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
   - 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
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**

**General**

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

**Liver Specific**
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 1 cm or greater and up to 5 cm or less in diameter or 2 to 3 tumors 1 cm or greater and up to 3 cm or less and without extrahepatic spread or macrovascular invasion. UNOS criteria, which were updated in 2013, may prioritize T2 HCC that meet specified staging and imaging criteria by allocating additional points equivalent to a MELD score predicting a 15% probability of death within 3 months. (1)

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. In addition, 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 are not eligible 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.

HIV-positive patients who meet the following criteria, as stated in the 2001 guidelines of the American Society of Transplantation, could be considered candidates for liver transplantation:

- CD4 count >100 cells per cubic microliter, <200 cells/microliter (without history of opportunistic infection)
- CD4 count >200 cells per cubic microliter during 3 months before transplantation
- Undetectable HIV viral load while receiving antiretroviral HIV therapy
- Detectable HIV viral load due to intolerance of HAART, HIV can be suppressed post-tx
- Documented compliance with a stable antiretroviral regimen
- Absence of opportunistic infection
- Absence of chronic wasting or severe malnutrition
- Donor free of hepatitis C

**Cholangiocarcinoma**

According to the OPTN policy on liver allocation, candidates with cholangiocarcinoma (CCA) meeting the following criteria will be eligible for a MELD/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 and biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (eg, primary sclerosing cholangitis).
- If cross-sectional imaging studies (computed tomography scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be 3 cm or less.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.
- Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

**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

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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| Individuals: With hepatocellular disease | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
| Individuals: With primary hepatocellular carcinoma | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management  
- Liver resection | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
| Individuals: With extrahepatic cholangiocarcinoma | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
| Individuals: With intrahepatic cholangiocarcinoma | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
| Individuals: With metastatic neuroendocrine tumors | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
| Individuals: With pediatric hepatoblastoma | Interventions of interest are:  
- Liver transplant | Comparators of interest are:  
- Medical management | Relevant outcomes include:  
- Overall survival  
- Morbid events  
- Treatment-related mortality  
- Treatment-related morbidity |
Liver transplantation is currently performed routinely as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS). The severity of illness is determined by the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scores.

For individuals who have hepatocellular disease who receive liver transplant, the evidence includes case series, registry studies, and systematic reviews. Relevant outcomes include overall survival (OS), morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis find 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. In addition, survival can be improved by eradication of hepatitis virus before transplantation. For patients with nonalcoholic steatohepatitis, OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatocellular carcinoma who receive liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The long-term outcome in patients with primary hepatocellular malignancies was poor (19%) in the past compared with the OS of liver transplant recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria diameter, has dramatically improved OS rates. In appropriately selected patients, liver transplant has been shown to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have extrahepatic cholangiocarcinoma who receive liver transplant, the evidence includes a systematic review and meta-analysis of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported as high as 76%. Society guidelines also support liver transplant in select patients with extrahepatic cholangiocarcinoma that is unresectable. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

For individuals who have pediatric hepatoblastoma who receive liver transplant, the evidence includes case series. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is included in 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 liver retransplant, the evidence includes observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for an original liver transplantation are met for retransplantation. While some evidence suggests outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. The evidence is sufficient to determine
that the technology results in a meaningful improvement in the net health outcome.

For individuals with indications for liver and kidney transplant who receive combined liver-kidney transplant (CLKT), the evidence includes registry studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for 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 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.

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and thus, may be considered medically necessary for the indications listed in the Policy Statement and in those 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 significantly worsen comorbid conditions. Based on survival data and clinical vetting input, 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. There was support from clinical vetting for retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent nonneoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.

**Background**

**Recipients**

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by OPTN and UNOS. The original liver allocation system was based on assignment to status 1, 2A, 2B, or 3. Status 2A, 2B, and 3 were based on the Child-Turcotte-Pugh score, which included a subjective assessment of symptoms as part of the scoring system. In February 2002, status 2A, 2B, and 3 were replaced with 2 disease severity scales: MELD and PELD for patients younger than age 12 years scoring systems. In June 2013, OPTN/UNOS published its most recent allocation system, which previously expanded status1 to status 1A and 1B in September 2012. Status 1A patients have acute liver failure with a life expectancy of less than 7 days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis and acute Wilson
disease. Status 1A patients must be recertified as status 1A every 7 days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease listed as: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to status 1A on age 18 but still qualify for pediatric indications.

