Policy Statement

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

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

Islet transplantation is considered investigational in all other situations.

Policy Guidelines

CPT code 48160 explicitly describes autologous pancreas islet cell transplantation at the time of pancreatectomy.

CPT instructs the use of code 48999 (unlisted procedure, pancreas) for transplantation of islet cells as a stand-alone procedure.

Three HCPCS codes are specific to these procedures:

- **G0341:** Percutaneous islet cell transplant, includes portal vein catheterization and infusion
- **G0342:** Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
- **G0343:** Laparotomy for islet cell transplant, includes portal vein catheterization and infusion

Description

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

Related Policies

- Allogeneic Pancreas Transplant
- Chronic Intermittent Intravenous Insulin Therapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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

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

Rationale

Background

Islet Transplantation

In autologous islet transplantation during the pancreatectomy procedure, islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient’s liver. Once implanted, the beta cells in these islets begin to make and release insulin.

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. Allogeneic transplantation may be performed in the radiology department.

Chronic Pancreatitis

Primary risk factors for chronic pancreatitis include 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.

Type 1 Diabetes

Allogeneic islet transplantation has been used for type 1 diabetes to restore normoglycemia and, ultimately, to reduce or eliminate the long-term complications of diabetes such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Islet transplantation potentially offers an alternative to whole-organ pancreas transplantation. However, a limitation of islet transplantation is that two 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.

In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen was developed in Edmonton, AB, Canada, and is known as the “Edmonton protocol.”

Literature Review

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial that includes clinically relevant measures of health outcomes. Also known as surrogate outcome measures, intermediate outcome measures may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition. The following is a summary of the key literature to date on islet cell transplantation.
Chronic Pancreatitis
Systematic Reviews
There are several systematic reviews of the literature on chronic pancreatitis patients. In 2015, Wu et al published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis. 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 (total N=677 patients) met reviewers’ 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 studies regardless of design or sample size. After reviewing 84 studies, 15 observational studies met 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 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).

Nonrandomized Studies
Representative studies are described next. For example, in 2014, Wilson et al reported on 166 patients ages 14 or older with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center. Actuarial survival rate at 5 years was 94.6%. Five or more years of data were available for 112 (67%) patients. At 1 year, 38% of patients were insulin-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. 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.

In 2012, Sutherland et al reported on 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center. Fifty-three (13%) of the 409 patients were children between the ages of 5 and 18 years. Actuarial 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 and 55% of children). A survey of quality of life outcomes was initiated in 2008; responses were available for 102 patients. At baseline, all 102 patients reported using narcotics for pain. At 12 months, the proportion of patients on narcotics decreased to 56% (n=52), and at 24 months, 41% of respondents (n=21) reported using narcotics.

Section Summary: Chronic Pancreatitis
Autologous islet transplantation is frequently performed in cases of total or near total pancreatectomies for chronic pancreatitis. Evidence from case series 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**

According to U.S. Food and Drug Administration industry guidance on evaluating allogeneic pancreatic islet cell products published in 2009, single-arm trials with historical controls may be acceptable alternatives to randomized controlled trials for evaluating the safety and efficacy of islet cell products in patients with metabolically unstable type 1 diabetes. Attainment of normal range hemoglobin A1c (HbA1c) level (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.

In 2004, TEC published a systematic review of evidence on islet cell transplantation in type 1 diabetes. TEC 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 have reportedly minimized risks of these adverse events. No procedure-related deaths, cytomegalovirus infection, or posttransplantation lymphoproliferative disease have been reported for islet-alone transplantation.

The 2008 report from the Collaborative Islet Transplant Registry, which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, assessed data on 325 adult recipients. Three years after the first infusion, 23% of islet-alone recipients were insulin-independent (defined as insulin independent ≥2 weeks), 29% were insulin-dependent with detectable C-peptide, 26% had lost function, and 22% had missing data. Seventy percent achieved insulin independence at least once, 71% of whom were still insulin-independent 1 year later and 52% at 2 years. Factors that favored primary outcomes were a higher number of islet infusions, a greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size.

The Collaborative Islet Transplant Registry updated its report in 2012; the focus was changes in outcomes over time. 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 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.

