoglycemic

unawareness, metabolic lability with documented severe hypoglycemia, or ketoacidosis despite intensive insulin therapy (N=10); (44, 45) a single-arm, open-label phase 3 trial with similar eligibility criteria (N=20); (46) and an expanded access protocol with similar eligibility criteria. (47, 48) In the FDA analysis of these trials (as described in the product labeling), median participant age was 46.5 years (range, 21 to 67 years); 80% of participants were female, 100% were White, and 97% were of non-Hispanic ethnicity. (49) Patients received up to 3 islet cell infusions; among 30 participants in the approval trials, 11 received 1 islet cell infusion, 12 received 2 infusions, and 7 received 3 infusions. Twenty-five participants (83%) achieved exogenous insulin independence (defined as not requiring exogenous insulin to achieve adequate glycemic control) of any duration, including 4 patients (13.3%) with independence for less than 1 year, 12 patients (36.7%) with independence for 1 to 5 years, and 9 patients (33.3%) with independence for more than 5 years. Mean duration of exogenous insulin dependence in the phase 1/2 and phase 3 studies were 5.1 years (standard deviation [SD] 4.2, range 0.2 to 12.8) and 3.2 years (SD 3.1, range 0 to 9.9), respectively. Serious adverse reactions were reported in 90%, including 2 deaths (7%) from multiorgan failure with sepsis (1.6 years after first infusion) and progressive confusion, global atrophy, and micro-ischemic disease (9.7 years after first infusion); most serious adverse reactions were attributed to immunosuppression. Infections were reported in 26 patients (87%), totaling 211 episodes, 1 of which was classified as life-threatening and 22 as severe. Malignancy was reported in 11 subjects (37%), including 12 skin cancers and 1 each of posttransplant lymphoproliferative disease, breast cancer, and thyroid cancer. Common adverse events included, but were not limited to nausea, fatigue, anemia, diarrhea, abdominal pain, asthenia, headache, and hyponatremia. Most adverse reactions were low-grade by Common Terminology Criteria for Adverse Events, version 5; the most common grade ≥3 adverse events included low density lipoprotein elevations (37%), anemia (27%), and pneumonia (17%).

The FDA also reviewed the Clinical Islet Transplantation (CIT) consortium's phase 3, open-label, single-arm, multicenter trial (CIT-07) data. (50) The trial enrolled patients with hypoglycemia unawareness and a history of severe hypoglycemic episodes. Although 8 centers participated in the trial, only the 4 patients from the single site who were treated with the particular donislecel-jujn product were included in the review. All patients received 1 or 2 islet transplants. The primary endpoint was the proportion of subjects who achieved a HbA1c less than 7% at 1 year with no hypoglycemic events from Day 28 to Day 365 after transplantation. Analysis of the primary endpoint was limited because 2 subjects had HbA1c levels less than 7% at baseline and another had near target HbA1c (7.3%). Severe hypoglycemic events were not reported. The 3 subjects who completed Day 730 follow up, were insulin independent at that time.

The FDA Biologics License Application Clinical Review Memorandum states numerous protocol deviations across the above studies that could impair the interpretation of both efficacy and safety data, as well as provides examples of missing and incongruent data and insufficient data monitoring during the study. (50) Multiple information requests were generated by the FDA in order to achieve adequate data for a substantive, complete review. Given that the studies were conducted at a single site raises concern; and other factors that might affect occurrence or

duration of insulin independence were not able to be elucidated from the existing studies, including cell product factors (number of cells, viability, purity, and potency) and delivery device (e.g., type of catheter).

Section Summary: Donislecel-jujn for Pancreatic Islet Cell Transplantation in Type 1 Diabetes
Allogeneic islet transplantation with donislecel-jujn has been investigated in the treatment of type 1 diabetes. A single-arm prospective trial of the allogeneic islet cellular therapy product donislecel-jujn demonstrated insulin independence for over 1 year in a majority of participants, with mean insulin independence of approximately 5 years, resulting in donislecel-jujn's FDA approval for certain adults with type 1 diabetes. A single-arm, open- label study reviewed by the FDA (CIT-07) included data from 4 patients who received donislecel-jujn. However, the primary outcome was intended to evaluate the proportion of patients with a HbA1c less than 7% and low baseline HbA1c..

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 (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 mellitus 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 with donislecel-jujn (i.e., Lantidra), the evidence includes single-arm prospective trials conducted at a single study site without strict protocols demonstrating insulin independence for over 1 year in a majority of participants, with mean insulin independence of approximately 5 years, resulting in Food and Drug Administration approval of donislecel for adults who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education and for use in conjunction with concomitant immunosuppression. Additional well-designed 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, therefore allogeneic pancreas islet transplantation with donislecel-juin (i.e., Lantidra) is considered not medically necessary.

