Small Bowel Transplant, Small Bowel/Liver Transplant and Multivisceral Transplant

Policy # 00112
Original Effective Date: 01/28/2002
Current Effective Date: 10/17/2018

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.

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 small bowel/liver transplant or multivisceral transplant for pediatric and adult patients to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be considered for pediatric and adult patients with intestinal failure when all of the following criteria are met:

- Have intestinal failure; and
- Have been managed with long-term total parenteral nutrition (TPN); and
- Have developed evidence of impending end-stage liver failure.

Evidence of intolerance of total parental nutrition includes, but is not limited to, multiple and prolonged hospitalizations to treat total parental nutrition related complications, or the development of progressive but reversible 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 total parental nutrition, thus avoiding the necessity of a multivisceral transplant.

Human immunodeficiency virus positive transplant recipients will be considered eligible for coverage when all of the additional criteria are met:

- CD4 count >200 cells per cubic millimeter for >6 months; and
- HIV-1 RNA undetectable; and
- On stable anti-retroviral therapy >3 months; and

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- No other complications from acquired immune deficiency syndrome (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidiose mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm); and
- All other criteria for transplantation are met.

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

When patient selection criteria have not been met, small bowel transplant, small bowel/liver transplant and multivisceral transplant are considered investigational.*

Potential contraindications subject to the judgment of the transplant center:
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 disease not attributed to intestinal failure
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 ability to adhere to therapy

Note: 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.

Isolated Small Bowel Transplant

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 small bowel transplant using cadaveric intestine in adult and pediatric patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who have established long-term dependency on total parenteral nutrition (TPN) and are developing or have developed severe complications due to TPN to be eligible for coverage.
Based on review of available data, the Company may consider a small bowel transplant using a living donor only when a cadaveric intestine is not available for transplantation in a patient who meets criteria for a cadaveric intestinal transplant to be **eligible for coverage**.

**When Services Are Considered Not Medically Necessary**

Based on review on available data, the Company considers the use of a small bowel transplant using living donors in all other situations to be **not medically necessary.**

**When Services Are Considered Investigational**

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

Based on the review of available data, a small bowel transplant for adults and pediatric patients with intestinal failure who are able to tolerate TPN is considered to be **investigational.**

**Background/Overview**

**SMALL BOWEL SYNDROME**

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, gastroschisis, volvulus, necrotizing enterocolitis, and congenital atresia are predominant causes.

**Treatment**

The small intestine, particularly the ileum, can 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 micronutrient 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. Patients with complications from total parenteral nutrition 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 2016, 147 intestinal transplants were performed in the United States; all were from cadaver donors.
SHORT BOWEL SYNDROME

Small bowel transplants are typically performed in patients with short bowel syndrome, defined as an inadequate absorbing surface of the small intestine due to extensive disease or surgical removal of a large portion of small intestine. In some instances, short bowel syndrome is associated with liver failure, often due to the long-term complications of total parenteral nutrition.

Treatment

These patients may be candidates for a small bowel/liver transplant or a multivisceral transplant, which includes the small bowel and liver with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, and/or colon. The type of transplantation depends on the underlying etiology of intestinal failure, quality of native organs, presence or severity of liver disease, and history of prior abdominal surgeries. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant. Complications following small bowel/liver and multivisceral transplants include acute or chronic rejection, donor-specific antibodies, infection, lymphoproliferative disorder, graft-versus-host disease, and renal dysfunction.

FDA or Other Governmental Regulatory Approval

Centers for Medicare and Medicaid Services (CMS)

Medicare will cover intestinal transplantation for the purposes of restoring intestinal function in patients with irreversible intestinal failure only when performed for patients who have failed TPN and only when performed in centers that meet approved criteria. The criteria for approval of centers will be based on an annual volume of 10 intestinal transplants per year with a 1-year actuarial survival of 65% (these criteria were reviewed again in 2006 and upheld).

Effective for services performed on or after April 1, 2001, this procedure is covered only when performed for patients who have failed 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.

