Liver Transplant and Combined Liver-Kidney Transplant

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for a liver transplant when it is determined to be medically necessary because the criteria shown below are met.

If the transplant is not specifically listed in the member’s list of Covered Organ Transplant Services, it will be considered a non-covered procedure.

When Policy Topic is covered
A liver transplant, using a cadaver or living donor, is 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 cirrhosis
   ▪ Viral hepatitis (either A, B, C, or non-A, non-B)
   ▪ Autoimmune hepatitis
   ▪ α1-Antitrypsin deficiency
   ▪ Hemochromatosis
   ▪ Non-alcoholic steatohepatitis
   ▪ Protoporphyria
   ▪ Wilson’s disease
B. Cholestatic liver diseases
   ▪ Primary biliary cirrhosis
   ▪ Primary sclerosing cholangitis with development of secondary biliary cirrhosis
   ▪ Biliary atresia
C. Vascular disease
   ▪ Budd-Chiari syndrome
D. Primary hepatocellular carcinoma (See Considerations 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 Considerations for patient selection criteria).

Liver transplantation may be considered medically necessary in pediatric patients with non-metastatic Hepatoblastoma.

Liver retransplantation may be considered medically necessary in patients with:
  - primary graft non-function
  - 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.

When Policy Topic is not covered
Liver transplantation is considered 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 situations:
  - Patients with hepatocellular carcinoma that has extended beyond the liver (see Considerations)
  - 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.

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

**Liver Specific 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/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. The MELD/PELD score 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 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 UNOS criteria.

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

**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
**UNOS 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 these 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 T2 tumors will lose the additional allocation points.

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

**Cholangiocarcinoma**
According to the OPTN policy on liver allocation, candidates with cholangiocarcinoma (CCA) meeting the following criteria will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase every 3 months:

- Centers must submit a written protocol for patient care to the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol
should include data collection as deemed necessary by the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee.

- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and one of the following: carbohydrate antigen 19-9 100 U/mL, or biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (e.g., primary sclerosing cholangitis).
- If cross-sectional imaging studies (computed tomography 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.

**Donor Criteria – Living Donor Liver Transplant**

Donor morbidity and mortality are prime concerns in donors undergoing right lobe, left lobe, or left lateral segment donor partial hepatectomy as part of living-donor liver transplantation. Partial hepatectomy is a technically demanding surgery, the success of which may be related to the availability of an experienced surgical team. In 2000, the American Society of Transplant Surgeons proposed the following guidelines for living donors:

- 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
- Should undergo evaluation to assure that they fully understand the procedure and associated risks
- Should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- Should be emotionally related to the recipients
- Must be excluded if the donor is felt or known to be coerced
- Needs 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 kidney transplant policy.

**Transplant Benefit**

Liver transplant and Combined Liver-Kidney transplant should be considered for coverage under the transplant benefit.
What is covered under the scope of the human organ transplant (HOT) benefit needs to be considered.

Typically, the following are covered under the HOT benefit:

- 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.

Expenses incurred in the evaluation and procurement of organs and tissues are benefits when billed by the hospital. Included in these expenses may be 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 prior to transplant);
- when the benefit ends (at the time of discharge from the hospital or at the end of required followup, including the immunosuppressive drugs administered on an outpatient basis).

Coverage usually is not provided for:

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

### Description of Procedure or Service

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Liver Transplant and Combined Liver-Kidney Transplant 7.03.06
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.

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<td>With indications for liver and kidney transplant</td>
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<td>Medical management</td>
<td>Overall survival, Morbid events, Treatment-related mortality, Treatment-related morbidity</td>
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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.