Following status 1, donor livers will be prioritized to those with the highest scores on MELD or PELD. With this allocation system, the highest priority for liver transplantation is given to patients receiving the highest number of points. The scoring system for MELD and PELD is a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (ie, international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet, waiting time was found to be a poor predictor of the urgency of liver transplant because some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation systems, patients with a higher mortality risk and higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer.5 Status 7 describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation. Pediatric patients who turn 18 are status X.

Donors
Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, split graft refers to dividing a donor liver into 2 segments that can be used for 2 recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient’s condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

Rationale
This evidence review was created in 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 22, 2017. Relevant outcomes for studies on liver transplantation include waiting time duration, dropout rates, survival time, and recurrence. As experience with liver transplant has matured, patient selection criteria have broadened to include a wide variety of etiologies.
Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

HEPATOCELLULAR DISEASE

Viral Hepatitis
The presence of hepatitis B virus (HBV) 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, registry data have indicated a long-term survival rate (7 years) of 47% in HBV-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%).(3) Recurrence of HCV infection in transplant recipients has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years.(4)

Mukherjee and Sorrell (2008), reviewing controversies in liver transplantation for hepatitis C, indicated that the greatest opportunity for HCV eradication is pretransplant before hepatic decompensation.(5) Challenges of treatment posttransplantation include immunosuppressive drugs and abnormal hematologic, infectious, and liver function parameters. The authors listed the following factors 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 (ACR) with steroid boluses, cytomegalovirus disease, and year of transplantation (worse with recent transplants).

Nonalcoholic Steatohepatitis
Liver transplantation is a treatment option for patients with nonalcoholic steatohepatitis (NASH) who progress to liver cirrhosis and failure. In a 2013 systematic review and meta-analysis, Wang et al (2014) evaluated 9 studies comparing liver transplantation outcomes in patients with and without NASH.(6) Patients with NASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (OR=0.21; 95% CI, 0.05 to 0.89; p=0.03). However, NASH 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 liver transplant patients.
Section Summary: Hepatocellular Disease
The evidence on liver transplantation for hepatocellular disease includes case series, registry studies, and systematic reviews. Long-term survival rates in patients with viral hepatitis are significant in a group of patients who have no other treatment options. In addition, survival can be improved by eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival rates are similar to other indications for liver transplantation.

HEPATOCELLULAR CARCINOMA

Liver Transplantation vs Liver Resection for Hepatocellular Carcinoma
In 2013, Zheng et al reported on a meta-analysis of 62 cohort studies (total N=10,170 patients) comparing liver transplantation with liver resection for hepatocellular carcinoma (HCC).(7) 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 over resection (OR=1.47; 95% CI, 1.18 to 1.84; p<0.001; OR=1.77; 95% CI, 1.45 to 2.16; p<0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than in liver resection patients at 1, 3, and 5 years, all respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR=0.20; 95% CI, 0.15 to 0.28; p<0.001).

Patient Selection Criteria
Patient selection criteria for liver transplantation for HCC have focused mainly on the number and size of tumors. In 1996, Mazzafaro et al identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis.(8) This patient selection criteria became known as the Milan criteria and specifies patients may have either a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or less. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. United Network of Organ Sharing (UNOS) adopted the Milan criteria, combined with 1 additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. Interest in expanding liver transplant selection criteria for HCC and other indications is ongoing. Important outcomes in assessing expanded criteria include waiting time duration, death, or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence (or related outcomes such as disease-free survival). Survival time can be estimated beginning when the patient is placed on the waiting list, using the intention-to-treat principal, or at the time of transplantation.

