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MEDICAL POLICY – 7.03.509

Liver Transplant and Combined Liver-Kidney Transplant

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RELATED MEDICAL POLICIES:

7.03.01	Kidney Transplant
8.01.11	Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | APPENDIX | HISTORY

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Introduction

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

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Transplant	Medical Necessity
Liver transplant using a cadaver or living donor	**A liver transplant using a cadaver or living donor may be considered medically necessary for carefully selected 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 o Alcoholic liver disease o Viral hepatitis (either A, B, C, or non-A, non-B) o Autoimmune hepatitis o α1-Antitrypsin deficiency o Hemochromatosis o Nonalcoholic steatohepatitis o Protoporphyria o Wilson disease B. Cholestatic liver diseases o Primary biliary cirrhosis o Primary sclerosing cholangitis with development of secondary biliary cirrhosis o Biliary atresia C. Vascular disease o Budd-Chiari syndrome D. Primary hepatocellular carcinoma (see **Related Information** for individual selection criteria) E. Inborn errors of metabolism F. Trauma and toxic reactions G. Miscellaneous o Familial amyloid polyneuropathy
Liver transplantation	**Liver transplantation may be considered medically necessary in individuals with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.**

Transplant	Medical Necessity

	Liver transplantation may be considered medically necessary in individuals with unresectable hilar cholangiocarcinoma (see Related Information for individual selection criteria).
	
	Liver transplantation may be considered medically necessary in pediatric individuals with nonmetastatic hepatoblastoma.
	
	Liver transplantation is considered not medically necessary in the following individuals:
	• Individuals with hepatocellular carcinoma that has extended beyond the liver (see **Related Information** for individual selection criteria)
	• Individuals with ongoing alcohol and/or drug abuse **except** for those with:
	  ○ Objective failure of therapy for severe acute alcoholic hepatitis.[73] (See **Appendix** for Lille protocol), **or**
	  ○ Critical decompensation in alcohol related cirrhotic individuals as judged by Model for End-stage Liver Disease score (MELD-Na ≥21)[68] predicting mortality prior to completion of required abstinence
	
	Note: Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.

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

Transplant	Investigational
Liver transplantation	**Liver transplantation is considered investigational in the following situations:** • Individuals with intrahepatic cholangiocarcinoma • Individuals with neuroendocrine tumors metastatic to the liver **Liver transplantation is considered investigational in all other situations not described above.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the relevant history and physical supporting that the individual has end stage liver disease due to an irreversibly damaged liver from one of the listed etiologies. Request for liver transplant, combined liver/kidney transplant, or liver retransplantation is specified.

Note: Combined liver-kidney transplant would be reported with the codes in this policy along with the codes in the policy on kidney transplant (See **Related Policies**).

Coding

Code	Description
CPT	
47135	Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age
HCPCS	
S2152	Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor (s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre and posttransplant care in the global definition

Related Information

Contraindications

Potential contraindications for solid organ transplant are subject to the judgment of the transplant center and include the following:

- Known current malignancy, including metastatic cancer
- Recent malignancy with high risk of recurrence
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end-stage diseases not attributed to liver disease
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

Liver-Specific Criteria

The Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during 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.

UNOS Stage T2 Criteria

A single tumor 2 cm or greater and up to 5 cm or less or two to three tumors 1 cm or greater and up to 3 cm or less and without extrahepatic spread or macrovascular invasion. UNOS criteria were updated in 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 three-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 three months:

- Centers must submit a written protocol for individual 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 one of the following: carbohydrate antigen 19-9 100 U/mL, or biopsy or cytology results demonstrating malignancy, or aneuploidy. The

tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (e.g., primary sclerosing cholangitis).

- If cross-sectional imaging studies (computed tomography scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be 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 three 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.

Benefit Application

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

Evidence Review

Description

Liver transplantation is currently the treatment of last resort for individuals 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 (OPTN) and the United Network of Organ Sharing (UNOS). The severity of illness is determined by the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores.