For individuals who have a hepatocellular disease who receive a liver transplant, the evidence includes case series, registry studies, and systematic reviews. The relevant outcomes include overall survival (OS), morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis have found that survival is lower than for other liver diseases. Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rates are significant in a group of 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 a meaningful 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. The 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 (eg, 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 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported as high as 76%. 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Five-year survival rates after liver transplantation in patients with cholangiocarcinoma are less than 30%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have metastatic neuroendocrine tumors who receive a liver transplant, the evidence includes systematic reviews of case
series. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In select 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is among 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some 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 combined liver-kidney transplant, the evidence includes registry studies. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for combined liver-kidney transplant in children are rare and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney. In both adults and children, comparisons with either liver or kidney transplantation alone would suggest that combined liver-kidney transplant is no worse, and possibly better, for graft and patient survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and may be considered medically necessary for the indications listed in the Policy section and inpatients otherwise meeting United Network of Organ Sharing criteria. Liver transplantation is investigational in patients in whom the procedure is expected to
be futile due to comorbid disease or in whom posttransplantation care is expected to worsen comorbid conditions significantly. Based on survival data, transplantation in patients with hilar cholangiocarcinoma who meet strict eligibility criteria may be considered medically necessary; transplantation for neuroendocrine tumors metastatic to the liver is considered investigational. Clinical vetting supported retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection, or certain recurrent non-neoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initially failed liver transplant may be considered medically necessary in these situations.

**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 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 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 an acute liver failure with a life expectancy of fewer than seven days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis, and acute Wilson disease. Status 1A patients must be recertified every seven days. Status 1B patients are pediatric patients (age range, 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 the listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. Status seven 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 two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

Management
Management of acute rejection of liver transplant using 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 10, 2019.

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, two domains are examined: the relevance, and 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 a 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 a hepatocellular disease?

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

Patients
The relevant population of interest are individuals with a hepatocellular disease, such as viral hepatitis or nonalcoholic steatohepatitis.

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 nonalcoholic steatohepatitis do not abuse alcohol.

Interventions
The therapy being considered is a liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

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 (eg, 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.

**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 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 (odds ratio[OR], 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, 63061 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 a 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 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 PICOs were used to select literature to inform this review.

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

**Interventions**
The therapy being considered is a liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

**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). Short-
Liver Transplantation vs Liver Resection for HCC
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. 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=10170 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 (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<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 four 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.\textsuperscript{10}

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.\textsuperscript{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.\textsuperscript{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 one 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 two validation cohorts.

Mazzafaro et al (1996) identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis.\textsuperscript{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 three 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 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.\textsuperscript{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.\textsuperscript{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 (SLT) and primary liver transplant (PLT) 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 SLT (74.30%) than PLT (77.01%, OR 0.86, 95% CI 0.75–0.98, p=0.03). SLT also had higher 3-year (55.69% and 59.07%, respectively; OR 0.85, 95% CI 0.76–0.96, p=0.01) and 5-year (48.67% and 52.32%, respectively; OR 0.85, 95% CI 0.76–0.96, p=0.009) OS than PLT. One-year (OR 0.86, 95% CI 0.75–0.99, p=0.03), 3-year (OR 0.56, 95% CI 0.39–0.81, p=0.002), and 5-year DFS (OR 0.75, 95% CI 0.66–0.86, p<0.001) were worse for PLT (70.03%, 74.08%, and 47.09%, respectively) than for SLT (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the 2 groups for postoperative biliary complications (p=0.19) or sepsis (p=0.68). 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 (CLRT) with those who received a liver transplant, stratified by liver disease stage, the extent of cancer, and whether SLT was offered.17 Among the 48 studies selected, 9835 patients were analyzed. For all categories of CLRT 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<0.01). Intention-to-treat analysis showed no significant difference in 5-year OS (OR=1.0; 95% CI, 0.6 to 1.7) between CLRT followed by SLT when SLT was offered after CLRT, though noninferiority could not be shown. Only 32.5% of patients with HCC after CLRT received SLT because the rest were medically ineligible. DFS was worse with CLRT and SLT 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 (total n=319 patients) assessing SLT after primary hepatic resection for HCC.19 Reviewers found that OS and DFS outcomes with SLT were similar to reported primary liver transplantation outcomes. Median OS rates for SLT patients were 89%, 80%, and 62% at 1, 3, and 5 years, respectively. DFS rates were 86%, 68%, and 67% at 1, 3, and 5 years, respectively. SLT 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 SLT 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 DFS,
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 SLT might be a viable option in these patients.

**Section Summary: Liver Transplant for HCC**

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 three 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 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 PICO$s$ were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with extra- or intrahepatic cholangiocarcinoma.

**Interventions**
The therapy being considered is a liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.
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 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.

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 (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.

