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Liver Transplant and Combined Liver-Kidney Transplant

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Texas ONLY: For policies (IFM, Student, Small Group, Mid-Market, Large Group, fully-insured Municipalities/Counties/Schools, State Employee Plans, PPO, HMO, POS) delivered, issued for delivery, or renewed on or after January 1, 2024, TIC Chapter 1380 (§§ 1380.001 – 1380.003 [SB 1040 Human Organ Transplant]) prohibits coverage of a human organ transplant or post-transplant care if the transplant operation is performed in China or another country known to have participated in forced organ harvesting; or the human organ to be transplanted was procured by a sale or donation originating in China or another country known to have participated in forced organ harvesting. The commissioner of state health services may designate countries who are known to have participated in forced organ harvesting. Forced organ harvesting is defined as the removal of one or more organs from a living person by means of coercion, abduction, deception, fraud, or abuse of power or a position of vulnerability.

Coverage

NOTE 1: Liver transplantation and combined liver-kidney transplantation may be considered medically necessary for the indications listed below for individuals meeting the Organ Procurement and Transplantation Network policy criteria.

A liver transplant using a cadaver donor or a 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 may include, but are not limited to, the following:

A. Hepatocellular diseases:
   - Alcoholic liver disease;
   - Viral hepatitis (types A, B, C, non-A, or non-B);
   - Autoimmune hepatitis;
   - Alpha-1 antitrypsin deficiency;
   - Hemochromatosis;
   - Metabolic dysfunction-associated steatohepatitis (MASH);
   - Protoporphyria;
   - Wilson disease.
B. Cholestatic liver diseases:
   - Primary biliary cirrhosis;
   - Primary sclerosing cholangitis with development of secondary biliary cirrhosis;
   - Biliary atresia.
C. Vascular disease:
   - Budd-Chiari syndrome.
D. Primary hepatocellular carcinoma (see Policy Guidelines section for individual selection criteria).
E. Inborn errors of metabolism.
F. Trauma and toxic reactions.
G. Miscellaneous:
   - Familial amyloid polyneuropathy.

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

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

Liver transplantation **may be considered medically necessary** in pediatric individuals with non-metastatic hepatoblastoma.

Liver *retransplantation* **may be considered medically necessary** in individuals with:
- Primary graft non-function;
- Hepatic artery thrombosis;
- Chronic rejection;
- Ischemic type biliary lesions after donation after cardiac death; or

- Recurrent non-neoplastic disease-causing late graft-failure.

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

Liver transplantation **is considered not medically necessary** in individuals with:
- Individuals with hepatocellular carcinoma that has extended beyond the liver (see Policy Guidelines section for individual selection criteria);
- Individuals with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.)

Liver transplantation **is considered experimental, investigational and/or unproven** in all other situations not described above, including but not limited to individuals with:
- Neuroendocrine tumors metastatic to the liver;
- Intrahepatic cholangiocarcinoma;
- Hepatic adenoma;
- Unresectable colorectal cancer liver metastases;
- Epithelioid hemangioendothelioma (HEHE).

Policy Guidelines

Contraindications
Potential contraindications for solid organ transplant are subject to the judgment of the transplant center and include the following:
- Known current malignancy, including metastatic cancer;
- Recent malignancy with high risk of recurrence;
- Untreated systemic infection making immunosuppression unsafe, including chronic infection;
- Other irreversible end-stage diseases not attributed to liver disease;
- History of cancer with a moderate risk of recurrence;
- Systemic disease that could be exacerbated by immunosuppression;
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

Liver-Specific Criteria
The Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during an individual's tenure on the waiting list.

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

Tobacco consumption is a contraindication.

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

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

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

Hepatocellular Carcinoma

Criteria used for selection of individuals with hepatocellular carcinoma (HCC) 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. See Supplemental Information for current OPTN 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 should be 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 (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 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 (85):

- 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.

Description

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. (2) Many advances have been made in the last several decades to reduce perioperative complications. Available data support 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 the 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 (e.g., acute liver failure with a life expectancy of fewer than 7 days without a liver transplant) or Status 1B (pediatric patients with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into 2 segments that can be used for 2 recipients. Living donor (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.

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

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

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Liver Transplant for Hepatocellular Disease
Clinical Context and Therapy Purpose
The purpose of a liver transplant for individuals who have a hepatocellular disease (i.e., viral hepatitis or metabolic dysfunction-associated steatohepatitis) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with a hepatocellular disease, such as viral hepatitis or metabolic dysfunction-associated steatohepatitis (MASH).

Viral hepatitis is an infection that causes liver inflammation and damage. Hepatitis B, C, and D viruses can cause acute, chronic infections and lead to cirrhosis, liver failure, and liver cancer.

Metabolic dysfunction-associated steatohepatitis is caused by a buildup of fat in the liver, which leads to inflammation and damage. While many individuals have no symptoms or problems, in some cases, the condition can worsen to cause liver scarring and cirrhosis.

Interventions
The therapy being considered is a liver transplant.

Comparators
The following practice is currently being used to make decisions about the end-stage hepatocellular disease: medical management.

Outcomes
The general outcomes of interest are overall survival (OS) and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Viral Hepatitis
The presence of hepatitis B virus and hepatitis C virus (HCV) have been controversial indications for liver transplantation because of the high potential for recurrence of the virus and subsequent recurrence of liver disease. However, in a review of registry data, Belle et al. (1995) have indicated a long-term survival rate (7 years) of 47% in hepatitis B virus-positive transplant recipients, which is lower than that seen in other primary liver diseases such as primary biliary cirrhosis (71%) or alcoholic liver disease (57%). (2) Recurrence of HCV infection in transplant

recipients who are not treated pretransplant has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years. (3)

Historical data demonstrating inferior survival in transplant recipients with HCV is not applicable to the current treatment landscape with the availability of direct acting antiviral agents, which are associated with sustained virological response rates of over 95%. (4) Timing the receipt of direct acting antiviral agents either before or after transplantation is still controversial and the decision should be individualized based the presence of compensated/ decompensated disease, Model for End-Stage Liver Disease (MELD) score, current quality of life, and the proportion of HCV-positive donors in the local and regional areas.

Metabolic Dysfunction-associated Steatohepatitis

Systematic Reviews

Liver transplantation is a treatment option for patients with MASH who progress to liver cirrhosis and failure. In a systematic review and meta-analysis, Wang et al. (2014) evaluated 9 studies of 717 patients with MASH and 3520 without MASH comparing liver transplantation outcomes. (5) Patients with MASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as patients without MASH. Patients with MASH also had lower graft failure risk than those without MASH (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.05 to 0.89; p=.03). However, MASH-related liver transplant patients had a greater risk of death related to cardiovascular disease (OR, 1.65; 95% CI, 1.01 to 2.70; p=.05) and sepsis (OR, 1.71; 95% CI, 1.17 to 2.50; p=.006) than non-MASH-related liver transplant patients.

Yong et al. (2021) presented an updated meta-analysis and systematic review analyzing 15 studies of 119,327 patients who received liver transplants. (6) The pooled prevalence of MASH across studies was 20.2%. The pooled 1-, 5-, and 10-year all-cause mortality in MASH patients after liver transplant were 12.5%, 24.4%, and 37.9%, respectively. Overall survival was comparable between liver transplant recipients with MASH versus non-MASH (hazard ratio [HR], 0.91; 95% CI, 0.76 to 1.10; p=.34). There was no significant difference between patients with MASH or without MASH for all secondary outcomes, including infection rates, biliary complications, cardiovascular disease events, cardiac failure, cerebrovascular accident, and length of stay. Additionally, there were no significant differences in graft survival between patients who underwent liver transplantation for MASH versus non-MASH (n=6 studies; HR, 0.95; 95% CI, 0.88 to 1.03; p=.20). Meta-regression demonstrated that a higher MELD score was associated with significantly worse overall survival in patients with MASH compared to patients without MASH after liver transplantation (95% CI, -0.0856 to -0.0181; p=.0026). There was no evidence of publication bias from the funnel plot conducted. This analysis is limited by large heterogeneity between studies, and a lack of information on donor quality to fully explore the association between higher MELD scores and early versus late mortality for MASH patients with liver transplantation.

