# Protocol

# Liver Transplant and Combined Liver-Kidney Transplant

(70306)

*(Formerly Liver Transplant)*

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| **Medical Benefit** | | **Effective Date**: 07/01/18 | **Next Review Date**: 03/19 |
| **Preauthorization** | Yes | **Review Dates**: 09/09, 09/10, 09/11, 01/12, 01/13, 01/14, 03/14, 03/15, 03/16, 03/17, 03/18 | |

***Preauthorization is required and must be obtained through Case Management.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With hepatocellular disease | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With primary hepato-cellular carcinoma | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management<br>• Liver resection | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With extrahepatic cholangiocarcinoma | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With intrahepatic cholangiocarcinoma | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With metastatic neuroendocrine tumors | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With pediatric hepatoblastoma | Interventions of interest are:<br>• Liver transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |

| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| Individuals:<br>• With a failed liver transplant | Interventions of interest are:<br>• Liver retransplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |
| Individuals:<br>• With indications for liver and kidney transplant | Interventions of interest are:<br>• Combined liver-kidney transplant | Comparators of interest are:<br>• Medical management | Relevant outcomes include:<br>• Overall survival<br>• Morbid events<br>• Treatment-related mortality<br>• Treatment-related morbidity |

**Description**

Liver transplantation is currently performed routinely as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with a liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (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.

**Summary of Evidence**

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

For individuals who have primary hepatocellular carcinoma who receive 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, recent use of standardized patient selection criteria (e.g., the Milan criteria diameter) has dramatically improved OS rates. In appropriately selected patients, liver transplant has been shown to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

For individuals who have metastatic neuroendocrine tumors who receive 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 there may be centers that perform liver transplants on select patients with neuroendocrine tumors, the available studies are limited by their heterogeneous populations. Further studies are needed to determine appropriate selection criteria. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pediatric hepatoblastoma who receive 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 included in UNOS criteria for patients eligible for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a failed liver transplant who receive 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 an original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

**Policy**

A liver transplant using a cadaver or living donor may be considered **medically necessary** for carefully selected patients with end-stage liver failure due to irreversibly damaged livers.

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

A. Hepatocellular diseases

- Alcoholic liver disease
- Viral hepatitis (either A, B, C, or non-A, non-B)
- Autoimmune hepatitis
- $\alpha_1$-Antitrypsin deficiency

- Hemochromatosis
- Nonalcoholic steatohepatitis
- Protoporphyria
- Wilson disease

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

C. Vascular disease
- Budd-Chiari syndrome

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

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
- Familial amyloid polyneuropathy

Liver transplantation may be considered **medically necessary** in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.

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

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

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

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

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

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

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

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

- Patients with hepatocellular carcinoma that has extended beyond the liver(see Policy Guidelines for patient selection criteria)

- Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of three months is required.)

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

**Policy Guidelines**

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at **their** facility.

*General*

Potential contraindications subject to the judgment of the transplant center:

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

*Liver-Specific Patient Selection Criteria*

The MELD and PELD scores range from six (less ill) to 40 (gravely ill). The MELD and PELD scores will change during the course of a patient's tenure on the waiting list.

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

Tobacco consumption is a contraindication.

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

- Enlargement of liver impinging on respiratory function
- Extremely painful enlargement of liver
- Enlargement of liver significantly compressing and interfering with function of other abdominal organs.

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

<u>Hepatocellular Carcinoma</u>

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

MILAN CRITERIA

A single tumor 5 cm or less in diameter or two to three tumors 3 cm or less

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO EXPANDED CRITERIA

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

UNOS T2 CRITERIA

A single tumor 1 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, which were updated in 2017, may prioritize T2 (HCC that meet specified staging and imaging criteria by allocating additional points equivalent to a MELD score predicting a 15% probability of death within three months). (https://optn.transplant.hrsa.gov/governance/policies/pfs/policy)

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

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

Additionally, nodules identified through imaging of cirrhotic livers are given a Class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent loco-regional treatment after being automatically approved upon initial application or extension. A single Class 5A nodule (greater than 1 cm and less than 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 are not eligible for automatic exception points. Nodules less than one 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.

HIV-positive patients who meet the following criteria, as stated in the 2013 guidelines of the American Society of Transplantation, could be considered candidates for liver transplantation:

- CD4 count >100 cells per cubic microliter, <200 cells/microliter (without history of opportunistic infection)
- CD4 count >200 cells per cubic microliter during three months before transplantation
- Undetectable HIV viral load while receiving antiretroviral HIV therapy
- Detectable HIV viral load due to intolerance of HAART, HIV can be suppressed post-transplant
- Documented compliance with a stable antiretroviral regimen
- Absence of opportunistic infection
- Absence of chronic wasting or severe malnutrition
- Donor free of hepatitis C

Cholangiocarcinoma

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

- Centers must submit a written protocol for patient care to the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee.
- Candidates must satisfy diagnostic criteria for hilar CCA: 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 [CT] scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be 3 cm or less.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 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 patients with obvious metastases before neoadjuvant therapy is initiated.
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

*Donor Criteria: Living Donor Liver Transplant*

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. In 2000, the American Society of Transplant Surgeons proposed the following guidelines for living donors:

- 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 assure 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.

**Medicare Advantage**

If a transplant is needed, we arrange to have the Medicare–approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

**Background**

*Liver Transplant*

Recipients

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by OPTN and UNOS. The original liver allocation system was based on assignment to status 1, 2A, 2B, or 3. Status 2A, 2B, and 3 were based on the Child-Turcotte-Pugh score, which included a subjective assessment of symptoms as part of the scoring system. In 2002, status 2A, 2B, and 3 were replaced with two disease severity scales: MELD and PELD for patients younger than age 12 years. In 2013, the OPTN and UNOS published its most recent allocation system, which previously expanded status 1 to status 1A and 1B in September 2012. Status 1A patients have acute liver failure with a life expectancy of less than seven days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis, and acute Wilson disease. Status 1A patients must be recertified every seven days. Status 1B patients are pediatric patients (age range, zero-17 years) with chronic liver disease, which may include the following: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to status 1A at age 18 but still qualify for pediatric indications.

Following status 1, donor livers will be prioritized to those with the highest scores on MELD or PELD. With this allocation system, the highest priority for liver transplantation is given to patients receiving the highest number of points. The scoring system for MELD and PELD is a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (i.e., international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from six to 40. The PELD score incorporates albumin, bilirubin, INR, growth failure, and age at listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet, waiting time was found to be a poor predictor of the urgency of liver transplant because some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation systems, patients with a higher mortality risk and higher MELD and PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer.[1] Status 7 describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation. Pediatric patients who turn 18 are status X.

Donors

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

develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

Management

Management of acute rejection of liver transplant using plasmapheresis is discussed separately in the Plasma Exchange Protocol. Also, the role of chemoembolization or radiofrequency ablation as a bridge to transplant in patients with hepatocellular cancer is addressed in the Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies Protocol and the Radiofrequency Ablation of Primary or Metastatic Liver Tumors Protocol respectively.

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Liver transplants are included in these regulations.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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