Practice Guidelines and Position Statements: Islet Cell Transplantation
National Institute for Health and Care Excellence (NICE)
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. (51) 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)." (52)

American Diabetes Association

In 2023, 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. (53) The standards of care note that islet cell transplantation may have a role in type 1 diabetes. Because of the need for immunosuppressive agents posttransplantation, the guidelines note 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. (54) 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 ongoing and unpublished trials that might influence this policy 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
NCT00706420	Islet Transplantation Alone (ITA) in Patients With Difficult to Control Type I Diabetes Mellitus Using a Glucocorticoid-free Immunosuppressive Regimen	17	Dec 2023
NCT00306098	Islet Cell Transplantation Alone in Patients With Type 1 Diabetes Mellitus: Steroid-Free Immunosuppression	40	May 2026
NCT03698396	A Phase I/II, Open-Arm Study Evaluating the Safety of Islet Transplant in Patients With Type I Diabetes	10	Dec 2023
NCT01897688	A Phase 3 Single Center Study of Islet Transplantation in Non-uremic Diabetic Patients	40	Mar 2027
NCT00679042[a]	Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol, Phase 3	21	Dec 2026
NCT05662267	Targeted Trial Emulation of Kidney Alone Versus Islet-After-Kidney inType 1 Diabetic Transplant Recipients: A French Nationwide CohortStudy	500	Mar 2023

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0584T, 0585T, 0586T, 48160
HCPCS Codes	C9399, G0341, G0342, G0343, J3590, S2102

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Tillou JD, Tatum JA, Jolissaint JS, et al. Operative management of chronic pancreatitis: A review. Am J Surg. Aug 2017; 214(2):347-357. PMID 28325588

2. Vantyghem MC, de Koning EJP, Pattou F, et al. Advances in β-cell replacement therapy for the treatment of type 1 diabetes. Lancet. Oct 05 2019; 394(10205):1274-1285. PMID 31533905
3. U.S. Food & Drug Administration (FDA). FDA Approves First Cellular Therapy to Treat Patients with Type 1 Diabetes. June 28, 2023. Available at <https://fda.gov> (accessed July 2, 2023).
4. Chinnakotla S, Radosevich DM, Dunn TB, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg. Apr 2014; 218(4):530-543. PMID 24655839
5. Zhang YJ, Duan DD, Yuan H. Efficacy and safety of islet autotransplantation after total pancreatectomy in chronic pancreatitis: A systematic review and meta-analysis including 17 studies. Clin Res Hepatol Gastroenterol. Sep 2020; 44(4):598-608. PMID 31523018
6. Kempeneers MA, Scholten L, Verkade CR, et al. Efficacy of total pancreatectomy with islet autotransplantation on opioid and insulin requirement in painful chronic pancreatitis: A systematic review and meta-analysis. Surgery. Sep 2019; 166(3):263-270. PMID 31085044
7. Wu Q, Zhang M, Qin Y, et al. Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients. Endocr J. Mar 30 2015; 62(3):227-234. PMID 25735805
8. Dong M, Parsaik AK, Erwin PJ, et al. Systematic review and meta-analysis: islet autotransplantation after pancreatectomy for minimizing diabetes. Clin Endocrinol (Oxf). Dec 2011; 75(6):771-779. PMID 21605156
9. Cameron JL, Mehigan DG, Broe PJ, et al. Distal pancreatectomy and islet autotransplantation for chronic pancreatitis. Ann Surg. Mar 1981; 193(3):312-317. PMID 6782958
10. Hinshaw DB, Jolley WB, Hinshaw DB, et al. Islet autotransplantation after pancreatectomy for chronic pancreatitis with a new method of islet preparation. Am J Surg. Jul 1981; 142(1):118-122. PMID 6266268
11. Toledo-Pereyra LH. Islet cell autotransplantation after subtotal pancreatectomy. Arch Surg. Jul 1983; 118(7):851-858. PMID 6407457
12. Fontana I, Arcuri V, Tommasi GV, et al. Long-term follow-up of human islet autotransplantation. Transplant Proc. Apr 1994; 26(2):581. PMID 8171565
13. Rastellini C, Shapiro R, Corry R, et al. Treatment of isolated pancreatic islets to reverse pancreatectomy-induced and insulin-dependent type I diabetes in humans: a 6-year experience. Transplant Proc. Feb-Mar 1997; 29(1-2):746-747. PMID 9123507
14. Jindal RM, Fineberg SE, Sherman S, et al. Clinical experience with autologous and allogeneic pancreatic islet transplantation. Transplantation. Dec 27 1998; 66(12):1836-1841. PMID 9884286
15. Rabkin JM, Olyaei AJ, Orloff SL, et al. Distant processing of pancreas islets for autotransplantation following total pancreatectomy. Am J Surg. May 1999; 177(5):423-427. PMID 10365884
16. Oberholzer J, Triponez F, Mage R, et al. Human islet transplantation: lessons from 13 autologous and 13 allogeneic transplantations. Transplantation. Mar 27 2000; 69(6):1115-1123. PMID 10762216
17. Berney T, Mathe Z, Bucher P, et al. Islet autotransplantation for the prevention of surgical