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 that survival in the MELD era was similar to survival in patients without HCC.(9) The subgroup of patients with larger (3-5 cm) tumors, serum alpha-fetoprotein level 455 mg/mL or greater, or a MELD score 20 or greater, however, had poor transplantation survival. A predicting cancer recurrence scoring system was developed by Chan et al based on a retrospective
review and analysis of liver transplants at 2 centers to determine factors associated with recurrence of HCC.(10) Of 116 patients with findings of HCC in their explanted livers, 12 developed recurrent HCC. Four independent significant explant factors were identified by stepwise logistic regression: size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio (OR). The accuracy of the method was confirmed in 2 validation cohorts.

In 2010, Guiteau et al reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4.(11) On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of 1 lesion less than 6 cm, 3 or less lesions, none greater than 5 cm and total diameter less than 9 cm. Patient allograft and recurrence-free survival at 3 years did not differ significantly between patients meeting Milan criteria vs patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2% and 90.5% and 86.9%, all respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in Region 4 and that outcomes may be different in other regions with different waiting times.

Additionally, the authors noted that a report from a 2010 national HCC consensus conference on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement.(12)

**Salvage Liver Transplantation**

Liver transplantation is the criterion standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A.(13) In patients who have a recurrence of HCC 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 primary transplant. In a 2013 meta-analysis of 14 nonrandomized comparative studies by Zhu et al, (n=1272 for primary transplant, n=236 for salvage),(14) overall survival at 1, 3, and 5 years and disease-free survival at 1 and 3 years was not significantly different between groups. Disease-free survival, however, was significantly lower at 5 years in salvage liver transplantation compared with primary transplantation (OR=0.62; 95% CI, 0.42 to 0.92; p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria, but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting salvage liver transplantation may be a viable option in these patients.
In 2013, Chan et al systematically reviewed 16 nonrandomized studies (n=319) on salvage liver transplantation after primary hepatic resection for HCC.(15) Reviewers found that overall and disease-free survival outcomes with salvage liver transplantation were similar to reported primary liver transplantation outcomes. The median overall survival for salvage liver transplantation patients was 89%, 80% and 62% at 1, 3, and 5 years, respectively. Disease-free survival was 86%, 68% and 67% at 1, 3, and 5 years, respectively. Salvage liver transplantation studies had median overall survival rates of 62% (range, 41%-89%) compared with a range of 61% to 80% in the literature for primary liver transplantation. Median disease-free survival rates for salvage liver transplantation were 67% (range, 29%-100%) compared with a range of 58% to 89% for primary liver transplantation.

Section Summary: Hepatocellular Carcinoma
Use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of ≤5 cm, or up to 3 tumors ≤3 cm and without extrahepatic spread or macrovascular invasion), has led to improved overall survival rates. In a systematic review of liver transplant for HCC in 2012, Maggs et al found 5-year overall survival rates ranged from 65% to 94.7% in reported studies.(16) Liver transplant was also been shown in a 2013 meta-analysis to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. 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 UCSF or other criteria.

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

EXTRAHEPATIC CHOLANGIOCARCINOMA (HILAR OR PERIHILAR)
In 2012, Gu et al reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma.(17) Most studies reported on patients with extrahepatic/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 and were 83% (95% CI, 57% to 98%), 57% (95% CI, 18% to 92%), and 65% (95% CI, 40% to 87%), respectively.

With Table 1 displaying the largest case series, among the individual centers, the Mayo Clinic in Minnesota has the most experience and most favorable results.(18,19) Between 1993 and 2006, 65 patients underwent liver transplantation for unresectable perihilar cholangiocarcinoma or had perihilar
tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and 5-year survival was 76%.

In 2012, Darwish Murad et al reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar cholangiocarcinoma followed by liver transplantation.(20) 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. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy (p<0.001).

In a 2008 review, Heimbach considers the published outcomes of the combined protocol in the context of data on outcomes for surgical resection and concludes that outcomes of neoadjuvant chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar cholangiocarcinoma, which is unresectable, or arising in the setting of primary sclerosing cholangitis are comparable to transplantation for patients with HCC and other chronic liver diseases and superior to resection.(21)

**Mixed Populations With Intrahepatic or Extrahepatic Cholangiocarcinoma**

The European Liver Transplant Registry was cited by a review article.(22) Among 186 patients with intrahepatic cholangiocarcinoma, 1-year survival was 58%, and 5-year survival was 29%. In 169 patients with extrahepatic cholangiocarcinoma, the probabilities were 63% and 29%, respectively.

