Liver Transplant and Combined Liver-Kidney Transplant

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

A. Hepatocellular diseases
   - Alcoholic liver disease
   - Viral hepatitis (either A, B, C, or non-A, non-B)
   - Autoimmune hepatitis
   - α1-Antitrypsin deficiency
   - Hemochromatosis
   - Nonalcoholic steatohepatitis
   - Protoporphyria
   - Wilson disease.

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

C. Vascular disease
   - Budd-Chiari syndrome.
Liver Transplant and Combined Liver-Kidney Transplant

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

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
  - Familial amyloid polyneuropathy.

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

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

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

Liver retransplantation may be considered medically necessary in patients with:
  - primary graft nonfunction
  - hepatic artery thrombosis
  - chronic rejection
  - ischemic type biliary lesions after donation after cardiac death
  - recurrent 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 investigational in the following situations:
  - Patients with intrahepatic cholangiocarcinoma
  - Patients with neuroendocrine tumors metastatic to the liver.

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

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

POLICY GUIDELINES

CONTRAINDICATIONS
Potential contraindications for solid organ transplant are subject to the judgment of the transplant center and include the following:
  - Known current malignancy, including metastatic cancer
  - Recent malignancy with high risk of recurrence
  - Untreated systemic infection making immunosuppression unsafe, including chronic infection
  - Other irreversible end-stage disease not attributed to liver disease
  - History of cancer with a moderate risk of recurrence
  - Systemic disease that could be exacerbated by immunosuppression

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- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

**LIVER-SPECIFIC CRITERIA**
The Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during a patient's tenure on the waiting list.

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

Tobacco consumption is a contraindication.

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

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

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

**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 expanded criteria, and United Network of Organ Sharing (UNOS) criteria.

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

**University of California, San Francisco Expanded Criteria**
A single tumor 6.5 cm or less or up to 3 tumors 4.5 cm or less, and a total tumor size of 8 cm or less.

**UNOS Stage T2 Criteria**
A single tumor 2 cm or greater and up to 5 cm or less or 2 to 3 tumors 1 cm or greater and up to 3 cm or less and without extrahepatic spread or macrovascular invasion. UNOS criteria were updated in 2018 (https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09)

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
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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 consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and ineligible for automatic priority points. Nodules less than 1 cm are considered indeterminate and are not considered for additional priority. Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list.

Cholangiocarcinoma
According to the Organ Procurement and Transplantation Network (OPTN) policy on liver allocation, candidates with cholangiocarcinoma meeting the following criteria will be eligible for a MELD or PELD exception with a 10% mortality equivalent increase every 3 months:

- Centers must submit a written protocol for patient care to the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with cholangiocarcinoma. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude 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 one of the following: carbohydrate antigen 19-9 100 U/mL, or and biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (eg, primary sclerosing cholangitis).
- If cross-sectional imaging studies (computed tomography scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be 3 cm or less.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 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
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- They should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure
- They should undergo evaluation to ensure that they fully understand the procedure and associated risks
- They should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- They should be emotionally related to the recipients
- They must be excluded if the donor is felt or known to be coerced
- They need to have the ability and willingness to comply with long-term follow-up.

Combined liver-kidney transplant would be reported with the codes in this policy along with the codes in the evidence review on kidney transplant (7.03.01).

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

Transplants, such as a liver or a liver-kidney transplant, should be considered for coverage under the transplant benefit and should be evaluated for charge in accordance with traditional transplant benefits.

Which expenses are incurred during the evaluation and procurement of organs and tissues should be compared with the scope of human organ transplant benefits for coverage determination. Typically, the following are considered human organ transplant benefits:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- prehospital workup and hospitalization of a living donor undergoing a partial hepatectomy should be considered as part of the recipient transplant costs;
- evaluation tests requiring hospitalization to determine the suitability of both potential and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis;
- hospital room, board, and general nursing in semiprivate rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians’ services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ;
- diagnostic services;
- drugs that require a prescription by federal law.

