Liver Transplant and Combined Liver-Kidney Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a liver transplant using a cadaver or living donor, for carefully selected patients with end-stage liver failure due to irreversibly damaged livers to be **eligible for coverage.**

Etiologies of end-stage liver disease include, but are not limited to, the following:

A. Hepatocellular diseases
- Alcoholic liver disease
- Viral hepatitis (either A, B, C, or non-A, non-B)
- Autoimmune hepatitis
- Alpha-1 antitrypsin deficiency
- Hemochromatosis
- Nonalcoholic steatohepatitis (NASH)
- 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 (HCC)
(See Policy Guidelines section for patient selection criteria)

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
- Familial amyloid polyneuropathy

Based on review of available data, the Company may consider liver transplantation in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment to be **eligible for coverage.**

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Based on review of available data, the Company may consider liver transplantation in patients with unresectable hilar cholangiocarcinoma (CCA) to be **eligible for coverage.** (See Policy Guidelines section for patient selection criteria).

Based on review of available data, the Company may consider liver transplantation in pediatric patients with nonmetastatic hepatoblastoma to be **eligible for coverage.**

Based on review of available data, the Company may consider liver *retransplantation* to be **eligible for coverage** in patients with:

- Primary graft nonfunction
- Hepatic artery thrombosis
- Chronic rejection
- Ischemic type biliary lesions after donation after cardiac death
- Recurrent nonneoplastic disease causing late graft failure

Based on review of available data, the Company may consider combined liver-kidney transplantation (CLKT) in patients who qualify for liver transplantation and have advanced irreversible kidney disease to be **eligible for coverage.**

When Services Are Considered Not Medically Necessary
Based on review on available data, the Company considers the use of liver transplantation to be **not medically necessary** in the following patients:

- Patients with HCC that has extended beyond the liver (See Policy Guidelines section for patient selection criteria).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers liver transplantation to be **investigational*** in the following situations:

- Patients with intrahepatic CCA
- Patients with neuroendocrine tumors (NETs) metastatic to the liver

Based on review of available data, the Company considers liver transplantation in all other situations not described above to be **investigational.***

Policy Guidelines

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

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

Tobacco consumption is a contraindication.

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

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

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

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

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

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

UNOS T2 Criteria
A single tumor 1 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, which were updated in 2017, 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) (http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf).

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 stage T2 will lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given a class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent locoregional treatment after being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and 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.

Human immunodeficiency virus (HIV)-positive patients who meet the following criteria, as stated in the 2013 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 highly active antiretroviral therapy (HAART), HIV can be suppressed post-treatment
- 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 Organ Procurement and Transplantation Network (OPTN) policy on liver allocation, candidates with CCA meeting the following criteria will be eligible for a MELD or PELD exception with a 10% mortality equivalent increase every 3 months:

- Centers must submit a written protocol for patient care to the OPTN and UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with 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 (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 (LDLT). 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:

- They should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure
- They should undergo evaluation to ensure that they fully understand the procedure and associated risks

- They should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- They should be emotionally related to the recipients
- They must be excluded if the donor is felt or known to be coerced
- They need to have the ability and willingness to comply with long-term follow-up.

Combined liver-kidney transplant would be reported with the codes in this policy.

Background/Overview

LIVER TRANSPLANTATION

Recipients

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by 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 2002, status 2A, 2B, and 3 were replaced with 2 disease severity scales: MELD and PELD for patients younger than age 12 years. In 2013, the OPTN and UNOS published its most recent allocation system, which previously expanded status 1 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 every 7 days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease, which may include the following: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to status 1A at age 18 but still qualify for pediatric indications.

Following status 1, donor livers 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 (i.e., international normalized ratio), and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. 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 and PELD scores will always be considered before those with lower scores, even if some patients with lower scores

have waited longer.[1] 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. 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 either intravenous immunoglobulin or plasmapheresis is discussed separately in medical policies 00170 and 00249, respectively. Also, the role of chemoembolization or radiofrequency ablation as a bridge to transplant in patients with hepatocellular cancer is addressed separately in medical policies 00227 and 00182, respectively.

FDA or Other Governmental Regulatory Approval

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

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

- The patient is not a candidate for subtotal liver resection;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

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 CCA, liver metastases due to a neuroendocrine tumor, and hemangioendothelioma. Adult liver transplantation is excluded for other malignancies.

