Introduction

An organ transplant is the surgical process of replacing a severely diseased organ with a healthy one from a donor. The donated organ can come from a living person or a person who passed away from an accident or illness. Organ failure is the most common reason a transplant is needed. Organ failure can occur because of illness, injury, or birth defect. There are many factors that go into finding a donor organ that matches. These include blood type and the size of the organ. Other factors include how long a person has been on the waiting list, the level of illness, and the distance the donated organ must be transported. This policy describes when transplanting a liver or a liver/kidney combined may be considered medically necessary. This policy notes that a plan physician will review solid organ transplant requests together with the criteria of the transplant center.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Transplant</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Liver transplant using a cadaver or living donor | A liver transplant using a cadaver or living donor may be considered medically necessary for carefully selected patients with end-stage liver failure due to irreversibly damaged livers. Etiologies of end-stage liver disease include, but are not limited to, the following:  
A. Hepatocellular diseases  
o Alcoholic liver disease  
o Viral hepatitis (either A, B, C, or non-A, non-B)  
o Autoimmune hepatitis  
o α1-Antitrypsin deficiency  
o Hemochromatosis  
o Nonalcoholic steatohepatitis  
o Protoporphyria  
o Wilson disease  
B. Cholestatic liver diseases  
o Primary biliary cirrhosis  
o Primary sclerosing cholangitis with development of secondary biliary cirrhosis  
o Biliary atresia  
C. Vascular disease  
o Budd-Chiari syndrome  
D. Primary hepatocellular carcinoma (see Related Information section for patient selection criteria)  
E. Inborn errors of metabolism  
F. Trauma and toxic reactions  
G. Miscellaneous  
o Familial amyloid polyneuropathy |
| Liver transplantation | Liver transplantation may be considered medically necessary in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.  
Liver transplantation may be considered medically necessary in patients with unresectable hilar cholangiocarcinoma (see Related Information section for patient selection criteria).  
Liver transplantation may be considered medically necessary in pediatric patients with nonmetastatic hepatoblastoma. |
<table>
<thead>
<tr>
<th>Transplant</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation is considered not medically necessary in the following patients:</td>
<td></td>
</tr>
<tr>
<td>• Patients with hepatocellular carcinoma that has extended beyond the liver (see Related Information section for patient selection criteria)</td>
<td></td>
</tr>
<tr>
<td>• Patients with ongoing alcohol and/or drug abuse except for those with:</td>
<td></td>
</tr>
<tr>
<td>o Objective failure of therapy for severe acute alcoholic hepatitis.⁶⁴ (See Appendix for Lille protocol).</td>
<td></td>
</tr>
<tr>
<td>o Critical decompensation in alcohol related cirrhotic patients as judged by MELD score (MELD-Na ≥21)⁶⁵ predicting mortality prior to completion of required abstinence</td>
<td></td>
</tr>
<tr>
<td>Note: Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.</td>
<td></td>
</tr>
<tr>
<td>Liver retransplantation</td>
<td>Liver retransplantation may be considered medically necessary in patients with:</td>
</tr>
<tr>
<td>• primary graft nonfunction</td>
<td></td>
</tr>
<tr>
<td>• hepatic artery thrombosis</td>
<td></td>
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<tr>
<td>• chronic rejection</td>
<td></td>
</tr>
<tr>
<td>• ischemic type biliary lesions after donation after cardiac death</td>
<td></td>
</tr>
<tr>
<td>• recurrent non-neoplastic disease-causing late graft failure</td>
<td></td>
</tr>
<tr>
<td>Combined liver-kidney transplantation</td>
<td>Combined liver-kidney transplantation may be considered medically necessary in patients who qualify for liver transplantation and have advanced irreversible kidney disease.</td>
</tr>
<tr>
<td>Transplant</td>
<td>Investigational</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>Liver transplantation is investigational in the following situations:</td>
</tr>
<tr>
<td>• Patients with intrahepatic cholangiocarcinoma</td>
<td></td>
</tr>
<tr>
<td>• Patients with neuroendocrine tumors metastatic to the liver</td>
<td></td>
</tr>
<tr>
<td>Liver transplantation is considered investigational in all other situations not described above.</td>
<td></td>
</tr>
<tr>
<td>HCV (hepatits C) viremic solid organs</td>
<td>The transplantation of HCV-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to an HCV non-viremic</td>
</tr>
</tbody>
</table>
Investigational recipient combined with direct-acting antiviral treatment for HCV is considered investigational.

