Policy Statement

A small bowel transplant using cadaveric intestine may be considered medically necessary in adult and pediatric patients when all of the following criteria have been met:

- Intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance)
- Established long-term dependency on total parenteral nutrition (TPN)
- Developing or have developed severe complications due to TPN

A small bowel transplant using a living donor may be considered medically necessary only when a cadaveric intestine is not available for transplantation in a patient who meets the criteria noted above for a cadaveric intestinal transplant.

A small bowel retransplant may be considered medically necessary after a failed primary small bowel transplant.

A small bowel transplant using living donors is considered not medically necessary in all other situations.

A small bowel transplant is considered investigational for adults and pediatric patients with intestinal failure who are able to tolerate TPN.

Policy Guidelines

General
Potential contraindications that are subject to the judgment of the transplant center:

- Known current malignancy, including metastatic cancer
- Recent malignancy with high risk of recurrence
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end-stage disease not attributed to intestinal failure
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

Small Bowel-Specific
Intestinal failure results from surgical resection, congenital defect, or disease-associated loss of absorption, and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance. Short-bowel syndrome is one case of intestinal failure.

Patients who are developing or have developed severe complications due to total parenteral nutrition (TPN) include, but are not limited to, the following: multiple and prolonged hospitalizations to treat TPN-related complications (especially repeated episodes of catheter-related sepsis) or the development of progressive liver failure. In the setting of progressive liver failure, small bowel transplant may be considered a technique to avoid end-stage liver failure related to chronic TPN, thus avoiding the necessity of a multivisceral transplant. In those receiving TPN, liver disease with jaundice (total bilirubin greater than 3 mg/dL) is often associated with development of irreversible progressive liver disease. The inability to maintain venous access is another reason to consider small bowel transplant in those who are dependent on TPN.
Description

A small bowel transplant may be performed as an isolated procedure or in conjunction with other visceral organs, including the liver, duodenum, jejunum, ileum, pancreas, or colon. Isolated small bowel transplant is commonly performed in patients with short bowel syndrome. Small bowel/liver transplants and multivisceral transplants are considered in Blue Shield of California Medical Policy: Small Bowel/Liver and Multivisceral Transplant.

Related Policies

- Small Bowel/Liver and Multivisceral Transplant

Benefit Application

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

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

Regulatory Status

Small bowel transplantation is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Rationale

Background

A small bowel transplant is typically performed in patients with short bowel syndrome. This is a condition in which the absorbing surface of the small intestine is inadequate due to extensive disease or surgical removal of a large portion of small intestine. In adults, etiologies of short bowel syndrome include ischemia, trauma, volvulus, and tumors. In children, gastrochisis, volvulus, necrotizing enterocolitis, and congenital atresias are predominant causes.

The small intestine, particularly the ileum, does have the capacity to adapt to some functions of the diseased or removed portion over a period of 1 to 2 years. Prognosis for recovery depends on the degree and location of small intestine damage. Therapy is focused on achieving adequate macro- and micro-nutrient uptake in the remaining small bowel. Pharmacologic agents have been studied to increase villous proliferation and slow transit times, and surgical techniques have been advocated to optimize remaining small bowel. However, some patients with short bowel syndrome are unable to obtain adequate nutrition from enteral feeding and become chronically dependent on total parenteral nutrition (TPN). Patients with complications from TPN may be considered candidates for small bowel transplant. Complications include catheter-related mechanical problems, infections, hepatobiliary disease, and metabolic bone disease. While cadaveric intestinal transplant is the most commonly performed transplant, there has been recent interest in using living donors.

Intestinal transplants (including multivisceral and bowel/liver) represent a small minority of all solid organ transplants. In 2011, 129 intestinal transplants were performed in the United States, of
which all but 1 was from deceased donors. In 2012, 106 intestinal transplants were performed in the United States; all were from deceased donors.