Other examples of benefits include: specific charges for participation with registries for organ procurement, operating rooms, supplies, use of hospital equipment, and transportation of the tissue or organ to be evaluated.

Administration of products with a specific transplant benefit needs to be defined as to:

- when the benefit begins (at the time of admission for the transplant or once the patient is determined eligible for a transplant, which may include tests or office visits before transplant);
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- when the benefit ends (at the time of discharge from the hospital or at the end of required follow-up, including the immunosuppressive drugs administered on an outpatient basis).

Coverage usually is not provided for:

- human organ transplant services, for which the cost is covered or funded by governmental, foundational, or charitable grants;
- organs sold rather than donated to the recipient;
- an artificial organ.

BACKGROUND

LIVER TRANSPLANTATION

Recipients
Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network of Organ Sharing. The liver allocation system adopted included the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Scoring on the MELD and PELD uses a continuous disease severity scale based entirely on objective laboratory values. In 2013, the Organ Procurement and Transplantation Network and United Network of Organ Sharing updated its allocation system. Status 1A patients have acute liver failure with a life expectancy of fewer than 7 days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis, and acute Wilson disease. Status 1A patients must be recertified every 7 days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease, which may include the following: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to status 1A at age 18 but still qualify for pediatric indications.

Following status 1, donor livers are prioritized to those with the highest scores on MELD or PELD. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (ie, international normalized ratio), and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. Status 7 describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation. Pediatric patients who turn 18 are status X.

Donors
Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into 2 segments that can be used for 2 recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient’s condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.
Management
Management of acute rejection of liver transplant using intravenous immunoglobulin or plasmapheresis is discussed separately in evidence reviews 8.01.05 and 8.02.02, respectively. Also, the role of chemoembolization or radiofrequency ablation as a bridge to transplant in patients with hepatocellular cancer is addressed separately in evidence reviews 8.01.11 and 7.01.91, respectively.

REGULATORY STATUS
Liver and liver-kidney transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

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

RATIONALE
This evidence review was created in December 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 21, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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 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 Test Purpose
The purpose of a liver transplant for patients who have hepatocellular disease (ie, 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 net health outcomes in individuals with hepatocellular disease?

The following PICOTS were used to select literature to inform this review.
**Patients**
The relevant population of interest is individuals with a hepatocellular disease, such as viral hepatitis or nonalcoholic steatohepatitis.

**Interventions**
The therapy being considered is a liver transplant.

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

**Outcomes**
The general outcomes of interest are overall survival (OS) and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

**Timing**
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.

**Setting**
Liver transplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

**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%).

Recurrence of HCV infection in transplant recipients has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years.

Mukherjee and Sorrell (2008), reviewing controversies in liver transplantation for hepatitis C, indicated that the greatest opportunity for HCV eradication is pretransplant before hepatic decompensation. Challenges of treatment posttransplantation include immunosuppressive drugs and abnormal hematologic, infectious, and liver function parameters. The authors listed the following factors as associated with poor outcomes in liver transplantation for recurrent HCV: high HCV-RNA level pretransplant, non-Caucasian ethnicity, advanced donor age, T cell-depleting therapies, inappropriate treatment of Banff A1 acute cellular rejection with steroid boluses, cytomegalovirus disease, and year of transplantation (outcomes tend to be worse with recent transplants).

**Nonalcoholic Steatohepatitis**

**Systematic Reviews**
Liver transplantation is a treatment option for patients with nonalcoholic steatohepatitis (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. 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 (OR [odds ratio], 0.21; 95% confidence interval [CI], 0.05 to 0.89; p=0.03). 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=0.05) and sepsis (OR=1.71; 95% CI, 1.17 to 2.50; p=0.006) 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. In all, 63,061 patients underwent liver transplant from 2003 to 2014. NASH 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 hepatitis C (72.15%; 95% CI, 71.37 to 72.93; p<0.001). 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<0.001).

Section Summary: Liver Transplant for Hepatocellular Disease
The evidence on liver transplantation for hepatocellular disease includes case series, 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 Test 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 UNOS criteria.