2. Approved Transplant Facilities
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.

Rationale/Source
SMALL BOWEL TRANSPLANTATION
This evidence review has been informed by 2 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 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 those 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 vs small bowel transplant, transplantation may be considered a reasonable option in select adults.

The published literature consists of case series, mainly reported by single centers in the United States, Japan, and Europe. Tables 1 and 2 summarize the characteristics and results of the case series, respectively. Many case series have included small bowel/liver transplantations and multivisceral transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off TPN. Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multivisceral transplantations (see Table 2).

Several investigators have reported higher survival rates in transplantations conducted more recently than those conducted earlier. Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex 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 has indicated 1-year patient survival rates between 78% and 85% and 5-year or more survival rates between 56% and 61%. Concerning 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.

Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

**Table 1. Summary of Key Case Series Characteristics for Transplantations**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>N</th>
<th>Median Age (Range), y</th>
<th>Interventions</th>
<th>Treatment</th>
<th>Follow-Up (Range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al (2017)</td>
<td>France</td>
<td>110</td>
<td>5.3 (0.4-19)</td>
<td>• Isolated IT</td>
<td>60</td>
<td>17 at &lt;5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Combined liver IT</td>
<td>45</td>
<td>17 at 5-10 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Multivisceral graft</td>
<td>5</td>
<td>21 at ≥10 y</td>
</tr>
<tr>
<td>Garcia Aroz et al (2017) a</td>
<td>U.S.</td>
<td>10</td>
<td>1.5 (0.7-13)</td>
<td>• Isolated IT</td>
<td>7</td>
<td>6/7 alive at follow-up &gt;10 y</td>
</tr>
<tr>
<td>Dore et al (2016)</td>
<td>U.S.</td>
<td>30</td>
<td>0.2 (0.1-18)</td>
<td>• Isolated IT</td>
<td>6</td>
<td>28 (4-175)</td>
</tr>
<tr>
<td>Rutter et al (2016)</td>
<td>U.K.</td>
<td>60</td>
<td>1.8 (0-8)</td>
<td>• Isolated IT</td>
<td>16</td>
<td>21.3 (0-95)</td>
</tr>
<tr>
<td>Lauro et al (2014)</td>
<td>Italy</td>
<td>46</td>
<td>34 (NR)</td>
<td>• Isolated IT</td>
<td>34</td>
<td>51.3</td>
</tr>
<tr>
<td>Ueno et al (2014) b</td>
<td>Japan</td>
<td>24</td>
<td>0-2 y: 6 a 3-6 y: 6 7-18 y: 8 ≥19 y: 4</td>
<td>• Isolated IT</td>
<td>23</td>
<td>NR</td>
</tr>
<tr>
<td>Benedetti et al (2006) a</td>
<td>U.S.</td>
<td>11</td>
<td>27 (1.5-50)</td>
<td>• Isolated IT</td>
<td>11</td>
<td>NR</td>
</tr>
</tbody>
</table>

IT: intestinal transplantation; NR: not reported.
a All living donors.
b Twelve living donors and 12 cadaveric donors.
c Reported as age range and n.

