Allogeneic Pancreas Transplant

Policy # 00092
Original Effective Date: 11/22/1993
Current Effective Date: 01/08/2020

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: Islet cell transplantation is considered in medical policy 00007.

When Services May Be 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 a combined pancreas-kidney transplant in insulin dependent diabetic patients with uremia to be **eligible for coverage.****

Based on review of available data, the Company may consider pancreas transplant after a prior kidney transplant in patients with insulin dependent diabetes to be **eligible for coverage.****

Based on review of available data, the Company may consider pancreas transplant alone in patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile insulin dependent diabetes that persists in spite of optimal medical management to be **eligible for coverage.****

Based on review of available data, the Company may consider pancreas retransplant after a failed primary pancreas transplant in patients who meet criteria for pancreas transplantation to be **eligible for coverage. ****

Pancreas transplantation, when the transplant recipient is human immunodeficiency virus (HIV) positive, may be considered for coverage when all of the additional criteria are met:

- CD4 count >200 cells/mm-3 for more than six months; and
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least six months; and
- Demonstrable adherence and a stable HAART regimen for at least six months; and

- Absence of AIDS-defining illness following successful immune reconstitution after HAART; and
- All other transplant criteria are met.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of pancreas transplant when patient selection criteria are not met is considered **investigational.***

The use of pancreas transplant in HIV positive recipients when patient selection criteria and additional HIV positive patient selection criteria are not met is considered **investigational.***

Based on review of available data, pancreas re-transplantation after two or more prior failed pancreas transplants is considered **investigational.***

Policy Guidelines

General Criteria

Potential contraindications for solid organ transplant are subject to the judgment of the transplant center include the following:

1. Known current malignancy, including metastatic cancer
2. Recent malignancy with high-risk of recurrence
3. Untreated systemic infection making immunosuppression unsafe, including chronic infection
4. Other irreversible end-stage diseases not attributed to kidney disease
5. History of cancer with a moderate risk of recurrence
6. Systemic disease that could be exacerbated by immunosuppression
7. Psychosocial conditions or chemical dependency affecting the ability to adhere to therapy.

Pancreas-Specific Criteria

Candidates for pancreas transplant alone should also meet one of the following severity of illness criteria:

- Documentation of severe hypoglycemia unawareness as evidenced by chart notes or emergency department visits or
- Documentation of potentially life-threatening labile diabetes, as evidenced by chart notes or hospitalization for diabetic ketoacidosis.

Additionally, most pancreas transplant patients will have type 1 diabetes. Those transplant candidates with type 2 diabetes, in addition to being insulin-dependent, should also not be obese (body mass index should be ≤32 kg/m2). According to International Pancreas Transplant Registry data, in 2010, 7% of pancreas transplant recipients had type 2 diabetes (Gruessner [2011]).

Multiple Transplant Criteria
Although there are no standard guidelines for multiple pancreas transplants, the following information may aid in case review:

- If there is early graft loss resulting from technical factors (eg, venous thrombosis), a retransplant may generally be performed without substantial additional risk.
- Long-term graft losses may result from chronic rejection, which is associated with increased risk of infection following long-term immunosuppression, and sensitization, which increases the difficulty of finding a negative cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

Background/Overview

Pancreas transplantation occurs in several different scenarios such as (1) a diabetic patient with renal failure who may receive a simultaneous cadaveric pancreas plus kidney transplants; (2) a diabetic patient who may receive a cadaveric or living-related pancreas transplant after a kidney transplantation (pancreas after kidney); or (3) a nonuremic diabetic patient with specific severely disabling and potentially life-threatening diabetic problems who may receive a pancreas transplant alone. The total number of adult pancreas transplants (pancreas and pancreas plus kidney) in the U. S. peaked at 1484 in 2004 and has since steadily declined. In 2017, 213 received a pancreas transplant alone and 789 simultaneous pancreas plus kidneys were performed in the U. S.

According to the International Pancreas Transplant Registry data, the proportion of pancreas transplant recipients worldwide who have type 2 diabetes has increased over time, from 2% in 1995

to 7% in 2010. In 2010, approximately 8% of simultaneous pancreas plus kidney transplants, 5% of pancreas transplant after kidney transplant, and 1% of a pancreas transplant alone were performed in patients with type 2 diabetes.

Small bowel/liver and multivisceral transplantation are surgical procedures and, as such, are not subject to regulation by the U.S. Food and Drug Administration.
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. Pancreas transplants are included in these regulations.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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Rationale/Source

Transplantation of a healthy pancreas is a treatment for patients with insulin-dependent diabetes. Pancreas transplantation can restore glucose control and prevent, halt, or reverse the secondary complications from diabetes.

For individuals who have insulin-dependent diabetes who receive a pancreas transplant after a kidney transplant, the evidence includes case series and registry studies. The relevant outcomes are overall survival (OS), change in disease status, and treatment-related mortality and morbidity. Data from national and international registries have found relatively high patient survival rates with a pancreas transplant after a kidney transplant (eg, a 3-year survival rate of 93%). A 2012 analysis of data from a single-center found similar patient survival and death-censored pancreas graft survival rates with a pancreas transplant after a kidney transplant or a simultaneous pancreas and kidney

(SPK) transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have insulin-dependent diabetes with uremia who receive SPK transplants, the evidence includes registry studies. The relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. Data from national and international registries have found relatively high patient survival rates after SPK transplant. A retrospective analysis found a higher survival rate in patients with type 1 diabetes who had an SPK transplant vs those on a waiting list. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have insulin-dependent diabetes and severe complications who receive pancreas transplant alone, the evidence includes registry studies. The relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. Data from international and national registries have found that graft and patient survival rates after pancreas transplant alone have improved over time (eg, 3-year survival of 95%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had a prior pancreas transplant who still meet criteria for a pancreas transplant who receive pancreas retransplantation, the evidence includes case series and registry studies. The relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. National data and specific transplant center data have generally found similar graft and patient survival rates after pancreas retransplantation compared with initial transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Organ Procurement and Transplantation Network

The Organ Procurement and Transplantation Network updated its comprehensive list of transplant-related policies, most recently in May 2019.