Registry Studies

Cholankeril et al. (2017) published a retrospective cohort analysis of records from 2003 to 2014 in the United Network Organ Sharing (UNOS) and Organ Procurement and Transplantation Network (OPTN) database to evaluate the frequency of MASH-related liver transplantation. (7) In all, 63,061 patients underwent liver transplant from 2003 to 2014. Metabolic dysfunction-associated steatohepatitis accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to MASH increased by 162.0%, a greater increase than either hepatitis C (33.0% increase) and alcoholic liver disease (55.0% increase). Five-year survival posttransplant in patients who had MASH (77.81%; 95% CI, 76.37 to 79.25) was higher than patients who had HCV (72.15%; 95% CI, 71.37 to 72.93; p<.001). Patients with MASH also demonstrated significantly higher posttransplant survival than patients with HCV (HR, 0.75; 95% CI, 0.71 to 0.79; p<.001).

Section Summary: Liver Transplant for Hepatocellular Disease

The evidence on liver transplantation for a hepatocellular disease includes registry studies and systematic reviews. Long-term survival rates in patients with viral hepatitis 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 MASH, a 2013 systematic review has indicated that OS rates are similar to other indications for liver transplantation.

Liver Transplant for Primary Hepatocellular Carcinoma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have primary hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies. The criteria used to select individuals with HCC eligible for liver transplant include the Milan criteria, the University of California, San Francisco expanded criteria, and UNOS criteria.

The following PICO was used to select literature to inform this policy.

Patients

The relevant population of interest is individuals with HCC. See the detailed discussion in the Recipient Selection Criteria section below.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practices are currently being used to make decisions about managing HCC: medical management, including chemotherapy, and medical procedures, including surgery.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to

10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Liver Transplantation Versus Liver Resection for Hepatocellular Carcinoma

Systematic Reviews

Schoenberg et al. (2017) published a systematic review and meta-analysis of 54 retrospective studies (N=13,794) comparing liver resection (n=7990) with transplantation (n=5804) in patients with HCC. (8) At 1-year follow-up, survival rates were higher in those receiving resection than in those receiving liver transplant (86.17% vs 80.58%; OR, 1.19; 95% CI, 0.99 to 1.43; p=.07). At 5-year follow-up, survival rates were better for those who received transplantation (61.26%) than for those receiving surgery (51.9%; OR, 0.62; 95% CI, 0.50 to 0.76; p<.001). When a subgroup of patients with early HCC (8 studies) was analyzed, 1-year follow-up showed comparable survival rates between surgically treated patients (92.14%) and transplanted patients (90.38%; OR, 0.97; 95% CI, 0.63 to 1.50; p=.89). At 5 years, transplanted patients had a significantly higher survival rate (66.67%) than surgically treated patients (60.35%; OR, 0.60; 95% CI, 0.45 to 0.78; p<.001). Review limitations included a high level of heterogeneity between the studies analyzed.

Zheng et al. (2014) reported on a meta-analysis of 62 cohort studies (N=10,170) comparing liver transplantation with liver resection for HCC. (9) Overall 1-year survival was similar between procedures (OR, 1.08; 95% CI, 0.81 to 1.43; p=.61). However, overall 3- (OR, 1.47; 95% CI, 1.18 to 1.84; p<.001) and 5-year survival (OR, 1.77; 95% CI, 1.45 to 2.16; p<.001) significantly favored liver transplantation over resection. Disease-free survival (DFS) in liver transplant patients was 13%, 29%, and 39% higher than in liver resection patients at 1, 3, and 5 years, all respectively (p<.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR, 0.20; 95% CI, 0.15 to 0.28; p<.001).

Recipient Selection Criteria

Liver transplantation selection criteria for patients with HCC have focused mainly on the number and size of tumors. Guiteau et al. (2010) reported on 445 patients who received transplants for HCC in a multicenter, prospective study in UNOS Region 4. (10) On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria; these expanded criteria consisted of 1 lesion less than 6 cm, 3 or fewer lesions, none greater than 5 cm, and a total diameter less than 9 cm. Patient allograft survival and recurrence-free

survival at 3 years did not differ significantly between patients meeting Milan criteria and patients not meeting the expanded criteria (71% vs 70.2% and 90.5% vs 86.9%, respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in region 4 and that outcomes might differ in other regions with different waiting times. Additionally, the authors noted that a report from a 2010 national consensus conference on liver allocation for patients with HCC did not recommend expanding Milan criteria nationally and encouraged regional agreement. (11)

Ioannou et al. (2008) analyzed UNOS data pre- and post-adoption of the MELD allocation system, finding a 6-fold increase in recipients with HCC and survival rates in the MELD era similar to survival rates in patients without HCC. (12) The subgroup of patients with larger (3 to 5 cm) tumors, serum a-fetoprotein level of 455 mg/mL or greater, or a MELD score of 20 or greater, however, had poor transplantation survival. A predictive cancer recurrence scoring system was developed by Chan et al. (2008) based on a retrospective review and analysis of liver transplants at 2 centers. (13) Of 116 patients with findings of HCC in their explanted livers, 12 developed recurrent HCC. Four independent significant explant factors were identified by stepwise logistic regression: the size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, while the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds. The accuracy of the method was confirmed in 2 validation cohorts.

Mazzafaro et al. (1996) identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis. (14) These selection criteria became known as the Milan criteria and specify that patients may have either a solitary tumor with a maximum diameter of 5 cm or less or up to 3 tumors 3 cm or less. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. The UNOS adopted the Milan criteria, combined with additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. Interest in expanding liver transplant selection criteria for HCC and other indications is ongoing. Important outcomes in assessing expanded criteria include waiting time duration, death, or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence (or related outcomes such as DFS). Survival time can be estimated beginning when the patient is placed on the waiting list, using the intention-to-treat principle, or at the time of transplantation.

Newer algorithms for selecting transplant recipients, which review more than the number and size of tumors, have been proposed as alternatives to the Milan criteria. (15) However, these criteria are preliminary and need prospective evaluation.

Salvage Liver Transplantation

Liver transplantation is the criterion standard treatment for HCC meeting Milan criteria in decompensated livers, as is the case in patients with Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is used for early HCC in livers classified as Child-Pugh class A. (16) In patients who have an HCC recurrence after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection,

chemotherapy, or other local therapies such as radiofrequency ablation, transarterial chemoembolization, percutaneous ethanol ablation, or cryoablation.

Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared with the primary transplant.

Yadav et al. (2018) published a systematic review and meta-analysis comparing salvage liver transplant and primary liver transplant for individuals with HCC. (17) Twenty retrospective studies (10 of which were also included in Murali et al. [2017]) with a total of 9879 patients were included in the analysis. One-year OS was better for salvage liver transplant (74.30%) than primary liver transplant (77.01%; OR, 0.86; 95% CI, 0.75 to 0.98; p=.03). Salvage liver transplant also had higher 3-year (55.69% and 59.07%, respectively; OR, 0.85; 95% CI, 0.76 to 0.96; p=.01) and 5-year OS (48.67% and 52.32%, respectively; OR, 0.85; 95% CI, 0.76 to 0.96; p=.009) than primary liver transplant. One-year (OR, 0.86; 95% CI, 0.75 to 0.99; p=.03), 3-year (OR, 0.56; 95% CI, 0.39 to 0.81; p=.002), and 5-year DFS (OR, 0.75; 95% CI, 0.66 to 0.86; p<.001) were worse for primary liver transplant (70.03%, 74.08%, and 47.09%, respectively) than for salvage liver transplant (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the 2 groups for postoperative biliary complications (p=.19) or sepsis (p=.68). No limitations to the analysis were reported.

Murali et al. (2017) conducted a systematic review and meta-analysis of studies comparing survival of patients treated who received locoregional therapy with curative intent to those who received a liver transplant, stratified by liver disease stage, the extent of cancer, and whether a salvage liver transplant was offered. (18) Among the 48 studies selected, 9835 patients were analyzed. For all categories of locoregional therapy with curative intent combined, 5-year OS and DFS were worse than for primary liver transplant (OR for OS, 0.59; 95% CI, 0.48 to 0.71; p<.01). Intention-to-treat analysis showed no significant difference in 5-year OS (OR, 1.0; 95% CI, 0.6 to 1.7) between locoregional therapy with curative intent followed by salvage liver transplant when salvage liver transplant was offered after locoregional therapy with curative intent, though noninferiority could not be shown. Only 32.5% of patients with HCC after locoregional therapy with curative intent received salvage liver transplant because the rest were medically ineligible. Disease-free survival was worse with locoregional therapy with curative intent and salvage liver transplant than with liver transplant (OR, 0.31; 95% CI, 0.2 to 0.6).