**Table 2. Summary of Key Case Series Results for Transplantations**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Interventions</th>
<th>Survival</th>
<th>Off Total Parenteral Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Years</th>
<th>%</th>
<th>Measure</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al (2017)</td>
<td>Isolated IT</td>
<td>60</td>
<td>10</td>
<td>59</td>
<td>All combined at last follow-up</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Combined liver</td>
<td>45</td>
<td>10</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivisceral graft</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia Aroz et al (2017)*</td>
<td>Isolated IT</td>
<td>7</td>
<td>All combined: 70</td>
<td></td>
<td>All combined at last follow-up</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Combined liver IT</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dore et al (2016)</td>
<td>Isolated IT</td>
<td>6</td>
<td>9</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined liver IT</td>
<td>6</td>
<td>10</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivisceral graft</td>
<td>18</td>
<td>2.5</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutter et al (2016)</td>
<td>Isolated IT</td>
<td>16</td>
<td>1</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivisceral graft</td>
<td>35</td>
<td>1</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Modified multivisceral</td>
<td>9</td>
<td>1</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lauro et al (2014)</td>
<td>Isolated IT</td>
<td>34</td>
<td>1</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined liver IT</td>
<td>6</td>
<td>3</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivisceral graft</td>
<td>6</td>
<td>5</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueno et al (2014)b</td>
<td>Isolated IT</td>
<td>23</td>
<td>1</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined liver IT</td>
<td>1</td>
<td>5</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benedetti et al (2006)a</td>
<td>Isolated IT</td>
<td>11</td>
<td>1</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IT: intestinal transplantation; NR: not reported.

* All living donors.
b Twelve living donors and 12 cadaveric donors.

### Adverse Events

One issue discussed in intestinal transplantation literature is earlier referral to avoid combined liver and intestine transplantation. It has been suggested that removing the restriction on intestinal transplantation to patients who have severe complications from TPN and recommending earlier transplantation may improve survival. However, in a review of the status of intestinal transplantation, Vianna et al (2008) identified no randomized trials that compared intestinal transplantation with long-term TPN; therefore, optimal timing for earlier transplantation has not been established.

In 2016, Wu et al investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (N=175). Patients were 25 years of age. Acute ABMR was diagnosed by clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free small intestine grafts, 36% included a liver graft, and 6.3% were retransplantations. Eighteen

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cases of acute ABMR were identified, 14 (14%) among the patients undergoing first liver-free transplantation, 2 (3%) among patients undergoing liver/small bowel transplantations, and 2 (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

Florescu et al (2012) 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% CI, 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, in 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 developed 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 an 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. 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 caloric intake. One patient was weaned off TPN.

Tables 1 and 2 provide details on additional case series that used living donors (Garcia Aroz et al [2017], Ueno et al [2014], Benedetti et al [2006]). In general, survival rates of recipients with living donors are comparable to rates for recipients of cadaveric donations. Living related donors were reported to have an uneventful recovery. Weight loss and diarrhea were reported among donors, but recovery was without complications.
HIV-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, which has markedly changed the natural history of the disease.

The 2013 HIV Organ Policy Equity Act in the United States permitted scientists to research organ donations from a person with HIV to another HIV-infected person. In 2015, the Organ Procurement and Transplant Network updated its policies to be consistent with the HIV Organ Policy Equity Act. The Organ Procurement and Transplant Network and United Network for Organ Sharing (UNOS) policies specify that organs from HIV-positive patients be used only for HIV-positive transplant recipients.

In 2006, the British HIV Association and the British Transplantation Society published joint guidelines an kidney transplantation in patients with HIV disease. These criteria may be extrapolated to other organs. The guidelines, which are similar to the UNOS guidelines, have recommended 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/mL for at least 6 months.
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months.
- Demonstrable adherence and a stable highly active antiretroviral therapy regimen for at least 6 months.
- The absence of AIDS-defining illness following successful immune reconstitution after highly active antiretroviral therapy.

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 RETRANSPANTATION

Two case series from single institutions and one analysis using data from the UNOS database (Desai et al, 2012) have provided evidence on the use of retransplantation in patients who failed primary small bowel transplant. Case series characteristics and results are detailed in Tables 3 and 4, respectively.
Desai et al (2012) has 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 1987 and 2009.