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

The following PICOTS were 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 (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Timing
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.

Setting
Liver transplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Liver Transplantation vs Liver Resection for Hepatocellular Carcinoma
Schoenberg et al (2017) published a systematic review and meta-analysis of 54 retrospective studies (N=13,794) comparing liver resection (n=7990) with transplantation (n=5804) in patients with HCC. At 1-year follow-up, survival rates were higher in those receiving resection (86.17%) than in those receiving liver transplant (80.58%), (OR=1.19; 95% CI, 0.99 to 1.43; p=0.07). 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<0.001). 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=0.89). 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<0.001). Review limitations included a high level of heterogeneity between studies analyzed.

Zheng et al (2014) reported on a meta-analysis of 62 cohort studies (total N=10,170 patients) comparing liver transplantation with liver resection for HCC. Overall 1-year survival was similar between procedures (OR=1.08; 95% CI, 0.81 to 1.43; p=0.61). However, overall 3- and 5-year survival significantly favored liver transplantation (OR=1.47; 95% CI, 1.18 to 1.84; p=0.001) over resection (OR=1.77; 95% CI, 1.45 to 2.16; p=0.001). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than in liver resection patients at 1, 3, and 5 years, all respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR=0.20; 95% CI, 0.15 to 0.28; p<0.001).

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. 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.
Ioannou et al (2008) analyzed UNOS data pre- and postadoption of the Model for End-stage Liver Disease (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 \(\alpha\)-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: size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, while the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds. The accuracy of the method was confirmed in 2 validation cohorts.

Mazzafaro et al (1996) identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis.\(^{13}\) 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. 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 disease-free survival). Survival time can be estimated beginning when the patient is placed on the waiting list, using the intention-to-treat principle, or at the time of transplantation.

Newer algorithms for selecting transplant recipients, which review more than the number and size of tumors, have been proposed as alternatives to 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. 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 (CLRT) with those who received a liver transplant, stratified by liver disease stage, the extent of cancer, and whether salvage liver transplant was offered.\(^{16}\) Among the 48 studies selected, 9835 patients were analyzed. For all categories of CLRT combined, 5-year OS and disease-free survival were worse than for primary liver transplant (OR for OS=0.59; 95% CI, 0.48 to 0.71; \(p<0.01\)). Intention-to-treat analysis showed no significant different in 5-year OS (OR=1.0; 95% CI, 0.6 to 1.7) between CLRT followed by salvage liver transplant when salvage liver transplant was offered after CLRT, though noninferiority could not be shown. Only 32.5% of patients with HCC after CRLT received salvage liver transplant because the rest were medically ineligible. Disease-free survival was worse with CLRT 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.\(^\text{17}\)

Chan et al (2014) systematically reviewed 16 nonrandomized studies (total N=319 patients) assessing salvage liver transplantation after primary hepatic resection for HCC.\(^\text{18}\) Reviewers found that OS and disease-free survival outcomes with salvage liver transplantation were similar to reported primary liver transplantation outcomes. Median OS rates for salvage liver transplantation 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 transplantation 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 disease-free survival rate for salvage liver transplantation 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 disease-free survival at 1 and 3 years did not differ significantly between groups (n=1272 for primary transplant, n=236 for salvage).\(^\text{19}\) 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=0.02). 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 transplantation 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 $\leq$ 5 cm, or up to 3 tumors $\leq$ 3 cm and without extrahepatic spread or macrovascular invasion), has led to improved overall survival rates. A 2012 systematic review reported 5-year OS rates ranged from 65% to 94.7%. 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 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 CHOLANGIOCARCINOMA**

Reports on outcomes after liver transplantation for cholangiocarcinoma or bile duct carcinoma distinguish between extrahepatic and intrahepatic tumors, the former including hilar or perihilar tumors. Recent efforts have focused on pretransplant downstaging of disease with neoadjuvant radiochemotherapy.

