BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 7.03.06 Liver Transplant and Combined Liver-Kidney Transplant

Annual Effective Policy Date: January 1, 2024

Original Policy Date: December 2011

Related Policies:

None

Liver Transplant and Combined Liver-Kidney Transplant

Description

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.

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 individuals 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
- α_1-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 individual 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 individuals with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.

Liver transplantation may be considered **medically necessary** in individuals with unresectable hilar cholangiocarcinoma (see Policy Guidelines section for individual selection criteria).

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

Liver *retransplantation* may be considered **medically necessary** in individuals 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 individuals who qualify for liver transplantation and have advanced irreversible kidney disease.

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

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

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

- Individuals with hepatocellular carcinoma that has extended beyond the liver (see Policy Guidelines section for individual selection criteria)
- Individuals 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.

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 an individual's tenure on the waiting list.

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

Tobacco consumption is a contraindication.

Individuals 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.

Individuals 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 individuals may not be candidates for liver transplant alone due to coexisting cardiac disease.

Hepatocellular Carcinoma

Criteria used for selection of hepatocellular carcinoma (HCC) individuals 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.

United Network for Organ Sharing 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. United Network for Organ Sharing criteria were updated in 2022.

Individuals with HCC are appropriate candidates for liver transplant only if the disease remains confined to the liver. Therefore, the individual should be periodically monitored while on the waiting list, and if metastatic disease develops, the individual 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 individuals do not receive any priority on the waiting list. All individuals 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 consists 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 individuals 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 1 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 less than 3 cm.

- 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 individuals 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 (7.03.01).

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.

RATIONALE

Summary of Evidence

For individuals who have a hepatocellular disease who receive a liver transplant, the evidence includes 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 an 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 an 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 and individual registry 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, 5-year survival rates have been reported as high as 76%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have intrahepatic cholangiocarcinoma who receive a liver transplant, the evidence includes registry studies and a systematic review of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In a registry study comparing outcomes in patients with intrahepatic cholangiocarcinoma who received liver transplantation to those who received surgical resection of the liver, no differences were found in OS, length of stay, or unplanned 30-day readmission rates between groups. Additional studies reporting survival rates in patients with intrahepatic cholangiocarcinoma or in mixed populations of patients with extrahepatic and intrahepatic cholangiocarcinoma have reported 5-year survival rates of less than 30%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 the United Network for Organ Sharing criteria for patients eligible for liver transplantation. The evidence is sufficient to determine that the technology results in an 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 an 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 a systematic review of retrospective observational studies in adults and several individual 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 transplant is no worse, and possibly better, for graft and patient survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Consensus Conference

In 2010, an International Consensus Conference, including representation from the U.S., convened with the goal of reviewing current practice regarding liver transplantation in patients with hepatocellular carcinoma (HCC).[64,] The Conference ultimately came up with recommendations beginning from the assessment of candidates with HCC for liver transplantation and managing patients on waitlists, to the role of liver transplantation and post-transplant management. Some notable recommendations are described.

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 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 (AASLD) and the American Society of Transplantation (AST) issued joint guidelines on evaluating patients for a liver transplant.[65,] 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 from complications of cirrhosis
- Liver-based metabolic condition with systemic manifestations
    - α_1-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 [Human Immunodeficiency Virus] 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 [acquired immunodeficiency syndrome]
- 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 AASLD, AST, , and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition issued joint guidelines on the evaluation of the pediatric patients for liver transplant.[66,] 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 AASLD guideline on alcohol-associated liver disease provided recommendations on the timing of referral and selection of candidates for liver transplant.[67,] 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.

In 2023, the AASLD released a practice guideline on the management of hepatocellular carcinoma.[68,] Evidence recommendations by the expert panel are rated based on the Oxford Center for Evidence-Based Medicine and the strength of recommendations are categorized based on the level of evidence, risk - benefit ratio, and patient preferences. Recommendations regarding liver transplantation are listed below.

- "Liver transplantation should be the treatment of choice for transplant-eligible patients with early-stage HCC occurring in the setting of clinically significant portal hypertension and/or decompensated cirrhosis (Level 2, Strong Recommendation)
- AASLD advises the use of pre-transplant locoregional bridging therapy for patients being evaluated or listed for liver transplantation, if they have adequate hepatic reserve, to reduce the risk of waitlist dropout in the context of anticipated prolonged wait times for transplant (Level 3, Strong Recommendation)
- AASLD advises patients with decompensated cirrhosis who develop T1 HCC and are eligible for LT be monitored with cross-sectional imaging at least every 3 months until criteria are met for MELD exception before pursuing LRT [locoregional therapy] (Level 3, Weak Recommendation)
- Patients who are otherwise transplant-eligible except with initial tumor burden exceeding the Milan criteria, especially those meeting United Network of Organ Sharing (UNOS) downstaging criteria, should be considered for LT following successful downstaging to within Milan criteria after a 3-to-6-month period of observation (Level 2, Strong Recommendation)