Background

Solid organ transplantation offers a treatment option for individuals with different types of end stage organ failure that can be lifesaving or provide significant improvements to an individual's quality of life.[1] 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. Individuals are prioritized for transplant by mortality risk and severity of illness criteria developed by OPTN and UNOS.

Liver Transplantation

Liver transplantation is routinely performed as a treatment of last resort for individuals with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Certain populations are prioritized as Status 1A (e.g., acute liver failure with a life expectancy of fewer than 7 days without a liver transplant) or Status 1B (pediatric individuals with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the MELD and 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 two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

Summary of Evidence

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

For individuals who have primary HCC who receive a liver transplant, the evidence includes systematic reviews of observational studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In the past, long-term outcomes in individuals with primary hepatocellular malignancies had been poor (19%) compared with the OS of liver transplant recipients. However, the recent use of standardized individual selection criteria (e.g., the Milan criteria diameter) has dramatically improved OS rates. In the appropriately selected

individuals, a liver transplant has been shown to result in higher survival rates than resection. In individuals 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For individuals 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In a registry study comparing outcomes in individuals 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 individuals with intrahepatic cholangiocarcinoma or in mixed populations of individuals 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 (NETs) who receive a liver transplant, the evidence includes systematic reviews of case series. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In select individuals 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 individuals 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is among the UNOS criteria for individuals

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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some individuals, 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 (CLKT), the evidence includes a systematic review of retrospective observational studies in adults and several individual registry studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for CLKT in children are rare and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney. In both adults and children, comparisons with either liver or kidney transplantation alone would suggest that CLKT is no worse, and possibly better, for graft and individual survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05717842	Simultaneous Prospective Kidney Transplant Assessment in Combined Liver Kidney	15	Feb 2025
Ongoing			
NCT03500315	HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients	209	Dec 2022 (completed)

NCT: national clinical trial

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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

2012 Input

In response to requests, input was received from three physician specialty societies and five 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 individuals 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 individuals 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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a United States (US) professional society, an international society with US representation, or National Institute for Health and Care Excellence. 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 US, convened with the goal of reviewing current practice regarding liver transplantation in individuals with HCC.[65] The Conference ultimately came up with recommendations beginning from the assessment of candidates with HCC for liver transplantation and managing individuals 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 individual selection, although it was suggested that the Milan criteria might be modestly expanded based on data from expansion studies that demonstrated outcomes are comparable with outcomes from studies using the Milan criteria. Candidates for liver transplantation should also have a predicted survival of five years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining individual prognosis.

Regarding liver retransplantation, the consensus criteria issued a weak recommendation for retransplantation after graft failure of a living donor transplant for HCC in individuals 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 individuals 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 individuals for a liver transplant.[66] These guidelines indicated liver transplantation for severe acute or advanced chronic liver disease after all effective medical treatments have been attempted. The formal evaluation should confirm the irreversible nature of the liver disease and lack of effective alternative medical therapy.

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

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

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

- "Tobacco consumption should be prohibited in LT [liver transplant] candidates."
- "Patients with HIV [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 individuals for liver transplant.[67] The guidelines stated that "disease categories suitable for referral to a pediatric LT program are similar to adults: acute liver failure, autoimmune, cholestasis, metabolic or genetic, oncologic, vascular, and infectious. However, specific etiologies and outcomes differ widely from adult patients, justifying independent pediatric guidelines." The indications listed for liver transplantation included biliary atresia, Alagille syndrome, pediatric acute liver failure, hepatic tumors, HCC, hemangioendothelioma, cystic fibrosis-associated liver disease, urea cycle disorders, immune-mediated liver disease, along with other metabolic or genetic disorders.

The American Association for the Study of Liver Diseases

In 2019, the AASLD guideline on alcohol-associated liver disease provided recommendations on the timing of referral and selection of candidates for liver transplant.[68] The guidance notes that the individual'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 individuals into higher- or lesser-risk strata for relapse.