**Documentation Requirements**

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the relevant history and physical supporting that patient has end stage liver disease due to irreversibly damaged livers from one of the listed etiologies. Request for liver transplant, combined liver/kidney transplant, or liver retransplantation is specified.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age</td>
</tr>
<tr>
<td>S2152</td>
<td>Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor (s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre and posttransplant care in the global definition</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

**Contraindications**

Potential contraindications for solid organ transplant are subject to the judgment of the transplant center and include the following:
• 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 diseases not attributed to liver disease

• 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.

**Liver-Specific Criteria**

The Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during a patient’s tenure on the waiting list.

Patients with liver disease related to alcohol or drug abuse must be actively involved in a substance abuse treatment program.

Tobacco consumption is a contraindication.

Patients with polycystic disease of the liver do not develop liver failure but may require transplantation due to the anatomic complications of a hugely enlarged liver. The MELD and PELD score may not apply to these cases. One of the following complications should be present:

• Enlargement of liver impinging on respiratory function

• Extremely painful enlargement of liver

• Enlargement of liver significantly compressing and interfering with function of other abdominal organs.

Patients with familial amyloid polyneuropathy do not experience liver disease per se but develop polyneuropathy and cardiac amyloidosis due to the production of a variant transthyretin molecule by the liver. MELD and PELD exception criteria and scores may apply to these cases. Candidacy for liver transplant is an individual consideration based on the morbidity of the polyneuropathy. Many patients may not be candidates for liver transplant alone due to coexisting cardiac disease.
Hepatocellular Carcinoma

Criteria used for patient selection of hepatocellular carcinoma (HCC) patients eligible for liver transplant include the Milan criteria, which is considered the criterion standard, the University of California, San Francisco expanded criteria, and United Network of Organ Sharing (UNOS) criteria.

**Milan Criteria**

A single tumor 5 cm or less or 2 to 3 tumors 3 cm or less.

**University of California, San Francisco Expanded Criteria**

A single tumor 6.5 cm or less or up to 3 tumors 4.5 cm or less, and a total tumor size of 8 cm or less.

**UNOS Stage T2 Criteria**

A single tumor 2 cm or greater and up to 5 cm or less or two to three tumors 1 cm or greater and up to 3 cm or less and without extrahepatic spread or macrovascular invasion. UNOS criteria were updated in 2018 ([https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09](https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09)).

Patients with HCC are appropriate candidates for liver transplant only if the disease remains confined to the liver. Therefore, the patient should be periodically monitored while on the waiting list, and if metastatic disease develops, the patient should be removed from the transplant waiting list. Also, at the time of transplant, a backup candidate should be scheduled. If locally extensive or metastatic cancer is discovered at the time of exploration before hepatectomy, the transplant should be aborted, and the backup candidate scheduled for transplant.

Note that liver transplantation for those with T3 HCC is not prohibited by UNOS guidelines, but such patients do not receive any priority on the waiting list. All patients with HCC awaiting
transplantation are reassessed at 3-month intervals. Those whose tumors have progressed and are no longer stage T2 will lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given a class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and ineligible for automatic exception points. Nodules less than 1 cm are considered indeterminate and are not considered for additional priority. Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list.

**Cholangiocarcinoma**

According to the Organ Procurement and Transplantation Network (OPTN) policy on liver allocation, candidates with cholangiocarcinoma meeting the following criteria will be eligible for a MELD or PELD exception with a 10% mortality equivalent increase every three months:

- Centers must submit a written protocol for patient care to the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with cholangiocarcinoma. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee.