In 2011, Friman et al reported on 53 patients who received liver transplants for cholangiocarcinoma during the period of 1984-2005, in Norway, Sweden, and Finland.(23) 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 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. 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. The authors suggest transplantation may have acceptable outcomes in select patients.

The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic cholangiocarcinoma, finding a 1-year survival of 72% and a 5-year rate of 23%.(24) The multicenter Spanish report included 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.(25) One-year survival was 82% and 77%, while 5-year survival was 30% and 23% in the 2 groups, respectively.

**Table 1. Percent Overall Survival Following Liver Transplantation in Patients With Intrahepatic or Extrahepatic (Hilar or Perihilar) Cholangiocarcinoma**

<table>
<thead>
<tr>
<th>Years</th>
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Table:

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<th>Group</th>
<th>1</th>
<th>3</th>
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<tbody>
<tr>
<td>Darwish Murad et al (2012)²⁰ multicenter</td>
<td></td>
<td>287</td>
<td>EH perihilar</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Liver Transplant Registry; Pascher et al (2003) review²²</td>
<td></td>
<td>186</td>
<td>IH</td>
<td>58</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>European Liver Transplant Registry; Pascher et al (2003) review²²</td>
<td></td>
<td>169</td>
<td>EH</td>
<td>63</td>
<td>38</td>
<td>29</td>
</tr>
</tbody>
</table>

EH: extrahepatic; IH: intrahepatic; Y: year.
a Unresectable CCA, cholangiohepatoma;
b Hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental. c Aggressive neoadjuvant radiochemotherapy, d Unresectable CCA.

Section Summary: Cholangiocarcinoma

The evidence on liver transplant in patients with cholangiocarcinoma includes registry studies and a systematic review and meta-analysis of observational studies. The 5-year survival rate following liver transplantation in patients with cholangiocarcinoma is less than 30%. In addition, intrahepatic cholangiocarcinoma is listed as a contraindication for liver transplantation in society guidelines.

However, for patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, survival rates have been reported to be as high as 76%. Society guidelines have also supported liver transplant in select patients with extrahepatic cholangiocarcinoma that is unresectable.

METASTATIC NEUROENDOCRINE TUMORS

Two systematic reviews of case series have been identified on metastatic neuroendocrine tumors (NETs). NETs are relatively rare neoplasms that are generally slow-growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection.

In 2014, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin.(²⁷) A total of 706 patients were included in the studies reviewed. Reported overall 5-year survival rates ranged from 0 to 100%, while 5-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the 5-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after liver transplantation were reported in most studies.
In 2011 Mathe et al conducted a systematic review of the literature to evaluate patient survival after liver transplant for pancreatic NETs. Data from 89 transplanted patients from 20 clinical studies were included in the review. 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 rate was 54.45 (6.31) months, and the median calculated survival rate was 41 months (95% CI, 22 to 76 months).

**Section Summary: Metastatic Neuroendocrine Tumors**
The evidence on liver transplant for NETs includes systematic reviews of NETs for metastases of any origin. In select patients with nonresectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms. While there may be centers that perform liver transplantation on select patients with NETs, the available studies are limited by their heterogeneous populations. Further studies are needed to determine appropriate selection criteria.

**PEDIATRIC HEPATOBlastOMA**
Pediatric hepatoblastoma is a rare condition, and the available evidence consists of small case series. For example, in 2011 Barrena et al reported on 15 children with hepatoblastoma requiring liver transplantation. Overall survival after liver transplant was 93.3% (6.4%) at 1, 5, and 10 years. In 2010, Malek et al 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 overall survival was 93%. In 2008, Browne et al reported on 14 hepatoblastoma patients treated with liver transplantation. Mean follow-up was 46 months, with overall survival in 10 of 14 patients (71%). Tumor recurrence caused all 4 deaths. In the 10 patients receiving primary liver transplantation, 9 survived while only 1 of 4 patients transplanted after primary resection survived (90% vs 25%, p=0.02).