**Literature Review**

**Small Bowel Transplantation**

This evidence review is based on 2 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessments conducted in the 1990s. A 1995 TEC Assessment concluded that, in children, small bowel transplant was associated with improved survival rates compared with total parenteral nutrition (TPN) because the associated adverse outcomes for small bowel transplant were offset by severe TPN-related complications. This Assessment also concluded that, in adults, the outcomes for small bowel transplant were worse than that associated with TPN. A 1999 TEC Assessment reevaluated the data on adults and concluded that, because it is not possible to predict which patients would survive longer on TPN versus small bowel transplant, transplantation may be considered a reasonable option in selected adults.

Much of the published literature consists of relatively small case series. For example, in 2014, Ueno et al in Japan reported on 21 intestinal transplant patients; all but 1 received an isolated small bowel transplant for intestinal failure. Overall 1- and 5-year survival rates were 86% and 68%, respectively. In the 15 patients who underwent transplantation after 2006, 1-year survival was 92% and 5-year survival was 83%.

These reports, as well as reviews of observational data, have noted that while outcomes continue to improve, obstacles remain to long-term survival. Recurrent and chronic rejections and complications of immunosuppression are significant issues in bowel transplantation.

One obstacle is timely referral for intestinal transplantation to avoid combined liver and intestine transplantation. It has been suggested that improvements in survival may justify removing the restriction of intestinal transplantation to patients who have severe complications of TPN. However, Vianna et al (2008) have reported on the status of intestinal transplantation, no randomized trials were identified that have compared intestinal transplantation with long-term TPN, and optimal timing for earlier transplantation has not been established.

Another obstacle is the rate of various complications after small bowel transplant. Florescu et al have published several retrospective reviews of complications in a cohort of 98 pediatric patients. Twenty-one (21.4%) of these children had an isolated small bowel transplant; the remainder had combined transplants. Their 2012 study reported that 68 (69%) of the 98 patients developed at least 1 episode of bloodstream infection. Among patients with an isolated small bowel transplant, the median time to infection for those who developed one was 4.5 months (95% confidence interval, 2.4 to 6.7 months). Also in 2012, these researchers reported that 7 (7%) of 98 patients developed cytomegalovirus disease; only 1 had an isolated small bowel transplant. In 2010, Florescu et al reported that 25 (25.5%) of 98 cases reviewed who developed at least 1 episode of fungal infection; Candida infection was most common. Mortality rates did not differ significantly between patients who did (32.3%) and did not develop a fungal infection (29.8%; p=0.46).

Several other series have reported on renal failure after intestinal transplantation. In 2013, a research group in France reported that 7 of 12 children who had an isolated small bowel transplant with renal function complications at some point after surgery. Before treatment, all patients had normal renal functioning. In 2014, Calvo Pulido et al in Spain reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants. Thirteen (62%) patients experienced renal failure; the etiology included high ileostomy output, immunosuppression, and medical treatment.

**Living Donor Transplants**

Cadaveric intestines have been most commonly used, but recently there has been interest in using a portion of intestine harvested from a living, related donor. Potential advantages of a
Living donor include the ability to plan the transplantation electively and better antigen matching, leading to improved management of rejection. Small case reports from the 1990s have reported on 1 or 2 patients with different lengths of the ileum or jejunum. While there appear to be minimal complications to the donors, of the 6 cases reported, 5 recipients remain on TPN for at least part of their nutrition. One patient was weaned off TPN.

Benedetti et al (2006) reported outcomes from 4 children and 7 adults who underwent 12 living small bowel transplantations between 1998 and 2004. All related donors were reported to have had uneventful recovery following removal of up to 40% of the small intestine. The 3-year transplant patient survival was 82%, with graft survival of 75%. Longer follow-up from the earlier cases was not reported. Gangemi and Benedetti (2006) published a literature review of living donor small bowel transplantation reports from 2003 to 2006; all reports listed Benedetti as coauthor. Reviewers commented that, “Due to the excellent result in modern series of deceased donor bowel transplantation, widespread use of the procedure [living donor] should not be recommended, in consideration of the potential risks to donor. Furthermore, few centers have acquired the necessary experience with the procedure.”

