Aetna considers liver transplantation medically necessary for the indications listed below for adolescents and adults with either (i) a Model of End-stage Liver Disease (MELD) score (see Appendix) greater than 10; or (ii) who are approved for transplant by the United Network for Organ Sharing (UNOS) Regional Review Board, and for children less than 12 years of age who meet the transplanting institution's selection criteria. Requests for liver transplantation for adolescents and adults with a MELD score of 10 or less who have not been approved by the UNOS Regional Review Board are subject to medical necessity review. In the absence of an institution's selection criteria, Aetna considers liver transplantation medically necessary for adolescents and adults with a MELD score greater than 10 or who are approved by the UNOS Regional Review Board and for children who meet the medical necessity criteria specified below.

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
I. Medically Necessary Indications (not an all-inclusive list)

Aetna considers orthotopic (normal anatomical position) liver transplantation (with cadaveric organ, reduced-size organ, living related organ, and split liver) medically necessary for members with end-stage liver disease (ESLD) due to any of the following conditions.

A. Cholestatic diseases:

1. Biliary atresia
2. Familial cholestatic syndromes
3. Primary biliary cirrhosis
4. Primary sclerosing cholangitis with development of secondary biliary cirrhosis

B. Hepatocellular diseases:

1. Alcoholic cirrhosis
2. Chronic active hepatitis with cirrhosis (hepatitis B or C)
3. Cryptogenic cirrhosis
4. Idiopathic autoimmune hepatitis
5. Post-necrotic cirrhosis due to hepatitis B surface antigen negative state

C. Malignancies:

1. Primary hepatocellular carcinoma confined to the liver when all of the following criteria are met:

   a. Any lung metastases that have been shown to be responsive to chemotherapy; and
   b. Member is not a candidate for subtotal liver resection; and
   c. Member meets UNOS criteria for tumor size and number; and
   d. There is no identifiable extra-hepatic spread of tumor to surrounding lymph nodes, abdominal organs, bone or other sites; and
   e. There is no macrovascular involvement.

Note: These criteria are intended to be consistent with UNOS guidelines for selection of liver transplant
candidates for hepato-cellular carcinoma (HCC).

2. Hepatoblastomas in children when all of the following criteria are met:

   a. Member is not a candidate for subtotal liver resection; and
   b. Member meets UNOS criteria for tumor size and number; and
   c. There is no identifiable extra-hepatic spread of tumor to surrounding lungs, abdominal organs, bone or other sites. (Note: Spread of hepatoblastoma to veins and lymph nodes does not disqualify a member for coverage of a liver transplant.)

3. Epithelioid hemangioendotheliomas;
4. Intra-hepatic cholangiocarcinomas (i.e., cholangiocarcinomas confined to the liver);
5. Large, unresectable fibrolamellar HCCs;
6. Metastatic neuroendocrine tumors (carcinoid tumors, apudomas, gastrinomas, glucagonomas) in persons with severe symptoms and with metastases restricted to the liver, who are unresponsive to adjuvant therapy after aggressive surgical resection including excision of the primary lesion and reduction of hepatic metastases.

D. Vascular diseases:

   1. Budd-Chiari syndrome
   2. Veno-occlusive disease.

E. Metabolic disorders and metabolic liver diseases with cirrhosis (not an all-inclusive list):

   1. Alpha 1-antitrypsin deficiency
   2. Hemochromatosis
   3. Inborn errors of metabolism
   4. Protoporphyria
   5. Wilson’s disease.

F. Miscellaneous:

   1. Familial amyloid polyneuropathy
2. Polycystic disease of the liver
3. Porto-pulmonary hypertension (pulmonary hypertension associated with liver disease or portal hypertension) in persons with a mean pulmonary artery pressure by catheterization of less than 35 mm Hg
4. Toxic reactions (fulminant hepatic failure due to mushroom poisoning, acetaminophen (Tylenol) overdose, etc.)
5. Trauma
6. Hepato-pulmonary syndrome when the following selection criteria are met:

- Arterial hypoxemia (PaO2 less than 60 mm Hg or AaO2 gradient greater than 20 mm Hg in supine or standing position); and
- Chronic liver disease with non-cirrhotic portal hypertension; and
- Intrapulmonary vascular dilatation (as indicated by contrast-enhanced echocardiography, technetium-99 macroaggregated albumin perfusion scan, or pulmonary angiography).

II. Retransplantation

Aetna considers retransplantation following a failed liver transplant medically necessary if the initial transplant was performed for a covered indication.

III. Contraindications

Aetna considers liver transplantation not medically necessary for members with any of the following absolute contraindications to liver transplantation:

A. Active alcoholism or active substance abuse
B. Active sepsis outside the biliary tract
C. Other effective medical treatments or surgical options are available
D. Presence of significant organ system failure other than kidney, liver or small bowel.
IV. Experimental and Investigational Procedures

Aetna considers the following indications/procedures regarding liver transplantation experimental and investigational because their safety and effectiveness has not been established:

A. Bioartificial liver transplantation
B. Ectopic or auxiliary liver transplantation
C. Hepatocellular (hepatocyte) transplantation
D. Malignancies other than those listed as covered above
E. Molecular Adsorbent Recirculating System (MARS) for the treatment of progressive familial intrahepatic cholestasis
F. Normothermic machine perfusion of donor liver
G. Peri-operative use of vasopressin in liver transplantation
H. Peri-operative use of sorafenib in liver transplantation
I. Use of everolimus to prevent organ rejection after liver transplantation
J. Use of ursodeoxycholic acid (UDCA) as an adjuvant treatment to prevent acute cellular rejection after liver transplantation
K. Xenotransplantation.