Table 3. Summary of Key Case Series Characteristics for Retransplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>n</th>
<th>Median Age (Range), y</th>
<th>Interventions</th>
<th>Follow-Up (Range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al (2017)</td>
<td>France</td>
<td>10</td>
<td>13 (5-16)</td>
<td>• Isolated IT</td>
<td>3</td>
</tr>
<tr>
<td>Desai et al (2012)</td>
<td>U.S.</td>
<td>72 (adults) 77 (children)</td>
<td>NR</td>
<td>Adults: • Isolated IT</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Children: • Isolated IT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Combined liver IT</td>
</tr>
<tr>
<td>Abu-Elmagd et al (2009)</td>
<td>U.S.</td>
<td>47</td>
<td>NR</td>
<td>• Isolated IT</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Combined liver IT</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multivisceral graft</td>
</tr>
</tbody>
</table>

IT: intestinal transplantation; NR: not reported.

Table 4. Summary of Key Case Series Results for Retransplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Interventions</th>
<th>Survival</th>
<th>Off TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al (2017)</td>
<td>• Isolated IT 3</td>
<td>All combined at last follow-up: 30</td>
<td>NR</td>
</tr>
<tr>
<td>Desai et al (2012)</td>
<td>Adults: • Isolated IT 41</td>
<td>1/3/5 80/47/29</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>• Combined liver IT 31</td>
<td>1/3/5 63/56/47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: • Isolated IT 28</td>
<td>1/3/5 81/74/57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Combined liver IT 49</td>
<td>1/3/5 42/42/42</td>
<td></td>
</tr>
<tr>
<td>Abu-Elmagd et al (2009)</td>
<td>• Isolated IT 31</td>
<td>All combined:</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>• Combined liver IT 7</td>
<td>1 69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivisceral graft 9</td>
<td>5 47</td>
<td></td>
</tr>
</tbody>
</table>

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

Section Summary: Small Bowel Retransplantation

Data from a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data have suggested reasonably high survival rates after small bowel retransplantation 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 worsen comorbid conditions significantly. 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 a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data have suggested a reasonably high survival rate after small bowel retransplantation 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.

TRANSPLANTATION OF SMALL BOWEL/LIVER OR MULTIVISCERAL ORGANS

A 1999 TEC Assessment focused on multivisceral transplantation and offered the following conclusions: “Multivisceral transplantation in patients with small bowel syndrome, liver failure, and/or other gastrointestinal problems such as pancreatic failure, thromboses of the celiac axis and the superior mesenteric artery, or pseudo-obstruction affecting the entire gastrointestinal tract is associated with poor patient and graft survival. Pediatric and adult patients have a similar 2- and 5-year survival of 33% to 50%. However, without this procedure, it is expected that these patients would face 100% mortality.”

The published literature consists of case series, mainly reported by single centers in the United States and Europe. Tables 1 and 2 summarize the characteristics and results of the case series, respectively. Many case series have included isolated small bowel transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off TPN. Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multivisceral transplants (see Table 2).
Several investigators have reported higher survival rates in transplants conducted more recently than those conducted earlier. Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex procedure. Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

Table 1. Summary of Key Case Series Characteristics for Transplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>N</th>
<th>Median Age (Range), y</th>
<th>Interventions</th>
<th>Follow-Up (Range)</th>
</tr>
</thead>
</table>
| Lacaille et al (2017) | France   | 110 | 5.3 (0.4-19)          | • Isolated IT  
• Combined liver IT  
• Multivisceral graft | 45 (60, 5) Of 55 alive:  
17 at <5 y  
17 at 5-10 y  
21 at ≥10 y |
| Garcia Aroz et al (2017) | United States | 10  | 1.5 (0.7-13)          | • Isolated IT  
• Combined liver IT | 7 (3) 6/7 alive at follow-up ≥10 y |
| Dore et al (2016) | United States | 30  | 0.2 (0.1-18)          | • Isolated IT  
• Combined liver IT  
• Multivisceral graft | 6 (6) 18 28 (4-175) mo |
| Rutter et al (2016) | United Kingdom | 60  | 1.8 (0-8)             | • Isolated IT  
• Multivisceral graft  
• Modified multivisceral | 16 (35, 9) 21.3 (0-95) mo |
| Lauro et al (2014) | Italy     | 46  | 34 (NR)               | • Isolated IT  
• Combined liver IT  
• Multivisceral graft | 34 (6) 6 51.3 mo |
| Varkey et al (2013) | Sweden    | 20  | Adults:  
• 44 (20-67)  
Children:  
• 6 (0.5-13) | • Isolated IT  
• Combined liver IT  
• Multivisceral graft | 4 (1) 15 NR |
| Mangus et al (2013) | United States | 100 | Adults:  
• 48 (NR to 66)  
Children:  
• 1 (0.6 to NR) | • Multivisceral graft  
• Modified multivisceral | 84 (16) 25 mo |