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
Unresectable patients underwent neoadjuvant radiochemotherapy. The 1-year survival rate was 91%, and the 5-year survival rate was 76% (see Table 2).

**Systematic Reviews**

Data from the European Liver Transplant Registry was assessed in a review article by Pascher et al (2003; see Table 1). 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). 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). In a multicenter study by Robles et al (2004) reported on 36 patients with hilar tumors and 23 with the peripheral intrahepatic disease. One-year survival was 82% and 77%, while 5-year survival was 30% and 23% for those with hilar tumors compared with the 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>Casavilla et al (1997)</td>
<td>U.S.</td>
<td>54</td>
<td>Liver transplant</td>
<td>6.8</td>
</tr>
</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>
<tbody>
<tr>
<td>Heimbach et al (2006); Rea et al (2005)</td>
<td>Liver transplant</td>
<td>EH perihilar</td>
<td>91</td>
<td>76</td>
</tr>
<tr>
<td>Casavilla et al (1997)</td>
<td>Liver transplant</td>
<td>IH</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td>Friman et al (2011)</td>
<td>Liver transplant</td>
<td>IH/EH</td>
<td>70</td>
<td>29</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

Clinical Context and Test Purpose
The purpose of a liver transplant for patients who have metastatic 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 PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with metastatic NETs.
The therapy being considered is a liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

**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 (eg, 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.

**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 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. 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 NETs**
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 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 PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are children with pediatric hepatoblastoma.

Interventions
The therapy being considered is a liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

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). 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.

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 four 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 as 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 PICOs were used to select literature to inform this review.

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

Interventions
The therapy being considered is a liver retransplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

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). 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.

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 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 PICOs were used to select literature to inform this review.

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

**Interventions**
The therapy being considered is a CLKT, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.
Comparators
The following tools and practices are currently being used to make decisions about managing CLKT: medical management or single organ transplant.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (eg, 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.

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. 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%. 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. 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=10084) and, for an isolated kidney transplant, 90% at 10 years (n=14800). 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. 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 two 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: CLKT**
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 six 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 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.47,48,49,50.

In December 2000, the National Institutes of Health convened a workshop focusing on living donor liver transplantation. Shiffman et al (2002) summarized this workshop.51. 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 arelationship 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.51.

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.52. For DFS 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.

**Human Immunodeficiency Virus-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. 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 hepatitis C virus (HCV) and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older. Patient and graft survival reductions were significantly associated with only one 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 three-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. The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease. 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. 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 case series, registry studies, and systematic reviews. The 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 NASH, OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in 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. The 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 (eg, 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 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported as high as 76%. 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Five-year survival rates after liver transplantation in patients with cholangiocarcinoma are less than 30%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have NETs who receive a liver transplant, the evidence includes systematic reviews of case series. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In select 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited but case series have
demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is among 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for original liver transplantation are met for retransplantation. While some evidence has suggested outcomes after retransplantation may be less favorable than for initial transplantation in some 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. The relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for CLKT in children are rare and often congenital and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney. In both adults and children, comparisons with either liver or kidney transplantation alone would suggest that CLKT is no worse, and possibly better, for graft and 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 three physician specialty societies and five 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 five 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 a 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.

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 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
- Fulminating 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 (2014) issued joint guidelines on the evaluation of the pediatric patients for liver transplant. 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 NCCN guidelines on hepatobiliary cancers (v.2.2019) 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, 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. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors (v.1.2019) indicate that liver transplantation for neuroendocrine liver metastases is considered investigational despite "encouraging" 5-year survival rates.60.

**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.61,62, 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 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>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03500315</td>
<td>HOPE in Action Prospective Multicenter, Clinical Trial of Deceased HIVD+ Kidney Transplants for HIV+ Recipients</td>
<td>360</td>
<td>Aug 2022</td>
</tr>
<tr>
<td>NCT02878473</td>
<td>Liver Transplantation for the Treatment of Early Stages of Intrahepatic Cholangiocarcinoma in Cirrhotics</td>
<td>30</td>
<td>Jan 2029</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


Billing Coding/Physician Documentation Information

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 (ie, 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 (ie, 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

Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each

ICD10 Codes

B15.0- B15.9 Acute hepatitis A; code range

B16.0- B16.9 Acute hepatitis B; code range

B17.0- B17.9 Other acute viral hepatitis; code range

B18.0- B18.9 Chronic viral hepatitis; code range

B19.0- B19.9 Unspecified viral hepatitis; code range

B25.1 Cytomegaloviral hepatitis

B66.1 Clonorchiasis

B66.5 Fasciolopsiasis

C22.0- C22.9 Malignant neoplasm of liver and intrahepatic bile ducts; code range (includes hepatoblastoma)

D64.0- D64.9 Other anemias; code range

D81.810 Biotinidase deficiency

D84.0- D84.9 Other immunodeficiencies; code range

E72.00- E72.09 Disorders of amino-acid metabolism; code range

E72.09- E74.00 Other disorders of carbohydrate metabolism; code range

E74.9- E78.0 Disorders of lipoprotein metabolism and other lipidemias; code range

E78.9- E80.0 Disorders of porphyrin and bilirubin metabolism; code range

E80.7- E83.0 Disorders of copper metabolism; code range

E83.0- E83.19 Disorders of iron metabolism; code range

E83.19- E85.0 Amyloidosis; code range

E85.9- E88.9 Metabolic disorder, unspecified

G60.0- G60.9 Hereditary and idiopathic neuropathy; code range

I74.8 Embolism and thrombosis of other arteries (includes hepatic artery thrombosis)

I82.0 Budd-Chiari syndrome

I99.9 Unspecified disorder of circulatory system

K71.10- K71.9 Toxic liver disease
Fibrosis and cirrhosis of liver; code range
Nonalcoholic steatohepatitis (NASH)
Liver disorders in diseases classified elsewhere (code first underlying disease)
Other diseases of biliary track; code range
Congenital Cystic disease of liver
Injury of liver and gallbladder and bile duct; code range
Liver transplant rejection
Liver transplant failure
Liver donor

Additional Policy Key Words
N/A

Policy Implementation/Update Information
12/1/01 New policy. Added to Surgery section
12/1/02 Added cryptogenic cirrhosis as a medically necessary indication, added 2002 scoring system.
12/1/03 No policy statement changes
12/1/04 No policy statement changes. Added new codes for living donor hepatectomy; added to Transplant section;
12/1/05 Removed HIV positivity as an investigational indication.
2/1/06 Policy statement updated to include epithelioid hemangioendothelioma as medically necessary.
4/1/06 Added general criteria to the Considerations section.
12/1/06 No policy statement changes.
12/1/07 No policy statement changes.
12/1/08 No policy statement changes.
12/1/09 No policy statement changes.
12/1/10 No policy statement changes.
12/1/11 Policy statements for medically necessary indications unchanged; neuroendocrine tumor metastases added to investigational statement. Policy statements on hepatocellular carcinoma that has extended beyond the liver and ongoing alcohol and/or drug abuse moved from investigational to not medically necessary. Removed “Patients with an active infection” from the investigational policy statement.
12/1/12 No policy statement changes.
3/1/13 Policy statements revised as follows: non-alcoholic steatohepatitis cirrhosis added to the medically necessary policy statement; a statement added that retransplantation may be considered medically necessary; a statement added that extrahepatic peri-hilar or hilar cholangiocarcinoma may be considered medically necessary. Other intrahepatic or extrahepatic malignancies including non-peri-hilar or non-hilar cholangiocarcinoma and recurrent hepatocellular carcinoma
salvage treatment added to the investigational policy statement

3/1/14  Policy statement on polycystic liver disease moved to a separate policy statement. Pediatric non-metastatic hepatoblastoma added as may be medically necessary. Policy statement added that liver transplantation is considered investigational in all other situations not described.

3/1/15  No policy statement changes.
3/1/16  No policy statement changes.
3/1/17  No policy statement changes.
11/1/17  Removed Cryptogenic cirrhosis and Epithelioid hemangioendothelioma from medically necessary statement. Combined liver-kidney transplantation added to policy; considered medically necessary. Contraindication for smoking and HIV criteria added to Considerations. Policy title changed to “Liver Transplant and Combined Liver-Kidney Transplant”.

3/1/18  No policy statement changes.
3/1/19  No policy statement changes.
3/1/20  No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.