Note: For policy on hepatitis B immune globulin for prophylaxis of recurrent hepatitis B infection in HbsAg positive liver transplant recipients, see CPB 0544 - Immune Globulins for Post-exposure Prophylaxis (0544.html).

Background

Progressive liver diseases that result in death either in short-term or long-term is known as end-stage liver disease (ESLD), which is evidenced by irreversible, progressive liver dysfunction, variceal bleeding, encephalopathy, synthetic dysfunction, poor growth, or poor nutritional status. The most common causes of ESLD include infection (e.g., acute or chronic hepatitis), toxic effects (e.g., alcohol, medications), disorders of metabolism (e.g., hemochromatosis, Wilson's disease), tumors (primary or metastatic), and malformations (e.g., primary biliary atresia). Liver transplantation is an effective treatment for fulminant (acute) hepatic failure and for many chronic liver diseases.
A liver transplant is usually positioned in the normal anatomical position (orthotopic) following a total hepatectomy of the recipient. In auxiliary liver transplantation, a second liver is implanted ectopically and the recipient's own liver remains in-situ. A major concern of ectopic transplantation is the recipient's diseased liver may harbor bacterial, fungal or viral infection or cancer. Advances in surgical techniques and immunosuppressive drugs have resulted in increased survival rates (with 1-year survival rates in the 85 to 90 % range, and 5-year survival rates exceeding 70 %). Currently, 10 to 20 % of liver transplanted patients are retransplanted with a success rate of greater than 50 %.

Hepatitis C cirrhosis is the most common indication for liver transplantation. Alcoholic liver disease remains a controversial indication for liver transplantation but carefully selected patients do well. Some of the common indications for liver transplantation are as follows:

1. Alcoholic liver disease (after a period of abstinence)
2. Chronic active hepatitis (usually secondary to hepatitis B and C)
3. Cryptogenic cirrhosis
4. Primary biliary cirrhosis
5. Primary sclerosing cholangitis

Hepato-cellular carcinoma (HCC) complicates many chronic liver diseases. However, a small tumor is not a contraindication to transplantation since tumor rarely recurs in these patients. In contrast, most patients with large (greater than 5 cm in diameter) or multiple hepatomas or most other types of cancer are not considered for transplantation since tumors recur rapidly. At present, there is insufficient evidence that liver transplantation is an effective treatment for other malignancies that affect the liver such as metastatic disease, bile duct carcinoma, and epitheloid hemangioendothelioma, among others. An assessment by the Agency for Healthcare Research and Quality (Beavers et al, 2001) on liver transplantation for malignancies other than HCC concluded that “[t]he available evidence does not provide a clear profile of patients who might be optimal candidates for such
therapy.” Contraindications to liver transplantation include extra-hepatic malignancy, severe cardiopulmonary disease, systemic sepsis, and an inability to comply with regular pharmacotherapy.

Liver transplantation is an effective treatment for a variety of acute and chronic diseases of the liver in the pediatric (less than 18 years of age) population. Approximately 15% of the liver transplantations performed yearly in the United States are in pediatric patients. Most children who need liver transplantation are young (age less than 3 years) and small (body weight less than 45 pounds). Size-matched organs are given preference in organ allocation. However, because of the severe scarcity of pediatric donor livers, techniques such as reduced size (“cut down”) and split (a liver is split between 2 recipients) liver transplantations are used to reduce the size of adult donor livers to fit pediatric recipients. Donation of the left lobe of the liver by a living adult relative (“living related donor”) is also an option.

Liver transplantation in children is indicated for ESLD from any etiology in the absence of contraindications. The most common indication for pediatric liver transplantation is biliary atresia, often after failure to respond to a porto-enterostomy. In addition, unresectable tumors and liver-based metabolic deficiencies may be indications for liver transplantation.

The Model for End-Stage Liver Disease (MELD) is a numerical scale, ranging from 6 (less ill) to 40 (gravely ill), that is used for adult liver transplant candidates. It gives each individual a 'score' (number) based on how urgently he or she needs a liver transplant within the next 3 months. The number is calculated by a formula using bilirubin, prothrombin time, and creatinine. Candidates under the age of 12 are placed in categories according to the Pediatric End-stage Liver Disease (PELD) scoring system. PELD is similar to MELD but uses some different criteria to recognize the specific growth and development needs of children. PELD scores may also range higher or lower than the range of MELD scores. The PELD scoring system takes into account the patient’s bilirubin, prothrombin time, albumin, growth failure, and whether the child is less than 1 year old. A liver transplantation is rarely necessary for persons with a MELD score of less than 10. According to data from the United Network
for Organ Sharing (UNOS), of almost 5,000 liver transplants that were performed in 2002, only 181 transplants were performed on patients with a MELD score of less than 10.

The MELD/PELD score is a well-validated measure of short-term mortality from liver disease; however, referring physicians who believe a patient faces a greater mortality risk than predicted by the MELD/PELD score can request accelerated listing. UNOS Regional Review Boards can approve or deny these requests, and a study by Voight et al (2004) concluded that these boards fairly and accurately distinguish between high- and low-risk patients. The study found that the denials of physicians' requests for accelerated listings did not increase mortality for those patients.

To determine the effect of UNOS Regional Review Board decisions on the mortality of physician-referred patients, investigators analyzed 1,965 nationwide referrals to UNOS Regional Review Boards. They noted which cases were approved and which were denied, and gathered information about patient deaths while awaiting transplantation. The investigators found that there was no significant difference in survival to transplantation whether accelerated listing was approved or denied for adult or pediatric cases. In addition, the researchers examined whether or not referring physicians predicted death better than the MELD/PELD score. The investigators found that the physicians had poor predictive capacity and added no additional information to the risk assessment by the MELD/PELD score. The investigators concluded that the MELD-PELD score is a better predictor of mortality than the judgement of the referring physician, but the UNOS Regional Review Board process adds additional information (e.g., Voight et al, 2004).