In a systematic review of liver transplantation for HCC, Maggs et al. (2012) found 5-year OS rates ranged from 65% to 94.7% in reported studies. (19)

Chan et al. (2014) systematically reviewed 16 nonrandomized studies (N=319 patients) assessing salvage liver transplant after primary hepatic resection for HCC. (20) Reviewers found that OS and DFS outcomes with salvage liver transplant were similar to reported primary liver transplantation outcomes. Median OS rates for salvage liver transplant patients were 89%, 80%, and 62% at 1, 3, and 5 years, respectively. Disease-free survival rates were 86%, 68%, and 67% at 1, 3, and 5 years, respectively. Salvage liver transplant studies had a median OS rate of 62%

(range, 41% to 89%) compared with a range of 61% to 80% in the literature for primary liver transplantation. The median DFS rate for salvage liver transplant was 67% (range, 29% to 100%) compared with a range of 58% to 89% for primary liver transplantation.

In a meta-analysis of 14 nonrandomized comparative studies by Zhu et al. (2013), OS at 1, 3, and 5 years and DFS at 1 and 3 years did not differ significantly between groups (n=1272 for primary transplant, n=236 for salvage). (21) Disease free survival, however, was significantly lower at 5 years with salvage liver transplantation than with primary transplantation (OR, 0.62; 95% CI, 0.42 to 0.92; p=.02). There were insufficient data to evaluate outcomes in patients exceeding Milan criteria; but, in patients meeting Milan criteria, survival outcomes did not differ significantly, suggesting salvage liver transplant might be a viable option in these patients.

Section Summary: Liver Transplant for Primary Hepatocellular Carcinoma

Use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of ≤5 cm, or up to 3 tumors ≤3 cm and without extrahepatic spread or macrovascular invasion), has led to improved OS rates. A 2012 systematic review reported 5-year OS rates ranged from 65% to 94.7%. A liver transplant was also shown in a 2013 meta-analysis to result in higher survival rates than resection. Similar outcomes were identified in a 2017 meta-analysis, in which transplantation showed a significantly improved survival benefit, especially for patients with early HCC. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach.

Note that expansion of patient selection criteria, bridging to transplant, or downstaging of disease to qualify for liver transplantation, is frequently studied. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded University of California, San Francisco or other criteria.

Liver Transplant for Extrahepatic Cholangiocarcinoma (Hilar or Perihilar)

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have extrahepatic cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with extrahepatic cholangiocarcinoma.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing cholangiocarcinoma: medical management.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Cambridge et al. (2021) reported on a systematic review and meta-analysis/meta-regression of 20 observational studies (N=428) on orthotopic liver transplantation for unresectable perihilar cholangiocarcinoma. (22) Pooled 1- (n=265), 3- (n=240), and 5-year (n=309) survival rates were 76.9% (95% CI, 69.5 to 83.5), 55.3% (95% CI, 43.7 to 66.5), and 44.9% (95% CI, 31.4 to 58.8), respectively. In patients who received neoadjuvant chemoradiation, 1- (n=109), 3- (n=89), and 5-year (n=210) pooled survival rates improved to 82.8% (95% CI, 73 to 90.8), 65.5% (95% CI, 48.7 to 80.5), and 65.1% (95% CI, 55.1 to 74.5), respectively.

Gu et al. (2012) reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma. (23) Most studies reported on patients with extrahepatic or hilar cholangiocarcinoma. Overall 1-, 3-, and 5-year pooled survival rates from 605 study patients were 73% (95% CI, 65 to 80), 42% (95% CI, 33 to 51), and 39% (95% CI, 28 to 51), respectively. When patients received adjuvant therapies preoperatively, 1-, 3-, and 5-year pooled survival rates improved to 83% (95% CI, 57 to 98), 57% (95% CI, 18 to 92), and 65% (95% CI, 40 to 87), respectively.

In a review, Heimbach (2008) considered the published outcomes of the combined protocol in the context of data on outcomes for surgical resection. (24) Heimbach (2008) concluded that outcomes were comparable between transplantation for patients with HCC and other chronic liver diseases and neoadjuvant chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar cholangiocarcinoma, which is unresectable, or arose in the setting of primary sclerosing cholangitis. The reviewer further concluded that both methods were superior to resection.

Observational Studies

Darwish Murad et al. (2012) reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar cholangiocarcinoma followed by liver transplantation (see Table 1). (25) Intention-to-treat survival (after a loss of 71 patients before liver transplantation) was 68% at 2 years and 53% at 5 years, and recurrence-free survival rates posttransplant were 78% at 2 years and 65% at 5 years (see Table 2). Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria because they had a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy ($p<.001$).

Heimbach et al. (2006) reported on 65 patients who underwent liver transplantation for unresectable perihilar cholangiocarcinoma or for perihilar tumor due to primary sclerosing cholangitis between 1993 and 2006 (see Table 1). (26, 27) Unresectable patients underwent neoadjuvant radiochemotherapy. The 1-year survival rate was 91%, and the 5-year survival rate was 76% (see Table 2).

Populations With Extrahepatic or Mixed Cholangiocarcinoma

Systematic Reviews

Data from the European Liver Transplant Registry was assessed in a review article by Pascher et al. (2003). (28) In 169 patients with extrahepatic cholangiocarcinoma, the probabilities for 1- and 5-year survival were 63% and 29%, respectively. Among 186 patients with intrahepatic cholangiocarcinoma, the 1-year survival rate was 58%, and the 5-year survival rate was 29%.

Observational Studies

Studies on hepatic cholangiocarcinoma are described in Tables 1 and 2.

Friman et al. (2011) reported on 53 patients who received liver transplants for cholangiocarcinoma from 1984 to 2005, in Norway, Sweden, and Finland. (29) The 5-year survival rate was 25% overall, 36% in patients with TNM stage 2 or less, and 10% in patients with TNM greater than stage 2. On further analysis using only data from those patients transplanted after 1995, the 5-year survival rate increased to 38% versus 0% for those transplanted before 1995 (see Table 2). Additionally, the 5-year survival rate increased to 58% in those patients transplanted after 1995 with TNM stage 2 or less and a CA 19-9 level of 100 or less.

Meyers et al. (2000) reported on data from 207 patients with intrahepatic or extrahepatic cholangiocarcinoma from the Cincinnati Transplant Registry, finding a 1-year survival of 72% and a 5-year rate of 23%. (30) In a multicenter study, Robles et al. (2004) reported on 36 patients with hilar tumors and 23 with peripheral intrahepatic disease. (31) One-year survival was 82% and 77%, while 5-year survival was 30% and 23% for those with hilar tumors compared with peripheral intrahepatic disease, respectively.

Table 1. Summary of Key Case Series Characteristics for Extrahepatic or Intrahepatic Cholangiocarcinoma

Study	Country	Participants	Treatment	Follow-Up, years

Darwish Murad et al. (2012) (25)	U.S.	287	Liver transplant	5
Friman et al. (2011) (29)	Norway, Sweden, Finland	53	Liver transplant	5
Heimbach et al. (2006) (26); Rea et al. (2005) (27)	U.S.	65	Liver transplant	5
Robles et al. (2004) (31)	Spain	59	Liver transplant	5
Meyer et al. (2000) (30)	U.S.	207	Liver transplant	5
Casavilla et al. (1997) (32)	U.S.	54	Liver transplant	6.8

U.S.: United States.

Table 2. Summary of Key Case Series Results for Extrahepatic or Intrahepatic Cholangiocarcinoma

Study	**Treatment**	**Group**	**Overall Survival, %**		
			Years		
			1	**3**	**5**
Darwish Murad et al. (2012) (25)	Liver transplant	EH perihilar			53
Heimbach et al. (2006) (26); Rea et al. (2005) (27)[c]	Liver transplant	EH perihilar	91		76
Meyer et al. (2000) (30)[a]	Liver transplant	IH/EH	72		23
Robles et al. (2004) (31)[b]	Liver transplant	EH Hilar	82	53	30
		IH	77	65	23
Casavilla et al. (1997) (32)	Liver transplant	IH	70	29	18
Friman et al. (2011) (29)[d]	Liver transplant	IH/EH			25

EH: extrahepatic; IH: intrahepatic.

[a] Unresectable cholangiohepatoma;

[b] Hilar or peripheral cholangiohepatoma; unresectable, postoperative recurrent, or incidental;

[c] Aggressive neoadjuvant radiochemotherapy;

[d] Unresectable cholangiohepatoma.