- Candidates must satisfy diagnostic criteria for hilar cholangiocarcinoma: malignant-appearing stricture on cholangiography and one of the following: carbohydrate antigen 19-9 100 U/mL, or biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (eg, primary sclerosing cholangitis).

- If cross-sectional imaging studies (computed tomography scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be 3 cm or less.
• Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.

• Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.

• Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

Living Donor Criteria

Donor morbidity and mortality are prime concerns in donors undergoing right lobe, left lobe, or left lateral segment donor partial hepatectomy as part of living donor liver transplantation. Partial hepatectomy is a technically demanding surgery, the success of which may be related to the availability of an experienced surgical team. The American Society of Transplant Surgeons proposed the following guidelines for living donors (American Society of Transplant Surgeons: Ethics Committee. American Society of Transplant Surgeons' position paper on adult-to-adult living donor liver transplantation. Liver Transplant. 2000;6(6):815-817. PMID 11084076):

• They should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure

• They should undergo evaluation to ensure that they fully understand the procedure and associated risks

• They should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent

• They should be emotionally related to the recipients

• They must be excluded if the donor is felt or known to be coerced

• They need to have the ability and willingness to comply with long-term follow-up.
Benefit Application

See member’s plan contract language for organ transplant benefits and specific benefits related to transport, lodging, and donor services. Please note limitations in coverage based on the transplant benefit, if applicable.

Evidence Review

Description

Liver transplantation is currently the treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with a liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network and the United Network of Organ Sharing. The severity of illness is determined by the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores.

Background

Liver transplantation

Recipients

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network of Organ Sharing. The liver allocation system adopted included the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Scoring on the MELD and PELD uses a continuous disease severity scale based entirely on objective laboratory values. In 2013, the Organ Procurement and Transplantation Network and United Network of Organ Sharing updated its allocation system. Status 1A patients have an acute liver failure with a life expectancy of fewer than seven days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic
artery thrombosis, and acute Wilson disease. Status 1A patients must be recertified every seven days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease, which may include the following: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to status 1A at age 18 but still qualify for pediatric indications.

Following status 1, donor livers are prioritized to those with the highest scores on MELD or PELD. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (ie, international normalized ratio), and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at the listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility.¹ Status seven describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation. Pediatric patients who turn 18 are status X.

**Donors**

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient’s condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

**Management**

Management of acute rejection of liver transplant using intravenous immunoglobulin or plasmapheresis is not addressed in this policy. Also, the role of chemoembolization or radiofrequency ablation as a bridge to transplant in patients with hepatocellular cancer is addressed in a [Related Policy](#).
Summary of Evidence

