Islet Transplantation

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**Effective Date** December 1, 2016

**Revision Date(s)** 11/08/16; 07/14/15; 07/14/14; 08/12/13; 08/14/12; 08/09/11; 09/14/10; 07/14/09; 06/09/09; 03/11/08; 09/12/06; 12/13/05; 03/08/05; 11/13/01

**Replaces** N/A

*Medicare has a policy

**Policy**

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.

**Related Policies**

None

**Policy Guidelines**

**Coding**

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<thead>
<tr>
<th>CPT</th>
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<tr>
<td>48160</td>
<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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**HCPCS**

<table>
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<tr>
<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
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<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
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<tr>
<td>G0343</td>
<td>Laparatomy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>S2102</td>
<td>Islet cell tissue transplant from pancreas; allogeneic</td>
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</table>
Autologous islet transplantation, performed in conjunction with pancreatectomy, 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.

Background
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 the 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 pancreatitis, 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. Autologous islet transplantation has been investigated as a technique to prevent this serious morbidity.

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 2 or more donor organs are usually required for successful transplantation, although experimentation with single-donor transplantation is occurring. A pancreas that is rejected for whole-organ transplant is typically used for islet transplantation. Therefore, islet transplantation has generally been reserved for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management.

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.”

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

Scope
Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Benefit Application

When the criteria for total or near total pancreatectomy with autologous islet cell transplantation are met, the surgical costs will be adjudicated under the Medical benefit.

When the criteria for pancreatectomy with allogeneic islet cell transplantation are met, the surgical costs will be adjudicated under the Transplant benefit.

Islet transplantation is a specialized procedure that may require referral to an out-of-network facility.

Rationale

This policy was created in 2001 and was updated regularly with searches of the MEDLINE database. The most recent literature review was conducted through October 10, 2016. Following is a summary of the key literature to date on islet cell transplantation.

Chronic Pancreatitis

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. (1) 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. (2) 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% 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% to 33%) and at 2 years (3 studies) was 21% (95% CI: 16% to 27%).

Representative studies are described next.

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. (3) 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. (4) 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. (5) Fifty-three of the 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.

**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 RCTs for evaluating the safety and efficacy of islet cell products in patients with metabolically unstable type 1 diabetes. (6) Attainment of normal range HbA1c level (i.e., ≤6.5%) and elimination of hypoglycemia are acceptable primary end points. To assess 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 April 2004, in its capacity as an Evidence-based Practice Center for the Agency for Healthcare Research and Quality, TEC published a systematic review of evidence on islet cell transplantation in type 1 diabetes. (7) The report 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, lack of standardized methods of reporting clinical outcomes. In addition, rare, serious adverse events have occurred in patients given islet transplants, although recent procedure modifications reportedly minimize 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 (CITR), which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, published a report with data on 325 adult recipients. (8) Three years after 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 higher number of islet infusions, greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size.

CITR published an updated report in 2012; the focus of the article was changes in outcomes over time. (9) The number of patients receiving islet transplants was 214 during 1999-2002, 255 between mid-2003 and 2006, and 208 from 2007 to 2010. A total of 575 of the 677 (85%) 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) versus islet cell transplantation in patients with type 1 diabetes. (10) The article reported on 45 patients; at the time of data analysis, 32 had received islet cell transplants. Median follow-up was 47 months pretransplant and 66 months post-transplant. The overall mean HbA1c was 7.8% pretransplant and 6.7% posttransplant; this difference was statistically significant (p<0.001). In the 16 patients for whom sufficient data were available on renal outcomes, the median decline in glomular filtration rate (in milliliters per minute per month) was -6.7 pretransplant and -1.3 post-transplant (p=0.01). Retinopathy was assessed using the International Scale, which categorizes nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 of 82 (12%) eyes pretransplant versus 0 of 51 post-transplant (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 may 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 these tend to report some success and also adverse events.(11-13) 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.(12) Fourteen patients (82%) attained the primary end point, which was an HbA1c 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 of the 17 (41%) patients developed mild lymphopenia and 1 developed Clostridium difficile colitis; these all responded to treatment. Eight patients developed anemia shortly after transplant and 1 required a blood transfusion. Procedure-related complications included 1 partial portal vein thrombosis and 3 postoperative bleeds; 2 of the bleeds required transfusion.