**Clinical Context and Test Purpose**

The purpose of a liver transplant for patients who have 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 PICOTS were used to select literature to inform this review.
MP 7.03.06
Liver Transplant and Combined Liver-Kidney Transplant

**Patients**
The relevant population of interest is individuals with extra- or intrahepatic 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 (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

**Timing**
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.

**Setting**
Liver transplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

**Extrahepatic Cholangiocarcinoma (Hilar or Perihilar)**

**Systematic Reviews**
Gu et al (2012) reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma. 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. Heimbach 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.

**Case Series**
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). 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<0.001).
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).23,24 Unresectable patients underwent neoadjuvant radiochemotherapy. The 1-year survival rate was 91%, and the 5-year survival rate was 76% (see Table 2).

**Mixed Populations With Extrahepatic or Intrahepatic Cholangiocarcinoma**

**Systematic Reviews**
Data from the European Liver Transplant Registry was assessed in a review article by Pascher et al (2003; see Table 1).25 In 169 patients with extrahepatic cholangiocarcinoma, the probabilities 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%.

**Case Series**
Friman et al (2011) reported on 53 patients who received liver transplants for cholangiocarcinoma from 1984 to 2005, in Norway, Sweden, and Finland (see Table 1).26 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% vs 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 19-9 100 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% (see Table 1).27 In a multicenter study by Robles et al (2004) reported on 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.28 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friman et al (2011)26</td>
<td>Norway, Sweden, Finland</td>
<td>53</td>
<td>Liver transplant</td>
<td>5</td>
</tr>
<tr>
<td>Casavilla et al (1997)29</td>
<td>U.S.</td>
<td>54</td>
<td>Liver transplant</td>
<td>6.8</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Group</th>
<th>Overall Survival, %</th>
<th>Years</th>
</tr>
</thead>
</table>

**Original Policy Date:** December 1995
### MP 7.03.06
Liver Transplant and Combined Liver-Kidney Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Location</th>
<th>Year</th>
<th>1</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darwish Murad et al (2012)²²</td>
<td>Liver transplant</td>
<td>EH perihilar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casavilla et al (1997)²⁹</td>
<td>Liver transplant</td>
<td>IH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friman et al (2011)²⁶ᵈ</td>
<td>Liver transplant</td>
<td>IH/EH</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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 Cholangiocarcinoma
The evidence on a liver transplant in patients with cholangiocarcinoma includes registry studies and systematic reviews of observational studies.

For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma treated with a liver transplant and adjuvant chemotherapy, survival rates have been reported to be as high as 76%.

For patients with intrahepatic cholangiocarcinoma who received liver transplantation, the 5-year survival rate was less than 30%.

### LIVER TRANSPLANT FOR INDIVIDUALS WITH METASTATIC NEUROENDOCRINE TUMORS
Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection.

### Clinical Context and Test 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 PICOTS were used to select literature to inform this review.

**Patients**
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.
Outcomes
The general outcomes of interest are OS and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Timing
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.

Setting
Liver transplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Systematic Reviews
Two systematic reviews of case series have assessed metastatic NETs. NETs 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 (total N=706 patients) on liver transplantation for NET liver metastases of any origin. Reported overall 5-year survival rates ranged from 0% to 100%, while 5-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the 5-year OS rate and disease-free survival 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. Data from 89 transplanted patients treated at 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 on 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 Test 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 PICOTS were used to select literature to inform this review.
Patients
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 (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Timing
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.

Setting
Liver retransplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

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. 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. 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. 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. 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=0.02).

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. UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation.
LIVER RETRANSPLANT FOR A FAILED LIVER TRANSPLANT

Clinical Context and Test Purpose
The purpose of a liver transplant 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 PICOTS were used to select literature to inform this review.

Patients
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 (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Timing
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.

Setting
Liver retransplantation is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Cohort Studies
Bellido et al (2012) reported on a retrospective cohort using registry data on 68 consecutive adults with liver retransplantations. Survival estimates using Kaplan-Meier curves to compare 21 urgent with 47 elective retransplantations were calculated. OS 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. When compared with primary liver transplantation patients, retransplantation patients had significantly lower 6-year survival rates (80% vs 58%, respectively; p<0.001). 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. 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 Test Purpose
The purpose of a combined liver-kidney transplant (CLKT) 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 CLKT improve net health outcomes in individuals with indications for liver and kidney transplant?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The therapy being considered is a CLKT.