For individuals who have a hepatocellular disease who receive a liver transplant, the evidence includes case series, registry studies, and systematic reviews. The relevant outcomes include overall survival (OS), morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis have found that survival is lower than for other liver diseases. Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rates are significant in a group of patients who have no other treatment options. Also, survival can be improved by the eradication of the hepatitis virus before transplantation. For patients with nonalcoholic steatohepatitis (NASH), OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary hepatocellular carcinoma (HCC) who receive a liver transplant, the evidence includes systematic reviews of observational studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In the past, long-term outcomes in patients with primary hepatocellular malignancies had been poor (19%) compared with the OS of liver transplant recipients. However, the recent use of standardized patient selection criteria (e.g., the Milan criteria diameter) has dramatically improved OS rates. In the appropriately selected patients, a liver transplant has been shown to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have extrahepatic cholangiocarcinoma who receive a liver transplant, the evidence includes systematic reviews of observational studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported as high as 76%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have intrahepatic cholangiocarcinoma who receive a liver transplant, the evidence includes registry studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Five-year survival rates after liver transplantation in patients with cholangiocarcinoma are less than 30%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have neuroendocrine tumors (NETs) who receive a liver transplant, the evidence includes systematic reviews of case series. The relevant outcomes include OS, morbid
events, and treatment-related morbidity and mortality. In select patients with nonresectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms. While some centers may perform liver transplants on select patients with neuroendocrine tumors, the available studies are limited by their heterogeneous populations. Further studies are needed to determine the appropriate selection criteria. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pediatric hepatoblastoma who receive a liver transplant, the evidence includes case series. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is among in United Network for Organ Sharing criteria for patients eligible for liver transplantation. 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 liver transplant who receive a liver retransplant, the evidence includes observational studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with indications for liver and kidney transplant who receive a combined liver-kidney transplantation (CLKT), the evidence includes registry studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for CLKT in children are rare and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney. In both adults and children, comparisons with either liver or kidney transplantation alone would suggest that CLKT is no worse, and possibly better, for graft and patient survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a report from a single-site prospectively evaluating 55 recipients of HCV antibody (Ab)+/nucleic acid test (NAT)- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and
loss were comparable between groups, as was mortality by one year of follow-up. Seroconversion was detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully treated with an appropriate HCV antiviral therapy and subsequent sustained virologic response (SVR). A fifth recipient died before treatment of non-HCV related causes. Several case reports have published outcomes for a total of 12 adults who received HCV viremic liver transplants. A notable finding in the reports is that the majority of recipients had prior HCV infection and had successfully achieved an SVR using genotype-specific direct-acting antiviral agents (DAA) when reinfection was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT03500315</td>
<td>HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients</td>
<td>360</td>
<td>Aug 2022</td>
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<tr>
<td>NCT02878473</td>
<td>Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics</td>
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<td>Jan 2029</td>
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<td>NCT03208127</td>
<td>Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Liver Transplant</td>
<td>10</td>
<td>Sep 2020</td>
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<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT01756794</td>
<td>Validation of the Procedure of Early Liver Transplantation in Alcoholic Hepatitis Resisting to Medical Treatment (QuickTrans)</td>
<td>263</td>
<td>Jan 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
Clinical Input Received 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, input was received from three physician specialty societies and five academic medical centers while this policy was under review. There was a consensus among reviewers that liver transplantation may be medically necessary for end-stage liver failure due to irreversibly damaged livers from various disease states such as those considered during the report update. There was also a consensus among reviewers that liver retransplantation is appropriate in patients with acute or chronic liver failure such as primary graft nonfunction, ischemic-type biliary injury after donation after cardiac death, hepatic artery thrombosis, chronic rejection or recurrent diseases such as primary sclerosing cholangitis, autoimmune hepatitis, and hepatitis C resulting in end-stage liver failure. There was general support for the use of liver transplantation as a treatment for cholangiocarcinoma in patients who meet strict eligibility criteria. In general, there was no support for the use of liver transplantation for a neuroendocrine tumor metastatic to the liver.

Practice Guidelines and Position Statements

*International Consensus Conference*

The Milan criteria were recommended for use as the benchmark for patient selection, although it was suggested that the Milan criteria might be modestly expanded based on data from expansion studies that demonstrated outcomes are comparable with outcomes from studies using the Milan criteria. Candidates for liver transplantation should also have a predicted survival of five years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

Regarding liver retransplantation, the consensus criteria issued a weak recommendation for retransplantation after graft failure of a living donor transplant for hepatocellular carcinoma (HCC) in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued against liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria. Also, the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC would not be appropriate.
However, a de novo case of HCC may be treated as a new tumor, and retransplantation may be considered even though data to support this is limited.

**American Association for the Study of Liver Diseases et al**

The American Association for the Study of Liver Diseases and the American Society of Transplantation (2013) issued joint guidelines on evaluating patients for a liver transplant. These guidelines indicated liver transplantation for severe acute or advanced chronic liver disease after all effective medical treatments have been attempted. The formal evaluation should confirm the irreversible nature of the liver disease and lack of effective alternative medical therapy.