In 2011, Thompson et al in Canada published findings from a prospective crossover study of intensive medical therapy (pretransplant) vs islet cell transplantation in patients with type 1 diabetes. The article reported on 45 patients; at the time of data analysis, 32 had received islet cell transplants. Median follow-up was 47 months pretransplant and 66 months posttransplant. The overall mean HbA1c level was 7.8% pretransplant and 6.7% posttransplant; this difference was statistically significant (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 (in milliliters per minute per month) was -6.7 mL/min/1.73 m²/y pretransplant and -1.3 mL/min/1.73 m²/y posttransplant (p=0.01). Retinopathy was assessed using a scale that categorizes nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 (12%) of 82 eyes pretransplant vs 0 of 51 posttransplant (p<0.01). (The numbers of patients in the retinopathy analyses were not reported.) The rate of change in nerve
conduction velocity did not differ significantly between groups (exact numbers not reported). The authors noted that their finding of reduced microvascular complications after islet transplantation might be due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil.

Small case series continue to be published, and they tend to report some success and also adverse events. For example, in 2013, O’Connell et al reported on 17 patients with type 1 diabetes and severe hypoglycemia who underwent islet transplantation in Australia. Fourteen (82%) patients attained the primary end point, which was an HbA1c level 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 postoperative bleeds; 2 of the bleeds required transfusion.

A systematic review by Health Quality Ontario in 2015 reported on islet transplantation for patients with type 1 diabetes. Most of the evidence was from case series derived at single centers. 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.

Section Summary: Type 1 Diabetes

Allogeneic islet transplantation has been investigated in the treatment of type 1 diabetes. Evidence from case series and systematic reviews has demonstrated that varying ranges of insulin independence occurs posttransplantation. There is conflicting evidence that allogeneic islet transplantation reduces long-term diabetic complications. Long-term comparative studies are required to determine the effects of allogeneic islet transplantation in type 1 diabetics and posttransplant immunosuppression.

Summary of Evidence

For individuals with chronic pancreatitis undergoing total or near total pancreatectomy who receive autologous pancreas islet transplantation, the evidence includes case series 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 case series and systematic reviews. Relevant outcomes are overall survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. 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
Guidance from the National Institute for Care Excellence, published in 2008, indicated the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes has shown that serious complications may occur, and the long-term immunosuppression required is associated with risk of adverse events. A related 2008 guidance addressed autologous islet cell transplantation for improved glycemic control after pancreatectomy stated that studies have shown some short-term efficacy, although most patients require insulin therapy in the long term. Complications mainly result from the major surgery involved in pancreatectomy rather than from the islet cell transplantation.

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

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT00679042</td>
<td>Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol</td>
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<td>NCT00706420</td>
<td>Islet Transplantation Alone (ITA) in Patients With Difficult to Control Type 1 Diabetes Mellitus Using a Glucocorticoid-free Immunosuppressive Regimen</td>
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<td>NCT02505893</td>
<td>Minimal Islet Transplant at Diabetes Onset (MITO)</td>
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<td>NCT00160732</td>
<td>Allogenic Islet Cell Transplantation</td>
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<td>Oct 2018</td>
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<tr>
<td>NCT01897688</td>
<td>A Phase 3 Single Center Study of Islet Transplantation in Nonuremic Diabetic Patients</td>
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<td>NCT019909245</td>
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<td>NCT00306098</td>
<td>Islet Cell Transplantation Alone in Patients With Type 1 Diabetes Mellitus: Steroid-Free Immunosuppression</td>
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<td>Allogenic Islet Transplantation for the Treatment of Type 1 Diabetes (GRIIF)</td>
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<td>Jan 2022</td>
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NCT: National Clinical Trial.

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

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

## Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<tr>
<th>Type</th>
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<th>Description</th>
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<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
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<td>48999</td>
<td>Unlisted procedure, pancreas</td>
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<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
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<td></td>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
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<td></td>
<td>S2102</td>
<td>Islet cell tissue transplant from pancreas; allogeneic</td>
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<td>Introduction of Autologous Pancreatic Islet Cells into Peripheral Vein, Percutaneous Approach</td>
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<td>Introduction of Autologous Pancreatic Islet Cells into Biliary and Pancreatic Tract, Percutaneous Approach</td>
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<td>Introduction of Autologous Pancreatic Islet Cells into Biliary and Pancreatic Tract, Via Natural or Artificial Opening</td>
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## Policy History

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

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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

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

### Prior Authorization Requirements (as applicable to your plan)

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

Questions regarding the applicability of this policy should also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal at www.blueshieldca.com/provider.

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