Dimmock et al (2008) noted that deoxyguanosine kinase (DGUOK) deficiency is the commonest type of mitochondrial DNA depletion associated with a hepato-cerebral phenotype. These researchers assessed predictors of survival and therapeutic options in patients with DGUOK deficiency. A systematic search of MEDLINE, LILAC, and SCIELO was performed to identify peer-reviewed clinical trials, randomized controlled trials, meta-analyses, and other studies with clinical pertinence. Deoxyguanosine kinase deficiency was searched with the terms dGK, DGUOK,
mitochondrial DNA depletion, mtDNA, and hepatocerebral. Bibliographies of identified articles were reviewed for additional references. A total of 13 identified studies met the inclusion criteria and were used in this study. The analysis revealed that DGUOK deficiency is associated with a variable clinical phenotype. Long-term survival is best predicted by the absence of profound hypotonia, significant psychomotor retardation, or nystagmus. In the presence of these features, there is increased mortality, and liver transplantation does not confer increased survival. The authors concluded that liver transplantation appears to be futile in the presence of specific neurological signs or symptoms in patients affected with DGUOK deficiency. Conversely, in the absence of these neurological features, liver transplantation may be considered a potential treatment.

Bioartificial Liver Transplantation:

Artificial and bioartificial livers have been developed for use as a bridge to transplant in patients with liver failure or to allow recovery in persons with acute liver failure. Liu et al (2004) reported on the results of a meta-analysis of 12 trials of artificial or bioartificial support systems versus standard medical therapy, involving 483 patients, and 2 trials comparing different artificial support systems, involving 105 patients. Most trials had unclear methodological quality. Compared to standard medical therapy, support systems had no significant effect on mortality (relative risk [RR] 0.86; 95 % confidence interval [CI]: 0.65 to 1.12) or bridging to liver transplantation (RR 0.87; 95 % CI: 0.73 to 1.05), but a significant beneficial effect on hepatic encephalopathy (RR 0.67; 95 % CI: 0.52 to 0.86). Subgroup analysis indicated that artificial and bioartificial livers may reduce mortality by 1/3 in acute-on-chronic liver failure (RR 0.67; 95 % CI: 0.51 to 0.90), but not in acute liver failure (RR 0.95; 95 % CI: 0.71 to 1.29). The authors noted that the incidence of adverse events was inconsistently reported. They concluded that, although artificial support systems may reduce mortality in acute-on-chronic liver failure, “considering the strength of the evidence additional randomised clinical trials are needed before any support system can be recommended for routine use.”
More recently, Demetriou et al (2004) reported on the first prospective, randomized controlled trial of bioartificial liver, the HepatAssist Liver Support System in 171 patients with severe acute liver failure, including both fulminant/subfulminant hepatic failure and primary non-function following liver transplantation. For the entire patient population, survival at 30 days was 71 % for patients assigned to the bioartificial liver versus 62 % for patients in the control group (p = 0.26). After exclusion of primary non-function patients, survival was 73 % for persons assigned to the bioartificial liver versus 59 % for persons in the control group (p = 0.12). When survival was analyzed accounting for confounding factors, in the entire patient population, there was no difference between the 2 groups (risk ratio = 0.67; p = 0.13). However, differences in survival between bioartificial liver and control patients with fulminant/subfulminant hepatic failure reached marginal statistical significance (risk ratio = 0.56; p = 0.048). The authors concluded that this study demonstrated improved survival in patients with fulminant/subfulminant hepatic failure. These results would need to be confirmed in additional prospective randomized studies before conclusions can be drawn about the effectiveness of the bioartificial liver.

**Peri-Operative Use of Sorafenib:**

Qi and colleagues (2015) examined if the application of sorafenib during the peri-operative period of LT improves prognosis in liver cancer patients. These investigators searched PubMed, EMBASE and MEDLINE for eligible articles. A total of 4 studies were found that fulfilled the previously agreed-upon standards. They then performed a systematic review and meta-analysis on the enrolled trials that met the inclusion criteria. Out of the 104 studies identified in the database, 82 were not clinical experiments, and 18 did not fit the inclusion standards. Among the remaining 4 articles, only 1 was related to the pre-operative use of sorafenib, whereas the other 3 were related to its post-operative use. As the heterogeneity among the 4 studies was high, with an I(2) of 86 %, a randomized effect model was applied to pool the data. The application of sorafenib before LT had a hazard ratio (HR) of 3.29 (95 % CI: 0.33 to 32.56). The use of sorafenib after LT had an HR of 1.44 (95 %CI: 0.27 to 7.71). The overall pooled HR was 1.68
(95 %CI: 0.41 to 6.91). The authors concluded that the results showed that the use of sorafenib during the peri-operative period of LT did not improve patient survival significantly. In fact, sorafenib could even lead to a worse prognosis, as its use may increase the hazard of poor survival.