The guidelines also stated that liver transplant is indicated for the following conditions:

- Acute liver failure complications of cirrhosis
- Liver-based metabolic condition with systemic manifestations
  - α1-Antitrypsin deficiency
  - Familial amyloidosis
  - Glycogen storage disease
  - Hemochromatosis
  - Primary oxaluria
  - Wilson disease
- Systemic complications of chronic liver disease.

The guidelines also included 1-A recommendations (strong recommendation with high-quality evidence) for a liver transplant that:

- "Tobacco consumption should be prohibited in LT [liver transplant] candidates."
- "Patients with HIV infection are candidates for LT if immune function is adequate and the virus is expected to be undetectable by the time of LT."
- "LT candidates with HCV [hepatitis C virus] have the same indications for LT as for other etiologies of cirrhosis."
Contraindications to liver transplant included:

- "MELD [Model for End-stage Liver Disease] score < 15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system."

The American Association for the Study of Liver Diseases, the American Society of Transplantation, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (2014) issued joint guidelines on the evaluation of the pediatric patients for liver transplant. The guidelines stated that “disease categories suitable for referral to a pediatric LT program are similar to adults: acute liver failure, autoimmune, cholestasis, metabolic or genetic, oncologic, vascular, and infectious. However, specific etiologies and outcomes differ widely from adult patients, justifying independent pediatric guidelines.” The indications listed for liver transplantation included biliary atresia, Alagille syndrome, pediatric acute liver failure, hepatic tumors, HCC, hemangioendothelioma, cystic fibrosis-associated liver disease, urea cycle disorders, immune-mediated liver disease, along with other metabolic or genetic disorders.

**The American Association for the Study of Liver Diseases**

The American Association for the Study of Liver Diseases (2019) issued practice guidance on the diagnosis and treatment of alcohol-related liver diseases. The guidance recommended:
• Patients with decompensated alcohol-related cirrhosis, Child-Turcotte-Pugh C or MELD-Na \( \geq 21 \) should be referred and considered for liver transplantation.

• Candidate selection for liver transplantation in alcohol-related cirrhosis should not be solely based on a fixed interval of abstinence.

The practice guidance also recommended:

• Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe alcoholic hepatitis (AH) not responding to medical therapy.

**The American Society of Transplantation**

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients and concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers (v.2.2019) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting United Network of Organ Sharing criteria of a single tumor measuring 2 to 5 cm, or two to three tumors 3 cm or less with no macrovascular involvement or extrahepatic disease. Patients should be referred to the transplant center. Patients should be referred to the transplant center before the biopsy. In patients who are ineligible for transplant and in select patients with Child-Pugh class A or B liver function with tumors that are resectable, the NCCN indicates resection is the preferred treatment option; locoregional therapy may also be considered. Patients with unresectable HCC should be evaluated for liver transplantation; if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. The NCCN guidelines on hepatobiliary cancers also indicate the same. These are level 2A recommendations based on lower-level evidence and uniform consensus.
The NCCN guidelines on neuroendocrine tumors (v.1.2019) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite “encouraging” 5-year survival rates.

**Medicare National Coverage**

Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility approved by the Centers for Medicare & Medicaid Services as meeting institutional coverage criteria for liver transplants. The following conditions must be met for coverage of HCC:

- "The patient is not a candidate for subtotal liver resection;
- The patient’s tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone; and
- The transplant is furnished in a facility that is approved by CMS [Centers for Medicare & Medicaid Services] …"

Beginning in June 2012, on review of this national coverage decision for new evidence, Medicare began covering adult liver transplantation, at Medicare administrative contractor discretion, for extrahepatic unresectable cholangiocarcinoma, liver metastases due to a neuroendocrine tumor, and hemangioendothelioma. Adult liver transplantation is excluded from other malignancies.

Pediatric liver transplantation is covered for children (<18 years of age) when performed at pediatric hospitals approved by the Centers for Medicare & Medicaid Services. Coverage includes extrahepatic biliary atresia or any other form of end-stage liver disease, except for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.