Section Summary: Liver Transplant for Extrahepatic Cholangiocarcinoma

The evidence on liver transplantation in patients with extrahepatic (hilar or perihilar) cholangiocarcinoma includes registry studies and systematic reviews of observational studies. For patients with extrahepatic cholangiocarcinoma treated with a liver transplant and adjuvant chemotherapy, 5-year survival rates have been reported to be as high as 76%.

Liver Transplant for Intrahepatic Cholangiocarcinoma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have intrahepatic cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with intrahepatic cholangiocarcinoma.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing intrahepatic cholangiocarcinoma: medical management.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review and meta-analysis conducted by Ziogas et al. (2021) pooled available data to assess liver transplantation for intrahepatic cholangiocarcinoma. (33) They included 18 studies with 355 patients, including Casavilla et al. (1997) and Friman et al. (2011), noted below, and a registry study of 385 patients. The pooled 1-, 3-, and 5-year OS rates were 75% (95% CI, 64 to 84), 56% (95% CI, 46 to 67), and 42% (95% CI, 29 to 55), respectively. The pooled 1-, 3-, and 5-year recurrence-free survival rates were 70% (95% CI, 63 to 75), 49% (95% CI, 41 to 57), and 38% (95% CI, 27 to 50), respectively. Cirrhosis was positively associated with recurrence-free survival, but incidental diagnosis was not. The pooled overall recurrence rate was 42% (95% CI, 33 to 53) over a mean follow-up of 40.6$\pm$37.7 months. Patients with very early (single $\leq$2 cm) intrahepatic cholangiocarcinoma exhibited superior pooled 5-year recurrence-

free survival (67%; 95% CI, 47 to 86) versus advanced intrahepatic cholangiocarcinoma (34%; 95% CI, 23 to 46). This study is limited by the retrospective nature of the articles included and the potential presence of publication bias regarding the pooled OS data.

Observational Studies

Hue et al. (2020) used registry data from the National Cancer Database to compare outcomes among patients with intrahepatic cholangiocarcinoma who received liver transplantation (n=74) to those who received surgical resection of the liver (n=1879). (34) Median OS was not significantly different when comparing patients who received liver resection versus those who received a liver transplant, respectively, at 1- (82.6% vs 89.4%), 3- (50.2% vs 53%), or 5-years (33% vs 40.8%) posttransplant; the overall median survival was 36.1 months in both groups (p=.34). Length of stay and unplanned 30-day readmission rates were also similar between groups (p=.11 and.18, respectively). These differences all remained nonsignificant in a propensity score matched analysis (n=57 patients in each group).

One additional observational study reported on survival rates for 54 patients with intrahepatic cholangiocarcinoma. (32) Survival rates at 1-, 3-, and 5-years posttransplant were reported to be 70%, 29%, and 18%, respectively. In studies of mixed populations of patients with extrahepatic or intrahepatic cholangiocarcinoma (see Tables 1 and 2 above), a single study reported a 1-year survival rate of 72%. (30) Five-year survival rates ranged between 23% and 25% in 2 studies. (30, 29)

Section Summary: Liver Transplant for Intrahepatic Cholangiocarcinoma

The evidence on liver transplantation in patients with intrahepatic cholangiocarcinoma includes registry studies and a systematic review of observational studies. 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%.

Liver Transplant for Individuals with Metastatic Neuroendocrine Tumors

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have metastatic neuroendocrine tumors (NETs) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with metastatic NETs.

Interventions

The therapy being considered is a liver transplant.

Comparators
The following practice is currently being used to make decisions about managing metastatic NETs: medical management. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Three systematic reviews of case series have assessed metastatic NETs. Neuroendocrine tumors are relatively rare neoplasms that are slow-growing but rarely cured when metastatic to the liver.

Palaniappan et al. (2023) conducted a systematic review of 15 studies (N=755 patients) focusing on long-term outcomes of liver transplantation for the management of neuroendocrine neoplasms. (35) Across studies, the median overall survival was 87% at 1 year (range 73% to 100%; 11 studies), 65% at 5 years (range 36% to 97.2%, 11 studies), and 50% at 10 years (range 46.1% to 88.8%; 3 studies). Reported disease-free/recurrence-free survival at 1 year was 70% (range 56% to 80%; 7studies) and 36.5% at 5 years (range 11% to 86.9%; 8 studies).

Fan et al. (2015) reported on a systematic review of 46 studies (N=706 patients) on liver transplantation for NET liver metastases of any origin. (36) Reported overall 5-year survival rates ranged from 0% to 100%, while 5-year DFS rates ranged from 0% to 80%. In studies with more than 100 patients, the 5-year OS rate and DFS rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after liver transplantation were reported in most studies.

Mathe et al. (2011) conducted a systematic review of the literature on patient survival after liver transplant for pancreatic NETs. (37) Data from 89 transplanted patients treated in 20 clinical studies were reviewed. Sixty-nine patients had primary endocrine pancreatic tumors, 9 patients were carcinoids, and 11 patients were not further classified. Survival rates at 1, 3, and 5 years were 71%, 55%, and 44%, respectively. The mean calculated survival was 54.45 months, and the median calculated survival was 41 months (95% CI, 22 to 76 months).

Section Summary: Liver Transplant for Metastatic Neuroendocrine Tumors

The evidence on liver transplant for NETs includes systematic reviews of NETs for metastases of any origin. 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 transplantation in select patients with NETs, the available studies were limited by their heterogeneous populations. Further studies are needed to define the appropriate selection criteria.

Liver Transplant for Individuals with Unresectable Colorectal Liver Metastases

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have unresectable colorectal liver metastases is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with unresectable metastatic colorectal liver metastases.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing colorectal liver metastases: medical management. Treatment options to control or downstage the disease include chemotherapy and/or locoregional treatments such as ablation.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Adam et al. (2024) published the first RCT (TransMet) comparing chemotherapy alone to chemotherapy plus liver transplant in patients with unresectable colorectal liver metastases. (38) A total of 94 patients were enrolled and followed up at a median of 59.3 months. Five-year OS was significantly improved with transplant. Tables 3 and 4 summarize the characteristics and results or the TransMet trial. Limitations can be found in Tables 5 and 6.

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Adam et al. (2024); TransMet (38)	EU	20	2016-2021	Adults with unresectable CRLM (n=94) responsive to systemic chemotherapy and no extrahepatic disease	Liver transplant + chemotherapy (n=47)	Chemotherapy alone (n=47)

CRLM: colorectal liver metastases; EU: European Union; RCT: randomized controlled trial.

Table 4. Summary of Key RCT Results

Study	5-year OS[a]	Median survival	5-year PFS[b]	Serious AEs	Any toxicity ≥3
Adam et al. (2024); TransMet (38)	n=94	n=94	n=72	NR	n=62
Transplant + chemotherapy	56.6% (95% CI, 43.2-74.1)	Not reached	19.9% (95% CI, 9.0-44.1)	110 events in 32 patients	36%
Chemotherapy alone	12.6% (95% CI, 5.2-30.1)	26.6 months (95% CI, 16.5-35.7)	0%	69 events in 45 patients	47%

HR (95% CI); p	0.37 (0.21-0.65); p=.0003	0.16 (0.07-0.33); p<.0001	0.34 (0.20-0.57); p<.0001	NR	NR

AE: adverse event; CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression free survival; RCT: randomized controlled trial.
[a] Intention to treat analysis.
[b] Per protocol analysis.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Adam et al. (2024); TransMet (38)	4. Conducted entirely in Europe		2. Chemotherapy regimens were not standardized		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Adam et al. (2024); TransMet (38)		1. Open-label trial				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing

data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Hagness et al. (2013) reported the results of the SECA-I study, which included 21 patients with unresectable colorectal liver-only metastases. (39) Median follow-up was 27 months (range, 8 to 60 months). Estimated 1-, 3-, and 5-year OS were 95%, 68%, and 60%, respectively. A total of 33% of patients required reintervention for complications.

Dueland et al. (2020) reported the results of the SECA-II study, which enrolled 15 patients with unresectable colorectal liver-only metastases. (40) Median follow-up was 36 months (range, 5 to 60 months). Estimated 1-, 3-, and 5-year OS were 100%, 83%, and 83%, respectively. Median disease-free survival was 13.7 months with 1, 2, and 3-year disease-free survival of 53%, 44%, and 35%. A total of 47% of patients required reintervention for complications.