Mancuso et al (2015) stated that data on survival and safety of sorafenib for hepatocellular carcinoma recurrence after LT are still equivocal. These researchers performed a meta-analysis of published studies, with the aim of estimating the 1-year rates of survival, analyzing the variability in survival rates and, finally, identifying the factors associated with a longer survival. Data from 8 of the 17 selected studies were pooled, while the other 9 were excluded because survival rates were missing. All included studies were retrospective. Overall, the 1-year survival ranged from 18 % to 90 %. Tumor progression was the main cause of death. The second cause was bleeding, reported only in patients undergoing m-Tor inhibitor therapy. The pooled estimate of 1-year survival was 63 %. There was a significant heterogeneity among studies (p < 0.0001). Among the 34 variables assessed by univariate meta-regression, 5 were associated with an increase in the 1-year survival rate: (i) male gender (p = 0.001); (ii) time to progression (p = 0.038); and adverse drug events, divided in (iii) gastrointestinal (p = 0.038), (iv) cardiovascular (p = 0.029), and (v) dermatological (p = 0.014). The authors concluded that additional data from multi-center prospective studies are needed to clearly determine if sorafenib is a safe and acceptable treatment in hepatocellular carcinoma recurrence after LT. Nevertheless, its association with m-Tor inhibitors should be discouraged.

An UpToDate review on “Long-term management of adult liver transplant recipients” (Gaglio and Cotler, 2015) does not mention the use of sorafenib as a management agent.

**Split Liver Transplantation versus Whole Liver Transplantation:**

Wan and colleagues (2015) noted that split liver transplantation (SLT) has proven to be an effective technique to reduce the mortality of children on the waiting list, but whether creating 2
split grafts from 1 standard-criteria whole liver would compromise outcomes of adult recipients remains uncertain. These investigators conducted this meta-analysis to compare outcomes of right lobe SLT and whole liver transplantation (WLT) in adult patients. PubMed, Embase, and the Cochrane Library were searched for relevant articles published before December 2014. Outcomes assessed were patient survival, graft survival and major surgical complications after transplantation. Pooled odds ratios (OR) with 95 % CI were calculated to synthesize the results. A total of 17 studies with a total of 4,8457 patients met the full inclusion criteria. Patient survival and graft survival rates were all found to be equivalent between SLT and WLT recipients. However, SLT was associated with higher rates of overall biliary complications (OR = 1.66, 95 % CI: 1.29 to 2.15, p < 0.001), bile leaks (OR = 4.30, 95 % CI: 2.97 to 6.23, p < 0.001), overall vascular complications (OR = 1.81, 95 % CI:1.29 to 2.53, p < 0.001), hepatic artery thromboses (OR = 1.71, 95 % CI: 1.17 to 2.50, p = 0.005) and outflow tract obstructions (OR = 4.17, 95 % CI: 1.75 to 9.94, p = 0.001). No significant difference was observed in incidences of biliary stricture, portal vein complications, post-operative bleeding requiring surgical treatments, primary non-function and re-transplantations. In subgroup analyses, biliary and vascular complications only increased after ex-vivo SLT rather than in-situ SLT, and SLT recipients had more re-transplantations if they matched with WLT recipients in terms of urgent status. The authors concluded that adult right lobe SLT was associated with increased biliary and vascular complications compared with WLT, but it did not show significant inferiority in patient and graft survivals.

Ursodeoxycholic Acid for Prevention of Acute Cellular Rejection after Liver Transplantation:

Deng et al (2014) noted that acute cellular rejection (ACR) after LT is one of the most common problems faced by transplant recipients in spite of advances in immunosuppressive therapy. Recently, clinical trials reported that ursodeoxycholic acid (UDCA) reduced the incidence of ACR significantly. However, others have shown contradictory conclusion. Therefore, these investigators performed a meta-analysis of rigorous randomized controlled
trials (RCTs) to determine the effectiveness of UDCA in reducing ACR after LT. All RCTs that evaluated effectiveness of UDCA as an adjuvant treatment to prevent ACR after LT were searched from PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ScienceDirect databases and Web of Science (from January 1981 to March 2012). There was no language limitation in these searches. Relevant abstracts of international meetings were also searched. References of each included study were searched manually. A total of 234 patients from 4 high-quality RCTs (Jadad score 4 to 5) were included in this meta-analysis. Prophylactic use of UDCA did not decrease the incidence of ACR (RR: 0.94, 95 % CI: 0.77 to 1.16, p > 0.05), steroid-resistant rejection (RR: 0.77, 95 % CI: 0.47 to 1.27, p > 0.05) and the number of patients with the multiple episodes of ACR (RR: 0.60, 95 % CI: 0.28 to 1.30, p > 0.05). Different intervention programs (high-dose versus low-dose UDCA; early versus delayed UDCA treatment) also did not alter the outcomes.

The authors concluded that UDCA, as an adjuvant treatment, was not able to prevent ACR and steroid-resistant rejection after LT. They stated that further trials should be done to determine whether higher dose of UDCA will be beneficial.

An UpToDate review on “Long-term management of adult liver transplant recipients” (Gaglio and Cotler, 2015) does not mention the use of ursodeoxycholic acid as a management agent.

**Xenotransplantation:**

The success of transplantation has led to a marked increase in the number of candidates to over 16,000 places on the national waiting list. However, there has been little growth in the supply of available cadaveric organs, resulting in an organ shortage crisis. With waiting times often exceeding 1 to 2 years, the waiting list death rate now exceeds 10 % in most regions. Researchers have investigated novel approaches such as xenotransplantation, hepato-cellular transplantation and bioartificial liver to address the growing disparity between the limited supply and excessive demand for suitable organs. However, all these approaches are considered investigational in nature at this juncture.
Studies on xenotransplantation are performed using primates (e.g., baboons, and smaller monkeys). Transmission of diseases, which can be transmitted from animals to humans under natural conditions (zoonoses) as well as hyper-acute rejection remains major concerns in xenotransplantation. Hepatocellular transplantation is used either to temporarily or permanently replace the diseased liver. Hepatocytes are seeded onto biodegradable polymer that serves as a temporary extra-cellular matrix and to induce vascular in-growth. The seeded polymer is then implanted into a vascular rich area, such as the mesentery of the small intestine. Other techniques including direct injection into the spleen or liver. A bioartificial liver is designed to treat liver disease in the manner similar to a dialysis machine treats renal disease. Investigators use porcine hepatocytes or a transformed line of hepatocytes housed in a bioreactor allowing plasma from patients with liver failure to perfuse through it. It can be used either as a bridge to liver transplantation or to allow recovery of the native liver.