In 2023, the AASLD released a practice guideline on the management of HCC.[69] 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 individual 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 HCC (v 2.2024) recommend referral to a liver transplant center or bridge therapy for individuals with HCC meeting UNOS criteria of a single tumor measuring 2 to 5 cm, or two to three tumors 1 to 3 cm in diameter with no macrovascular involvement or extrahepatic disease.[16] In individuals who are ineligible for transplant and in select individuals 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. Individuals with unresectable HCC should be evaluated for liver transplantation; if the individual 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 individuals 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.[70]

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 (CMS) as meeting institutional coverage criteria for liver transplants. [71,72] 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 CMS. Coverage includes extrahepatic biliary atresia or any other form of end-stage liver disease, except for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.

Regulatory Status

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

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

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Appendix

Lille Protocol

Severe acute alcoholic hepatitis defined as Maddrey's discriminant function > 32. Calculation available at: **https://www.mdcalc.com/maddreys-discriminant-function-alcoholic-hepatitis** Accessed September 4, 2024.

- Non-responsive to medical therapy defined as a Lille model [77] score > 0.45 or more after 7 days of medical therapy. Calculation available at: **https://www.mdcalc.com/lille-model-alcoholic-hepatitis** Accessed September 4, 2024.
    - Medical therapy consists of standard medical care for liver insufficiency and use of glucocorticoids (40 mg per day of prednisolone for at least 7 days); **OR**
    - As a continuous increase in the Model for End-Stage Liver Disease (MELD) score
- Severe alcoholic hepatitis as the first liver-decompensating event
- Presence of close supportive family members
- Absence of severe coexisting or psychiatric disorders
- Agreement by individuals (with support from family members) to adhere to lifelong total abstinence
- Selection process consists of 4 medical teams who independently meet the individual and family members
    - Team 1: (closest to the individual): nurses, one resident, one fellow
    - Team 2: specialist in addiction
    - Team 3: senior hepatologists
    - Team 4: anesthesiologist and transplant surgeon
- The 4 evaluating teams have to reach complete consensus on selection

Source: Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790-800. PMID: 22070476.

History

Date	Comments
07/01/02	Add to Surgery Section - New Policy. Replaces other transplant policies (PR.7.03.100, 102, 103, 104, 105, and 106)
05/13/03	Replace Policy - Scheduled review. References added and CPT code table updated.
01/01/04	Replace Policy - CPT code updates only.
05/11/04	Replace Policy - Policy reviewed by Nancy Aceto no changes needed at this time; new review date only. Appendices removed—no value.
09/01/04	Replace Policy - Policy renumbered from PR.7.03.109. No changes to dates.
05/10/05	Replace Policy - Scheduled review. References added. No change to policy statement.
02/06/06	Codes updated - No other changes.
05/09/06	Replace Policy - Scheduled review. References added; no change to policy statement.
05/26/06	Scope and Disclaimer Updates - No other changes.
02/26/07	Codes Updated - No other changes.
05/08/07	Replace Policy - Policy updated with literature review; reference added. No change in policy statement.
05/21/07	References Updated - Policy updated with information on Medicare coverage of heart transplants.
05/13/08	Replace Policy - Policy updated with literature search. Policy statement to include using a cadaver or living donor under kidney transplants as a medically necessary indication. Also to include "imminent end-stage liver failure" for patients under liver transplants as medically necessary.
03/10/09	Replace Policy - Policy updated with literature search; references added. No change to policy statement.
02/09/10	Replace Policy - Policy updated with literature search. No change to policy statement.
01/11/11	Replace Policy - Policy updated with literature search. No change to policy statement.
01/06/12	Replace Policy – Policy updated with literature search; references added. No change to policy statement.
12/03/12	Update title to Related Policy 7.03.11.