- AASLD advises surveillance for detection of post-transplant HCC recurrence using multiphasic contrast-enhanced abdominal CT [computed tomography] or MRI [magnetic resonance imaging] and chest CT scan (Level 2, Strong Recommendation)"

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v 1.2023) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting UNOS 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.[16,] 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 and who fit UNOS criteria/ extended criteria, the NCCN indicates that these patients could be considered for resection or transplant. 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 also indicate that patients with unresectable disease who are not a transplant candidate should receive locoregional therapy with ablation, arterially directed therapies, or external beam radiation therapy or may receive systemic therapy, best supportive care, or be enrolled in a clinical trial. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors (v.2.2022) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite "encouraging" 5-year survival rates.[69,]

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.[70,71,] 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

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21 st century. Ann Transl Med. Oct 2018; 6(20): 409. PMID 30498736
2. Belle SH, Beringer KC, Detre KM. An update on liver transplantation in the United States: recipient characteristics and outcome. Clin Transpl. 1995: 19-33. PMID 8794252
3. Sheiner P, Rochon C. Recurrent hepatitis C after liver transplantation. Mt Sinai J Med. 2012; 79(2): 190-8. PMID 22499490
4. Gadiparthi C, Cholankeril G, Perumpail BJ, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. World J Gastroenterol. Jan 21 2018; 24(3): 315-322. PMID 29391754
5. Wang X, Li J, Riaz DR, et al. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. Mar 2014; 12(3): 394-402.e1. PMID 24076414
6. Yong JN, Lim WH, Ng CH, et al. Outcomes of Nonalcoholic Steatohepatitis After Liver Transplantation: An Updated Meta-Analysis and Systematic Review. Clin Gastroenterol Hepatol. Jan 2023; 21(1): 45-54.e6. PMID 34801743

7. Cholankeril G, Wong RJ, Hu M, et al. Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. Dig Dis Sci. Oct 2017; 62(10): 2915-2922. PMID 28744836
8. Schoenberg MB, Bucher JN, Vater A, et al. Resection or Transplant in Early Hepatocellular Carcinoma. Dtsch Arztebl Int. Aug 07 2017; 114(31-32): 519-526. PMID 28835324
9. Zheng Z, Liang W, Milgrom DP, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Transplantation. Jan 27 2014; 97(2): 227-34. PMID 24142034
10. Guiteau JJ, Cotton RT, Washburn WK, et al. An early regional experience with expansion of Milan Criteria for liver transplant recipients. Am J Transplant. Sep 2010; 10(9): 2092-8. PMID 20883543
11. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. Liver Transpl. Mar 2010; 16(3): 262-78. PMID 20209641
12. Ioannou GN, Perkins JD, Carithers RL. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology. May 2008; 134(5): 1342-51. PMID 18471511
13. Chan EY, Larson AM, Fix OK, et al. Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. Liver Transpl. Jul 2008; 14(7): 956-65. PMID 18581511
14. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. Mar 14 1996; 334(11): 693-9. PMID 8594428
15. Firl DJ, Kimura S, McVey J, et al. Reframing the approach to patients with hepatocellular carcinoma: Longitudinal assessment with hazard associated with liver transplantation for HCC (HALTHCC) improves ablate and wait strategy. Hepatology. Oct 2018; 68(4): 1448-1458. PMID 29604231
16. National Comprehensive Cancer Network. Hepatocellular Carcinoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf. Accessed June 12, 2023.
17. Yadav DK, Chen W, Bai X, et al. Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma. Ann Transplant. Aug 03 2018; 23: 524-545. PMID 30072683
18. Murali AR, Patil S, Phillips KT, et al. Locoregional Therapy With Curative Intent Versus Primary Liver Transplant for Hepatocellular Carcinoma: Systematic Review and Meta-Analysis. Transplantation. Aug 2017; 101(8): e249-e257. PMID 28282359
19. Maggs JR, Suddle AR, Aluvihare V, et al. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. Aliment Pharmacol Ther. May 2012; 35(10): 1113-34. PMID 22432733
20. Chan DL, Alzahrani NA, Morris DL, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol. Jan 2014; 29(1): 31-41. PMID 24117517
21. Zhu Y, Dong J, Wang WL, et al. Short- and long-term outcomes after salvage liver transplantation versus primary liver transplantation for hepatocellular carcinoma: a meta-analysis. Transplant Proc. Nov 2013; 45(9): 3329-42. PMID 24182812
22. Cambridge WA, Fairfield C, Powell JJ, et al. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. Ann Surg. Feb 01 2021; 273(2): 240-250. PMID 32097164
23. Gu J, Bai J, Shi X, et al. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. Int J Cancer. May 01 2012; 130(9): 2155-63. PMID 21387295
24. Heimbach JK. Successful liver transplantation for hilar cholangiocarcinoma. Curr Opin Gastroenterol. May 2008; 24(3): 384-8. PMID 18408469
25. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. Jul 2012; 143(1): 88-98.e3; quiz e14. PMID 22504095
26. Heimbach JK, Gores GJ, Haddock MG, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation. Dec 27 2006; 82(12): 1703-7. PMID 17198263
27. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. Sep 2005; 242(3): 451-8; discussion 458-61. PMID 16135931
28. Pascher A, Jonas S, Neuhaus P. Intrahepatic cholangiocarcinoma: indication for transplantation. J Hepatobiliary Pancreat Surg. 2003; 10(4): 282-7. PMID 14598146
29. Friman S, Foss A, Isoniemi H, et al. Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results. Scand J Gastroenterol. Mar 2011; 46(3): 370-5. PMID 21073376
30. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation. Apr 27 2000; 69(8): 1633-7. PMID 10836374
31. Robles R, Figueras J, Turrin VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg. Feb 2004; 239(2): 265-71. PMID 14745336
32. Casavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg. Nov 1997; 185(5): 429-36. PMID 9358085
33. Ziogas IA, Giannis D, Economopoulos KP, et al. Liver Transplantation for Intrahepatic Cholangiocarcinoma: A Meta-analysis and Meta-regression of Survival Rates. Transplantation. Oct 01 2021; 105(10): 2263-2271. PMID 33196623
34. Hue JJ, Rocha FG, Ammori JB, et al. A comparison of surgical resection and liver transplantation in the treatment of intrahepatic cholangiocarcinoma in the era of modern chemotherapy: An analysis of the National Cancer Database. J Surg Oncol. Mar 2021; 123(4): 949-956. PMID 33400841
35. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. HPB (Oxford). Jan 2015; 17(1): 23-8. PMID 24992381
36. Mth Z, Tagkalos E, Paul A, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation. Mar 15 2011; 91(5): 575-82. PMID 21200365