**Everolimus for Prevention of Organ Rejection:**

National Institute for Health and Care Excellence (NICE)’s clinical practice guideline on “Everolimus for preventing organ rejection in liver transplantation” (2015) stated that “Everolimus is not recommended within its marketing authorisation for preventing organ rejection in people having a liver transplant”.

An UpToDate review on “Liver transplantation in adults: Long-term management of transplant recipients” (Gaglio and Cotler, 2016) states that “Everolimus may be another alternative, though its role in the management of patients following liver transplantation has yet to be established”. Furthermore, UpToDate reviews on “Treatment of acute cellular rejection in liver transplantation” (Cotler, 2016) and “” ( ) do not mention everolimus as a management option.

**Peri-Operative Immuno-Nutrition:**

Lei and colleagues (2015) stated that no consensus has been reached concerning the effects of peri-operative immuno-
nutrition in patients undergoing liver transplantation. These researchers conducted a meta-analysis to evaluate the effects of peri-operative immuno-nutrition on clinical outcomes and liver function in patients undergoing liver transplantation. The PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and google scholar were searched to identify all available RCTs that compared peri-operative immuno-nutrition support (arginine, glutamine, ribonucleic acids, and ω-3 polyunsaturated fatty acids) with standard nutrition. The data analysis was performed using Revman 5.2 software. A total of 7 RCTs involving 501 patients were included. Peri-operative immuno-nutrition significantly reduced the risk of infectious complications (RR: 0.51; 95 % CI: 0.27 to 0.98, p = 0.04) and shortened the post-operative hospital stay [weighted mean difference (WMD): -3.89; 95 % CI: -7.42 to -0.36; p = 0.03]. Furthermore, peri-operative immuno-nutrition improved liver function by decreasing the levels of aspartate aminotransferase (AST) in the blood (WMD: -25.4; 95 % CI: -39.9 to -10.9, p = 0.0006). However, these investigators did not find statistically significant differences in serum alanine aminotransferase (ALT), total bilirubin (TB) and direct bilirubin (DB) levels. There were no statistically significant differences in mortality and rejection reaction. The authors concluded that peri-operative nutrition support adding immuno-nutrients like arginine, glutamine, ribonucleic acids, and ω-3 polyunsaturated fatty acids may improve outcomes in patients undergoing liver transplantation. Moreover, they stated that due to the limited sample size of the included trials, further large-scale and rigorously designed RCTs are needed to confirm these preliminary findings.

**Peri-Operative Use of Vasopressin:**

In a meta-analysis, Won and associates (2015) evaluated the effect of peri-operative terlipressin (an analog of vasopressin) on post-operative renal function in patients who have undergone living donor liver transplantation (LDLT) and analyzed the hemodynamic data during transplantation surgery. These investigators assessed the post-operative peak serum creatinine level and changes in the hemodynamic data (e.g., the mean arterial pressure, heart rate, and systemic vascular resistance).
They collected RCTs from PubMed, Embase Drugs and Pharmacology, Cochrane Controlled Trials Register, and Cochrane Database on Systematic Reviews. Analysis was conducted using RevMan 5.2. Data from each trial were pooled and weighted by their mean differences and corresponding 95% CI. A heterogeneity assessment was performed. A total of 3 trials (151 patients) were included. The difference in the mean (95% CI) peak serum creatinine (mg/dL) levels post-operatively was not significant between the intervention and control groups (WMD: -0.27; CI: -0.55 to 0.01; p = 0.06). Terlipressin significantly decreased heart rate during the anhepatic phase (WMD: -6.58; 95% CI: -8.85 to -4.31; p < 0.00001) with a low heterogeneity (I² = 41%) and significantly decreased heart rate during the neohepatic phase (WMD: -9.82; 95% CI: -11.96 to -7.68; p < 0.00001), although the heterogeneity was high (I² > 50%). The authors concluded that an iv infusion of terlipressin peri-operatively for LDLT had no effect on the creatinine values post-operatively. Moreover, they stated that larger RCTs on terlipressin infusions during liver transplantation are needed.