Date	Comments
01/29/13	Replace policy. Policy updated with literature search. No change to policy statement. References updated.
02/12/13	Update Related Policies, change title for 8.02.02.
05/30/13	Update Related Policies. Change title for 7.03.510.
02/10/14	Replace policy. Retransplant policy statements added to kidney, heart, heart/lung. Literature updated. References 35-39 added. ICD-9 Diagnosis codes were listed for informational purposes only and have been removed from the policy.
03/11/14	Coding Update. Codes 33.50, 33.51, 33.52, 33.6, 37.5, 50.4, 50.51, 50.59, 52.80, 52.81, 52.82, 52.83, and 55.69 were removed per ICD-10 mapping project; these codes are not utilized for adjudication of policy.
03/31/15	Annual Review. Alphabetized names of organ transplants in policy statements. Related policy 7.03.05 added. Rationale section extensively reorganized by alphabetizing organ transplants and updated based on a literature review through December, 2014. References extensively renumbered and some references removed. Policy statements unchanged.
08/19/15	Update Related Policies. Remove 7.03.510 and 8.02.02 then add 8.03.05 and 7.03.04.
09/24/15	Coding update. ICD-9 Procedure codes removed; these are informational only.
01/12/16	Annual Review. Policy updated with literature search; references added. No change to the policy statement.
01/29/16	Coding update. Added HCPCS code S2152.
11/01/16	Update related policies. Removed 7.03.05 from related policies section as it was deleted (contents moved to 7.03.04).
01/01/17	Coding Update. Transplant benefit-related codes removed. Coding table moved to Policy Guidelines section. Updated titles of some Related Policies.
03/01/17	Annual Review, approved February 14, 2017. Policy updated with literature review through October 25, 2016; references renumbered. Policy statements unchanged.
04/14/17	Coding update; added HCPCS code S2060.
04/18/17	Coding update; added HCPCS code S2065.
09/01/17	Policy moved to new format. No changes to policy statement.
07/27/18	Coding update; added CPT 33935 to policy as it was inadvertently removed.
11/01/18	Annual Review, approved October 26, 2018. Policy updated with literature review through June 2018; references 42, 51, 56, 82, 87, 89, 94, 109, 111, 118, 120,136, 158, 164, 178,183, 184, and 201 added. Examples of end-stage cardiac and pulmonary diseases added for clarity under heart and lung transplant. Etiologies of end-stage liver disease added for clarity, polycystic disease of the liver, unresectable hilar cholangiocarcinoma, pediatric patients with nonmetastatic hepatoblastoma are added as medically necessary indications for liver transplantation. Indications for liver

Date	Comments
	retransplantation were added. Indications where liver transplantation is not medically necessary or is considered investigational were added, otherwise policy statements unchanged.
04/01/19	Minor update, added Documentation Requirements section.
11/01/19	Annual Review approved October 8, 2019. Policy title changed from "Solid Organ Transplants" to "Liver Transplant and Combined Liver-Kidney Transplant". Previous content of Solid Organ Transplants is now addressed in individual policies (7.03.01, 7.03.02, 7.03.07, 7.03.08, 7.03.09) except for liver and combined liver-kidney transplant. Policy updated with literature review through June 2019. References added. Added exception criteria for patients with ongoing alcohol abuse. Added policy statement on transplantation of HCV viremic organs which is taken from BCBSA policy 7.03.14.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.
11/01/20	Annual Review, approved October 22, 2020. Policy updated with literature review through July 2020; references added. Policy statements unchanged.
11/01/21	Annual Review, approved October 5, 2021. Policy updated with literature review through July 6, 2021; references added. Policy statements unchanged.
11/01/22	Annual Review, approved October 24, 2022. Policy updated with literature review through June 27, 2022; references added and updated. Minor editorial refinements to policy statements; intent unchanged.
11/01/23	Annual Review, approved October 9, 2023. Policy updated with literature review through June 13, 2023; references added and updated. Removed the policy statement regarding the transplantation of HCV-viremic solid organs to an HCV non-viremic recipient combined with direct-acting antiviral treatment for HCV is considered investigational. Other minor editorial refinements to policy statements made for clarity; intent unchanged.
11/01/24	Annual Review, approved October 7, 2024. Policy updated with literature review through July 9, 2024; references added. Policy statements unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.