7.03.06	Liver Transplant and Combined Liver-Kidney Transplant		
Original Policy Date:	May 16, 1984	**Effective Date:**	October 1, 2021
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Policy Statement

A liver transplant using a cadaver or living donor may be considered **medically necessary** for carefully selected patients with end-stage liver failure due to irreversibly damaged livers. Etiologies of end-stage liver disease include, but are not limited to, the following:

- **I. Hepatocellular diseases**
  - A. Alcoholic liver disease
  - B. Alpha-1 Antitrypsin deficiency
  - C. Autoimmune hepatitis
  - D. Hemochromatosis
  - E. Nonalcoholic steatohepatitis
  - F. Protoporphyria
  - G. Viral hepatitis (either A, B, C, or non-A, non-B)
  - H. Wilson disease
- **II. Cholestatic liver diseases**
  - A. Biliary atresia
  - B. Primary biliary cirrhosis
  - C. Primary sclerosing cholangitis with development of secondary biliary cirrhosis
- **III. Vascular disease**
  - A. Budd-Chiari syndrome
- **IV. Primary hepatocellular carcinoma***
- **V. Inborn errors of metabolism**
- **VI. Trauma and toxic reactions**
- **VII. Miscellaneous**
  - A. Familial amyloid polyneuropathy

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

Liver transplantation may be considered **medically necessary** in patients with unresectable hilar cholangiocarcinoma*.

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

Liver *retransplantation* may be considered **medically necessary** in patients with **any** of the following:

I. Chronic rejection
II. Hepatic artery thrombosis
III. Ischemic type biliary lesions after donation after cardiac death
IV. Primary graft nonfunction
V. Recurrent non-neoplastic disease-causing late graft failure

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

Liver transplantation is considered **investigational** in **any** of the following situations:

I. Patients with intrahepatic cholangiocarcinoma
II. Patients with neuroendocrine tumors metastatic to the liver

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

I. Patients with hepatocellular carcinoma that has extended beyond the liver*
II. Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required)

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

* See Policy Guidelines section for patient selection criteria.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational.**

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

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

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

Renal-Specific Criteria
Both creatinine and glomerular filtration rates (GFR) are significant markers to consider. Other factors such as symptoms or comorbidities may be considered when making the decision when to begin wait listing or for transplant. Indications for renal transplant include a creatinine level of greater than 8 mg/dL, or greater than 6 mg/dL in symptomatic diabetic patients or a glomerular filtration rate (GFR) of <15; however, consideration for listing for renal transplant may start well before the creatinine or GFR levels reach this point, based on the anticipated time that a patient may spend on the waiting list.

Living donor renal transplants in patients with progressive renal failure may be indicated at creatinine or GFR levels below that typically associated with end stage chronic kidney disease (Stage 5 chronic kidney disease [CKD]). Discussions about renal transplants and other treatment options may start much earlier at Stage 3B or Stage 4.

Five Stages of Kidney Disease

- **Stage** 1: with normal or high GFR (GFR > 90 mL/min)
- **Stage** 2: Mild **CKD** (GFR = 60-89 mL/min)
- **Stage** 3A: Moderate **CKD** (GFR = 45-59 mL/min)
- **Stage** 3B: Moderate **CKD** (GFR = 30-44 mL/min)
- **Stage** 4: Severe **CKD** (GFR = 15-29 mL/min)
- **Stage 5**: End **Stage CKD** (GFR <15 mL/min)

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 a patient's tenure on the waiting list.

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

Tobacco consumption is a contraindication.

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

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

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

Hepatocellular Carcinoma
Criteria used for patient selection of hepatocellular carcinoma (HCC) patients eligible for liver transplant include the Milan criteria, which is considered the criterion standard, the University of California, San Francisco (UCSF) expanded criteria, and United Network of Organ Sharing (UNOS) criteria.

Milan Criteria
A single tumor 5 cm or less or 2 to 3 tumors 3 cm or less.

University of California, San Francisco (UCSF) 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 in diameter 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 (UNOS) criteria were updated in 2021.

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

Note that liver transplantation for those with T3 HCC is not prohibited by UNOS guidelines, but such patients do not receive any priority on the waiting list. All patients 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 (greater than 1 cm and less than 2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and 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 (CCA). This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee.