**Regulatory Status**

Liver and liver-kidney transplants are a surgical procedure 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. Liver transplants are included in these regulations.

References


74. Friedman SL. Liver transplantation for alcoholic liver disease. In: UpToDate, Robson, KM (Ed), UpToDate, Waltham, MA, 2019.
Appendix

Lille Protocol


- Non-responsive to medical therapy defined as a Lille model\(^{69}\) score > 0.45 or more after 7 days of medical therapy. Calculation available at: [https://www.mdcalc.com/lille-model-alcoholic-hepatitis](https://www.mdcalc.com/lille-model-alcoholic-hepatitis) Accessed September 2019.

  - Medical therapy consists of standard medical care for liver insufficiency and use of glucocorticoids (40 mg per day of prednisolone for at least 7 days); OR

  - As a continuous increase in the Model for End-Stage Liver Disease (MELD) score

- Severe alcoholic hepatitis as the first liver-decompensating event

- Presence of close supportive family members

- Absence of severe coexisting or psychiatric disorders

- Agreement by patients (with support from family members) to adhere to lifelong total abstinence

- Selection process consists of 4 medical teams who independently meet the patient and family members

  - Team 1: (closest to the patient): nurses, one resident, one fellow

  - Team 2: specialist in addiction

  - Team 3: senior hepatologists

  - Team 4: anesthesiologist and transplant surgeon

- The 4 evaluating teams have to reach complete consensus on selection

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/02</td>
<td>Add to Surgery Section - New Policy. Replaces other transplant policies (PR.7.03.100, 102, 103, 104, 105, and 106)</td>
</tr>
<tr>
<td>05/13/03</td>
<td>Replace Policy - Scheduled review. References added and CPT code table updated.</td>
</tr>
<tr>
<td>01/01/04</td>
<td>Replace Policy - CPT code updates only.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy reviewed by Nancy Aceto no changes needed at this time; new review date only. Appendices removed—no value.</td>
</tr>
<tr>
<td>09/01/04</td>
<td>Replace Policy - Policy renumbered from PR.7.03.109. No changes to dates.</td>
</tr>
<tr>
<td>05/10/05</td>
<td>Replace Policy - Scheduled review. References added. No change to policy statement.</td>
</tr>
<tr>
<td>02/06/06</td>
<td>Codes updated - No other changes.</td>
</tr>
<tr>
<td>05/09/06</td>
<td>Replace Policy - Scheduled review. References added; no change to policy statement.</td>
</tr>
<tr>
<td>05/26/06</td>
<td>Scope and Disclaimer Updates - No other changes.</td>
</tr>
<tr>
<td>02/26/07</td>
<td>Codes Updated - No other changes.</td>
</tr>
<tr>
<td>05/08/07</td>
<td>Replace Policy - Policy updated with literature review; reference added. No change in policy statement.</td>
</tr>
<tr>
<td>05/21/07</td>
<td>References Updated - Policy updated with information on Medicare coverage of heart transplants.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Replace Policy - Policy updated with literature search. Policy statement to include using a cadaver or living donor under kidney transplants as a medically necessary indication. Also to include “imminent end-stage liver failure” for patients under liver transplants as medically necessary.</td>
</tr>
<tr>
<td>03/10/09</td>
<td>Replace Policy - Policy updated with literature search; references added. No change to policy statement.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Replace Policy - Policy updated with literature search. No change to policy statement.</td>
</tr>
<tr>
<td>01/11/11</td>
<td>Replace Policy - Policy updated with literature search. No change to policy statement.</td>
</tr>
<tr>
<td>01/06/12</td>
<td>Replace Policy – Policy updated with literature search; references added. No change to policy statement.</td>
</tr>
<tr>
<td>12/03/12</td>
<td>Update title to Related Policy 7.03.11.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>01/29/13</td>
<td>Replace policy. Policy updated with literature search. No change to policy statement. References updated.</td>
</tr>
<tr>
<td>02/12/13</td>
<td>Update Related Policies, change title for 8.02.02.</td>