IT: intestinal transplantation; NR: not reported.
a Living donors.

Table 2. Summary of Key Case Series Results for Transplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Interventions</th>
<th>Treatment n</th>
<th>Survival</th>
<th>Off TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al</td>
<td>• Isolated IT</td>
<td>60</td>
<td>• 59% at 10 y; 54% at 18 y</td>
<td>All treatments combined:</td>
</tr>
</tbody>
</table>
Complications

Several case series have focused on complications after small bowel and multivisceral transplantation. For example, in 2016, Nagai et al reported on cytomegalovirus (CMV) infection after intestinal or multivisceral transplantation at a single center in the United States. A total of 210 patients had either an intestinal transplant, multivisceral transplant, or modified multivisceral transplant between 2003 and 2014. The median length of follow-up was 2.1 years. Thirty-four (16%) patients developed CMV infection at a median of 347 days after transplantation. Nineteen patients had tissue invasive CMV disease. CMV infection was significantly associated with rejection (odds ratio, 2.6; p<0.01) and adversely affected patient survival (hazard ratio, 2.7; p<0.001). In a 2016 report from another U.S. center, 16 (19%) of 85 patients undergoing intestinal or multivisceral transplantation developed CMV infection a mean of 139 days (range, 14-243 days) postoperatively.

In 2016, Wu et al investigated the incidence and risk factors of ABMR among patients undergoing intestinal transplantation (N=175). All patients were 25 years of age. Acute ABMR was diagnosed by: clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free grafts, 36%...
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included a liver graft, and 6.3% were retransplantations. Eighteen cases of acute ABMR were identified—14 (14%) among the patients undergoing first liver-free transplantation, 2 (3%) among patients undergoing liver/small bowel transplantations, and 2 (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

In a 2016 series by Cromvik et al, 5 (19%) of 26 patients were diagnosed with graft-versus-host disease (GVHD) after intestinal or multivisceral transplantation. Risk factors for GVHD were: malignancy as a cause of transplantation; neoadjuvant chemotherapy; or brachytherapy before transplantation.

A 2012 retrospective study reported on bloodstream infections among 98 children (>18 years) with small bowel and combined organ transplants. Seventy-seven (79%) underwent small bowel transplant in combination with a liver, kidney, or kidney and pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients had survived. The 1-year survival rate was similar in patients with combined small bowel transplant (75%) and in those with isolated small bowel transplant (81%). In the first year after transplantation, 68 (69.4%) patients experienced at least 1 episode of bloodstream infection. The 1-year survival rate for patients with bloodstream infections was 72% compared with 87% in patients without bloodstream infections (p=0.056 for difference in survival in patients with and without bloodstream infections).

In 2011, Wu et al reported on 241 patients who underwent intestinal transplantation. Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants, and 29 (12%) had small bowel/liver transplants. Recipients included 151 (63%) children and 90 (37%) adults. Twenty-two (9%) patients developed GVHD. Children younger than 5 years old were most likely to develop this condition (13.2% [16/121]) than children between 5 and 18 years (6.7% [2/30] and adults older than 18 years (4.4% [9/90]).

HIV-Positive Transplant Recipients
No studies reporting on outcomes in HIV-positive patients who received small bowel/liver or multivisceral transplants were identified in literature reviews.