- Candidates must satisfy diagnostic criteria for hilar cholangiocarcinoma:
  - Malignant-appearing stricture on cholangiography and 1 of the following:
    - Carbohydrate antigen 19-9 100 U/mL
    - Biopsy or cytology results demonstrating malignancy
    - 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 patients with obvious metastases before neoadjuvant therapy is initiated
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures

Living Donor Criteria

Donor morbidity and mortality are prime concerns in donors undergoing right lobe, left lobe, or left lateral segment donor partial hepatectomy as part of living donor liver transplantation. Partial hepatectomy is a technically demanding surgery, the success of which may be related to the availability of an experienced surgical team. The American Society of Transplant Surgeons proposed the following guidelines for living donors (American Society of Transplant Surgeons:

Ethics Committee. American Society of Transplant Surgeons' position paper on adult-to-adult living donor liver transplantation. *Liver Transplant*. 2000;6(6):815-817. PMID 11084076):

- They should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure
- They should undergo evaluation to ensure that they fully understand the procedure and associated risks
- They should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- They should be emotionally related to the recipient
- 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

Coding

The following CPT code may be used:

- **47399**: Unlisted procedure, liver

Combined liver-kidney transplant would be reported with the codes in this policy along with the codes in Blue Shield of California Medical Policy: Kidney Transplant.

Description

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

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

Background

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.[1] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Liver transplantation

Liver transplantation is routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Certain populations are prioritized as Status 1A (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.

Literature Review

Evidence reviews 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 patients who have a hepatocellular disease (i.e., viral hepatitis or nonalcoholic steatohepatitis) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a liver transplant improve the net health outcome in individuals with hepatocellular disease?

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

Populations

The relevant population of interest is individuals with a hepatocellular disease, such as viral hepatitis or nonalcoholic steatohepatitis (NASH).

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.

Nonalcoholic steatohepatitis is caused by a buildup of fat in the liver, which leads to inflammation and damage. While many patients have no symptoms or problems, in some cases, the condition can worsen to cause liver scarring and cirrhosis. As noted by the name of the condition, patients with NASH do not abuse alcohol.

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 (out to at 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.

Review of Evidence

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 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.

Nonalcoholic Steatohepatitis
Systematic Reviews
Liver transplantation is a treatment option for patients with NASH 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 NASH and 3520 without NASH comparing liver transplantation outcomes.[5,] Patients with NASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.05 to 0.89; p=.03). However, NASH-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-NASH-related liver transplant patients.

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 NASH-related liver transplantation.[6,] In all, 63,061 patients underwent liver transplant from 2003 to 2014. Nonalcoholic steatohepatits accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to NASH 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 NASH (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 NASH also demonstrated significantly higher posttransplant survival than patients with hepatitis C (hazard ratio [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 NASH, a 2013 systematic review has indicated that OS rates are similar to other indications for liver transplantation

Liver transplant for Hepatocellular Carcinoma
Clinical Context and Therapy Purpose
The purpose of a liver transplant for patients who have 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 HCC patients eligible for liver transplant include the Milan criteria, the University of California, San Francisco expanded criteria, and United Network for Organ Sharing (UNOS) criteria.

The question addressed in this evidence review is: Does a liver transplant improve net health outcomes in individuals with HCC?

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

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.

Review of Evidence
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=13794) comparing liver resection (n=7990) with transplantation (n=5804) in patients with HCC.[7] 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 studies analyzed.

Zheng et al (2014) reported on a meta-analysis of 62 cohort studies (N=10170 patients) comparing liver transplantation with liver resection for HCC.[8] Overall 1-year survival was similar between procedures (OR, 1.08; 95% CI, 0.81 to 1.43; p=.61). However, overall 3- and 5-year survival significantly favored liver transplantation (OR, 1.47; 95% CI, 1.18 to 1.84; p<.001) over resection (OR, 1.77; 95% CI, 1.45 to 2.16; p<.001). 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.[9] 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.[10]

Ioannou et al (2008) analyzed UNOS data pre- and postadoption 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.[11] The subgroup of patients with larger (3-5 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.[12] 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.