*Molecular Adsorbent Recirculating System (MARS):*

Khuroo and colleagues (2004) stated that molecular adsorbent recirculating system (MARS), a non-cell based device, is an important option for patients with liver failure to give them additional time for recovery or to serve as a "bridge" to transplantation. However, its effect on survival for such patients is not well known. These researchers evaluated the treatment effects of MARS on patients with acute and acute-on-chronic liver failure. The outcomes measure evaluated was survival. They searched Medline (1966 to 2002) and Embase (1974 to 2002) using the terms liver failure, liver support systems, and MARS. The search was extended to the Cochrane Controlled Trials Registry Database, published abstracts from 5 international conferences, Teraklin (the manufacturer of MARS), known contacts, and bibliographies from each full-published report. They included trials published in English and non-English languages. Eligible studies were randomized and non-randomized controlled trials, which compared the treatment effects of MARS with standard medical treatment. Of the 206 articles screened, 4
randomized controlled trials (RCTs) including 67 patients were analyzed; 2 non-randomized trials with 61 patients were used for explorative analysis. The methodology, population, intervention, and outcomes of each selected trial were evaluated by duplicate independent review. Disagreements were resolved by consensus. In the primary meta-analysis, MARS treatment did not appear to reduce mortality significantly compared with standard medical treatment [relative risk (RR), 0.56; 95 % confidence interval (CI): 0.28 to 1.14; p = 0.11]. Only 1 of the 4 randomized trials analyzed showed significant reduction in mortality. Sensitivity analysis of 3 peer-reviewed trials did not reduce mortality significantly with MARS treatment (RR, 0.72; 95 % CI: 0.37 to 1.40; p = 0.33). Subgroup analysis of 2 trials for acute liver failure and another 2 trails for acute-on-chronic liver failure also did not reveal any benefit to survival with MARS treatment. In contrast, explorative analysis of 2 non-randomized trials showed a significant survival benefit with MARS treatment (risk ratio [RR], 0.36; 95 % CI: 0.17 to 0.76; p = 0.007). This was possibly related to bias in the selection of patients in the non-randomized trials. The authors concluded that MARS treatment had no significant survival benefit on patients with liver failure when compared with standard medical therapy. However, these investigators found only a few trials with a small number of patients for the analysis, allowing for the possibility of false negative and erroneous conclusions. They stated that well-conducted randomized trials are strongly recommended to define the role of MARS in the treatment of patients with liver failure.

Vaid and associates (2012) noted that MARS is an artificial liver support system that has been developed for patients with liver failure until the liver regains function or as a bridge to transplantation. These researchers conducted a meta-analysis to examine the effectiveness of this promising therapy. They searched Medline, Embase, and the Cochrane Registry of Controlled Trials databases, and abstracts from the proceedings of several scientific meetings. Patients with acute, acute on chronic, and hyper-acute liver failure were included and these investigators compared MARS with standard medical therapy. Randomized and non-randomized controlled trials were included and Molecular Adsorbent Recirculating System was the
intervention used. They evaluated net change in total bilirubin levels, improvement in hepatic encephalopathy and mortality; 9 RCTs and 1 non-randomized controlled study met criteria and were included. By meta-analysis, MARS resulted in a significant decrease in total bilirubin levels (net change -7.0 mg/dL; 95 % CI: -10.4 to -3.7; p < 0.001) and in an improvement in the West-Haven grade of hepatic encephalopathy (odds ratio [OR] 3.0; 95 % CI: 1.9 to 5.0; p < 0.001). There was no beneficial effect on mortality (OR 0.91; 95 % CI: 0.64 to 1.31; p = 0.62). The limitations of this study included a small sample size, an inability to blind with significant heterogeneity among studies, and variable definitions of liver failure. The authors concluded that the MARS is associated with a significant improvement in total bilirubin levels and hepatic encephalopathy; but has no impact on survival. They stated that large studies are needed to assess the merit of this promising therapy on patient-centered outcomes.

Saliba et al (2013) stated that albumin dialysis with the MARS (Gambro, Lund, Sweden), a non-cell artificial liver support device, may be beneficial in acute liver failure (ALF). In a RCT, these investigators examined if MARS improved survival in ALF. Subjects received conventional treatment (n = 49) or MARS with conventional treatment (n = 53), stratified according to whether paracetamol caused ALF. Outcome measures included 6-month survival and secondary end-points included adverse events. A total of 102 patients (mean age of 40.4 years [SD, 13]) were in the modified intention-to-treat (mITT) population. The per-protocol analysis (49 conventional, 39 MARS) included patients with at least 1 session of MARS of 5 hours or more. Six-month survival was 75.5 % (95 % CI: 60.8 % to 86.2 %) with conventional treatment and 84.9 % (CI: 71.9 % to 92.8 %) with MARS (p = 0.28) in the mITT population and 75.5 % (CI: 60.8 % to 86.2 %) with conventional treatment and 82.9 % (CI: 65.9 % to 91.9 %) with MARS (p = 0.50) in the per-protocol population. In patients with paracetamol-related ALF, the 6-month survival rate was 68.4 % (CI: 43.5 % to 86.4 %) with conventional treatment and 85.0 % (CI: 61.1 % to 96.0 %) with MARS (p = 0.46) in the mITT population; 66 of 102 patients had transplantation (41.0 % among paracetamol-induced ALF; 79.4 % among non-paracetamol-induced ALF) (p < 0.001). Adverse events did not significantly
diﬀer between groups. The authors concluded that this randomized trial of MARS in patients with ALF was unable to provide deﬁnitive safety or eﬀectiveness conclusions because many patients had transplantation before administration of the intervention; ALF not caused by paracetamol was associated with greater 6-month patient survival.

He and co-workers (2015) evaluated the treatment eﬀects of the MARS in patients with ALF and acute-on-chronic liver failure (AOCLF). They searched Medline, Embase, and the Cochrane Controlled Trials Registry database between January 1966 and January 2014. They included RCTs, which compared the treatment eﬀects of MARS with standard medical treatment. Study quality assessed according to Consolidated Standards of Reporting Trials (CONSORT) criteria. The RR was used as the eﬀect-size measure according to a ﬁxed-eﬀects model. The search strategy revealed 72 clinical studies, 10 of which were RCTs that met the criteria and were included; 4 addressed ALF (93 patients) and 6 addressed AOCLF (453 patients). The mean CONSORT score was 15 (range of 10 to 20). By meta-analysis, MARS signiﬁcantly improved survival in ALF (RR 0.61; 95 % CI: 0.38 to 0.97; p = 0.04). There was no signiﬁcant survival beneﬁt in AOCLF (RR 0.88; 95 % CI: 0.74, 1.06; p = 0.16). MARS signiﬁcantly improved survival in patients with ALF, however, there is no evidence that it improved survival in patients with AOCLF. The authors concluded that the present meta-analysis indicated that MARS therapy can improve survival in patients with ALF.