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

**RETRANSPLANTATION**
In 2012, Bellido et al reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data. Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent with 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%), which were mostly
related to chronic rejection. In 2011, Remiszewski et al examined factors influencing survival outcomes in 43 liver retransplantation patients. (34) 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. (35) Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than 1 prior liver transplant, need for mechanical ventilation, serum albumin 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 between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful in patient selection.

**Section Summary: Retransplantation**
Observational studies have evaluated risk factors for survival after liver retransplantation. Overall survival is reported as lower after retransplantation than after initial liver transplantation, but results in acceptable survival rates in appropriately selected patients.

**COMBINED LIVER-KIDNEY TRANSPLANTATION**
**Adults**
In 2012, Fong et al evaluated data from the Organ Procurement Transplant Network (OPTN) and UNOS database to compare outcomes of combined liver-kidney transplantation (CLKT) with liver transplantation alone for adult cirrhotic patients with renal failure. (36) The analysis evaluated cirrhotic patients with serum creatinine level 2.5 mg/dL or higher or who 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 who underwent CLKT. Patients who received the 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 who had a MELD score over 35 at listing, fewer who were hospitalized prior to transplant, and fewer who were 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 over 5 years). The liver allograft survival 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 2017 retrospective study, Lunsford et al evaluated factors for renal failure in patients who underwent CLKT.(37) Out of 145 patients who underwent 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 (Odds ratio [OR] 2.43 per log SD, p=0.008), kidney cold ischemia of more than 883 minutes (OR 3.43, p=0.011), kidney donor risk index (OR 1.96 per log SD, p=0.012), and recipient hyperlipidemia (OR 3.50, p=0.028).

In a series of 74 CLKT procedures performed at a single institution over a 23-year period, survival was 62% at 5 years.(38) However, in patients who were undergoing a second CLKT or liver retransplantation, survival was 30% at 3 months. This led to a recommendation to not 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**

In 2014, Calinescu et al evaluated outcomes of CLKT in children using the Scientific Registry of Transplant Recipients from OPTN.(39) There were 152 primary CLKTs performed in the period between 1987 and 2011. Liver graft survival was 72.6% at 10 years and kidney graft survival was 66.9%. Patient survival at 10 years after CLKT was 78.9%. In comparison, patient survival following isolated liver transplantation during the same period was 77.4% (n=10,084), and for isolated kidney transplant, 90% at 10 years (n=14,800). Thus, CLKT resulted in survival outcomes that were no worse than liver transplant alone, but were inferior to kidney transplant alone. Indications for CLKT were noted as primary hyperoxaluria and other liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney such as congenital hepatic fibrosis and polycystic kidney disease. A table of the indications for CLKT in children treated between 1987 and 2011 is included in this publication.

Some reports have suggested that liver transplantation may have a protective effect on kidney allografts. To test this hypothesis, de al Cerda et al (2010) evaluated kidney survival in children who had kidney only or CLKT.(40) Examination of the OPTN/UNOS database between 1995 and 2005 identified 111 combined liver-kidney transplantations and 3798 kidney only transplants in children. The patients in the CLKT group were younger on average (9 years vs 12 years, p=0.007) and more had inherited disease as the primary cause (42% vs 28%). More patients in the combined liver-kidney transplantation group lost their kidney graft within 6 months (20.1% vs 5.9%, p=0.001), however, late kidney graft survival was significantly better at 5 years posttransplant compared with the kidney only group (p<0.01). The authors described 2 situations when combined
liver-kidney transplant 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 liver transplant.

Section Summary: Combined Liver–Kidney Transplantation
The evidence on CLKT includes registry studies that compare 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. There are relatively few children who have received CLKT. Patient survival has been reported to be worse than following kidney transplantation alone, but no worse than for liver transplant alone. For kidney grafts that survive the first 6 months, organ survival 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 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 the major concern. For example, the surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia reported the results of their first 40 adult-to-adult living donor liver transplantations, performed between 1998 and 1999.(41) There were an equal number of related and unrelated donors. Minor complications occurred in 7 donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, 4 of the 5 deaths occurred in recipients who were classified as 2A (see Description section). In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living-donor transplant. Reports of several donor deaths reemphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team.(42-44)

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

Criteria for a recipient of a living-related liver were also controversial, with some groups advocating that living-related donor livers be only used in those most critically ill; while others state 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.