Comparators
The following tools and practices are currently being used to make decisions about managing CLKT: medical management

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Timing
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.

Setting
CLKT is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Adults
In a retrospective study, Lunsford et al (2017) evaluated factors for renal failure in patients who underwent CLKT. Of 145 patients who had CLKT, 30 (20.7%) had renal failure. Survival at 1 and 3 years in the CLKT group with renal failure (18.2% and 13.5%) was significantly worse than in CLKT patients without renal failure (92.6% and 83.7%, p<0.001). Multivariate predictors of renal failure were pretransplant dialysis duration (OR=2.43, p=0.008), kidney cold ischemia of more than 883 minutes
(OR=3.43, p=0.011), kidney donor risk index (OR=1.96, p=0.012), and recipient hyperlipidemia (OR=3.50, p=0.028).

Fong et al (2012) evaluated data from the OPTN and UNOS database to compare outcomes of CLKT with liver transplantation alone for adults with cirrhosis and renal failure.\textsuperscript{42} 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 CLKT. Patients who received CLKT 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 CLKT compared with liver transplant alone. At 5 years posttransplant, 67.4% of patients had survived in the CLKT arm compared with 62.9% in the liver alone arm (p<0.001). The liver allograft survival rate after 5 years was 65.3% in the CLKT arm and 58.9% in the liver transplantation alone (p<0.001). After adjusting for confounding factors, liver transplant alone remained a significant risk factor for liver allograft loss (HR=1.24; p=0.002) and mortality compared with CLKT transplantation (HR=1.16; p=0.043).

In a series of 74 CLKT procedures performed at a single institution over a 23-year period, Ruiz et al (2010) reported a 5-year survival rate of 62%.\textsuperscript{43} However, in patients who had a second CLKT or liver retransplantation, survival was 30% at 3 months. This finding led to a recommendation not to perform CLKT 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=0.001 over follow-up), and kidney graft survival was only 56% at 5 years.

**Children**

Calinescu et al (2014) evaluated CLKT outcomes in children using data from the Scientific Registry of Transplant Recipients from OPTN.\textsuperscript{44} There were 152 primary CLKTs 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 CLKT was 78.9%. In comparison, patient survival following isolated liver transplantation during the same period was 77.4% (n=10,084) and, for an isolated kidney transplant, 90% at 10 years (n=14,800). Thus, CLKT resulted in survival outcomes that were no worse than liver transplant alone but were inferior to kidney transplant alone. Indications for CLKT 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 CLKT.\textsuperscript{45} Examination of the OPTN/UNOS database between 1995 and 2005 identified 111 CLKTs and 3798 kidney-only transplants in children. The patients in the CLKT group were younger on average than those in the kidney-only group (9 years vs 12 years, p=0.007) and more had inherited disease as the primary cause (42% vs 28%), respectively. More patients in the CLKT group lost their kidney graft within 6 months (20.1% vs 5.9%, p=0.001); however, late kidney graft survival was significantly better at 5 years posttransplant compared with the kidney-only group (p<0.01). The authors described 2 situations when CLKT 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 Transplantation
The evidence on CLKT includes mostly registry studies that have compared combined organ transplantation with liver or with kidney transplantation alone. In adults undergoing liver transplant with kidney failure, CLKT results in a modest improvement in patient survival compared with liver transplantation alone. Liver allograft survival was also higher in the patients who received CLKT compared with patients who received a liver transplant alone. Relatively few children have received CLKT. Patient survival has been reported to be worse with CLKT 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 CLKT 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 CLKT in children are rare and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney.