Mazzafaroet al (1996) identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis.[13] These selection criteria became known as the Milan criteria and specify 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 reviewed more than the number and size of tumors, have been proposed as alternatives to Milan criteria.[14] 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.[15] 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.[16] 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, 0.75–0.99, p=.03), 3-year (OR, 0.56; 95% CI 0.39–0.81, p=.002), and 5-year DFS (OR, 0.75; 95% CI, 0.66–0.86, 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 salvage liver transplant was offered.[17.] 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.[18.]

Chan et al (2014) systematically reviewed 16 nonrandomized studies (N=319 patients) assessing salvage liver transplant after primary hepatic resection for HCC.[19.] 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%-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%-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).[20.] 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 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 patients who have extrahepatic cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a liver transplant improve net health outcomes in individuals with cholangiocarcinoma?

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

Populations

The relevant population of interest is individuals with extra hepatic 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.

Review of Evidence

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.[21,] 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.[22,] 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.[23] 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).[24] 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).[25,26] 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).[27] 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 CCA from 1984 to 2005, in Norway, Sweden, and Finland.[28] 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 on 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%.[29] In a multicenter study, Robles et al (2004) reported on 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.[30] 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)[24]	U.S.	287	Liver transplant	5
Friman et al (2011)[28]	Norway, Sweden, Finland	53	Liver transplant	5
Heimbach et al (2006)[25]; Rea et al (2005)[26]	U.S.	65	Liver transplant	5
Robles et al (2004)[30]	Spain	59	Liver transplant	5
Meyer et al (2000)[29]	U.S.	207	Liver transplant	5
Casavilla et al (1997)[31]	U.S.	54	Liver transplant	6.8

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)[24]	Liver transplant	EH perihilar			53
Heimbach et al (2006)[25]; Rea et al (2005)[26]	Liver transplant	EH perihilar	91		76
Meyer et al (2000)[29],[a]	Liver transplant	IH/EH	72		23
Robles et al (2004)[30],[b]	Liver transplant	EH hilar	82	53	30
		IH	77	65	23
Casavilla et al (1997)[31]	Liver transplant	IH	70	29	18
Friman et al (2011)[28],[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 patients who have intrahepatic cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a liver transplant improve net health outcomes in individuals with intrahepatic cholangiocarcinoma?

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

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.

Review of Evidence
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).[32] 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.[31] 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%.[29] Five-year survival rates ranged between 23% and 25% in 2 studies.[29,28]

Section Summary: Liver Transplant for Intrahepatic Cholangiocarcinoma
The evidence on liver transplantation in patients with intrahepatic cholangiocarcinoma includes registry 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 patients who have metastatic neuroendocrine tumors (NETs) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a liver transplant improve net health outcomes in individuals with metastatic NETs?

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

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.

Review of Evidence
Systematic Reviews
Two 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.

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.[33] 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.[34] 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 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 question addressed in this evidence review is: Does liver transplant improve net health outcomes in children with pediatric hepatoblastoma?

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

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.

Review of Evidence

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.[35] 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.[36] 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 primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007.[37] 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.[38] 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.[39.] The UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation.[40.]

Liver Retransplant for a Failed Liver Transplant
Clinical Context and Therapy Purpose
The purpose of a liver retransplant for patients who have a failed liver transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a liver retransplant improve net health outcomes in individuals with a failed liver transplant?

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

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.

Review of Evidence
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.[41.] 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.[42] 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 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.[43] 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.[44] 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 patients 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 question addressed in this evidence review is: Does a combined liver-kidney transplantation improve net health outcomes in individuals with indications for liver and kidney transplant?

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

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.

Review of Evidence
Adults

Systematic Reviews
Bouari et al (2021) performed a systematic review and meta-analysis of 4 retrospective observational studies (N=22736) comparing survival and other outcomes among adult patients who received combined liver-kidney transplant to those with renal dysfunction who received liver transplant alone.[45.] 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.[46.] 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.[47.] 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 transplant 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%.[48.] 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 (»30% at 5 years) than for patients who did not (»70%, 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.[49] 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=10084) and, for an isolated kidney transplant, 90% at 10 years (n=14800). 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.[50] 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
Review of Evidence

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.[51,52,53,54,]

In December 2000, the National Institutes of Health convened a workshop focusing on living donor liver transplantation. Shiffman et al (2002) summarized this workshop.[55,] 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 to 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 a 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.[55,]

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.[56,] 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 hazard ratio 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 LDLT and deceased donor liver transplants from 39 studies (N=38563; mainly retrospective in nature) of patients with end-stage liver disease.[57,] 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.[58,] 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.[59] 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.[60]

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[61] 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.