37. Hamilton EC, Balogh J, Nguyen DT, et al. Liver transplantation for primary hepatic malignancies of childhood: The UNOS experience. J Pediatr Surg. Oct 12 2017. PMID 29108844
38. Barrena S, Hernandez F, Miguel M, et al. High-risk hepatoblastoma: results in a pediatric liver transplantation center. Eur J Pediatr Surg. Jan 2011; 21(1): 18-20. PMID 20938901
39. Malek MM, Shah SR, Atri P, et al. Review of outcomes of primary liver cancers in children: our institutional experience with resection and transplantation. Surgery. Oct 2010; 148(4): 778-82; discussion 782-4. PMID 20728194
40. Browne M, Sher D, Grant D, et al. Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg. Nov 2008; 43(11): 1973-81. PMID 18970927
41. Czauderna P, Otte JB, Aronson DC, et al. Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer. May 2005; 41(7): 1031-6. PMID 15862752
42. Organ Procurement and Transplantation Network (OPTN). Policy 9: Allocation of Livers and Liver-Intestines. Updated March 16, 2023; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_01. Accessed June 12, 2023.
43. Salimi J, Jafarian A, Fakhar N, et al. Study of re-transplantation and prognosis in liver transplant center in Iran. Gastroenterol Hepatol Bed Bench. 2021; 14(3): 237-242. PMID 34221263
44. Bellido CB, Martnez JM, Artacho GS, et al. Have we changed the liver retransplantation survival?. Transplant Proc. 2012; 44(6): 1526-9. PMID 22841203
45. Remiszewski P, Kalinowski P, Dudek K, et al. Influence of selected factors on survival after liver retransplantation. Transplant Proc. Oct 2011; 43(8): 3025-8. PMID 21996216
46. Hong JC, Kaldas FM, Kositamongkol P, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. Ann Surg. Sep 2011; 254(3): 444-8; discussion 448-9. PMID 21817890
47. Bouari S, Rijkse E, Metselaar HJ, et al. A comparison between combined liver kidney transplants to liver transplants alone: A systematic review and meta-analysis. Transplant Rev (Orlando). Dec 2021; 35(4): 100633. PMID 34098490
48. Lunsford KE, Bodzin AS, Markovic D, et al. Avoiding Futility in Simultaneous Liver-kidney Transplantation: Analysis of 331 Consecutive Patients Listed for Dual Organ Replacement. Ann Surg. May 2017; 265(5): 1016-1024. PMID 27232249
49. Fong TL, Khemichian S, Shah T, et al. Combined liver-kidney transplantation is preferable to liver transplant alone for cirrhotic patients with renal failure. Transplantation. Aug 27 2012; 94(4): 411-6. PMID 22805440
50. Ruiz R, Jennings LW, Kim P, et al. Indications for combined liver and kidney transplantation: propositions after a 23-yr experience. Clin Transplant. 2010; 24(6): 807-11. PMID 20002463
51. Calinescu AM, Wildhaber BE, Poncet A, et al. Outcomes of combined liver-kidney transplantation in children: analysis of the scientific registry of transplant recipients. Am J Transplant. Dec 2014; 14(12): 2861-8. PMID 25274400
52. de la Cerda F, Jimenez WA, Gjertson DW, et al. Renal graft outcome after combined liver and kidney transplantation in children: UCLA and UNOS experience. Pediatr Transplant. Jun 2010; 14(4): 459-64. PMID 20070563
53. Marcos A, Ham JM, Fisher RA, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. Liver Transpl. May 2000; 6(3): 296-301. PMID 10827229
54. Malag M, Testa G, Marcos A, et al. Ethical considerations and rationale of adult-to-adult living donor liver transplantation. Liver Transpl. Oct 2001; 7(10): 921-7. PMID 11679994
55. Renz JF, Busuttil RW. Adult-to-adult living-donor liver transplantation: a critical analysis. Semin Liver Dis. 2000; 20(4): 411-24. PMID 11200412
56. Bak T, Wachs M, Trotter J, et al. Adult-to-adult living donor liver transplantation using right-lobe grafts: results and lessons learned from a single-center experience. Liver Transpl. Aug 2001; 7(8): 680-6. PMID 11510011
57. Shiffman ML, Brown RS, Olthoff KM, et al. Living donor liver transplantation: summary of a conference at The National Institutes of Health. Liver Transpl. Feb 2002; 8(2): 174-88. PMID 11862598
58. Grant RC, Sandhu L, Dixon PR, et al. Living vs. deceased donor liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. Clin Transplant. 2013; 27(1): 140-7. PMID 23157398
59. Tang W, Qiu JG, Cai Y, et al. Increased Surgical Complications but Improved Overall Survival with Adult Living Donor Compared to Deceased Donor Liver Transplantation: A Systematic Review and Meta-Analysis. Biomed Res Int. 2020; 2020: 1320830. PMID 32908865
60. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with synthetic cohort. AIDS. Mar 27 2011; 25(6): 777-86. PMID 21412058
61. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl. Jun 2012; 18(6): 716-26. PMID 22328294
62. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. Updated March 16, 2023; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed June 13, 2023.
63. Blumberg EA, Rogers CC. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. Sep 2019; 33(9): e13499. PMID 30773688
64. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. Jan 2012; 13(1): e11-22. PMID 22047762
65. American Association for the Study of Liver Diseases, American Society of Transplantation. Liver transplantation, evaluation of the adult patient. 2013; https://www.aasld.org/practice-guidelines/evaluation-adult-liver-transplant-patient. Accessed June 13, 2023.
66. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology. Jul 2014; 60(1): 362-98. PMID 24782219