Dueland et al. (2021) reported a comparative effectiveness study that compared patients with colorectal liver metastases who were enrolled in the above mentioned liver transplant studies (SECA-I and SECA-II; n=50), with database information from 53 patients who had received portal vein embolization and liver resection. (41) The 5-year OS rate for patients with high tumor load was 33.4%for those who underwent liver transplant and 6.7% for those who underwent pulmonary vein embolization. Among patients with high tumor load and left-sided primary tumors, the 5-year OS rate was 45.3% for transplant patients and 12.5% for those treated with embolization and resection. The inherent limitations of the study design and baseline differences between groups prohibit conclusions regarding the comparative effectiveness of these treatment options.

Table 7 summarizes key nonrandomized trial characteristics.

Table 7. Summary of Key Nonrandomized Trials

Study	Hagness et al. (2013); SECA-I (39)	Dueland et al. (2020); SECA-II (40)	Dueland et al. (2021) (41)
Study Type	Prospective cohort	Prospective cohort	Comparative effectiveness
Country	Norway	Norway	Norway
Dates	2006-2011	2012-2016	2006-2019
Participants	Patients with unresectable colorectal liver-only metastases (N=21)	Patients with unresectable colorectal liver-only metastases (N=15)	Patients with CRLM (n=50 enrolled in liver transplant studies and n=53

			who had received Portal vein embolization and resection)
Treatment	Liver transplant	Liver transplant	Liver transplant
Treatment	N/A	N/A	Portal vein embolization and resection
Follow-Up	NR	Up to 10 years	NR

CRLM: colorectal liver metastases; N/A: not applicable; NR: not reported.

Section Summary: Liver Transplant for Unresectable Colorectal Liver Metastases

The evidence on liver transplant for unresectable colorectal liver metastases includes one RCT and nonrandomized studies. Five-year OS was improved with liver transplant compared with standard of care in the RCT; however, the study is limited by the small sample size and heterogeneous standard of care. Nonrandomized studies indicate improved OS compared with historic controls.

Liver Transplant for Individuals with Unresectable Hepatic Epithelioid Hemangioendothelioma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have unresectable hepatic epithelioid hemangioendothelioma (HEHE) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with unresectable HEHE.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing HEHE: medical management with chemotherapy. There is currently no standard effective medical therapy.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Studies

Several studies have evaluated liver transplant for HEHE utilizing data from healthcare registries. Larson et al. (2025) published the largest and most recent study using the UNOS/OPTN database. (42) The authors compared post-transplant outcomes of 121 patients undergoing liver transplant for HEHE to those undergoing transplant for other diagnoses. Patients undergoing transplant for HEHE were younger, more likely to be female, and had lower body mass indices than other transplant recipients. Similar post-transplant survival was observed for recipients with HEHE (16.6 years) compared with other diagnoses (13.8 years; log-rank p=.28), even after adjusting for baseline donor and recipient characteristics (adjusted HR 1.28; 95% CI, 0.94 to 1.74; p=.12). An earlier analysis of the UNOS/OPTN database by Rodriguez et al. (2008) included HEHE patients transplanted from 1987 to 2005. (43) At a median follow-up duration of 24 months (range, 0 to 181 months), the 1-year, 3-year, and 5-year OS rates were 80%, 68%, and 64%, respectively. Lerut et al. (2007) reported the outcomes of 59 patients with HEHE from the European Liver Transplant Registry. (44) Overall survival rates at 1, 5, and 10 years (as calculated from time of transplant) were 93%, 83%, and 72%. A total of 14 (23.7%) patients had recurrent disease after a median of 49 months. Disease-free survival rates at 1, 5, and 10 years were 90%, 82%, and 64%.

Table 8. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Larson et al. (2025) (42)	Retrospective cohort	US	2002-2021	Adults with first liver transplant (N=111,558)	Liver transplant	Through 2023
Rodriguez et al. (2008) (43)	Retrospective cohort	US	1987-2005	Patients with HEHE who received liver transplant (N=110)	Liver transplant	NR
Lerut et al. (2007) (44)	Retrospective cohort	EU	1989-2004	Patients with HEHE who received liver transplant (N=59)	Liver transplant	NR

EU: European Union; HEHE: hepatic hemangioendothelioma; NR: not reported; US: United States.

Section Summary: Liver Transplant for Unresectable Hepatic Epithelioid Hemangioendothelioma

The evidence for liver transplant for HEHE is based on nonrandomized retrospective cohort studies. Liver transplant for HEHE has a similar OS as liver transplant for other indications. At this time, there is no standardized treatment for HEHE and RCTs are unlikely to be conducted.

Liver Transplant for Individuals with Hepatic Adenoma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have hepatic adenoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with hepatic adenoma.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing hepatic adenoma: medical management or surgical resection. Management is dependent upon the patient's symptoms, lesion size, and lesion progression.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Review

Ziogas et al. (2022) reviewed all patients listed or transplanted for hepatic adenoma from 1987 to 2020 (N=199) in the US and performed a systematic review of published literature. (45) From 199 patients listed, 142 underwent liver transplant. Most patients did not convert to hepatocellular carcinoma (89.4%), and at a median follow-up of 62.9 months, 18.3% of patients

died. Overall survival rates at 1, 3, and 5 years were 94.2%, 89.7%, and 86.3%, respectively. A total of 61 articles describing 99 patients who underwent liver transplant for hepatic adenoma were identified in the systematic review. Over a median follow-up of 36.5 months, 6% of patients died. Overall survival rates at 1, 3, and 5 years were all 95%. Posttransplant complications were reported in 25% of patients, including acute rejection in 13.1%; retransplantation was required in 2.3%. The authors noted a need for optimal selection criteria to further improve outcomes.

Section Summary: Liver Transplant for Hepatic Adenomas

The evidence for liver transplant for hepatic adenoma is based on a systematic review of published observational studies. The systematic review found 5-year OS rates of 95% but noted a lack of optimal selection criteria for patients with hepatic adenoma who would benefit from hepatic transplant.

Liver Transplant for Pediatric Hepatoblastoma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for children who have pediatric hepatoblastoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is children with pediatric hepatoblastoma.

Interventions

The therapy being considered is a liver transplant.

Comparators

The following practice is currently being used to make decisions about managing pediatric hepatoblastoma: medical management.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Case Series

Pediatric hepatoblastoma is a rare condition, and the available evidence consists of small case series. Most recently, Hamilton et al. (2017) reported on 376 children with hepatoblastoma requiring liver transplantation; this was part of a larger cohort of 544 children receiving a liver transplant from 1987 to 2012, as recorded in the UNOS database. (46) The 5-year patient survival rate after liver transplant for hepatoblastoma was 73%, with a 5-year graft survival rate of 74%. The recurrent or metastatic disease was the most common (57%) cause of death for this population. Barrena et al. (2011) reported on 15 children with hepatoblastoma requiring liver transplantation. (47) The OS rate after liver transplant was 93.3% at the 1-, 5-, and 10-year follow-up points. Malek et al. (2010) reported on liver transplantation results for 27 patients with a primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007. (48) Tumor recurrence occurred in 1 patient after liver transplantation, and the OS rate was 93%. Browne et al. (2008) reported on 14 hepatoblastoma patients treated with liver transplantation. The mean follow-up was 46 months, with OS in 10 (71%) of 14 patients. (49) Tumor recurrence caused all 4 deaths. In the 10 patients receiving primary liver transplantation, 9 survived while only 1 of 4 patients transplanted after primary resection survived (90% vs 25%, p=.02).

Section Summary: Liver Transplant for Pediatric Hepatoblastoma

Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, tumors are often not discovered until they are unresectable. In cases of unresectable tumors, liver transplantation with pre- and/or postchemotherapy is a treatment option with reports of good outcomes and high rates of survival. (50) The UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation. (51)

Liver Retransplant for a Failed Liver Transplant

Clinical Context and Therapy Purpose

The purpose of a liver retransplant for individuals who have a failed liver transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with a failed liver transplant.

Interventions

The therapy being considered is a liver retransplant.

Comparators

The following practice is currently being used to make decisions about failed liver transplant: medical management.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Cohort Studies
Salimi et al. (2021) reported on a retrospective cohort using records from 1030 patients who underwent liver transplantation at a liver transplantation center in Iran between the years 2000 and 2016; of these, 966 were initial transplants and 64 were retransplants. (52) The mortality rate was significantly higher among patients who underwent retransplantation (54.68%) compared to patients who underwent primary liver transplantation (21.32%; p<.001). Overall survival at 1-, 3-, and 5-years posttransplant was 82%, 80%, and 70%, respectively, for patients undergoing initial transplant and 59%, 43%, and 32%, respectively, for patients undergoing retransplant. Patients who underwent retransplantation also had significantly higher MELD scores (10.73±25.89) compared to patients who underwent primary liver transplantation (5.65±20.51; p=.004).