diabetes after extended pancreatectomy for the resection of benign tumors of the pancreas. Transplant Proc. May 2004; 36(4):1123-1124. PMID 15194391
18. Ahmad SA, Lowy AM, Wray CJ, et al. Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. J Am Coll Surg. Nov 2005; 201(5):680-687. PMID 16256909
19. Argo JL, Contreras JL, Wesley MM, et al. Pancreatic resection with islet cell autotransplant for the treatment of severe chronic pancreatitis. Am Surg. Jun 2008; 74(6):530-536; discussion 536-537. PMID 18556996
20. Dixon J, DeLegge M, Morgan KA, et al. Impact of total pancreatectomy with islet cell transplant on chronic pancreatitis management at a disease-based center. Am Surg. Aug 2008; 74(8):735-738. PMID 18705576
21. Sutherland DE, Gruessner AC, Carlson AM, et al. Islet autotransplant outcomes after total pancreatectomy: a contrast to islet allograft outcomes. Transplantation. Dec 27 2008; 86(12):1799-1802. PMID 19104425
22. Webb MA, Illouz SC, Pollard CA, et al. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. Pancreas. Oct 2008; 37(3):282-287. PMID 18815550
23. Jung HS, Choi SH, Kim SJ, et al. Delayed improvement of insulin secretion after autologous islet transplantation in partially pancreatectomized patients. Metab Clin Exp. Nov 2009; 58(11):1629-1635. PMID 19604519
24. Takita M, Naziruddin B, Matsumoto S, et al. Variables associated with islet yield in autologous islet cell transplantation for chronic pancreatitis. Proc (Bayl Univ Med Cent). Apr 2010; 23(2):115-120. PMID 20396418
25. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. Apr 2012; 214(4):409-42; discussion 424-426. PMID 22397977
26. Walsh RM, Saavedra JR, Lentz G, et al. Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. J Gastrointest Surg. Aug 2012; 16(8):1469-1477. PMID 22673773
27. Dorlon M, Owczarski S, Wang H, et al. Increase in postoperative insulin requirements does not lead to decreased quality of life after total pancreatectomy with islet cell autotransplantation for chronic pancreatitis. Am Surg. Jul 2013; 79(7):676-680. PMID 23815999
28. Garcea G, Pollard CA, Illouz S, et al. Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. Pancreas. Mar 2013; 42(2):322-328. PMID 23407482
29. Gruessner RW, Cercone R, Galvani C, et al. Results of open and robot-assisted pancreatectomies with autologous islet transplantations: treating chronic pancreatitis and preventing surgically induced diabetes. Transplant Proc. Jul-Aug 2014; 46(6):1978-1979. PMID 25131087
30. Wilson GC, Sutton JM, Abbott DE, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? Ann Surg. Oct 2014; 260(4):659-665; discussion 665-667. PMID 25203883
31. Chinnakotla S, Beilman GJ, Dunn TB, et al. Factors predicting outcomes after a total