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

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial 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.

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.

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 (1995) 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%). Recurrence of HCV infection in transplant recipients has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years.

Mukherjee and Sorrell (2008), reviewing controversies in liver transplantation for hepatitis C, indicated that the greatest opportunity for HCV eradication is pretransplant before hepatic decompensation. Challenges of treatment posttransplantation include immunosuppressive drugs and abnormal hematologic, infectious, and liver function parameters. The authors listed the following factors associated with poor outcomes in liver transplantation for recurrent HCV: high hepatitis C virus ribonucleic acid (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

Liver transplantation is a treatment option for patients with NASH who progress to liver cirrhosis and failure. In a 2014 systematic review and meta-analysis, Wang et al evaluated 9 studies comparing liver transplantation outcomes in patients with and without NASH. Patients with NASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had

lower graft failure risk than those without NASH (OR [odds ratio], 0.21; 95% confidence interval [CI], 0.05 to 0.89; p=0.03). However, NASH 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. Also, survival can be improved by eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival (OS) rates are similar to other indications for liver transplantation.

HEPATOCELLULAR CARCINOMA

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

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

Ioannou et al (2008) analyzed UNOS data pre- and postadoption of the MELD allocation system finding a 6-fold increase in recipients with HCC and survival rates in the MELD era similar to survival rates in patients without HCC. The subgroup of patients with larger (3-5 cm) tumors, serum alpha-fetoprotein level of 455 mg/mL or greater, or a MELD score of 20 or greater, however, had poor transplantation survival. A predictive cancer recurrence scoring system was developed by Chan et al based on a 2008 retrospective

review and analysis of liver transplants at 2 centers to determine factors. Of 116 patients with findings of HCC in their explanted livers, 12 developed recurrent HCC. Four independent significant explant factors were identified by stepwise logistic regression: size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, while the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds. The accuracy of the method was confirmed in 2 validation cohorts.

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

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. 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 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), OS at 1, 3, and 5 years and disease-free survival at 1 and 3 years did not differ significantly between groups. Disease-free survival, however, was significantly lower at 5 years with salvage liver transplantation than with primary transplantation (OR=0.62; 95% CI, 0.42 to 0.92; p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria; but, in patients meeting Milan criteria, survival outcomes did not differ significantly, suggesting salvage liver transplantation might be a viable option in these patients.

In 2014, Chan et al systematically reviewed 16 nonrandomized studies (total N=319 patients) assessing salvage liver transplantation after primary hepatic resection for HCC. Reviewers found that OS and disease-free survival outcomes with salvage liver transplantation were similar to reported primary liver transplantation outcomes. Median OS rates for salvage liver transplantation patients were 89%, 80%, and 62% at 1, 3, and 5 years, respectively. Disease-free survival rates were 86%, 68%, and 67% at 1, 3, and 5 years, respectively. Salvage liver transplantation studies had a median OS rate of 62% (range, 41%-89%)

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

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

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.

CHOLANGIOCARCINOMA
Reports on outcomes after liver transplantation for CCA, or bile duct carcinoma 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 CCA. Most studies reported on patients with extrahepatic or hilar CCA. 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.

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

In 2012, Darwish Murad et al reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar CCA 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 post-transplant 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 because they had a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy ($p<0.001$).

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

Mixed Populations With Intrahepatic or Extrahepatic Cholangiocarcinoma

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

In 2011, Friman et al reported on 53 patients who received liver transplants for CCA 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. 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 suggested transplantation might have acceptable outcomes in select patients.

The Cincinnati Transplant Registry reported in 2000 on 207 patients with intrahepatic or extrahepatic CCA, finding a 1-year survival of 72% and a 5-year rate of 23% (see Table 1). The 2004 multicenter Spanish report included 36 patients with hilar tumors and 23 with 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 peripheral intrahepatic disease, respectively.

