LOUISIANA BLUE

Liver Transplant and Combined Liver-Kidney Transplant

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a liver transplant using a cadaver or living donor, for carefully selected individuals with end-stage liver failure due to irreversibly damaged livers to be **eligible for coverage.****

Etiologies of end-stage liver disease include, but are not limited to, the following:

A. Hepatocellular diseases
   - Alcoholic liver disease (see Policy Guidelines section)
   - 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

Based on review of available data, the Company may consider liver transplantation in individuals with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment to be **eligible for coverage.****

Based on review of available data, the Company may consider liver transplantation in individuals with unresectable hilar cholangiocarcinoma (CCA) to be **eligible for coverage**** (See Policy Guidelines section for patient selection criteria).

Based on review of available data, the Company may consider liver transplantation in pediatric individuals with nonmetastatic hepatoblastoma to be **eligible for coverage.****

Based on review of available data, the Company may consider liver *retransplantation* to be **eligible for coverage**** in individuals with:

- Primary graft nonfunction
- Hepatic artery thrombosis
- Chronic rejection
- Ischemic type biliary lesions after donation after cardiac death
- Recurrent nonneoplastic disease causing late graft failure

Based on review of available data, the Company may consider combined liver-kidney transplantation (CLKT) in individuals who qualify for liver transplantation and have advanced irreversible kidney disease to be **eligible for coverage.****

When Services Are Considered Investigational

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

Based on review of available data, the Company considers liver transplantation to be **investigational*** in all other situations, including but not limited to:

- Individuals with intrahepatic cholangiocarcinoma (CCA)
- Individuals with neuroendocrine tumors (NETs) metastatic to the liver
- Individuals with HCC 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. A formal psychological evaluation can help stratify individuals into higher- or lesser-risk strata for relapse.)

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 (alcoholic liver disease or drug abuse must be actively involved in a substance abuse treatment program.

Patients who have alcoholic hepatitis (AH) are infrequently transplanted because the diagnosis of AH implies recent harmful alcohol use and because some patients will improve without transplantation. The chronic inflammatory state associated with AH has the potential to increase perioperative complications, although most studies found that long-term morbidity is related primarily to recurrent alcohol use disorder rather than acute complications of transplantation.

The number of patients undergoing liver transplantation for acute AH has been steadily increasing in the United States, with marked geographic variation because **a** limited number of centers perform transplantation for this indication. Criteria for patient selection remain highly variable among centers, and additional studies with long-term follow-up are needed to optimize criteria for liver transplantation. At most transplant centers, criteria for selecting patients with AH require that there is no prior history of liver decompensation because prior decompensation has been associated with higher risk of mortality and alcohol relapse.

Tobacco consumption is a contraindication. Documentation should include confirmation of patient enrollment into smoking cessation program and treatment plan if patient continues to smoke despite interventions.

Smoking remains an independent and significant risk factor for post-transplant morbidity and mortality. Moreover, long-term morbidity and mortality are also linked to continued smoking, which accelerates cardiovascular and cancer risk.

Some authorities have advocated removing individuals from the transplant waiting list who continue to smoke despite these interventions. Roughly 20 percent of transplant centers report that they will refuse to list individuals due to smoking. One report found that up to 40 percent of individuals who had undergone transplantation for alcoholic liver disease resumed smoking early in the post-

transplant course, underscoring the need for continued counseling and monitoring after transplantation.

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.

Background/Overview

Solid organ transplantation offers a treatment option for patients with different types of end stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life. Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. 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.

Liver transplantation
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 (eg, 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 (LD) liver transplantation (LT) 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 LD LT. In addition to addressing the problem of donor organ scarcity, LD LT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. Living donor LT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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. Individuals 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.

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review in 2012. 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
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). 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. 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. 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. 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. 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 2.2024) 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 1 to 3 cm in diameter with no macrovascular involvement or extrahepatic disease. 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.1.2024) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite "encouraging" 5-year survival rates.

The NCCN guidelines on colorectal cancer (v.1.2025) do not mention or recommend liver transplant as a treatment option for unresectable colorectal liver-only metastases.

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. 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.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02878473	Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics	30	Jan 2029
NCT05717842	Simultaneous Prospective Kidney Transplant Assessment in Combined Liver Kidney	15	Feb 2025
Unpublished			
NCT03500315	HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients	209	Dec 2022 (completed)

NCT: national clinical trial.

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Policy History

Original Effective Date: 05/21/2014
Current Effective Date: 04/01/2025
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. New policy.
03/05/2015 Medical Policy Committee review

03/20/2015	Medical Policy Implementation Committee approval. Removed requirement for "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.)".
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Policy title changed from "Liver Transplant" to "Liver Transplant and Combined Liver-Kidney Transplant." Combined liver-kidney transplantation added to policy as eligible for coverage. Policy Guidelines moved from the Background/Overview to a new Policy Guidelines section. Contraindication for smoking and HIV criteria added to Policy Guidelines.
01/01/2019	Coding update
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/10/2019	Coding update
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Added a reference to see the patient selection criteria in the Policy Guidelines section for liver transplantation in patients with unresectable hilar cholangiocarcinoma. Added a not medically necessary criteria bullet as follows: • 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.)
09/16/2020	Coding update
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Added information on tobacco consumption under Liver-Specific Criteria in the Policy Guidelines.
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/02/2023	Medical Policy Committee review

03/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Minor editorial refinements to policy statements changing "patients" to "individuals"; intent unchanged.
07/02/2024	Medical Policy Committee review
07/10/2024	Medical Policy Implementation Committee approval. Added a reference to see Policy Guidelines section for alcoholic liver disease in the coverage criteria. Removed the Not Medically Necessary section. Combined investigational statements into one statement. Added investigational bullet for HCC that has extended beyond the liver. Added two investigational bullets for individuals with ongoing alcohol and/or drug abuse addressing evidence for abstinence and for formal psychological evaluation. Added content to Policy Guidelines section under Liver-Specific Criteria and the related sources to the References.
03/06/2025	Medical Policy Committee review
03/12/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged..

Next Scheduled Review Date: 03/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147, 47399
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.