Hepatitis Infection
Terrault et al (2012) also reported on the group of patients with HCV.[59] 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 a systematic review. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis have found that survival is lower than for other liver diseases. Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rates are significant in a group of patients who have no other treatment options. Also, survival can be improved by the eradication of the hepatitis virus before transplantation. For patients with nonalcoholic steatohepatitis, OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have primary hepatocellular carcinoma who receive a liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In the past, long-term outcomes in patients with primary hepatocellular malignancies had been poor (19%) compared with the OS of liver transplant recipients. However, the recent use of standardized patient selection criteria (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. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In a registry study comparing outcomes in patients with intrahepatic cholangiocarcinoma who received liver transplantation to those who received surgical resection of the liver, no differences were found in OS, length of stay, or unplanned 30-day readmission rates between groups. Additional studies reporting survival rates in patients with intrahepatic cholangiocarcinoma or in mixed populations of patients with extrahepatic and intrahepatic cholangiocarcinoma have reported 5-year survival rates of less than 30%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have metastatic neuroendocrine tumors who receive a liver transplant, the evidence includes systematic reviews of case series. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In select patients with nonresectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms. While some centers may perform liver transplants on select patients with neuroendocrine tumors, the available studies are limited by their heterogeneous populations. Further studies are needed to determine the appropriate selection criteria. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pediatric hepatoblastoma who receive a liver transplant, the evidence includes case series. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is among the United Network for Organ Sharing criteria for patients eligible for liver transplantation. The evidence is sufficient to determine that the technology results in an l improvement in the net health outcome.

For individuals who have a failed liver transplant who receive a liver retransplant, the evidence includes observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with indications for liver and kidney transplant who receive a combined liver-kidney transplant, the evidence includes a systematic review of retrospective observational studies in adults and several individual registry studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for combined liver-kidney transplant in children are rare

and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney. In both adults and children, comparisons with either liver or kidney transplantation alone would suggest that combined liver-kidney transplant is no worse, and possibly better, for graft and patient survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers
The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.[68] Key findings and recommendations are summarized in Table 3.

Table 3. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

	Content Area	Key Point
1	Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2	Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV "positive" organs
3	Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4	OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5	Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

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

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies and 5 academic medical centers in 2012. There was a consensus among reviewers that liver transplantation may be medically necessary for end-stage liver failure due to irreversibly damaged livers from various disease states such as those considered during the report update. There was also a consensus among reviewers that liver retransplantation is appropriate in patients with acute or chronic liver failure such as primary graft nonfunction, ischemic-type biliary injury after donation after cardiac death, hepatic artery thrombosis, chronic rejection or recurrent diseases such as primary sclerosing cholangitis, autoimmune hepatitis, and hepatitis C resulting in end-stage liver failure. There was general support for the use of liver transplantation as a treatment for cholangiocarcinoma in patients who meet strict eligibility criteria. In general, there was no support for the use of liver transplantation for a neuroendocrine tumor metastatic to the liver.

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

International Consensus Conference
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 hepatocellular carcinoma (HCC) in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued against liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria. Also, the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC would not be appropriate. However, a de novo case of HCC may be treated as a new tumor, and retransplantation may be considered even though data to support this is limited.

American Association for the Study of Liver Diseases and American Society of Transplantation
In 2013, the American Association for the Study of Liver Diseases and the American Society of Transplantation issued joint guidelines on evaluating patients for a liver transplant.[62.] These guidelines indicated liver transplantation for severe acute or advanced chronic liver disease after all effective medical treatments have been attempted. The formal evaluation should confirm the irreversible nature of the liver disease and lack of effective alternative medical therapy.