In 2010, Sudan published a review of current literature on long-term outcomes after intestinal transplantation. Sudan noted that intestinal transplantation had become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series indicated a 1-year patient survival rate of 78% to 85% and a 5-year or more survival rate of 56% to 61%. With respect to pediatric intestinal transplant patients, most achieve normal growth velocity at 2 years posttransplant. However, oral aversion is common; tube feedings are necessary in 45% of children. Sudan also reported on parental surveys of quality of life for pediatric transplant patients in which intestinal transplant patients appear to have modestly improved quality of life compared with patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

**Human Immunodeficiency Virus-Positive Transplant Recipients**

Transplants for recipients with HIV infection have long been controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Although HIV-positive transplant recipients may be a research interest of some transplant centers, the minimal data on long-term outcome in these patients primarily consist of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons have argued that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

As of 2013, the United Network for Organ Sharing (UNOS) policy on HIV-positive transplant candidates stated: “A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy” (Policy 4, Identification of Transmissible Diseases in Organ Recipients).

In 2006, the British HIV Association and the British Transplantation Society published joint guidelines for kidney transplantation in patients with HIV disease. These criteria may be extrapolated to other organs.

The guidelines, which are similar to the UNOS guidelines, recommend that any patient with end-stage organ disease with a life expectancy of at least 5 years is considered appropriate for transplantation under the following conditions:

- CD4 200 cells/microliter for at least 6 months.
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months.
- Demonstrable adherence and a stable HAART regimen for at least 6 months.
- Absence of AIDS-defining illness following successful immune reconstitution after HAART.
Section Summary: Small Bowel Transplantation
Small bowel transplant is infrequently performed, and only relatively small case series, generally single-center, are available. Risks after small bowel transplant are high, particularly related to infection, but may be balanced against the need to avoid the long-term complications of TPN dependence. In addition, early small bowel transplant may obviate the need for a later combined liver/small bowel transplant. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation.

Small Bowel Retransplantation
Desai et al (2012) have published the most comprehensive reporting of outcomes after repeat small bowel transplant in the United States. They evaluated data in the UNOS database on patients who underwent small bowel transplants in the United States between October 1987 and August 2009.21 Investigators identified 41 repeat isolated small bowel transplants in adults and 28 in children. Thirty-nine (95%) of the adults and 27 (96%) of the children had a previous isolated small bowel transplant; the remaining patients had an initial combined small bowel and liver transplant.

Among adults, survival rates after retransplant were 80% after 1 year, 47% after 3 years, and 29% after 5 years. Comparable survival rates for primary isolated small bowel transplant were 84% after 1 year, 67% after 3 years, and 54% after 5 years. Survival was significantly lower after repeat isolated small bowel transplant compared with primary isolated small bowel transplant (p=0.005).

Among children, patient survival was 81% after 1 year, 74% after 3 years, and 58% after 5 years. These rates did not differ significantly from rates after primary isolated small bowel transplant (85% after 1 year, 71% after 3 years, 64% after 5 years, respectively).

Section Summary: Small Bowel Retransplantation
Data from only a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data after retransplantation have suggested reasonably high survival rates after small bowel in patients who continue to meet criteria for transplantation.

Summary of Evidence
For individuals who have intestinal failure who receive a small bowel transplant, the evidence includes case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. Small bowel transplant is infrequently performed, and only relatively small case series, generally single-center, are available. Risks after small bowel transplant are high, particularly related to infection, but may be balanced against the need to avoid the long-term complications of total parenteral nutrition dependence. In addition, early small bowel transplant may obviate the need for a later combined liver/small bowel transplant. Transplantation is contraindicated in patients in whom the procedure is expected to be futile due to comorbid disease or in whom posttransplantation care is expected to significantly worsen comorbid conditions. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have failed small bowel transplant without contraindication(s) for retransplant who receive a small bowel retransplant, the evidence includes case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. Data from only a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data after retransplantation have suggested a reasonably high survival rate after small bowel in patients who continue to meet criteria for transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Supplemental Information
Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received through 2 physician specialty societies and 2 academic medical centers in 2009. The consensus of those providing input was that small bowel transplant should be performed in patients who are developing severe total parenteral nutrition-related complications and that small bowel transplant from living donors may be considered when cadaveric intestinal transplants are not available.