POTENTIAL CONTRAINDICATIONS (APPLIES TO ALL PREVIOUS INDICATIONS)

Living Donor vs Deceased Donor Liver Transplant Recipient Outcomes
Due to the scarcity of donor organs and the success of living donation, living donor liver transplantation has become an accepted practice. The living donor undergoes hepartectomy of the right lobe, the left lobe, or the left lateral segment, which is then transplanted into the recipient. Because hepartectomy 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 hepartectomy of diseased or injured liver is associated with mortality rates of about 5%. However, reports have suggested that right hepartectomy in healthy donors has a lower morbidity and mortality. Reports of several donor deaths have been reported.46-49

In December 2000, the National Institutes of Health convened a workshop focusing on living donor liver transplantation. Shiffman et al (2002) summarized this workshop.50 According to their report, the risk of mortality to the donor undergoing right hepartectomy was estimated to be approximately 0.2% to 0.5%. The median complication rate reported by responding transplant centers was 21%. Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepartectomy must be voluntary and free of coercion; therefore, it was preferable that the donor has a significant long-term and established relationship with the recipient.

Criteria for a recipient of a living-related liver were also controversial, with some groups advocating that living-related donor livers be only used in those most critically ill, while others stated that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival.50

Grant et al (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for HCC.51 For disease-free survival after living donor liver transplantation, the combined HR was 1.59 (95% CI, 1.02 to 2.49) compared with deceased donor liver transplantation. For OS, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality.

HIV-Positive Patients
Solid organ transplant for patients who are HIV-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. HIV candidates
for liver transplantation 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.52 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.53 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.54

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.55 These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- Cluster of differentiation 4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least six months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

**Hepatitis Infection**

Terrault et al (2012) also reported on the group of patients with HCV.53 As reported above, HCV status was not significantly associated with reduced patient and graft survival.

**SUMMARY OF EVIDENCE**

For individuals who have hepatocellular disease who receive a liver transplant, the evidence includes case series, registry studies, and systematic reviews. Relevant outcomes include overall survival, 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 NASH, overall survival rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary HCC who receive a liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include overall survival, 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 overall survival of liver transplant recipients. However, the recent use of standardized patient selection criteria (eg, the Milan criteria diameter) has dramatically improved overall survival rates. In 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 a meaningful 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. Relevant outcomes include overall survival, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported as high as 76%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have NETs who receive a liver transplant, the evidence includes systematic reviews of case series. Relevant outcomes include overall survival, 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 the effects of the technology on health outcomes.

For individuals who have pediatric hepatoblastoma who receive a liver transplant, the evidence includes case series. Relevant outcomes include overall survival, 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 in United Network for Organ Sharing criteria for patients eligible for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review. 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

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 et al
The American Association for the Study of Liver Diseases and the American Society of Transplantation (2013) issued joint guidelines on evaluating patients for liver transplant. These guidelines indicated liver transplantation for severe acute or advanced chronic liver disease after all effective medical treatments have been attempted. The formal evaluation should confirm the irreversible nature of the liver disease and lack of effective alternative medical therapy.
Liver Transplant and Combined Liver-Kidney Transplant

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
  - $\alpha_1$-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 transplantation 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.”

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 patient for liver transplant in 2014. 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.
National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers (v.2.2018) 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. Patients should be referred to the transplant center. Patients should be referred to the transplant center before the biopsy. 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, 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. NCCN guidelines on hepatobiliary cancers also indicate that. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors (v.2.2018) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite “encouraging” 5-year survival rates.

Council of the British Transplant Society et al
Liver transplantation guidelines for nonalcoholic steatohepatitis were developed by the Council of the British Transplant Society and approved by the British Society of Gastroenterology, the British Association for the Study of Liver, and the National Health Service Blood and Transplant in 2012. These guidelines indicated liver transplantation might be considered for the treatment of nonalcoholic steatohepatitis cirrhosis with end-stage liver disease or HCC. These guidelines were based primarily on the consensus of expert opinion.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility approved by the Centers for Medicare & Medicaid Services as meeting institutional coverage criteria for liver transplants. The following conditions must be met for coverage of HCC:

- “The patient is not a candidate for subtotal liver resection;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone; and
- The transplant is furnished in a facility that is approve 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 for 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 unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT01201096</td>
<td>Neo-adjuvant Peptide Receptor Mediated Radiotherapy With 177Lutetium in Front of Curative Intended Liver Transplantation in Patients With Hepatic Metastasis of Neuroendocrine Tumors</td>
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<td>Sep 2018</td>
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<tr>
<td>NCT03500315</td>
<td>HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients</td>
<td>360</td>
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<tr>
<td>NCT02878473</td>
<td>Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics</td>
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<td>Jan 2029</td>
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NCT: national clinical trial.