In 2013, Grant et al 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. For disease-free survival after living donor liver transplantation, the combined hazard ratio (HR) was 1.59 (95% confidence interval [CI], 1.02 to 2.49) compared with deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality.

HIV-Positive Patients
This subgroup of recipients has long been controversial, due to the long-term prognosis for HIV positivity, the impact of immunosuppression on HIV disease, and the interactions of immunosuppressive therapy with antiretroviral therapy in the setting of a transplanted liver. For example, most antiretroviral agents are metabolized through the liver and can cause varying degrees of hepatotoxicity. HIV candidates for liver transplantation are frequently coinfected with hepatitis B or C, and viral coinfection can further exacerbate drug-related hepatotoxicities. Nevertheless, HIV positivity is not an absolute contraindication to liver transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease and the increasing experience with liver transplant in HIV-positive patients. Furthermore, UNOS states that asymptomatic HIV-positive patients should not necessarily be excluded for candidacy for organ transplantation, stating “A potential candidate for organ transplantation whose test for HIV is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality because of immunosuppressive therapy.” In 2001, the American Society of Transplantation proposed that the presence of AIDS could be considered a contraindication to kidney transplant unless the following criteria were present. These criteria may be extrapolated to other organs:

- CD4 count greater than 200 cells/mm3 for more than 6 months
- HIV-1 RNA undetectable
• On stable antiretroviral therapy more than 3 months
• No other complications from AIDS (e.g., opportunistic infection, including aspergillosis, tuberculosis, coccidiodomycosis, resistant fungal infections, Kaposi sarcoma, or other neoplasm).
• Meeting all other criteria for transplantation.

It is likely that each individual transplant center will have explicit patient selection criteria for HIV-positive patients.

In 2011, Cooper et al conducted a systematic review to evaluate liver transplantation in patients coinfected with HIV and hepatitis.(48) Reviewers included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI, 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI, 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared with those with detectable HIV viremia.

Terrault et al (2012) reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older.(49) Patient and graft survival reductions were significantly associated with only 1 factor: HIV infection. At 3 years, in the HCV only group, patient and graft survival rates were significantly better at 79% (95% CI, 72% to 84%) and 74% (95% CI, 66% to 79%), respectively, than the group with both HIV and HCV infection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.

**Hepatitis Infection**
Terrault et al (2012) reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HIV and HCV infection (n=89), patients with only HCV (n=235), and all transplant patients age 65 and older.(49) HCV status was not significantly associated with reduced patient and graft survival. 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 both HIV and HCV infection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%).

**Section Summary: Potential Contraindications**
Living donor liver transplantation has become accepted practice with careful screening of donors. Case series and case-control data indicate that HIV infection is not an absolute contraindication to liver transplant; for patients who meet selection criteria, these studies have demonstrated patient and graft survival rates are similar to those in the general population of liver transplant recipients. HCV status is not significantly associated with reduced patient survival. Although HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.
SUMMARY OF EVIDENCE
For individuals who have hepatocellular disease who receive liver transplant, the evidence includes case series, registry studies, and systematic reviews. Relevant outcomes include overall survival (OS), morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis find 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. In addition, survival can be improved by eradication of hepatitis virus before transplantation. For patients with nonalcoholic steatohepatitis, OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatocellular carcinoma who receive liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The long-term outcome in patients with primary hepatocellular malignancies was poor (19%) in the past compared with the OS of liver transplant recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria diameter, has dramatically improved OS rates. In appropriately selected patients, liver transplant has been shown to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

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

For individuals who have pediatric hepatoblastoma who receive liver transplant, the evidence includes case series. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is included in 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 liver retransplant, the evidence includes observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for an original liver transplantation are met for retransplantation. While some evidence suggests outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with indications for liver and kidney transplant who receive combined liver-kidney transplant (CLKT), the evidence includes registry studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Most of the evidence involves adults with cirrhosis and kidney failure. Indications for 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 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.