Bellido et al. (2012) reported on a retrospective cohort using registry data on 68 consecutive adults with liver retransplantations. (53) Survival estimates using Kaplan-Meier curves to compare 21 urgent with 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications, than in those undergoing elective procedures (76.5%), which were mostly related to chronic rejection. Remiszewski et al. (2011) examined factors influencing survival outcomes in 43 liver retransplantation patients. (54) When compared with primary liver transplantation patients, retransplantation patients had significantly lower 6-year survival rates (80% vs 58%, respectively; p<.001). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong et al. (2011) reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation. (55) Eight risk factors were identified as predictive of graft failure, including recipient age, MELD score greater than 27, more than 1 prior liver transplant, need for mechanical ventilation, serum albumin level of less than 2.5 g/dL, donor age older than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation of 15 to 180 days.

Section Summary: Liver Retransplant for a Failed Liver Transplant

Observational studies have evaluated the risk factors with a failed liver transplant for survival after liver retransplantation. Reported OS rates are lower after retransplantation than after initial liver transplantation, but survival rates are acceptable in appropriately selected patients given the lack of treatment-related options.

Combined Liver-Kidney Transplantation

Clinical Context and Therapy Purpose

The purpose of a combined liver-kidney transplantation for individuals who have indications for liver and kidney transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with indications for liver and kidney transplant.

Interventions

The therapy being considered is a combined liver-kidney transplantation.

Comparators

The following tools and practices are currently being used to make decisions about managing combined liver-kidney transplantation: medical management or single organ transplant.

Outcomes

The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Adults

Systematic Reviews

Bouari et al. (2021) performed a systematic review and meta-analysis of 4 retrospective observational studies (N=22,736) comparing survival and other outcomes among adult patients who received a combined liver-kidney transplant to those with renal dysfunction who received a liver transplant alone. (56) No significant difference in mortality was found between patients who received combined liver-kidney transplant and those who received liver transplant alone at 1 year (pooled risk ratio [RR], 1.03; 95% CI, 0.97 to 1.09; p=.31), 3 years (pooled RR, 1.06; 95% CI, 0.99 to 1.13; p=.11), or 5-years (pooled RR, 1.08; 95% CI, 0.98 to 1.19; p=.11) posttransplant. Pooled results from 2 studies showed that liver graft loss was not significantly different at 1 year, but was significantly increased at 3 years in patients who received liver transplant alone (RR, 1.15; 95% CI, 1.08 to 1.24; p<.0001). A single study reporting on liver graft survival at 5 years found no difference between groups.

Observational Studies

In a retrospective study, Lunsford et al. (2017) evaluated factors for renal failure in patients who underwent combined liver-kidney transplantation. (57) Of 145 patients who had combined liver-kidney transplantation, 30 (20.7%) had renal failure. Survival at 1 and 3 years in the combined liver-kidney transplant group with renal failure (18.2% and 13.5%) was significantly worse than in combined liver-kidney transplant patients without renal failure (92.6% and 83.7%; p<.001). Multivariate predictors of renal failure were pretransplant dialysis duration (OR, 2.43; p=.008), kidney cold ischemia of more than 883 minutes (OR, 3.43; p=.011), kidney donor risk index (OR, 1.96; p=.012), and recipient hyperlipidemia (OR, 3.50; p=.028).

Fong et al. (2012) evaluated data from the OPTN and UNOS database to compare outcomes of combined liver-kidney transplantation with liver transplantation alone for adults with cirrhosis and renal failure. (58) The analysis evaluated cirrhotic patients with serum creatinine levels of 2.5 mg/dL or higher or who had received dialysis at least twice during the week before liver transplantation. Between 2002 and 2008, 2774 patients had both liver and renal failure and received a liver transplant alone, and 1501 patients underwent combined liver-kidney transplantation. Patients who received combined liver-kidney transplantation were more likely to be over 60 years of age, have minimal liver disease, and have been on dialysis. Patients in the combined transplant group were also not as sick, with fewer patients having a MELD score over 35 at listing, fewer being hospitalized before the transplant and fewer on life support. Liver and patient survival were higher in patients who received combined liver-kidney transplantation compared with liver transplantation alone. At 5 years posttransplant, 67.4% of patients had survived in the combined liver-kidney transplantation arm compared with 62.9% in the liver alone arm (p<.001). The liver allograft survival rate after 5 years was 65.3% in the combined

liver-kidney transplantation arm and 58.9% in the liver transplantation alone (p<.001). After adjusting for confounding factors, liver transplant alone remained a significant risk factor for liver allograft loss (HR, 1.24; p=.002) and mortality compared with combined liver-kidney transplantation (HR, 1.16; p=.043).

In a series of 74 combined liver-kidney transplantation procedures performed at a single institution over a 23-year period, Ruiz et al. (2010) reported a 5-year survival rate of 62%. (59) However, in patients who had a second combined liver-kidney transplantation or liver retransplantation, survival was 30% at 3 months. This finding led to a recommendation not to perform combined liver-kidney transplantation in patients requiring liver retransplantation. There was no significant difference in survival between patients who were on hemodialysis pretransplantation and those who were not. However, survival in patients who required hemodialysis after transplantation was significantly worse (approximately 30% at 5 years) than for patients who did not (>50%, p=.001 over follow-up), and kidney graft survival was only 56% at 5 years.

Children

Observational Studies

Calinescu et al. (2014) evaluated combined liver-kidney transplantation outcomes in children using data from the Scientific Registry of Transplant Recipients from OPTN. (60) There were 152 primary combined liver-kidney transplants performed between 1987 and 2011. Liver graft survival was 72.6% at 10 years, and kidney graft survival was 66.9%. Patient survival at 10 years after combined liver-kidney transplantation was 78.9%. In comparison, patient survival following isolated liver transplantation during the same period was 77.4% (n=10,084) and, for an isolated kidney transplant, 90% at 10 years (n=14,800). Thus, combined liver-kidney transplantation resulted in survival outcomes that were no worse than liver transplant alone but were inferior to kidney transplant alone. Indications for combined liver-kidney transplantation were noted as primary hyperoxaluria and other liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney, such as congenital hepatic fibrosis and polycystic kidney disease.

Some reports have suggested that liver transplantation may have a protective effect on kidney allografts. To test this hypothesis, de la Cerda et al. (2010) evaluated kidney survival in children who had a kidney-only transplant or combined liver-kidney transplantation. (61) Examination of the OPTN/UNOS database between 1995 and 2005 identified 111 combined liver-kidney transplants and 3798 kidney-only transplants in children. The patients in the combined liver-kidney transplantation group were younger on average than those in the kidney-only group (9 years vs 12 years, p=.007), and more had inherited disease as the primary cause (42% vs 28%), respectively. More patients in the combined liver-kidney transplantation group lost their kidney graft within 6 months (20.1% vs 5.9%, p=.001); however, late kidney graft survival was significantly better at 5 years posttransplant compared with the kidney-only group (p<.01). The authors described 2 situations when combined liver-kidney transplantation would be indicated in children: end-stage liver disease when the kidneys go into prolonged irreversible failure, and severe renal failure from an underlying disease that can be improved with a liver transplant.

Section Summary: Combined Liver-Kidney Transplant

The evidence on combined liver-kidney transplantation includes a systematic review of retrospective observational studies in adult patients and several registry studies that have compared combined organ transplantation with liver or with kidney transplantation alone. In adults undergoing liver transplant with kidney failure, a systematic review did not find differences in 1-, 3-, or 5-year survival when comparing combined liver-kidney transplantation to liver transplantation alone. Individual registry studies showed that combined liver-kidney transplantation resulted in a modest improvement in patient survival compared with liver transplantation alone. Liver allograft survival was also higher in the patients who received combined liver-kidney transplantation compared with patients who received a liver transplant alone. Relatively few children have received combined liver-kidney transplantation. Patient survival has been reported to be worse with combined liver-kidney transplantation than with kidney transplantation alone, but no worse than for liver transplant alone. For kidney grafts that survive the first 6 months, the organ survival rate may be better than for a kidney graft alone. Together, these results would suggest that combined liver-kidney transplantation is no worse, and possibly better, for graft and patient survival in adults and children who meet the requirements for liver transplantation and have concomitant renal failure. Indications for combined liver-kidney transplantation 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.

