# Islet Transplantation

**Policy #** 00007
Original Effective Date: 08/26/2002
Current Effective Date: 11/21/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Chronic Intermittent Intravenous Insulin Therapy (CIIIT) is addressed separately in medical policy 00015.*

*Note: Allogeneic Pancreas Transplant is addressed separately in medical policy 00092.*

**When Services Are Eligible for Coverage**
*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous pancreas islet transplantation as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis to be **eligible for coverage**.

**When Services Are Considered Investigational**
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers allogeneic islet transplantation for the treatment of type 1 diabetes to be **investigational.***

Based on review of available data, the Company considers autologous or allogeneic islet transplantation for all other indications to be **investigational.***

## Background/Overview

**CHRONIC PANCREATITIS**
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.

**TYPE 1 DIABETES**
Glucose control is a challenge for individuals with type 1 diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease.

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**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.

Allogeneic islet transplantation potentially offers an alternative to whole-organ pancreas transplantation. 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. 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. Allogeneic transplantation may be performed in the radiology department.

In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen is known as the "Edmonton protocol."

## FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**
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.

**Centers for Medicare and Medicaid Services (CMS)**
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 are not.

## Rationale/Source

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**
The purpose of autologous pancreas islet transplantation for patients 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 question addressed in this evidence review is: Does autologous pancreas islet transplantation improve the net health outcome in individuals who have chronic pancreatitis who are undergoing total or near total pancreatectomy?

The following PICOTS were used to select literature to inform this review.

***Patients***
The relevant population of interest is individuals who have chronic pancreatitis who are undergoing total or near total pancreatectomy.

***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.

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

***Timing***
Short-term follow-up is required to monitor for transplant-related complications; long-term follow-up is required to establish durability of glucose control.

***Setting***
Islet transplantation is provided in a hospital setting with specialized staff who are equipped to perform the interventional radiology procedure and manage posttransplant care.

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*Study Selection Criteria*
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Systematic Reviews**
There are several systematic reviews of the literature on chronic pancreatitis patients. Wu et al (2015) published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis. Studies could use any design type but had to include at least 5 patients or have a median follow-up of at least 6 months. Twelve studies (total N=677 patients) met reviewers' inclusion criteria. The mean age was 38 years and the mean duration of pancreatitis was 6.6 years. A meta-analysis of the insulin-independence rate at 1 year (5 studies, 362 patients) was 28.4% (95% 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.

Dong et al (2011) published a systematic review that included studies irrespective of design or sample size. After reviewing 84 studies, 15 observational studies met eligibility criteria. Eleven studies assessed total pancreatectomy, 2 studies evaluated partial pancreatectomy, and 2 studies included both types of surgery. Sample sizes in individual studies ranged from 3 to 173 patients. Thirteen studies included patients with chronic pancreatitis and 2 included patients with benign pancreatic tumors. The pooled 30-day mortality rate was 5% (95% CI, 2% to 10%), and the cumulative mortality at 1 year (reported by 10 studies) was 4.9% (95% CI, 2.6% to 7.3%). In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100 person-years (95% CI, 1.53 to 7.62). The pooled rate of insulin independence was 27% (95% CI, 21% to 33%) at 1 year (5 studies) and 21% (95% CI, 16% to 27%) at 2 years (3 studies). Table 1 provides a crosswalk of studies included in the systematic reviews discussed. Tables 2 and 3 provide the characteristics and results of these systematic reviews.

**Table 1. Comparison of Studies Included in the Systematic Reviews**

| Study | Wu et al (2015) | Dong et al (2011) |
|---|---|---|
| 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) | | ● |

| Study | Wu et al (2015) | Dong et al (2011) |
|---|---|---|
| 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) | ● | |

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

| Study | Dates | Trials | Participants | N (Range) | Design | Duration, mo |
|---|---|---|---|---|---|---|
| Wu et al (2015) | 1977-2014 | 12 | Individuals with chronic pancreatitis | 677 (5-409) | Case series | 1-210 |
| Dong et al (2011) | 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 |
|---|---|---|
| Wu et al (2015) | | |
| 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) | | |
| 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) | |
| $I^2$, % | Not reported | |
| n | 201 | |
| 2-year follow-up (95% confidence interval) | 21 (16 to 27) | |
| $I^2$, % | Not reported | |

**Nonrandomized Studies**

Wilson et al (2014) reported on 166 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center. 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-independent and that declined to 27% at the 5-year follow-up. Daily insulin requirement, however, remained stable over the 5

years. Fifty-five percent of patients were independent of opioid analgesics at 1 year and this improved to 73% at 5 years.

Chinnakotla et al (2014) included 484 patients with chronic pancreatitis who underwent total pancreatectomy and immediate islet autotransplantation. The actuarial 10-year survival rate was 84%. Patient survival at 5 years was 90.3% in the 80 patients with hereditary/genetic pancreatitis and 89.7% in the 404 patients with nonhereditary pancreatitis; the difference between groups was not statistically significant. Pancreatitis pain decreased significantly after the procedures, and there was no statistically significant difference in the rate of pancreatitis pain between the groups.