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and thus, may be considered medically necessary for the indications listed in the Policy Statement and in those 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 significantly worsen comorbid conditions. Based on survival data and clinical vetting input, 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. There was support from clinical vetting for retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent nonneoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review. There was consensus of agreement by the 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 listed in the above policy statement. There was also consensus of agreement by the 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 for the treatment of cholangiocarcinoma for patients who meet strict eligibility criteria. In general, there was not support for the use of liver transplantation for NET metastatic to the liver.

PRACTICE GUIDELINES AND POSITION STATEMENTS

International Consensus Conference

In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for hepatocellular carcinoma (HCC).(50) Consensus criteria for selecting candidates for liver transplantation were developed at the conference. Milan criteria was recommended for use as the benchmark for patient selection, although it is noted the Milan criteria may be modestly expanded based on data from expansion studies that demonstrate outcomes that are comparable to outcomes from studies using the Milan criteria. Candidates for liver transplantation should also have a
predicted survival of 5 years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

In regard to liver retransplantation, the consensus criteria issued a weak recommendation indicating retransplantation after graft failure of a living donor transplant for HCC is acceptable in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued indicating liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria is not recommended. And the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC is not appropriate. However, a de novo HCC may be treated as a new tumor and retransplantation may be considered even though data to support this are limited.

**American Association for the Study of Liver Diseases and American Society of Transplantation**

In 2013, the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST) issued guidelines on evaluating patients for liver transplant.(51) 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 medical therapy.

The AASLD and AST guidelines stated that liver transplant is indicated for:

- Acute liver failure complications of cirrhosis
- Liver-based metabolic condition with systemic manifestations
  - α1-Antitrypsin deficiency
  - Familial amyloidosis
  - Glycogen storage disease
  - Hemochromatosis
  - Primary oxaluria
  - Wilson disease
- Systemic complications of chronic liver disease.

In addition, the guidelines included 1-A (strong recommendation with a high quality of evidence) recommendations for 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 have the same indications for LT as for other etiologies of cirrhosis.”

Contraindications to liver transplant are:

- “MELD score < 15
- Severe cardiac or pulmonary disease
- Aids
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system

American Association for the Study of Liver Diseases et al
The AASLD, AST, and American Society for Pediatric Gastroenterology, Hepatology, and Nutrition provided joint guidelines for the evaluation of the pediatric patient for liver transplant in 2014.(52) 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 listed indications for liver transplantation include biliary atresia, Alagille syndrome, pediatric acute liver failure, hepatic tumors, hepatocellular carcinoma, hemangioendothelioma, cystic fibrosis-associated liver disease, urea cycle disorders, immune-mediated liver disease, along with other metabolic or genetic disorders.

European Neuroendocrine Society
The European Neuroendocrine Society issued consensus guidelines in 2008 and updated in 2012 for the management of patients with liver metastases from neuroendocrine tumors (NETs).(53) The Society guidelines indicated, in a “minimal consensus” statement, that liver transplantation may be considered for diffuse unresectable NET metastases or when hormonal disturbances that are refractory to medical therapy are life-threatening.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers (v.2.2017) recommends referral to a liver transplant center or bridge therapy for patients with HCC meeting UNOS criteria of a single tumor 5 cm or less, or 2 to 3 tumors 3 cm or less with no macrovascular involvement or extrahepatic disease.(13) Patients should be referred to the transplant center before biopsy. In patients meeting UNOS criteria who are ineligible for transplant and in select patients with Child-Pugh class A or B liver function with tumors that are resectable, NCCN indicates resection is the preferred treatment option or locoregional therapy may be considered. Patients with unresectable HCC should be evaluated for liver transplantation and if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. NCCN guidelines on hepatobiliary cancers also indicate liver transplant is appropriate in select patients with extrahepatic cholangiocarcinoma, which is unresectable, but biliary and hepatic function is otherwise normal or when underlying chronic liver disease precludes surgery. These are level 2A recommendations based on lower-level evidence and uniform consensus.
The NCCN guidelines on NETs (v.3.2017) indicate liver transplantation for NET liver metastases is considered investigational.(54)

