I. Description

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.

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 may be considered medically necessary.

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 not covered.

II. Policy

Autologous pancreas islet transplantation is covered (subject to Limitations and Administrative Guidelines) as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

III. Limitations

Allogeneic islet transplantation is not covered for the treatment of type 1 diabetes as it is not known to be effective in improving health outcomes.
IV. Administrative Guidelines

A. Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA’s Precertification Request and mail or fax the form as indicated along with the required documentation.

B. Applicable codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
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<table>
<thead>
<tr>
<th>ICD-9 Procedure Codes</th>
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<tbody>
<tr>
<td>52.84</td>
<td>Autotransplantation of cells of islets of Langerhans</td>
</tr>
<tr>
<td>52.85</td>
<td>Allotransplantation of cells of islets of Langerhans</td>
</tr>
<tr>
<td>52.86</td>
<td>Transplantation of cells of islets of Langerhans, not otherwise specified</td>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
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C. Codes that do not meet payment determination criteria:

<table>
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>S2102</td>
<td>Transplant, islet cell tissue, allogeneic</td>
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</table>

D. ICD-10 codes are provided for your information. These will not become effective until the ICD-10 compliance date.

<table>
<thead>
<tr>
<th>ICD-10-PCS</th>
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<tr>
<td>3E033U0</td>
<td>Percutaneous administration, peripheral vein, pancreatic islet cells, autologous</td>
</tr>
<tr>
<td>3E0J3U0</td>
<td>Percutaneous administration, biliary and pancreatic tract, pancreatic islet cells, autologous</td>
</tr>
</tbody>
</table>
V. 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 include toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive (the 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, 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 (IND) regulation. While at least 35 IND applications have been submitted to the FDA, no center has submitted a biologics license application.
VI. Rationale

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. 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 by Dong and colleagues. 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%).

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. 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. 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.

A large single center series was reported by Sutherland and colleagues in 2012. The study included 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation between February 1977 and September 2011. 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. Attainment of normal range HbA1c level (ie, ≤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, TEC completed an evidence report on islet cell transplantation in type 1 diabetes in its capacity as an Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). The evidence report found that published data on clinical outcomes of islet-alone transplantation were limited by small patient numbers, few transplant centers, short duration of follow-up, and lack of standardized methods of reporting clinical outcomes. Rare, serious adverse events have occurred in patients given islet transplants; recent procedure modifications reportedly minimize risks of these adverse events. No procedure-related deaths, cytomegalovirus (CMV) infection, or post-transplantation lymphoproliferative disease (PTL) 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, had 325 adult recipients in their registry as of April 2008. Three years after first infusion, 23% of islet-alone recipients were insulin-independent (defined as insulin-independent 2 or more 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.

The CITR published an updated report in 2012; the focus of the article was changes in outcomes over time. The number of patients receiving islet transplants was 214 during 1999-2002, 255 between mid-2003-2006 and 208 from 2007-2010. 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 50-53% 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 and colleagues in Canada published findings from a prospective cross-over study of intensive medical therapy (pretransplant) versus 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 pre-transplant and 66 months post-transplant. The overall mean HbA1c was 7.8% pretransplant and 6.7% post-transplant; this difference was statistically significant, p<0.001. In the 16 patients for whom sufficient data pre- and post-transplant were available on renal outcomes, the median decline in glomular filtration rate (GFR, ml/min/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 was 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 (MMF).

Small case series continue to be published, and these 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.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.

Practice Guidelines and Position Statements

Guidance from the National Institute for Clinical Excellence (NICE), 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. Evidence on safety shows that serious complications may occur, and the long-term immunosuppression required is also associated with risk of adverse events. The procedure is particularly indicated for patients with hypoglycemia unawareness or those already on immunosuppressive therapy because of renal transplantation. A 2008 update of guidance 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.

**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.

**VII. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

**VIII. References**