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For pancreas registration:
"Each candidate registered on the pancreas waiting list must meet *one* of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency
- Require the procurement or transplantation of a pancreas as part of a multiple organ transplant for technical reasons."

For combined kidney plus pancreas registration: "Each candidate registered on the kidney-pancreas waiting list must be diagnosed with diabetes or have pancreatic exocrine insufficiency with renal insufficiency."

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

Medicare National Coverage
An allogeneic pancreas transplant is covered under Medicare when performed in a facility approved by Medicare as meeting institutional coverage criteria. The Centers for Medicare & Medicaid Services made the following national coverage decision on pancreas transplant for Medicare recipients.

A. General
Pancreas transplantation is performed to induce an insulin-independent, euglycemic state in diabetic patients. The procedure is generally limited to those patients with severe secondary complications of diabetes, including kidney failure. However, pancreas transplantation is sometimes performed on patients with labile diabetes and hypoglycemic unawareness.

B. Nationally Covered Indications
Effective … 1999, whole organ pancreas transplantation is nationally covered by Medicare when performed simultaneously with or after a kidney transplant. If the pancreas transplant occurs after the kidney transplant, immunosuppressive therapy begins with the date of discharge from the inpatient stay for the pancreas transplant.

Effective … 2006, pancreas transplants alone (PA) are reasonable and necessary for Medicare beneficiaries in the following limited circumstances:

1. PA will be limited to those facilities that are Medicare-approved for kidney transplantation.
    - Patients must have a diagnosis of type I diabetes:
    - Patient with diabetes must be beta-cell autoantibody-positive; or
2. Patient must demonstrate insulinopenia defined as a fasting C-peptide level that is less than or equal to 110% of the lower limit of normal of the laboratory's measurement method. Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose ≤225 mg/dL;
3. Patients must have a history of medically-uncontrollable labile (brittle) insulin-dependent diabetes mellitus with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization. Aforementioned complications include frequent hypoglycemia unawareness or recurring severe ketoacidosis, or recurring severe hypoglycemic attacks;
4. Patients must have been optimally and intensively managed by an endocrinologist for at least 12 months with the most medically recognized advanced insulin formulations and delivery systems;
5. Patients must have the emotional and mental capacity to understand the significant risks associated with surgery and to effectively manage the lifelong need for immunosuppression; and,
6. Patients must otherwise be a suitable candidate for transplantation."

Nationally non-covered indications include "Transplantation of partial pancreatic tissue or islet cells (except in the context of a clinical trial)."

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT01047865	Type 1 Diabetes Recurrence in Pancreas Transplants	400	May 2020
NCT01957696	A Prospective, Observational Study in Pancreatic Allograft Recipients: The Effect of Risk Factors, Immunosuppressive Level and the Benefits of Scheduled Biopsies - on Surgical Complications, Rejections, and Graft Survival	80	Oct 2028
NCT00238693	Transplant Registry: Patients Who May Require Transplantation and Those Who Have Undergone	13,767	Jan 2018

	Transplantation of Liver, Kidney and/or Pancreas		

NCT: national clinical trial.

References

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11/21/2001	Managed Care Advisory Council approval
11/18/2003	Medical Policy Committee review
01/26/2004	Managed Care Advisory Council approval
01/04/2005	Medical Director review
01/18/2005	Medical Policy Committee review. Format revision. No substance change to policy.
01/31/2005	Managed Care Advisory Council approval
02/01/2006	Medical Director review
03/15/2006	Medical Policy Committee approval. Format revision.
02/07/2007	Medical Director review
02/21/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
02/13/2008	Medical Director review
02/20/2008	Medical Policy Committee approval.
02/04/2009	Medical Director review
02/19/2009	Medical Policy Committee approval. Clarified 2nd, 3rd and 4th criteria bullets for HIV positive transplant recipients. No change to coverage eligibility.
02/04/2010	Medical Policy Committee approval
02/17/2010	Medical Policy Implementation Committee approval. No change to coverage.

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02/03/2011	Medical Policy Committee approval
02/16/2011	Medical Policy Implementation Committee approval. No change to coverage.
02/02/2012	Medical Policy Committee approval
02/15/2012	Medical Policy Implementation Committee approval. Patient selection criteria revised.
01/03/2013	Medical Policy Committee approval
01/09/2013	Medical Policy Implementation Committee approval. No change to coverage.
01/09/2014	Medical Policy Committee approval
01/15/2014	Medical Policy Implementation Committee approval. Patient selection criteria section removed.
01/08/2015	Medical Policy Committee approval
01/21/2015	Medical Policy Implementation Committee approval. Added "in patients who meet criteria for pancreas transplantation" in the criteria for pancreas retransplant after a failed primary pancreas transplant.
01/07/2016	Medical Policy Committee approval
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee approval
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage
01/04/2018	Medical Policy Committee approval
01/17/2018	Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
01/10/2019	Medical Policy Committee approval
01/23/2019	Medical Policy Implementation Committee approval. No change to coverage
01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 01/2021

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 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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	48550, 48551, 48552, 48554, 48556
HCPCS	S2065, S2152
ICD-10 Diagnosis	All related diagnoses

*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.

**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.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.