Sutherland et al (2012) reported on 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation at a single center. 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, 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 opioid analgesia for pain control. At 12 months, the proportion of patients on narcotics decreased to 56% (n=32), and at 24 months, 41% of respondents (n=21) reported using narcotics.

Tables 4 and 5 provide the characteristics and results of the nonrandomized studies assessed.

**Table 4. Summary of Key Nonrandomized Study Characteristics**

| Study | Study Type | Country | Dates | Participants | Treatment | F/U, y |
|---|---|---|---|---|---|---|
| Wilson et al (2014) | Cohort | U.S. | 2000-2013 | Individuals with chronic pancreatitis | Total pancreatectomy and islet auto-transplantation (n=166) | ≥ 5 |
| Chinnakotla et al (2014) | Cohort | U.S. | 1977-2012 | Individuals with chronic pancreatitis | Total pancreatectomy and islet auto-transplantation (n=484) | NR |
| Sutherland et al (2012) | 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) | 98.2 | 94.6 | 38 | NR | 27 |
| Chinnakotla et al (2014) | | | | | |
| 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) | 97 | 90 | 26 | 30 | NR |

NR: Not reported.

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**Section Summary: Chronic Pancreatitis**
Autologous islet transplantation is frequently performed as an adjunct to 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 pancreatectomies for the treatment of chronic pancreatitis.

**TYPE 1 DIABETES**
The purpose of allogeneic pancreas islet transplantation for patients who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does allogeneic pancreas islet transplantation improve the net health outcome in individuals with type 1 diabetes?

The following PICOTS were used to select literature to inform this review.

***Patients***
The relevant population of interest is individuals with type 1 diabetes.

***Interventions***
The therapy being considered is allogeneic pancreas islet transplantation.

***Comparators***
The following practice is currently being used to make decisions about managing type 1 diabetes: medical management.

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

According to U.S. Food and Drug Administration (2009) industry guidance on evaluating allogeneic pancreatic islet cell products, single-arm trials with historical controls may be acceptable alternatives to RCTs for evaluating the safety and efficacy of islet cell products in patients with metabolically unstable type 1 diabetes. Attainment of a normal hemoglobin $A_{1c}$ ($HbA_{1c}$) range (ie, ≤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.

***Timing***
Short-term follow-up is required to monitor for transplant-related complications; the long-term follow-up to assess the durability of glucose control and monitor immunosuppression is lifelong.

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***Setting***
Islet transplantation is provided in a hospital setting with specialized staff who are equipped to perform the interventional radiology procedure and manage posttransplant care.

*Study Selection Criteria*
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Systematic Reviews**
A systematic review by Health Quality Ontario (2015) reported on islet transplantation for patients with type 1 diabetes. Case series derived from single centers constitutes most of the evidence. 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.

TEC Assessment (2004) evaluated the evidence on islet cell transplantation in type 1 diabetes. The Assessment found that published data on clinical outcomes of islet-alone transplantation were limited by small sample sizes (ie, ≤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 reportedly minimized risks of these adverse events. No procedure-related deaths, cytomegalovirus infection, or posttransplantation lymphoproliferative disease have been reported for islet-alone transplantation.

**Randomized Controlled Trials**
Lablanche et al (2018) published a multicenter, open-label, RCT (TRIMECO trial) evaluating patients who had type 1 diabetes with severe hypoglycemia or after kidney transplantation. Patients received immediate islet transplantation (n=25) or intensive insulin therapy followed by delayed islet transplantation (n=22). Median follow-up was 6 months for both groups. The primary end point was a composite score (β score) which has not been validated and which reflected fasting glucose, $HbA_{1c}$ level, C-peptide, and insulin independence. At 6 months, 16 of 25 patients in the immediate transplantation group and none of 22 patients in the control group had a modified β score of 6 or higher ($p<0.001$). Of note, few patients in the insulin group used continuous glucose monitoring or other technologies to monitor for hypoglycemia. At 6 months, insulin independence was achieved in 44% of patients in the immediate transplantation group (n=25; $p<0.001$). After the entire cohort received islet transplantation, the 1-year insulin independence rate

was 59% (n=46; p<0.001). Subsequent to islet transplantation, 6% of patients had bleeding complications. Trial limitations included possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability.

**Registry Studies**
In a report from the Collaborative Islet Transplant Registry, which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, Alejandro et al (2008) assessed data on 325 adult recipients. Three years after the first cell infusions, 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 $HbA_{1c}$ levels, processing centers related to the transplant center, and larger islet size.

Barton et al (2012) updated the Collaborative Islet Transplant Registry report, which focused on 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 a range of 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.

Thompson et al (2011) 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 $HbA_{1c}$ level was 7.8% pretransplant and 6.7% posttransplant (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 was -6.7 mL/min/1.73 $m^2$/y pretransplant and -1.3 mL/min/1.73 $m^2$/y posttransplant (p=0.01). Retinopathy was assessed using a scale that categorized 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 authors noted that their finding of reduced microvascular complications after islet transplantation might have been due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil.