Potential Contraindications

Living Donor Versus Deceased Donor Liver Transplant Recipient Outcomes

Due to the scarcity of donor organs and the success of living donation, living donor (LD) liver transplantation (LT) has become an accepted practice. The living donor undergoes hepatectomy of the right lobe, the left lobe, or the left lateral segment, which is then transplanted into the recipient. Because hepatectomy involves resection of up to 70% of the total volume of the donor liver, the safety of the donor has been a major concern. For example, the surgical literature suggests that right hepatectomy of the diseased or injured liver is associated with mortality rates of about 5%. However, reports have suggested that right hepatectomy in healthy donors has lower morbidity and mortality. Reports of several donor deaths have been reported. (62-65)

In December 2000, the National Institutes of Health convened a workshop focusing on living donor liver transplantation. Shiffman et al. (2002) summarized this workshop. (66) According to their report, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. The median complication rate reported by responding transplant centers was 21%. Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor has a significant long-term and established relationship with the recipient.

Criteria for a recipient of a living-related liver were also controversial, with some groups advocating that living-related donor livers be only used in those most critically ill, while others stated that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival. (66)

Grant et al. (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between LD LT and deceased donor liver transplants for HCC. (67) For DFS after LD LT, the combined HR was 1.59 (95% CI, 1.02 to 2.49) compared with deceased donor liver transplantation. For OS, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Another systematic review and meta-analysis by Tang et al. (2020) compared outcomes between LD LT and deceased donor liver transplants from 39 studies (N=38,563; mainly retrospective in nature) of patients with end-stage liver disease. (68) Perioperative mortality, hospital length of stay, retransplantation rates, and recurrence rates for HCV and HCC were similar between groups. Living donor LT were associated with significant improvements in 1- (OR, 1.32; 95% CI, 1.01 to 1.72; p=.04), 3- (OR, 1.39; 95% CI, 1.14 to 1.69; p=.0010), and 5-year (OR, 1.33; 95% CI, 1.04 to 1.70; p=.02) OS and vascular (OR, 2.00; 95% CI, 1.31 to 3.07; p=.001) and biliary (OR, 2.23; 95% CI, 1.59 to 3.13; p<.00001) complication rates compared to deceased donor liver transplants.

Human Immunodeficiency Virus-Positive Patients

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

Cooper et al. (2011) conducted a systematic review to evaluate liver transplantation in patients coinfected with HIV and hepatitis. (69) Reviewers included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI, 81.1 to 87.8) at 12 months. Patients were 2.89 (95% CI, 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared with those with detectable HIV viremia.

Terrault et al. (2012) reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older. (70) Patient and graft survival reductions were significantly associated with only 1 factor: HIV infection. At 3 years, in the HCV-only group, patient and graft survival rates were significantly better at 79% (95% CI, 72 to 84) and 74% (95% CI, 66 to 79), respectively, than the group with HIV and HCV coinfection at 60% (95% CI, 47 to 71) and 53% (95% CI, 40 to 64). While HIV infection reduced 3 year survival rates

after liver transplantation in patients coinfected with HCV, most patients still experienced long-term survival.

Current OPTN policy permits HIV-positive transplant candidates. (71)

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients. (72) For liver transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 (CD4) count >100 cells/mL with no history of acquired immunodeficiency syndrome (AIDS)-defining illnesses such as opportunistic infection or malignancy or CD4 count >200 cells/mL for at least 3 months;
- Undetectable HIV viral load while receiving antiretroviral therapy or a detectable HIV viral load in patients with intolerance to antiretroviral therapy that can be suppressed posttransplant;
- Documented compliance with a stable antiretroviral therapy regimen;
- Absence of active opportunistic infection and malignancy;
- Absence of chronic wasting or severe malnutrition;
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring.

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

A recent observational, noninferiority study published by Durand et al. (2024) compared transplantation of kidneys from deceased donors with HIV and donors without HIV to recipients with HIV. (73) The primary outcome was a safety event (a composite of death from any cause, graft loss, serious adverse events, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection), assessed for noninferiority. One hundred ninety-eight enrolled candidates received a kidney from a deceased donor; 99 received a kidney from a donor with HIV and 99 from a donor without HIV. The adjusted HR for the composite primary outcome was 1.00 (95% CI, 0.73 to 1.38), which demonstrated noninferiority. Based on results, in individuals with HIV, transplantation from donors with HIV appeared to be noninferior to that of donors without HIV. While this study used kidney transplantation, results could impact all solid organ transplantations, including the liver.

Hepatitis Infection

Terrault et al. (2012) also reported on the group of patients with HCV. (70) As reported above, HCV status was not significantly associated with reduced patient and graft survival.

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 metabolic dysfunction-associated 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 (e.g., 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 unresectable colorectal liver metastases who receive a liver transplant, the evidence includes one randomized controlled trial (RCT) and nonrandomized studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Five-year OS was improved with liver transplant compared with standard of care in the RCT. Nonrandomized studies indicate improved OS compared with historic controls. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable hepatic epithelioid hemangioendothelioma (HEHE) who receive a liver transplant, the evidence includes nonrandomized, observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Posttransplant survival among patients with HEHE was similar to those undergoing liver transplant for other indications. Based on the lack of standard treatment and the rare tumor type, high-quality comparative trials are unlikely to be conducted for hepatic transplant in HEHE. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have hepatic adenomas who receive a liver transplant, the evidence includes nonrandomized observational studies and a systematic review of these studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The systematic review found 5-year OS rates of 95% but noted a lack of optimal selection criteria for patients with hepatic adenoma who would benefit from hepatic transplant. 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.

Practice Guidelines and Position Statements

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. (74) 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. (75) 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, hepatocellular carcinoma (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. (76) 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. (77) 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)"

In July 2025, AASLD published a critical update to the guidance based on newly published data. (78) However, the update was related to immunotherapy in the adjuvant setting, and did not change any previous recommendations related to transplantation.

<u>International Consensus Conference</u>

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 HCC. (79) 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.

In 2024, another international joint conference was held, convening the International Liver Transplantation Society (ILTS) and International Liver Cancer Association (ILCA) to update its consensus on liver transplantation for HCC and intrahepatic cholangiocarcinoma. (80) Similarly to 2010, the Conference came up with recommendations beginning from the assessment of candidates with HCC or intrahepatic cholangiocarcinoma and managing patients on waitlists, to the role of liver transplantation and post-transplantation management. Some notable recommendations are summarized in Table 9, below.

Table 9. Notable Recommendations From 2024 ILTS and ILCA Conference on Liver Transplantation in HCC and iCCA

Recommendation	Level of evidence	Strength of recommendation
HCC		
Liver transplantation should not be restricted to HCC patients who have a predicted 5-year survival rate comparable to non-HCC patients. However, organ availability in different regions should be considered in allocation policies to avoid disadvantaging non-HCC patients.	Moderate	Moderate
Criteria for listing patients with HCC for liver transplantation must not rely solely on tumor size and number and should consider biomarkers (mainly AFP) and their dynamics on the waitlist. Emerging data suggest the use of AFP-L3, DCP, and PET-CT can add prognostic value.	Moderate	Strong
Salvage liver transplantation in patients with HCC recurrence or liver insufficiency can be as safe and effective as primary transplantation for HCC in patients that meet transplantation criteria.	Weak	Moderate
Given that the outcomes with regards to overall and disease-free survival are on-par and, in certain cases, better than DDLT, LDLT should be considered as an oncologically durable and safe alternative to DDLT. In regions where the waiting time (>3 mo) or where LDLT is the predominant type of LT, LDLT may be a preferred option for HCC within and beyond standard criteria.	Moderate	Moderate

iCCA		
In cirrhotic patients with iCCA, liver transplantation may be considered as a potential therapeutic option in tumors ≤3 cm in diameter after a period of observation with stability and without extrahepatic metastasis, as it offers a chance of curative treatment and improved survival.	Moderate	Moderate
In non-cirrhotic patients with intrahepatic cholangiocarcinoma, liver transplantation is not routinely recommended but may be considered as part of investigational protocols for patients with unresectable, liver-confined disease after at least 6 mo of stability after systemic therapy. Limitations on tumor size and number should be explored in prospective clinical trials.	Moderate	Weak

AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; DDLT: deceased donor liver transplantation; HCC: hepatocellular carcinoma; iCCA: intrahepatic cholangiocarcinoma; ILCA: International Liver Cancer Association; ILTS: International Liver Transplantation Society; LDLT: living donor liver transplantation; LT: liver transplantation; mo: month(s); PET-CT: positron emission tomography-computed tomography

Many recommendations deferred to local or regional protocols, but there seemed to be interest in expansion of liver transplantation protocols from the 2010 consensus.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v.1.2025) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting United Network of Organ Sharing (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. (16) In patients who are ineligible for transplant and in select patients with Child-Pugh class A or B liver function with tumors that are resectable and who fit UNOS criteria/ extended criteria, the NCCN indicates that these patients could be considered for resection or transplant. Patients with unresectable HCC should be evaluated for liver transplantation; if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. The NCCN guidelines also indicate that patients with unresectable disease who are not a transplant candidate should receive locoregional therapy with ablation, arterially directed therapies, or external beam radiation therapy or may receive systemic therapy, best supportive care, or be enrolled in a clinical trial. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors (v.3.2025) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite "encouraging" 5-year survival rates. (81)

National Liver Review Board

In July 2025, the board revised guidance for specific clinical situations to evaluate common exception case requests for adult liver transplant candidates. (82) This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the review board. This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements." This guidance document is intended to provide recommendations for the review board considering hepatic neoplasm cases which are outside standard policy.