Tsipotis and colleagues (2015) stated that albumin dialysis is the best-studied extra-corporeal non-biologic liver support system as a bridge or destination therapy for patients with liver failure awaiting liver transplantation or recovery of liver function. These researchers performed a systematic review to examine the safety and eﬀectiveness of 3 albumin dialysis systems (MARS, fractionated plasma separation, adsorption and hemodialysis [Prometheus system], and single-pass albumin dialysis) in randomized trials for supportive treatment of liver failure. PubMed, Ovid, EMBASE, Cochrane's Library, and ClinicalTrials.gov were searched. Two authors independently screened citations
and extracted data on patient characteristics, quality of reports, efficacy, and safety end-points. A total of 10 trials (7 of MARS and 3 of Prometheus) were identified (620 patients). By meta-analysis, albumin dialysis achieved a net decrease in serum total bilirubin level relative to standard medical therapy of 8.0 mg/dL (95% CI: -10.6 to -5.4) but not in serum ammonia or bile acids. Albumin dialysis achieved an improvement in hepatic encephalopathy relative to standard medical therapy with a RR of 1.55 (95% CI: 1.16 to 2.08) but had no effect survival with a RR of 0.95 (95% CI: 0.84 to 1.07). Because of inconsistency in the reporting of adverse events, the safety analysis was limited but did not demonstrate major safety concerns. The authors concluded that the use of albumin dialysis as supportive treatment for liver failure is successful at removing albumin-bound molecules, such as bilirubin and at improving hepatic encephalopathy. They stated that additional experience is needed to guide its optimal use and address safety concerns.

In a prospective, randomized, cross-over study, Sponholz et al (2016) compared 2 devices (MARS and single-pass albumin dialysis (SPAD)) with particular focus on reduction of bilirubin levels (primary end-point) and influence on para-clinical and clinical parameters (secondary end-points) associated with liver failure. Patients presenting with liver failure were screened for eligibility and after inclusion were randomly assigned to be started on either conventional MARS or SPAD (with 4 % albumin and a dialysis flow rate of 700 ml/h). Statistical analyses were based on a linear mixed-effects model. A total of 69 cross-over cycles of extra-corporeal albumin dialysis (ECAD) in 32 patients were completed. Both systems significantly reduced plasma bilirubin levels to a similar extent (MARS: median -68 μmol/L, interquartile range [IQR] -107.5 to -33.5, p = 0.001; SPAD: -59 μmol/L, -84.5 to +36.5, p = 0.001). However, bile acids (MARS: -39 μmol/L, -105.6 to -8.3, p < 0.001; SPAD: -9 μmol/L, -36.9 to +11.4, p = 0.131), creatinine (MARS: -24 μmol/L, -46.5 to -8.0, p < 0.001; SPAD: -2 μmol/L, -9.0 to +7.0/L, p = 0.314) and urea (MARS: -0.9 mmol/L, -1.93 to -0.10, p = 0.024; SPAD: -0.1 mmol/L, -1.0 to +0.68, p = 0.523) were reduced and albumin-binding capacity was increased (MARS: +10 %, -0.8 to +20.9 %, p < 0.001; SPAD: +7 %, -7.5 to +15.5 %, p = 0.137) only by MARS. Cytokine
levels of interleukin (IL)-6 and IL-8 and hepatic encephalopathy were altered by neither MARS nor SPAD. The authors concluded that both procedures were safe for temporary extra-corporeal liver support. While in clinical practice routinely assessed plasma bilirubin levels were reduced by both systems, only MARS affected other para-clinical parameters (i.e., serum bile acids, albumin-binding capacity, and creatinine and urea levels).

Soo and associates (2016) noted that in children ALF is a rare but life-threatening condition from which 2/3 do not recover with supportive therapy. Treatment is limited by the availability of liver transplants. Molecular adsorbent recirculating system dialysis is a bridge to transplantation that enhances the chances of survival during the waiting period for a transplant, although it cannot improve survival. Open albumin dialysis (OPAL) is a new mode of albumin dialysis developed to further improve dialysis efficiency. These investigators reported a pediatric case of AOCLF and compared the 2 modes of albumin dialysis, namely, the MARS and OPAL, used to treat this patient's cholestatic pruritus. Removal of total and direct bilirubin, ammonia and bile acids were measured by serial blood tests. There was an increased removal of bile acids with the OPAL mode, whereas the removal of total and direct bilirubin and ammonia was similar in both modes. The patient reported better improvement in pruritus following OPAL compared to dialysis with the MARS. The authors concluded that the OPAL may offer a better solution than the MARS in the treatment of refractory pruritus in liver failure.

An UpToDate review on “Acute liver failure in adults: Management and prognosis” (Goldberg and Chopra, 2017) states that “Artificial hepatic assist devices and hepatocyte transplantation -- Attempts have been made to develop an artificial hepatic assist device for acute liver failure that would operate on the same basic principles as hemodialysis for renal failure. However, developing a machine that performs the functions of the liver is inherently more difficult than developing one that performs the excretory functions of the kidneys because the liver performs a large number of diverse and vital synthetic functions. Results in patients treated with these systems have largely been disappointing and the systems are not widely
available so they are generally not used in the management of patients with acute liver failure. Support systems designed to treat patients with liver failure fall into two main categories, non-cell-based systems, including plasmapheresis, plasma exchange, albumin dialysis, and charcoal-based hemadsorption, and systems that incorporate living hepatocytes or hepatic tissue, also known as bioartificial liver support systems”.