Other small case series have reported some success and also adverse events. For example, O'Connell et al (2013) reported on 17 patients with type 1 diabetes and severe hypoglycemia who underwent islet

transplantation in Australia. Fourteen (82%) patients attained the primary endpoint, which was an $HbA_{1c}$ level of 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.

**Section Summary: Type 1 Diabetes**
Allogeneic islet transplantation has been investigated in the treatment of type 1 diabetes. One RCT found that quality of life was significantly improved after islet transplantation; however, the short length of follow-up limits these conclusions. Evidence from case series and systematic reviews has demonstrated varying ranges of insulin independence 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 from chronic pancreatitis. The procedure appears to decrease significantly the incidence of diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. Also, this islet procedure is not associated with serious complications and is performed in patients who are already undergoing a pancreatectomy procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with type 1 diabetes who receive allogeneic pancreas islet transplantation, the evidence includes an RCT, case series, and systematic reviews. Relevant outcomes are overall survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Results of a 2018 randomized trial have suggested some reduction in the number of severe hypoglycemic incidence annually, but limited follow-up and other trial limitations reduce the certainty in conclusions drawn. 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.

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## Policy History

Original Effective Date: 08/26/2002
Current Effective Date: 11/21/2018
08/15/2002 Medical Policy Committee review
08/26/2002 Managed Care Advisory Council approval

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Original Effective Date: 08/26/2002
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| | |
|---|---|
| 08/31/2004 | Medical Director review |
| 09/21/2004 | Medical Policy Committee review. Format revision. No substance change to policy. |
| 09/27/2004 | Managed Care Advisory Council approval |
| 09/07/2005 | Medical Director review |
| 09/20/2005 | Medical Policy Committee review. Coverage eligibility changes. Investigational statement for allogeneic islet cell transplantation for treatment of type 1 diabetes added. Format revision. FDA approval information added. |
| 09/22/2005 | Quality Care Advisory Council approval |
| 09/06/2006 | Medical Director review |
| 09/20/2006 | Medical Policy Committee approval. No changes to policy guidelines. |
| 09/05/2007 | Medical Director review |
| 09/19/2007 | Medical Policy Committee approval. No change to coverage eligibility. |
| 09/03/2009 | Medical Policy Committee approval |
| 09/16/2009 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/09/2010 | Medical Policy Committee review |
| 09/15/2010 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 09/01/2011 | Medical Policy Committee review |
| 09/14/2011 | Medical Policy Implementation Committee approval. No change to coverage statement. |
| 09/06/2012 | Medical Policy Committee review |
| 09/19/2012 | Medical Policy Implementation Committee approval. Title changed to “Islet Transplantation”. The words pancreatic and cell were dropped from the coverage statements. |
| 09/05/2013 | Medical Policy Committee review |
| 09/18/2013 | Medical Policy Implementation Committee approval. No change to coverage. |
| 09/04/2014 | Medical Policy Committee review |
| 09/17/2014 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 09/03/2015 | Medical Policy Committee approval |
| 09/23/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 10/01/2016 | Coding update |
| 11/03/2016 | Medical Policy Committee approval |
| 11/16/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 11/02/2017 | Medical Policy Committee approval |
| 11/15/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 11/08/2018 | Medical Policy Committee review |
| 11/21/2018 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

Next Scheduled Review Date: 11/2019

## Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician*.

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims*

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*responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

*CPT is a registered trademark of the American Medical Association.*

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code | | | |
|---|---|---|---|---|
| CPT | 48160, 48999 | | | |
| HCPCS | G0341, G0342, G0343, S2102 | | | |
| ICD-10 Diagnosis | E08.3511-E08.3599 | E08.37X1-E08.37X9 | E09.3211-E09.3299 | E09.3311-E09.3399 |
| | E09.3311-E09.3399 | E09.3411-E09.3499 | E09.3511-E09.3599 | E09.37X1-E09.37X9 |
| | E10.21-E10.29 | E10.311-E10.359 | E10.3211-E10.3299 | E10.3311-E10.3399 |
| | E10.10-E10.11 | E08.3211-E08.3299 | E08.3311-E08.3399 | E08.3411-E08.3499 |
| | E10.3511-E10.3599 | E10.36 | E10.37X1-E10.37X9 | E10.39-E10.49 |
| | E10.51-E10.59 | E10.610 | E10.618 | E10.620-E10.628 |
| | E10.630-E10.638 | E10.641-E10.649 | E10.65 | E10.69 |
| | E10.8-E10.9 | E11.3211-E11.3299 | E11.3311-E11.3399 | E11.3411-E11.3499 |
| | E11.3511-E11.3599 | E11.37X1-E11.37X9 | E13.3211-E13.3299 | E13.3311-E13.3399 |
| | E13.3411-E13.3499 | E13.3511-E13.3599 | E13.37X1-E13.37X9 | K86.0-K86.1 |

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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