</tr>
<tr>
<td>05/30/13</td>
<td>Update Related Policies. Change title for 7.03.510.</td>
</tr>
<tr>
<td>02/10/14</td>
<td>Replace policy. Retransplant policy statements added to kidney, heart, heart/lung. Literature updated. References 35-39 added. ICD-9 Diagnosis codes were listed for informational purposes only and have been removed from the policy.</td>
</tr>
<tr>
<td>03/11/14</td>
<td>Coding Update. Codes 33.50, 33.51, 33.52, 33.6, 37.5, 50.4, 50.51, 50.59, 52.80, 52.81, 52.82, 52.83, and 55.69 were removed per ICD-10 mapping project; these codes are not utilized for adjudication of policy.</td>
</tr>
<tr>
<td>03/31/15</td>
<td>Annual Review. Alphabetized names of organ transplants in policy statements. Related policy 7.03.05 added. Rationale section extensively reorganized by alphabetizing organ transplants and updated based on a literature review through December, 2014. References extensively renumbered and some references removed. Policy statements unchanged.</td>
</tr>
<tr>
<td>08/19/15</td>
<td>Update Related Policies. Remove 7.03.510 and 8.02.02 then add 8.03.05 and 7.03.04.</td>
</tr>
<tr>
<td>09/24/15</td>
<td>Coding update. ICD-9 Procedure codes removed; these are informational only.</td>
</tr>
<tr>
<td>01/12/16</td>
<td>Annual Review. Policy updated with literature search; references added. No change to the policy statement.</td>
</tr>
<tr>
<td>01/29/16</td>
<td>Coding update. Added HCPCS code S2152.</td>
</tr>
<tr>
<td>11/01/16</td>
<td>Update related policies. Removed 7.03.05 from related policies section as it was deleted (contents moved to 7.03.04).</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Coding Update. Transplant benefit-related codes removed. Coding table moved to Policy Guidelines section. Updated titles of some Related Policies.</td>
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<tr>
<td>03/01/17</td>
<td>Annual Review, approved February 14, 2017. Policy updated with literature review through October 25, 2016; references renumbered. Policy statements unchanged.</td>
</tr>
<tr>
<td>04/14/17</td>
<td>Coding update; added HCPCS code S2060.</td>
</tr>
<tr>
<td>04/18/17</td>
<td>Coding update; added HCPCS code S2065.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>Policy moved to new format. No changes to policy statement.</td>
</tr>
<tr>
<td>07/27/18</td>
<td>Coding update; added CPT 33935 to policy as it was inadvertently removed.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Annual Review, approved October 26, 2018. Policy updated with literature review through June 2018; references 42, 51, 56, 82, 87, 89, 94, 109, 111, 118, 120, 136, 158, 164, 178, 183, 184, and 201 added. Examples of end-stage cardiac and pulmonary diseases added for clarity under heart and lung transplant. Etiologies of end-stage liver disease added for clarity, polycystic disease of the liver, unresectable hilar cholangiocarcinoma, pediatric patients with nonmetastatic hepatoblastoma are added as medically necessary indications for liver transplantation. Indications for liver</td>
</tr>
</tbody>
</table>
retransplantation were added. Indications where liver transplantation is not medically necessary or is considered investigational were added, otherwise policy statements unchanged.

04/01/19
Minor update, added Documentation Requirements section.

11/01/19
Annual Review approved October 8, 2019. Policy title changed from “Solid Organ Transplants” to “Liver Transplant and Combined Liver-Kidney Transplant”. Previous content of Solid Organ Transplants is now addressed in individual policies (7.03.01, 7.03.02, 7.03.07, 7.03.08, 7.03.09) except for liver and combined liver-kidney transplant. Policy updated with literature review through June 2019. References added. Added exception criteria for patients with ongoing alcohol abuse. Added policy statement on transplantation of HCV viremic organs which is taken from BCBSA policy 7.03.14.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
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Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-5797 (TDD)

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