**Organ Procurement and Transplantation Network**
The Organ Procurement and Transplantation Network’s new prioritization guidelines for simultaneous liver-kidney allocation became effective August 10, 2017.(55) The listed medical eligibility requirements related to kidney function are required in order for an adult liver-kidney candidate to receive a liver and kidney transplant from the same deceased donor.(56)

**Council of the British Transplant Society et al**
Liver transplantation guidelines for nonalcoholic steatohepatitis were developed by the Council of the British Transplant Society and approved by the British Society of Gastroenterology, the British Association for the Study of Liver and NHS Blood and Transplant in 2012. These guidelines indicated liver transplantation may be considered for the treatment of nonalcoholic steatohepatitis cirrhosis with end-stage liver disease or HCC.(57) These guidelines were based primarily on consensus of expert opinion.

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

**MEDICARE NATIONAL COVERAGE**
Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility which is approved by the Centers for Medicare & Medicaid Services (CMS) as meeting institutional coverage criteria for liver transplants.(58,59) 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.

Beginning June 21, 2012, on review of this national coverage decision for new evidence, Medicare began offering coverage for adult liver transplantation, at Medicare administrative contractor discretion, for extrahepatic unresectable cholangiocarcinoma, liver metastases due to a neuroendocrine tumor and hemangioendothelioma. Adult liver transplantation is excluded for other malignancies.

Pediatric liver transplantation is covered for children (<18 years of age) when performed in a CMS-approved pediatric hospital for extrahepatic biliary atresia or any other form of end-stage liver disease, except that coverage is not provided for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.
ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. 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>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01201096</td>
<td>Neo-adjuvant Peptide Receptor Mediated Radiotherapy With 177Lutetium in Front of Curative Intended Liver Transplantation in Patients With Hepatic Metastasis of Neuroendocrine Tumors</td>
<td>50</td>
<td>Sep 2018</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 2028</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>47133</td>
<td>Donor hepatectomy (including cold preservation), from cadaver donor</td>
</tr>
<tr>
<td>47135</td>
<td>Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age</td>
</tr>
<tr>
<td>47136</td>
<td>Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor, any age (CPT removed 1/1/2016)</td>
</tr>
<tr>
<td>47140</td>
<td>Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)</td>
</tr>
<tr>
<td>47141</td>
<td>Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)</td>
</tr>
<tr>
<td>47142</td>
<td>Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)</td>
</tr>
<tr>
<td>47143</td>
<td>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</td>
</tr>
<tr>
<td>47144</td>
<td>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])</td>
</tr>
<tr>
<td>47145</td>
<td>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])</td>
</tr>
</tbody>
</table>
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
47147  Backbench reconstruction of cadaver or living donor liver graft prior
to allotransplantation; arterial anastomosis, each

ICD10 Codes

B15.0-  Acute hepatitis A; code range
B15.9
B16.0-  Acute hepatitis B; code range
B16.9
B17.0-  Other acute viral hepatitis; code range
B17.9
B18.0-  Chronic viral hepatitis; code range
B18.9
B19.0-  Unspecified viral hepatitis; code range
B19.9
B25.1  Cytomegaloviral hepatitis
B66.1  Clonorchiasis
B66.5  Fasciolopsiasis
C22.0-  Malignant neoplasm of liver and intrahepatic bile ducts; code range
C22.9  (includes hepatoblastoma)
D64.0-  Other anemias; code range
D64.9
D81.810  Biotinidase deficiency
D84.0-  Other immunodeficiencies; code range
D84.9
E72.00-  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
E83.09
E83.1-  Disorders of iron metabolism; code range
E83.19
E85.0-  Amyloidosis; code range
E85.9
E88.9  Metabolic disorder, unspecified
G60.0-  Hereditary and idiopathic neuropathy; code range
G60.9
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- Toxic liver disease
K71.9
K74.0- Fibrosis and cirrhosis of liver; code range
K74.69
K75.81 Nonalcoholic steatohepatitis (NASH)
K77 Liver disorders in diseases classified elsewhere (code first underlying disease)
K83.0- Other diseases of biliary track; code range
K83.9
Q44.6 Congenital Cystic disease of liver
S36.12xA- Injury of liver and gallbladder and bile duct; code range
S36.13xS
T86.41 Liver transplant rejection
T86.42 Liver transplant failure
Z52.6 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.

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