Practice Guidelines and Position Statements
In 2003, the American Gastroenterological Association produced a medical position statement on short bowel syndrome and intestinal transplantation.22 It recommended dietary, medical, and surgical solutions. Indications for intestinal transplantation mirror those of the Centers for Medicare and Medicaid Services. The guidelines acknowledged the limitations of transplant for these patients. The statement recommended the following Medicare-approved indications, pending availability of additional data:
  1. “Impending or overt liver failure....
  2. Thrombosis of major central venous channels....
  3. Frequent central line-related sepsis....
  4. Frequent severe dehydration.”

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

Medicare National Coverage
“Effective for services performed on or after April 1, 2001, this procedure [intestinal and multivisceral transplantation] is covered only when performed for patients who have failed total parenteral nutrition (TPN) and only when performed in centers that meet approval criteria.
  1. Failed TPN
The TPN delivers nutrients intravenously, avoiding the need for absorption through the small bowel. TPN failure includes the following:
  • Impending or overt liver failure due to TPN induced liver injury. The clinical manifestations include elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding or hepatic fibrosis/cirrhosis.
  • Thrombosis of the major central venous channels; jugular, subclavian, and femoral veins. Thrombosis of two or more of these vessels is considered a life-threatening complication and failure of TPN therapy. The sequelae of central venous thrombosis are lack of access for TPN infusion, fatal sepsis due to infected thrombi, pulmonary embolism, Superior Vena Cava syndrome, or chronic venous insufficiency.
  • Frequent line infection and sepsis. The development of two or more episodes of systemic sepsis secondary to line infection per year that requires hospitalization indicates failure of TPN therapy. A single episode of line-related fungemia, septic shock and/or acute respiratory distress syndrome are considered indicators of TPN failure.
  • Frequent episodes of severe dehydration despite intravenous fluid supplement in addition to TPN. Under certain medical conditions such as secretory diarrhea and nonconstructable gastrointestinal tract, the loss of the gastrointestinal and pancreatic secretions exceeds the maximum intravenous infusion rates that can be tolerated by the cardiopulmonary system. Frequent episodes of dehydration are deleterious to all body organs particularly kidneys and the central nervous system.
with the development of multiple kidney stones, renal failure, and permanent brain
damage.

2. Approved Transplant Facilities
Intestinal transplantation is covered by Medicare if performed in an approved facility. The
criteria for approval of centers will be based on a volume of 10 intestinal transplants per year
with a 1-year actuarial survival of 65 percent using the Kaplan-Meier technique."^{23}

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials
that would likely influence this review.

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**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):
- Referring physician history and physical
- Gastroenterologist and/or Hepatology consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient’s ability to be an adequate candidate for transplant
- Radiology reports including:
  - Abdominal CT, ultrasound, and/or MRI
  - CXR
- GI procedure reports:
  - Colonoscopy if > 50 years of age
  - EGD
- Cardiology procedures and respiratory function reports:
  - EKG
  - Cardiac echocardiogram, stress test, and cardiac catheterization (if indicated)
  - Pulmonary function tests (PFTs)
- Laboratory reports

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<td>Donor enterectomy (including cold preservation), open; from cadaver donor</td>
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<td>Donor enterectomy (including cold preservation), open; partial, from living donor</td>
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HCPCS None

ICD-10 Procedure 0DY80Z0 | Transplantation of Small Intestine, Allogeneic, Open Approach

ICD-10 Diagnosis | All Diagnoses

Policy History

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

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<td>Policy Revision</td>
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Definitions of Decision Determinations

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

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

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

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

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

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

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