pancreatectomy and islet autotransplantation lessons learned from over 500 cases. Ann Surg. Oct 2015; 262(4):610-622. PMID 26366540
32. Georgiev G, Beltran del Rio M, Gruessner A, et al. Patient quality of life and pain improve after autologous islet transplantation (AIT) for treatment of chronic pancreatitis: 53 patient series at the University of Arizona. Pancreatology. Jan-Feb 2015; 15(1):40-45. PMID 25455347
33. Takita M, Lara LF, Naziruddin B, et al. Effect of the duration of chronic pancreatitis on pancreas islet yield and metabolic outcome following islet autotransplantation. J Gastrointest Surg. Jul 2015; 19(7):1236-1246. PMID 25933581
34. Tai DS, Shen N, Szot GL, et al. Autologous islet transplantation with remote islet isolation after pancreas resection for chronic pancreatitis. JAMA Sug. Feb 2015; 150(2):118-124. PMID 25494212
35. Wilson GC, Sutton JM, Smith MT, et al. completion pancreatectomy and islet cell autotransplantation as salvage therapy for patients failing previous operative interventions for chronic pancreatitis. Surgery. Oct 2015; 158(4):872-878; discussion 879-880. PMID 26173686
36. Mokadem M, Noureddine L, Howard T, et al. Total pancreatectomy with islet cell transplantation vs intrathecal narcotic pump infusion for pain control in chronic pancreatitis. World J Gastroenterol. Apr 28 2016; 22(16):4160-4167. PMID 27122666
37. Shahbazov R, Yoshimatsu G, Haque WZ, et al. Clinical effectiveness of a pylorus-preserving procedure on total pancreatectomy with islet autotransplantation. Am J Surg. Jun 2017; 213(6):1065-1071. PMID 27760705
38. Fan CJ, Hirose K, Walsh CM, et al. Laparoscopic total pancreatectomy with islet autotransplantation and intraoperative islet separation as a treatment for patients with chronic pancreatitis. JAMA Surg. Jun 01 2017; 152(6):550-556. PMID 28241234
39. Quartuccio M, Hall E, Singh V, et al. Glycemic predictors of insulin independence after total pancreatectomy with islet autotransplantation. J Clin Endocrinol Metab. Mar 01 2017; 102(3):801-809. PMID 27870552
40. Solomina J, Golebiewska J, Kijek MR, et al. Pain control, glucose control, and quality of life in patients with chronic pancreatitis after total pancreatectomy with islet autotransplantation: A preliminary report. Transplant Proc. Dec 2017; 49(10):2333-2339. PMID 29198673
41. Morgan KA, Lancaster WP, Owczarski SM, et al. Patient selection for total pancreatectomy with islet autotransplantation in the surgical management of chronic pancreatitis. J Am Coll Surg. Apr 2018; 226(4):446-451. PMID 29289751
42. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. Transplantation. Feb 15 2011; 91(3):373-378. PMID 21258272
43. Food and Drug Administration (FDA). Guidance for industry: Considerations for allogeneic pancreatic islet cell products. 2009. Available at <https://www.fda.gov> (accessed July 5, 2023).
44. Gangemi A, Salehi P, Hatipoglu B, et al. Islet transplantation for brittle type 1 diabetes: the UIC protocol. Am J Transplant. Jun 2008; 8(6):1250-1261. PMID 18444920
45. Qi M, Kinzer K, Danielson KK, et al. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience. Acta Diabetol. Oct 2014; 51(5):833-

43. PMID 25034311
46. ClinicalTrials.gov. Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol (NCT00679042). July 27, 2022. Available at <https://classic.clinicaltrials.gov> (accessed July 5, 2023).
47. ClinicalTrials.gov. Islet Transplantation in Type I Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol (NCT03791567). March 16, 2022. Available at <https://classic.clinicaltrials.gov> (accessed July 3, 2023).
48. U.S. Food and Drug Administration (FDA). Donislecel-jujn (Lantidra) approval letter. June 28, 2023. Available at <https://www.fda.gov> (accessed July 3, 2023).
49. U.S. Food and Drug Administration (FDA). Donislecel-jujn (Lantidra) package insert. June 30, 2023. Available at <https://www.fda.gov> (accessed July 5, 2023).
50. LANTRIDA. U.S. Food and Drug Administration. August 7, 2023. Available at <https://www.fda.gov> (accessed August 24, 2023).
51. National Institute for Health and Clinical Excellence (NICE). Allogenic pancreatic islet cell transplantation for type 1 diabetes mellitus [IPG257]. 2008. Available at <https://www.nice.org.uk> (accessed July 5, 2023).
52. National Institute for Health and Clinical Excellence (NICE). Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy [IPG274] (2008). Available at <https://www.nice.org.uk> (accessed July 3, 2023).
53. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care. Jan 01 2023; 46(Suppl 1): S140-S157. PMID36507650
54. Abu-El-Haija M, Anazawa T, Beilman GJ, et al. The role of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis: A Report from the International Consensus Guidelines in chronic pancreatitis. Pancreatology. Jun 2020; 20(4):762-771. PMID 32327370

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2025	Reviewed. No changes.

03/15/2024	New medical document originating from SUR703.013 Allogeneic Pancreas Transplant. Autologous pancreas islet transplantation may be considered medically necessary as an adjunct to a total or near-total pancreatectomy in individuals with chronic pancreatitis. Allogeneic islet transplantation using an FDA-approved cellular therapy product (donislecel-jujn [i.e., Lantidra]) is considered not medically necessary for the treatment of type 1 diabetes. Islet transplantation is considered experimental, investigational and/or unproven in all other situations. Added references 1-3, 44-50, 54; Some updated; others removed.