In 2001, the American Society of Transplantation proposed that the presence of HIV or AIDS could be considered a contraindication to kidney transplant unless the following criteria were present (these criteria may be extrapolated to other organs):

- CD4 count greater than 200 cells/mm³ for more than 6 months
- HIV-1 RNA undetectable
- On stable antiretroviral therapy for more than 3 months
- No other complications from AIDS (eg, opportunistic infection, including aspergillus, tuberculosis, coccidioidomycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm)
- Meeting all other criteria for transplantation.
In 2006, the British HIV Association and the British Transplantation Society published joint guidelines on kidney transplantation in patients with HIV disease. As noted, these criteria may be extrapolated to other organs. The guidelines recommended 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 greater than 200 cells/mL for at least 6 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- Demonstrable adherence and a stable highly active antiretroviral therapy regimen for at least 6 months
- Absence of AIDS-defining illness following successful immune reconstitution after highly active antiretroviral therapy.

The 2013 HIV Organ Policy Equity Act in the United States permitted scientists to research organ donations from a person with HIV to another HIV-infected person. In 2015, the Organ Procurement and Transplant Network updated its policies to be consistent with the HIV Organ Policy Equity Act. The Organ Procurement and Transplantation Network and United Network for Organ Sharing policies specify that organs from HIV-positive patients be used only for HIV-positive transplant recipients.

Section Summary: Transplantation of Small Bowel/Liver or Multivisceral Organs

Intestinal transplantation procedures are infrequently performed and only relatively small case series, generally single-center, are available. For patients experiencing significant complications from TPN, which can lead to liver failure and repeated infections, these case series have shown reasonably high posttransplant survival rates in patients who have a high probability of death without treatment. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation.

RETRANSPLANTATION OF SMALL BOWEL/LIVER OR MULTIVISCERAL ORGANS

Evidence for the use of retransplantation to treat individuals who have failed intestinal transplantations includes several case series, mostly from single institutions. One case series analyzed records from the United Network for Organ Sharing database. Among the case series described in Table 3, reasons for retransplantations include: acute rejection, chronic rejection, CMV, liver failure, lymphoproliferative disorder, and graft dysfunction. Survival rates for retransplantations are listed in Table 4.

Table 3. Summary of Key Case Series Characteristics for Retransplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>N</th>
<th>Median Age (Range), y</th>
<th>Interventions</th>
<th>Follow-Up, (Range), mo</th>
<th>Treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacaille et al</td>
<td>France</td>
<td>10</td>
<td>13 (5-16)</td>
<td>• Isolated IT</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>(2017)</td>
<td></td>
<td></td>
<td></td>
<td>• Combined liver IT</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desai et al</td>
<td>United States</td>
<td>72</td>
<td>(adults) NR</td>
<td>Adults: NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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- 77 (children)
- Isolated IT
- Combined liver IT
- Children:
- Isolated IT
- Combined liver IT

- Isolated IT
- Combined liver IT
- Multivisceral graft

- Isolated IT
- Combined liver IT
- Multivisceral graft

IT: intestinal transplantation; NR: not reported.

Table 4. Summary of Key Case Series Results for Retransplantations

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Interventions</th>
<th>Survival</th>
<th>Off TPN</th>
</tr>
</thead>
</table>
| Lacaille et al (2017)     | • Isolated IT
• Combined liver IT | All transplantations combined: NR     | NR          |
| Desai et al (2012)        | Adults:
• Isolated IT
• Combined liver IT
• Children:
• Isolated IT
• Combined liver IT | Adults:
• 80% at 1 y; 47% at 3 y; 29% at 5 y
• 63% at 1 y; 56% at 3 y; 47% at 5 y
• Children:
• 81% at 1 y; 74% at 3 y; 57% at 5 y
• 42% at 1 y; 42% at 3 y; 42% at 5 y | NR          |
| Abu-Elmagd et al (2009)   | • Isolated IT
• Combined liver IT
• Multivisceral graft | All transplantations combined: NR     | NR          |
| Mazariegos et al (2008)   | • Isolated IT
• Combined liver IT
• Multivisceral graft | All transplantations combined: 100%  |             |

