Liver Transplant and Combined Liver-Kidney Transplant

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 and Pediatric End-stage Liver Disease scores.

Liver transplantation is 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. Certain populations are prioritized as Status 1A (e.g., acute liver failure with a life expectancy of fewer than 7 days without a liver transplant) or Status 1B (pediatric patients with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. 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 2 segments that can be used for 2 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.
OBJECTIVE

The objective of this evidence review is to determine the appropriate indications for a liver transplant and combined liver-kidney transplant and whether transplant improves net health outcomes.

POLICY STATEMENT

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
   - Alcoholic liver disease
   - Viral hepatitis (either A, B, C, or non-A, non-B)
   - Autoimmune hepatitis
   - α1-Antitrypsin deficiency
   - Hemochromatosis
   - Nonalcoholic steatohepatitis
   - Protoporphyria
   - Wilson disease.

B. Cholestatic liver diseases
   - Primary biliary cirrhosis
   - Primary sclerosing cholangitis with development of secondary biliary cirrhosis
   - Biliary atresia.

C. Vascular disease
   - Budd-Chiari syndrome.

D. Primary hepatocellular carcinoma (see Policy Guidelines section for patient selection criteria)

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
   - Familial amyloid polyneuropathy.

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 Policy Guidelines section for patient selection criteria).

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Liver transplantation may be considered **medically necessary** in pediatric patients with nonmetastatic hepatoblastoma.

Liver **retransplantation** may be considered **medically necessary** in patients with:

- primary graft nonfunction
- hepatic artery thrombosis
- chronic rejection
- ischemic type biliary lesions after donation after cardiac death
- recurrent non-neoplastic disease-causing late graft failure.

Combined liver-kidney transplantation may be considered **medically necessary** in patients who qualify for liver transplantation and have advanced irreversible kidney disease.

Liver transplantation is **investigational** in the following situations:

- Patients with intrahepatic cholangiocarcinoma
- Patients with neuroendocrine tumors metastatic to the liver.

Liver transplantation is considered **not medically necessary** in the following patients:

- Patients with hepatocellular carcinoma that has extended beyond the liver (see Policy Guidelines section for patient selection criteria)
- Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.)

Liver transplantation is considered **investigational** in all other situations not described above.

**POLICY GUIDELINES**

**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.
Potential Contraindications (Applies to all indications)

Living vs Deceased Donor Liver Transplant Recipient Outcomes

Due to the scarcity of donor organs and the success of living donation, living donor liver transplantation has become an accepted practice. The living donor undergoes heptatectomy of the right lobe, the left lobe, or the left lateral segment, which is then transplanted into the recipient. Because heptatectomy involves resection of up to 70% of the total volume of the donor liver, the safety of the donor has been a major concern. For example, the surgical literature suggests that right heptatectomy of the diseased or injured liver is associated with mortality rates of about 5%. However, reports have suggested that right heptatectomy in healthy donors has lower morbidity and mortality. Reports of several donor deaths have been reported 47.48.49.50.

In December 2000, the National Institutes of Health convened a workshop focusing on living donor liver transplantation. Shiffman et al (2002) summarized this workshop 51. According to their report, the risk of mortality to the donor undergoing right heptatectomy was estimated to be approximately 0.2% to 0.5%. The median complication rate reported by responding to transplant centers was 21%. Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for heptatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor has a significant long-term and established a relationship with the recipient.

Criteria for a recipient of a living-related liver were also controversial, with some groups advocating that living-related donor livers be only used in those most critically ill, while others stated that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival 51.

Grant et al (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for HCC 52. For DFS after living donor liver transplantation, the combined HR was 1.59 (95% CI, 1.02 to 2.49) compared with deceased donor liver transplantation. For OS, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality.

Human Immunodeficiency Virus-Positive Patients

Solid-organ transplant for patients who are HIV-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. HIV candidates for liver transplantation are frequently coinfected with hepatitis B or C, and viral coinfection can further exacerbate drug-related hepatotoxicties. Hepatitis is discussed below.

Cooper et al (2011) conducted a systematic review to evaluate liver transplantation in patients coinfected with HIV and hepatitis 53. Reviewers included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI, 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI, 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared with those with detectable HIV viremia.

Terrault et al (2012) reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both hepatitis C virus (HCV) and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older 54. Patient and graft survival reductions were significantly associated with only 1 factor: HIV infection. At 3 years, in the HCV-only group, patient and graft survival rates were significantly better at 79% (95% CI, 72% to 84%) and 74% (95% CI, 66% to 79%), respectively, than the group with HIV and HCV coinfection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3 year survival rates after liver transplantation in patients coinfected with HCV, most patients still experienced long-term survival.