They should use this resource when considering MELD exception case requests for adult candidates with the following diagnoses:

- Hepatocellular Carcinoma (HCC);
- Intrahepatic Cholangiocarcinoma (iCCA);
- Neuroendocrine Tumors (NET);
- Colorectal Liver Metastases (CRLM);
- Hepatic Epithelioid Hemangioendothelioma (HEHE);
- Hepatic Adenomas.

Hepatocellular Carcinoma

Patients with the following are contraindications for HCC exception score:

- Macro-vascular invasion of main portal vein or hepatic vein;
- Extrahepatic metastatic disease;
- Ruptured HCC;
- T1 stage HCC.

Intrahepatic Cholangiocarcinoma

According to the OPTN policy on liver allocation, candidates with unresectable intrahepatic cholangiocarcinoma can be considered if all of the following criteria are met:

- Biopsy-proven, unresectable, solitary intrahepatic cholangiocarcinoma or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma;
- History of locoregional or systemic therapy;
- ≤3 cm tumor with stable disease for 6 months (no new lesions or extrahepatic disease) and imaging every 3 months to ensure tumor is ≤3 cm.

Neuroendocrine Tumors

According to the OPTN policy on liver allocation, candidates with unresectable neuroendocrine liver metastasis can be considered if all of the following criteria are met:

- Tumor must be of gastro-entero-pancreatic (GEP) origin with portal system drainage (neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland, and thyroid are not candidates for MELD exception);
- Resection of primary malignancy and extrahepatic disease without any evidence of recurrence for ≥6 months;
- Lower-intermediate grade following the WHO classification;

- No evidence for extrahepatic tumor recurrence based on metastatic radiologic workup ≥3 months prior to initial or extension MELD exception request (negative metastatic workup should include functional imaging).

Colorectal Liver Metastases
According to the OPTN policy on liver allocation, candidates with unresectable colorectal liver metastases can be considered if all of the following criteria are met:
- Primary diagnosis of colon/rectal adenocarcinoma that is BRAF wild type and microsatellite stable of at least 12 months duration;
- Standard resection of the primary tumor with negative resection margins and no evidence of local recurrence by colonoscopy within 12 months prior to request;
- No signs of extrahepatic disease or local recurrence;
- Received or receiving first-line chemo- or immunotherapy with stability or disease regression with systemic and/or locoregional therapy for at least 6 months;
- Individuals with synchronous colon lesions must also have resection of the primary tumor more than 6 months after initial diagnosis and a minimum of 6 months of chemotherapy after primary tumor resection with disease stability of at least 12 months after diagnosis.

Hepatic Epithelioid Hemangioendothelioma
According to the OPTN policy on liver allocation, candidates with unresectable hepatic epithelioid hemangioendothelioma (HEHE) can be considered if all of the following criteria are met:
- Biopsy-proven diagnosis of HEHE and exclude hemangiosarcoma;
- Absence of macrovascular invasion on biopsy or imaging;
- Lesions are unresectable.

Hepatic Adenoma
According to the OPTN policy on liver allocation, candidates with unresectable hepatic adenoma can be considered if one of the following criteria are met:
- Adenoma in the presence of glycogen storage disease or Abernethy malformation;
- Unresectable adenoma with β-catenin mutation;
- Unresectable adenoma in a candidate with liver adenomatosis (greater than 10 HA);
- Adenoma(s) with all 3 of the following criteria:
    - Unresectable;
    - Unresponsive to non-operative management (e.g., observation after withholding estrogen-containing medications, observation after efforts to maintain an ideal body weight, transarterial embolization, or radiofrequency ablation);
    - Progressive or with complications such as hemorrhage, rupture, or malignant transformation.

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. (83, 84) 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;
- 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 policy are listed in Table 10.

Table 10. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT05717842	Simultaneous Prospective Kidney Transplant Assessment in Combined Liver Kidney	15	Feb 2026

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147, 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, 50370, 50380, 50547
HCPCS Codes	S2152

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/01/2025	Document updated. The following changes were made to Coverage: 1) Changed “Non-alcoholic steatohepatitis (NASH)” to “Metabolic dysfunction-associated steatohepatitis (MASH)”; and 2) Added “hepatic adenoma” and “Epithelioid hemangioendothelioma (HEHE)” to experimental, investigational and/or unproven example list. Added references 38-45, 73, 78, 80, and 82-84; others updated and some removed.
02/01/2025	Document updated with literature review. The following change was made to Coverage: Added “Colorectal cancer that is metastatic to the liver” to the list of examples where liver transplant is considered experimental, investigational and/or unproven. References 35, 69 and 71-72 added; others updated.
12/01/2023	Reviewed. No changes.
01/01/2023	Document updated from literature review. Minor editorial changes to coverage, i.e., patients changed to individuals, with no change to intent. References 1, 6, 22, 33, 34, 43, 47, and 59 added; others removed.
12/01/2021	Reviewed. No changes.
11/15/2020	Document updated with literature review. Coverage unchanged. References 4, 6-7, 14, 16-17, 33, 55-56, and 60-62 added. Several references removed.
03/01/2019	Reviewed. No changes.
05/15/2018	Document updated with literature review. The following changes were made to Coverage: 1) Added “NOTE 1: Liver transplantation and combined liver-kidney transplantation may be considered medically necessary for the indications listed below for patients meeting the Organ Procurement and Transplantation Network policy criteria.”; 2) Modified statement on cholangiocarcinoma to be specific to hilar cholangiocarcinoma; 3) Added medically necessary statement for combined liver-kidney transplantation; and 4) Replaced “extrahepatic malignancy” on the experimental, investigational, and/or unproven statement with “intrahepatic cholangiocarcinoma”. Title changed from “Liver Transplant”.
05/15/2016	Reviewed. No changes.
09/01/2015	Document updated with literature review. The following was added to Coverage: “Liver transplant may be considered medically necessary in pediatric patients with non-metastatic hepatoblastoma”. The following was changed in Coverage: 1) The statement regarding polycystic disease was moved from the “Miscellaneous” category to be a separate statement, and was changed to be “Liver transplant may be considered medically necessary in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment”; 2) The statement “Liver transplant is considered experimental, investigational and/or unproven” was clarified with the addition of “in all other situations not described above, including but not limited to”.

05/15/2014	Document updated with literature review. The following was added: 1.) Examples of indications that may be considered medically necessary: alcoholic liver disease and non-alcoholic steatohepatitis (NASH); 2.) Liver retransplantation may be considered medically necessary for specific conditions; and 3) Neuroendocrine tumors metastatic to the liver are considered experimental, investigational and/or unproven. The following has now changed to being considered not medically necessary in patients with: 1) Hepatocellular carcinoma extending beyond the liver; and 2) Ongoing alcohol and/or drug abuse. Description and Rationale was significantly revised.
12/15/2009	Revised/updated entire document; liver transplant may be considered medically necessary for diagnosis of cholangiocarcinoma when specified criteria are met; references updated.
01/01/2007	Revised/updated entire document
07/01/2004	Revised/updated entire document
05/01/1996	Revised/updated entire document
04/01/1996	Revised/updated entire document
04/01/1994	Revised/updated entire document
07/01/1993	Revised/updated entire document
04/01/1993	Revised/updated entire document
01/01/1993	Revised/updated entire document
01/01/1992	Revised/updated entire document
05/01/1990	New medical document