REFERENCES


**CODES**

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<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td>47133</td>
<td>Donor hepatectomy (including cold preservation); from cadaver</td>
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</table>
MP 7.03.06  
Liver Transplant and Combined Liver-Kidney Transplant

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>47135</td>
<td>Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age</td>
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<tr>
<td>47140-47142</td>
<td>Donor hepatectomy from living donor, code range</td>
</tr>
<tr>
<td>47143-47145</td>
<td>Backbench standard preparation of cadaver liver graft, code range</td>
</tr>
<tr>
<td>47146-47147</td>
<td>Backbench reconstruction of cadaver or living donor liver graft, code range</td>
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<tr>
<td>47399</td>
<td>Unlisted procedure; liver</td>
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ICD-10-CM

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<th>Code Range</th>
<th>Description</th>
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<tbody>
<tr>
<td>B15.0-B15.9</td>
<td>Acute hepatitis A; code range</td>
</tr>
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<td>B16.0-B16.9</td>
<td>Acute hepatitis B; code range</td>
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<td>B17.0-B17.9</td>
<td>Other acute viral hepatitis; code range</td>
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<td>B18.0-B18.9</td>
<td>Chronic viral hepatitis; code range</td>
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<td>B19.0-B19.9</td>
<td>Unspecified viral hepatitis; code range</td>
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<td>B25.1</td>
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<td>B66.5</td>
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<td>Malignant neoplasm of liver and intrahepatic bile ducts; code range (includes hepatoblastoma)</td>
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<td>D64.0-D64.9</td>
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<td>D81.810</td>
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<td>E74.00-E74.9</td>
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<td>Disorders of lipoprotein metabolism and other lipidemias; code range</td>
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<td>E80.0-E80.7</td>
<td>Disorders of porphyrin and bilirubin metabolism; code range</td>
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<td>I99.9</td>
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<td>K74.0-K74.69</td>
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<td>K75.81</td>
<td>Nonalcoholic steatohepatitis (NASH)</td>
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<td>K77</td>
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<td>S36.12xA-S36.13xS</td>
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<td>T86.42</td>
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ICD-10-PCS

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MP 7.03.06
Liver Transplant and Combined Liver-Kidney Transplant

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<thead>
<tr>
<th>Type of service</th>
<th>Place of service</th>
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<table>
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POLICY HISTORY

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<td>01/09/14</td>
<td>Replace policy</td>
<td>Policy updated with literature search on December 18, 2013. Policy statement on polycystic liver disease moved to a separate policy statement. Pediatric nonmetastatic hepatoblastoma added as may be medically necessary. Policy statement added that liver transplantation is considered investigational in all other situations not described. References 3, 19, 34-35, 37-38, and 54-57 added. Reference 33 updated.</td>
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<td>01/15/15</td>
<td>Replace policy</td>
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<td>10/19/16</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review; no change to policy.</td>
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<td>09/28/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to policy, as noted effective 11/15/2017; Policy updated with literature review though June 22, 2017; references 36-40, 52, and 55-56 added; references 13, 51, and 54 updated. Combined liver-kidney transplantation added to policy; considered medically necessary. Contraindication for smoking and HIV criteria added to Policy Guidelines. Policy title changed to “Liver Transplant and Combined Liver-Kidney Transplant.”</td>
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<tr>
<td>08/20/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through June 21, 2018; references 5, 7, 14, 16, 32, and 55-56 added; references 15, 37, 58, and 60 updated. Policy statements unchanged.</td>
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