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

				Overall Survival, %		
				Years		
Study	Dates	N	Group	1	3	5
Darwish Murad et al (2012) (multicenter)		287	EH perihilar			53
Heimbach et al (2006); Rea et al (2005) (Mayo Clinic, Rochester, MN[c])	1993-2006	65	EH perihilar	91		76
Pascher et al (2003) (European Liver Transplant Registry)		186	IH	58	38	29
		169	EH	63	38	29
Meyer et al (2000) (Cincinnati Transplant Registry[a])		207	IH/EH	72		23
Robles et al (2004) (multicenter in Spain[b])	1988-2001	36	EH Hilar	82	53	30
		23	IH	77	65	23
Casavilla et al (1997) (University of Pittsburgh)	1981-1994	20	IH	70	29	18
Friman et al (2011) (Norway, Sweden, Finland[d])	1984-2005	53	IH/EH			25

EH: extrahepatic; IH: intrahepatic.
[a] Unresectable cholangiohepatoma;
[b] Hilar or peripheral cholangiohepatoma; unresectable, postoperative recurrent, or incidental.
[c] Aggressive neoadjuvant radiochemotherapy,

[d] Unresectable cholangiohepatoma.

Section Summary: Cholangiocarcinoma
The evidence on liver transplant in patients with CCA includes registry studies and a systematic review of observational studies.

However, for patients with extrahepatic (hilar or perihilar) CCA 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 unresectable extrahepatic CCA.

The 5-year survival rate following liver transplantation in patients with intrahepatic CCA was less than 30%. Intrahepatic CCA is also listed as a contraindication for liver transplantation in society guidelines.

METASTATIC NEUROENDOCRINE TUMORS
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. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection.

In 2015, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin. A total of 706 patients were selected 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 OS rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after liver transplantation were reported in most studies.

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 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: Metastatic Neuroendocrine Tumors
The evidence on liver transplant for NETs includes systematic reviews of NETs for metastases of any origin. In select patients with nonresectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms. While there may be centers that perform liver transplantation on select patients with NETs, the available studies were limited by their heterogeneous populations. Further studies are needed to define 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. The OS rate after liver transplant was 93.3% 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 OS rate was 93%. In 2008, Browne et al reported on 14 hepatoblastoma patients treated with liver transplantation. The mean follow-up was 46 months, with OS in 10 (71%) of 14 patients. Tumor recurrence caused all 4 deaths. In the 10 patients receiving primary liver transplantation, 9 survived while only 1 of 4 patients transplanted after primary resection survived (90% vs 25%, p=0.02).

Section Summary: Pediatric Hepatoblastoma

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

RETRANSPLANTATION

In 2012, Bellido et al reported on a retrospective cohort of 68 consecutive adults with liver retransplantations using registry data. Survival estimates using Kaplan-Meier curves with log-rank tests 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. In 2011, Remiszewski et al 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 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. The authors proposed this risk-stratification model could be highly predictive of long-term outcomes after adult liver retransplantation and useful in patient selection.

Section Summary: Retransplantation

Observational studies have evaluated risk factors for survival after liver retransplantation. OS has been 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 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 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 (hazard ratio [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. 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 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 2010 series of 74 CLKT procedures performed at a single institution over a 23-year period, survival was 62% at 5 years. However, in patients 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
In 2014, Calinescu et al evaluated CLKT outcomes in children using data from the Scientific Registry of Transplant Recipients from the 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=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 the Calinescu publication.

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 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 2 situations when CLKT would be indicated in children: end-stage liver disease when the kidneys go into prolonged irreversible failure, and severe renal failure from an underlying disease that can be improved with liver transplant.

Section Summary: Combined Liver-Kidney Transplantation
The evidence on CLKT includes registry studies that have compared combined organ transplantation with liver or with kidney transplantation alone. In adults undergoing liver transplant with kidney failure, CLKT results in a modest improvement in patient survival compared with liver transplantation alone. Liver allograft survival was also higher in the patients who received CLKT compared with patients who received a liver transplant alone. Relatively few children have received CLKT. Patient survival has been reported to be worse with CLKT than with kidney transplantation alone, but no worse than for liver transplant alone. For kidney grafts that survive the first 6 months, the organ survival rate may be better than for a kidney graft alone. Together, these results would suggest that CLKT is no worse, and possibly better, for graft and patient survival in adults and children who meet the requirements for liver transplantation and have concomitant renal failure. Indications for CLKT in children are rare and often congenital, and include liver-based metabolic abnormalities affecting the kidney, along with structural diseases affecting both the liver and kidney.

POTENTIAL CONTRAINDICATIONS (APPLIES TO ALL PREVIOUS INDICATIONS)

Living Donor vs Deceased Donor Liver Transplant Recipient Outcomes
Due to the scarcity of donor organs and the success of living donation, LDLT 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 a 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 have suggested that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia reported in 2000 on the results of their first 40 adult-to-adult LDLTs, performed between 1998 and 1999. 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. 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.