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

Section Summary: Retransplantation of Small Bowel/Liver or Multivisceral Organs
Evidence for retransplantations derives mostly from single-center case series, though 1 series used records from the United Network for Organ Sharing database. Although limited in quantity, the available follow-up data after retransplantation have suggested reasonably high survival rates after small bowel and liver transplants and multivisceral retransplantation in patients who continue to meet criteria for transplantation.
SUMMARY OF EVIDENCE
For individuals who have intestinal failure and evidence of impending end-stage liver failure who receive a small bowel and liver transplant alone or multivisceral transplant, the evidence includes a limited number of case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. These transplant procedures are infrequently performed and few reported case series exist. However, results from the available case series have revealed fairly high postprocedural survival rates. Given these results and bearing in mind the abysmal survival rates of patients who exhaust all other treatments, transplantation may prove not only to be the last option, but also a beneficial one. To be clear, transplantation is contraindicated for 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a failed small bowel and liver or multivisceral transplant without contraindications for retransplant who receive a small bowel and liver retransplant alone or multivisceral retransplant, the evidence includes case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. Although limited in quantity, the available post retransplantation data has suggested reasonably high survival rates. Given exceedingly poor survival rates without retransplantation of patients who have exhausted other treatments, evidence of postoperative survival from uncontrolled studies is sufficient to demonstrate that retransplantation provides a survival benefit in appropriately selected patients. Retransplantation is contraindicated for 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

References
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Policy History
Original Effective Date: 01/28/2002
Current Effective Date: 10/17/2018
12/16/2001 Medical Policy Committee review
01/28/2002 Managed Care Advisory Committee approval
06/24/2002 Format Revision. No substance change to policy.

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01/20/2004 Medical Policy Committee review. Format Revision Policy revision to include small bowel transplant alone. No change in coverage eligibility status.
01/26/2004 Managed Care Advisory Council approval
01/04/2005 Medical Director review
01/18/2005 Medical Policy Committee review
01/24/2005 Managed Care Advisory Council approval
02/01/2006 Medical Director review
02/15/2006 Medical Policy Committee review. Format Revisions.
02/23/2006 Quality Care Advisory Council approval
07/07/2006 Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007 Medical Director review
04/18/2007 Medical Policy Committee approval. Adequate cardiopulmonary status, absence of infection, no history of malignancy within five years of transplantation, excluding nonmelanomatous skin cancers, and documentation of patient compliance with medical management were added to the patient selection criteria.
04/02/2006 Medical Director review
05/07/2009 Medical Director review
05/20/2009 Medical Policy Committee approval. Coverage eligibility unchanged.
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2011 Medical Policy Committee review
05/18/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/14/2012 Medical Policy Committee review
06/20/2012 Medical Policy Implementation Committee approval. Contraindications added to policy. “Based on review of available data, the Company considers small bowel transplant using living donors to be investigational* for adults and children” was removed from policy.
08/01/2013 Medical Director review
08/21/2013 Medical Policy Implementation Committee approval. Statement added that small bowel/liver transplant or multivisceral retransplant may be considered medically necessary after a failed primary small bowel/liver transplant or multivisceral transplant.
08/07/2014 Medical Director review
08/20/2014 Medical Policy Implementation Committee approval. Added pediatric patients as investigational for small bowel transplant with intestinal failure who are able to tolerate TPN.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017 Medical Policy Committee review

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10/18/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/04/2018 Medical Policy Committee review
Next Scheduled Review Date: 10/2019

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<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>44120, 44121, 44132, 44133, 44135, 44136, 44137, 44715, 44720, 44721, 47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147, 47399</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2053, S2054, S2055</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>K72.00, K72.01, K72.10, K72.11, K72.90, K72.91, K76.2, K91.2</td>
</tr>
</tbody>
</table>

*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. 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 or other nonaffiliated technology evaluation center(s);
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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.

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