Current OPTN policy permits HIV-positive transplant candidates 55.

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients 56. For liver transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 (CD4) count >100 cells/mL with no history of AIDS-defining illnesses such as opportunistic infection or malignancy or CD4 count >200 cells/mL for at least 3 months

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- Undetectable HIV viral load while receiving antiretroviral therapy or a detectable HIV viral load in patients with intolerance to antiretroviral therapy that can be suppressed posttransplant
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring

The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled hepatitis B infection may be considered for transplant. Caution is recommended in hepatitis C-coinfected patients who have not been initiated on direct acting antiviral therapy.

Hepatitis Infection

Terrault et al (2012) also reported on the group of patients with HCV.\textsuperscript{54} As reported above, HCV status was not significantly associated with reduced patient and graft survival.

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.

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### 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 2 to 3 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 hepectomy, 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 3 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 and 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.

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• 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.

Combined liver-kidney transplant would be reported with the codes in this policy along with the codes in the evidence review on kidney transplant.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA 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. Solid organs used for transplantation are subject to these regulations.

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Rationale

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. 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, 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 who receive a liver transplant, the evidence includes systematic reviews of observational studies. 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 (eg, 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. 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. 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 metastatic neuroendocrine tumors who receive a liver transplant, the evidence includes systematic reviews of case series. 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. 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. 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 transplant, the evidence includes registry studies. 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 combined liver-kidney transplant 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 combined liver-kidney transplantation 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.

SUPPLEMENTAL INFORMATION

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 5 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 and American Society of Transplantation

In 2013, the American Association for the Study of Liver Diseases and the American Society of Transplantation 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.

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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."

In 2014, 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 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.

In 2019, the American Association for the Study of Liver Diseases guideline on alcohol-associated liver disease provides recommendations on the timing of referral and selection of candidates for liver transplant. The guidance notes that the patient's history of addiction to alcohol is a primary driver in selecting appropriate candidates for liver transplantation. Clinical characteristics that should trigger an evaluation and consideration for liver transplant include decompensated alcohol-associated cirrhosis, Child-Pugh-Turcotte class C cirrhosis, or a MELD-Na score ≥21. Additionally, the guideline notes that candidate selection "should not be based solely on a fixed interval of abstinence" and instead a formal psychological evaluation can help stratify patients into higher- or lesser-risk strata for relapse.

**National Comprehensive Cancer Network**

The NCCN guidelines on hepatobiliary cancers (v.4.2020) 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 2 to 3 tumors 3 cm or less with no
macrovascular involvement or extrahepatic disease. 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 that. 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.61

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.62 63 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.

REFERENCES


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<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2011</td>
<td>New policy</td>
<td>Policy updated; non-alcoholic steatohepatitis cirrhosis added to the medically necessary policy statement; a statement added that retransplantation may be considered medically necessary; a statement added that unresectable hilar cholangiocarcinoma may be considered medically necessary. Intrahepatic cholangiocarcinoma added to the investigational policy statement.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Replace policy</td>
<td>Policy updated. Policy statement on polycystic liver disease moved to a separate policy statement. Pediatric non-metastatic hepatoblastoma added as may be medically necessary. Policy statement added that liver transplantation is considered investigational in all other situations not described.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature search through December 18, 2014. No change to policy statements. References 52, 64, and 66 added.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review though June 22, 2017; references 36-40, 52, and 55-56 added; references 13, 51, and 54 updated. Combined liver-kidney transplantation added to policy; considered medically necessary. HIV criteria and contraindication for smoking added to Policy Guidelines. Policy title changed to “Liver Transplant and Combined Liver-Kidney Transplant.”</td>
</tr>
<tr>
<td>December 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review though June 22, 2017; references 36-40, 52, and 55-56 added; references 13, 51, and 54 updated. Combined liver-kidney transplantation added to policy; considered medically necessary. HIV criteria and contraindication for smoking added to Policy Guidelines. Policy title changed to “Liver Transplant and Combined Liver-Kidney Transplant.”</td>
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### FEP 7.03.06 Liver Transplant and Combined Liver-Kidney Transplant

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<tbody>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 21, 2018; references 5, 7, 14, 16, 32, and 55-56 added; references 15, 37, 58, and 60 updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 10, 2019; reference added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 6, 2020; references added. Policy statements unchanged.</td>
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