The guidelines also stated that liver transplant is indicated for the following conditions:
- Acute liver failure complications of cirrhosis
- Liver-based metabolic condition with systemic manifestations
  - 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 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
- 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 American Association for the Study of Liver Diseases, the American Society of Transplantation, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition issued joint guidelines on the evaluation of the pediatric patients for liver transplant.[63] The guidelines stated that "disease categories suitable for referral to a pediatric LT program are similar to adults: acute liver failure, autoimmune, cholestasis, metabolic or genetic, oncologic, vascular, and infectious. However, specific etiologies and outcomes differ widely from adult patients, justifying independent pediatric guidelines." The indications listed for liver transplantation included biliary atresia, Alagille syndrome, pediatric acute liver failure, hepatic tumors, HCC, hemangioendothelioma, cystic fibrosis-associated liver disease, urea cycle disorders, immune-mediated liver disease, along with other metabolic or genetic disorders.

In 2019, the American Association for the Study of Liver Diseases guideline on alcohol-associated liver disease provided recommendations on the timing of referral and selection of candidates for liver transplant.[64] 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.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers (v.3.2021) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting United Network of Organ Sharing criteria of a single tumor measuring 2 to 5 cm, or 2 to 3 tumors 3 cm or less with no macrovascular involvement or extrahepatic disease.[15] 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, the NCCN indicates resection is the preferred treatment option; locoregional therapy may also be considered. 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 on hepatobiliary cancers 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 (preferred) or may receive systemic therapy, best supportive care, or be enrolled in a clinical trial. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors (v.2.2021) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite "encouraging" 5-year survival rates.[65]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility approved by the Centers for Medicare & Medicaid Services as meeting institutional coverage criteria for liver transplants.[66,67] The following conditions must be met for coverage of HCC:

- "The patient is not a candidate for subtotal liver resection;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and

- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone; and
- The transplant is furnished in a facility that is approved by CMS [Centers for Medicare & Medicaid Services]..."

Beginning in June 2012, on review of this national coverage decision for new evidence, Medicare began covering adult liver transplantation, at Medicare administrative contractor discretion, for extrahepatic unresectable cholangiocarcinoma, liver metastases due to a neuroendocrine tumor, and hemangioendothelioma. Adult liver transplantation is excluded from other malignancies.

Pediatric liver transplantation is covered for children (<18 years of age) when performed at pediatric hospitals approved by the Centers for Medicare & Medicaid Services. Coverage includes extrahepatic biliary atresia or any other form of end-stage liver disease, except for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03500315	HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients	160	Aug 2022
NCT02878473	Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics	30	Jan 2029