67. American Association for the Study of Liver Diseases. Diagnosis and Treatment of Alcohol Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. https://www.aasld.org/practice-guidelines/alcohol-associated-liver-disease. Accessed June 13, 2023.
68. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. May 22 2023. PMID 37199193
69. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed June 13, 2023.
70. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Adult Liver Transplantation (260.1). 2012; https://www.cms.gov/medicare-coverage-database/details/ncd- details.aspx?NCAId=259&NcaName=Liver+Transplantation+for+Malignancies&ExpandComments=n&CommentPeriod=0&NCDId=70&ncdver=3&id=186&bc=gABAAAAAEEAAAA%3D%3D&. Accessed June 13, 2023.
71. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Pediatric Liver Transplantation (260.2). 1991; https://www.cms.gov/medicare-coverage-database/details/ncd- details.aspx?MCDId=17&ExpandComments=n&McdName=Clinical+Pharmacology+Compendium+Revision+Re quest+-+CAG-00392&mcdtypename=Compendia&MCDIndexType=6&NCDId=71&ncdver=1&bc=AgAEAAAAAgAA&. Accessed June 12, 2023.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
March 2013	Replace policy	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.
March 2014	Replace policy	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.
March 2015	Replace policy	Policy updated with literature search through December 18, 2014. No change to policy statements. References 52, 64, and 66 added.
December 2017	Replace policy	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.,
December 2018	Replace policy	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.
December 2019	Replace policy	Policy updated with literature review through June 10, 2019; reference added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through July 6, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through July 6, 2021; references added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through June 27, 2022; references added and updated. Minor editorial refinements to policy statements; intent unchanged.
December 2023	Replace policy	Policy updated with literature review through June 13, 2023; references added and updated. Minor editorial refinements to policy statements; intent unchanged.