In December 2000, the National Institutes of Health convened a workshop focusing on LDLT. 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 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.

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 LDLT, the combined HR was 1.59 (95% CI, 1.02 to 2.49) compared with deceased donor liver transplantation. For OS, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality.

HIV-Positive Patients
Transplantation for patient with HIV infection 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, which has markedly changed the natural history of the disease and the increasing experience with liver transplant in HIV-positive patients. Furthermore, UNOS has suggested 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 acquired immune deficiency syndrome (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/mm^3 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 aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi sarcoma, or other neoplasm)
- Meeting all other criteria for transplantation.

It is likely that each 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. 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. Patient and graft survival reductions were significantly associated with only 1 factor: HIV infection. At 3 years, in the HCV-only group, patient and graft survival rates were significantly better at 79% (95% CI, 72% to 84%) and 74% (95% CI, 66% to 79%), respectively, than the group with HIV and HCV coinfection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3-year survival rates after liver transplantation in patients coinfected with HCV, a majority of patients still experienced long-term survival.

Hepatitis Infection
Terrault et al (2012) also reported on the group of patients with HCV. 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 HIV and HCV at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%).

Section Summary: Potential Contraindications
LDLT has become accepted practice with careful donor screening. Case series and case-control data has indicated 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 coinfected with HCV, most patients still experienced 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 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 eradication of 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 liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In the past, long-term outcomes in patients with primary hepatocellular malignancies had been poor (19%) compared with the OS of liver transplant recipients. However, recent use of standardized patient selection criteria (e.g., 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have intrahepatic CCA 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 CCA are less than 30%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have metastatic NETs 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 transplants on select patients with NETs, 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 UNOS 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 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 combined liver-kidney transplant, 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 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.

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Policy History

Original Effective Date: 05/21/2014
Current Effective Date: 03/21/2018

05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. New policy.
03/05/2015	Medical Policy Committee review
03/20/2015	Medical Policy Implementation Committee approval. Removed requirement for "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.)".
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Policy title changed from "Liver Transplant" to "Liver Transplant and Combined Liver-Kidney Transplant." Combined liver-kidney transplantation added to policy as eligible for coverage. Policy Guidelines moved from the Background/Overview to a new Policy Guidelines section. Contraindication for smoking and HIV criteria added to Policy Guidelines.

Next Scheduled Review Date: 03/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147, 47399			
HCPCS	No codes			
ICD-10 Diagnosis	A52.15	B15.0	B15.9	B16.0-B16.9
	B17.10-B17.11	B17.8-B17.9	B18.0-B18.9	B19.10-B19.11
	B19.9	B25.1	B66.1	B66.3
	D64.0-D64.3	D81.810	D84.1	E70.0-E70.1
	E70.21-E70.29	E70.30	E70.310-E70.319	E70.320-E70.329
	E70.330-E70.339	E70.039	E70.40-E70.41	E70.49
	E70.5	E70.8-E70.9	E71.0	E71.110-E71.111
	E71.118	E71.120-E71.121	E71.128	E71.19
	E71.2	E71.30	E72.00-E72.09	E72.10-E72.19
	E72.20-E72.29	E72.3-E72.4	E72.50-E72.59	E72.8-E72.9
	E73.0-E73.9	E74.00-E74.39	E74.4	E74.8-E74.9
	E75.21-E75.22	E75.240-E75.249	E75.3	E75.5-E75.6
	E77.0-E77.9	E78.0-E78.6	E78.70-E78.79	E78.81-E78.89
	E78.9	E80.0-E80.1	E80.20-E80.29	E83.00-E83.19
	E85.0-E85.9	E88.1-E88.2	E88.89	E88.9
	G63	G65.0-G65.2	G70.00-G70.01	I74.8
	I82.0	I87.9	I99.9	K71.0
	K71.10-K71.11	K71.2-K71.4	K71.50-K71.51	K71.6-K71.9
	K74.3-K74.5	K75.2-K75.3	K75.81	K75.89
	K75.9	K76.0	K76.4	K76.89
	K77	K80.30-K80.37	K83.0-K83.1	K83.5
	K83.8	K87	M34.83	Q43.4-Q43.9
	S31.609A	S36.112A-S36.119A	T86.40-T86.49	Z52.6

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.