Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Transplant- Islet Cell (*Autologous*) for Chronic Pancreatitis

Description/Background

ISLET TRANSPLANTATION
Islet cell autotransplantation, also known as an autologous islet cell transplantation, is the infusion of a patient's own pancreatic islet cells into the portal vein of the liver.

Autologous islet cell transplantation is an option for persons undergoing total pancreatectomy for severe, refractory chronic pancreatitis. Near total or total pancreatic resection can alleviate pain in patients with severe chronic pancreatitis. Autologous islet cell transplantation can preserve islet cell function in patients undergoing pancreatectomy.

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.

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.

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.

Inclusionary and Exclusionary Guidelines

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

Exclusions:
- *Autologous* islet cell transplantation in individuals in all other situations.

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.):

N/A

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 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** 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.

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.

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.[43]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).”[44]

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.[45]

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.[46] 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
NCT05095532	Autologous Mesenchymal Stromal Cells and Islet Co-transplantation in TP-IAT	42	June 2026
NCT05453851	A Surgical Procedure (Total Pancreatectomy) With a Transplant Procedure (Islet Cell Autotransplantation) for the Treatment of Chronic Pancreatitis and Benign Pancreatic Tumors	12	July 2029

NCT: national clinical trial.

Government Regulations
National/Local:

There is no NCD or LCD regarding autologous islet cell transplantation for chronic pancreatitis.

(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)
- Lantidra™ (donislecel-jujn) Pharmacy policy

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2024, the date the research was completed.

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.
1/1/24	10/17/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
N/A	TABLED		Policy was discussed and tabled at the 12/19/24 JUMP meeting. Vendor managed: N/A (ds)
11/1/24	8/23/24		• Title changed to Transplant-

			Islet Cell (*Autologous)* • Removed code S2102 as it no longer belongs on this policy, the code remains E/I in the system • Allogeneic islet cell transplantation removed from MPS, exclusion section and rationale section as well as related references. • Removed NCD info from government section—did not apply to autologous islet cell transplant. • The policy status has changed to established. • Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2025

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: TRANSPLANT- ISLET CELL (AUTOLOGOUS) FOR CHRONIC PANCREATITIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy criteria
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.