In 2014, Qi et al reported on a 5-year phase 1/2 allogeneic islet transplantation clinical trial conducted at the University of Illinois at Chicago (UIC). Ten patients were enrolled in this single center, open label, and prospective trial in which patients received 1–3 transplants. The first four subjects underwent islet transplantation with the Edmonton immunosuppressive regimen and the remaining six subjects received the UIC immunosuppressive protocol (Edmonton plus etanercept and exenatide). All 10 patients achieved insulin independence after 1–3 transplants. At five years follow-up, six of the initial 10 patients were free of exogenous insulin. During the follow-up period, 7 of the 10 patients maintained positive C-peptide levels and a composite hypoglycemic (HYPO) score of 0. Most patients maintained HbA1c levels < 6.0% and a significantly improved ß-score. Throughout the 5-year follow-up period after transplant, a total of three patients were withdrawn due to localized breast cancer diagnosis 18 months after first transplant, graft rejection and the development of diabetic myonecrosis of the neck. The authors felt that this study demonstrated long-term islet graft function without using T-cell depleting induction, with an encouraging outcome that included 60% of patients remaining insulin independent after five years of initial transplantation.

Summary of Evidence
Although the published experience with autologous islet cell transplantation is limited, the procedure appears to significantly decrease the incidence of diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. In addition, this procedure is not associated with serious complications itself and is performed in patients who are already undergoing a pancreatectomy procedure. Thus, this technology may be considered medically necessary as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

The techniques for allogeneic islet cell transplants are evolving, and the impact on the net health outcome for patients with type 1 diabetes, not otherwise undergoing surgery, is still uncertain. Moreover, longer follow-up with larger numbers of patients is needed before conclusions can be drawn about the safety of allogeneic islet transplantation and its impact on diabetes mellitus and associated complications. Thus, this technology is considered investigational.

Practice Guidelines and Position Statements
Guidance from the National Institute for Clinical Excellence, published in 2008, states that the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy.(14) Evidence on safety shows that serious complications may occur, and the long-term immunosuppression required is also associated with risk of adverse events. A related NICE guidance document on autologous islet cell transplantation for improved glycemic control after pancreatectomy states that studies show 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.(15)

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

Medicare National Coverage
Effective October 1, 2004, Medicare will cover pancreatic islet transplantation in patients with type 1 diabetes participating in the context of a clinical trial sponsored by the National Institutes of Health. Partial pancreatic tissue transplantation or islet transplantation performed outside the context of a clinical trial will continue to not be covered.

References


Appendix

N/A
**History**

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<tr>
<td>11/13/01</td>
<td>Add to Surgery Section - New Policy</td>
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<td>03/08/05</td>
<td>Replace Policy - Policy reviewed; added information on islet transplantation for type 1 diabetes and statement that this indication is considered investigational; added Medicare coverage policy information on islet transplantation for type 1 diabetes; removed “autologous” from the policy title; HCPCS codes updated.</td>
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<td>12/13/05</td>
<td>Replace Policy - Policy reviewed with literature search; reference added. Policy statement and title updated with removal of “cell” when describing islet transplantation rather than “islet cell transplantation.”</td>
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<td>05/26/06</td>
<td>Scope and Disclaimer Updates - No other changes.</td>
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<td>09/12/06</td>
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<td>03/11/08</td>
<td>Replace Policy - Policy updated with literature search; no change to policy statement; reference added.</td>
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<tr>
<td>07/14/09</td>
<td>Replace Policy - Policy updated with literature search; no change to policy statement. Benefit Application section updated. References added.</td>
</tr>
<tr>
<td>09/14/10</td>
<td>Replace Policy - Policy updated with literature review; rationale section extensively edited. References numbers 16 – 18 have been added; the policy statements remain unchanged.</td>
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<td>Replace Policy – Policy updated with literature review. Reference numbers 13 and 17 added; other references renumbered or removed; policy statements unchanged. ICD-10 codes added to policy.</td>
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<td>08/20/12</td>
<td>Replace Policy. Rationale section revised based on literature review through April 2012. References 1-3 and 14 added, other references renumbered or removed. Policy statements unchanged.</td>
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<td>09/28/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<td>01/10/13</td>
<td>Coding update. CPT codes 0141T – 0143T removed from policy; they were deleted as of 1/1/12.</td>
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<td>08/16/13</td>
<td>Replace policy. Policy guidelines reformatted for readability. Rationale updated with literature review through April 18, 2013. Ongoing clinical trial added. Reference numbers 7,9,11 and 16 added; others renumbered or removed. Policy statements unchanged.</td>
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<td>Coding Update. Codes 52.85 and 52.86 were removed per ICD-10 mapping project; these codes are not utilized for adjudication of policy.</td>
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<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review through March 26, 2014. Reference numbers 4, 10, 11 and 20 added. Statement added that islet transplantation is considered investigational in all other situations.</td>
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<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through April 8, 2015; references 1, 3, 6, and 11 added. Policy statements unchanged. ICD-9 and ICD-10 procedure codes removed; these were listed for informational purposes only.</td>
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