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Hepatology consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for living liver transplant (when information is available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Abdominal Computerized Tomography (CT) scan, ultrasound, and/or Magnetic resonance imaging (MRI)
  - Chest x-ray (CXR)
- GI procedure reports:
  - Colonoscopy if more than 50 years of age
  - Esophagogastroduodenoscopy (EGD)
- Cardiology procedures and respiratory function reports:
  - Electrocardiogram (EKG)
  - Cardiac echocardiogram, stress test, and cardiac catheterization (if indicated)
  - Pulmonary function tests (PFTs)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	47133	Donor hepatectomy (including cold preservation), from cadaver donor
	47135	Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into 2 partial liver grafts (i.e., left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into 2 partial liver grafts (i.e., left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/16/1984	Policy adopted
10/12/1994	Policy Revision
05/17/2001	Policy clarification
07/02/2007	Policy Updated. Adopted from BCBSA MPP. Benefit Guidelines from BSC COE program.
02/05/2008	Coding Update
10/01/2010	Policy Revision
06/28/2013	Policy revision with position change
03/28/2014	Policy revision with position change
04/30/2015	Policy revision without position change
01/01/2016	Coding update
05/01/2017	Policy revision without position change
11/01/2017	Policy title change from Liver Transplant Policy revision without position change
10/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
11/01/2020	Annual review. No change to policy statement. Policy guidelines and literature updated.
10/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Liver Transplant and Combined Liver-Kidney Transplant 7.03.06 **Policy Statement:** A liver transplant using a cadaver or living donor may be considered **medically necessary** for carefully selected patients with end-stage liver failure due to irreversibly damaged livers. Etiologies of end-stage liver disease include, but are not limited to, the following: **I. Hepatocellular diseases** A. Alcoholic liver disease B. Alpha-1 Antitrypsin deficiency C. Autoimmune hepatitis D. Hemochromatosis E. Nonalcoholic steatohepatitis F. Protoporphyria G. Viral hepatitis (either A, B, C, or non-A, non-B) H. Wilson disease **II. Cholestatic liver diseases** A. Biliary atresia B. Primary biliary cirrhosis C. Primary sclerosing cholangitis with development of secondary biliary cirrhosis **III. Vascular disease** A. Budd-Chiari syndrome **IV. Primary hepatocellular carcinoma*** **V. Inborn errors of metabolism** **VI. Trauma and toxic reactions** **VII. Miscellaneous** A. Familial amyloid polyneuropathy Liver transplantation may be considered **medically necessary** in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment. Liver transplantation may be considered **medically necessary** in patients with unresectable hilar cholangiocarcinoma*.	**Liver Transplant and Combined Liver-Kidney Transplant 7.03.06** **Policy Statement:** A liver transplant using a cadaver or living donor may be considered **medically necessary** for carefully selected patients with end-stage liver failure due to irreversibly damaged livers. Etiologies of end-stage liver disease include, but are not limited to, the following: **I. Hepatocellular diseases** A. Alcoholic liver disease B. Alpha-1 Antitrypsin deficiency C. Autoimmune hepatitis D. Hemochromatosis E. Nonalcoholic steatohepatitis F. Protoporphyria G. Viral hepatitis (either A, B, C, or non-A, non-B) H. Wilson disease **II. Cholestatic liver diseases** A. Biliary atresia B. Primary biliary cirrhosis C. Primary sclerosing cholangitis with development of secondary biliary cirrhosis **III. Vascular disease** A. Budd-Chiari syndrome **IV. Primary hepatocellular carcinoma*** **V. Inborn errors of metabolism** **VI. Trauma and toxic reactions** **VII. Miscellaneous** A. Familial amyloid polyneuropathy Liver transplantation may be considered **medically necessary** in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment. Liver transplantation may be considered **medically necessary** in patients with unresectable hilar cholangiocarcinoma*.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Liver transplantation may be considered **medically necessary** in pediatric patients with nonmetastatic hepatoblastoma. Liver *retransplantation* may be considered **medically necessary** in patients with **any** of the following: I. Chronic rejection II. Hepatic artery thrombosis III. Ischemic type biliary lesions after donation after cardiac death IV. Primary graft non-function V. Recurrent non-neoplastic disease-causing late graft failure Combined liver-kidney transplantation may be considered **medically necessary** in patients who qualify for liver transplantation and have advanced irreversible kidney disease. Liver transplantation is considered **investigational** in **any** of the following situations: I. Patients with intrahepatic cholangiocarcinoma II. Patients with neuroendocrine tumors metastatic to the liver Liver transplantation is considered **not medically necessary** in **either** of the following patients: I. Patients with hepatocellular carcinoma that has extended beyond the liver* II. Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.) Liver transplantation is considered **investigational** in all other situations not described above. * See Policy Guidelines section for patient selection criteria. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational.**	Liver transplantation may be considered **medically necessary** in pediatric patients with nonmetastatic hepatoblastoma. Liver *retransplantation* may be considered **medically necessary** in patients with **any** of the following: I. Chronic rejection II. Hepatic artery thrombosis III. Ischemic type biliary lesions after donation after cardiac death IV. Primary graft nonfunction V. Recurrent non-neoplastic disease-causing late graft failure Combined liver-kidney transplantation may be considered **medically necessary** in patients who qualify for liver transplantation and have advanced irreversible kidney disease. Liver transplantation is considered **investigational** in **any** of the following situations: I. Patients with intrahepatic cholangiocarcinoma II. Patients with neuroendocrine tumors metastatic to the liver Liver transplantation is considered **not medically necessary** in **either** of the following patients: I. Patients with hepatocellular carcinoma that has extended beyond the liver* II. Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required) Liver transplantation is considered **investigational** in all other situations not described above. * See Policy Guidelines section for patient selection criteria. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational.**