Also, there is a phase II clinical trial on “Molecular Adsorbent Recirculating System (MARS®) in Hypoxic Hepatitis (MARS in HH)”; this study is currently recruiting participants. (Last verified September 2016).  https://clinicaltrials.gov/ct2/show/NCT01690845 (https://clinicaltrials.gov/ct2/show/NCT01690845).

Normothermic Machine Perfusion for Liver Transplantation:

Bral and co-workers (2017) stated that after extensive experimentation, outcomes of a first clinical normothermic machine perfusion of the liver (NMP-L) trial in the United Kingdom demonstrated feasibility and clear safety, with improved liver function compared with standard static cold storage (SCS).

These researchers presented a preliminary single-center North American experience using identical NMP technology. Total of 10 donor liver grafts were procured, 4 (40 %) from donation after circulatory death (DCD), of which 9 were transplanted. One liver did not proceed because of a technical failure with portal cannulation and was discarded. Transplanted NMP grafts were matched 1:3 with transplanted SCS livers. Median NMP was 11.5 hours (range of 3.3 to 22.5 hours) with 1 DCD liver perfused for 22.5 hours. All transplanted livers functioned, and serum transaminases, bilirubin, international normalized ratio, and lactate levels corrected in NMP recipients similarly to controls.

Graft survival at 30 days (primary outcome) was not statistically different between groups on an intent-to-treat basis (p = 0.25). Intensive care and hospital stays were significantly more prolonged in the NMP group. The authors concluded that this preliminary experience demonstrated feasibility as well as potential technical risks of NMP in a North American setting and highlighted a need for larger, randomized studies.
Laing and associates (2017) noted that NMP-L is a novel technology recently introduced into the practice of liver transplantation. These researchers discussed benefits of normothermic perfusion over conventional SCS and summarized recent publications in this area. The first clinical trials have demonstrated both safety and feasibility of NMP-L. They have shown that machine perfusion can entirely replace cold storage or be commenced following a period of cold ischemia. The technology currently allows transplant teams to extend the period of organ preservation for up to 24 hours. Results from the first RCT comparing NMP-L with SCS will be available soon. One major advantage of NMP-L technology over other parallel technologies is the potential to assess liver function during NMP-L. Several case series have suggested parameters usable for liver viability testing during NMP-L including bile production and clearance of lactic acidosis. NMP-L allows viability testing of high-risk livers. It has shown the potential to increase utilization of donor organs and improve transplant procedure logistics. The authors concluded that NMP-L is likely to become an important technology that will improve organ preservation as well as have the potential to improve utilization of extended criteria donor livers.

Ceresa and colleagues (2017) stated that preservation of the liver via NMP is rapidly becoming an area of great academic and clinical interest. These investigators described the benefits and limitations of NMP and where the role for SCS may lie. Clinical studies have recently been published reporting the use of NMP in liver preservation for transplantation. They have described the technology to be well-tolerated and feasible with potentially improved post-transplant outcomes; NMP facilitates extended preservation times as well as the potential to increase organ utilization through viability assessment and regeneration. However, this technology is considerably more costly than cold storage and carries significant logistical challenges. Cold storage remains the gold standard preservation for standard criteria livers with good long-term patient and graft survival. The authors concluded that NMP is an exciting new technological advancement in liver preservation, which is likely to have a positive impact in liver transplantation. However, they stated that
RCTs are needed to justify its inclusion into standard practice and provide evidence to support its effectiveness

**Appendix**

A tool to calculate MELD score is available at the following website: [http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=8](http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=8).

### CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>CPT codes covered if selection criteria are met:</th>
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<tbody>
<tr>
<td>47133</td>
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<td>47146</td>
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**Other CPT codes related to the CPB:**

- **47120 - 47130** Hepatectomy, resection of liver; partial lobectomy; trisegmentectomy; total left lobectomy; or total right lobectomy

**HCPCS codes not covered for indications listed in the CPB:**

- **B4155** Enteral formula, nutritionally incomplete/modular nutrients, includes specific nutrients, carbohydrates (e.g., glucose polymers), proteins/amino acids (e.g., glutamine, arginine), fat (e.g., medium chain triglycerides) or combination, administered through an enteral feeding tube, 100 calories = 1 unit

- **J8561** Everolimus, oral, 0.25 mg

**ICD-10 codes covered if selection criteria are met:**

- **B16.0, B16.2, B18.0 - B18.1, B19.11** Acute hepatitis B with hepatic coma
- **B16.1, B16.9, B19.10** Acute hepatitis B without mention of hepatic coma
- **B17.10** Acute hepatitis C without hepatic coma
- **B17.11** Acute hepatitis C with hepatic coma
- **B18.2** Chronic viral hepatitis C
- **B19.20 - B19.21** Unspecified viral hepatitis C
- **C22.0** Liver cell carcinoma
- **C22.1** Intrahepatic bile duct carcinoma
- **C22.2** Hepatoblastoma [in children]
<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>D37.6</td>
<td>Neoplasm of uncertain behavior of liver, gallbladder and bile ducts [Epithelioid hemangioendotheliomas]</td>
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<td>Disorders of aromatic amino-acid metabolism, disorders of branched-chain amino-acid metabolism and fatty-acid metabolism and other disorders of amino-acid metabolism</td>
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<td>E80.0</td>
<td>Hereditary erythropoietic porphyria [Erythropoietic protoporphyria]</td>
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<td>E83.01</td>
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<td>E83.10, E83.19</td>
<td>Other and unspecified disorders of iron metabolism</td>
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<td>E83.110 - E83.119</td>
<td>Hereditary hemochromatosis</td>
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<td>E85.1</td>
<td>Neuropathic heredofamilial amyloidosis</td>
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<td>I82.0</td>
<td>Budd-Chiari syndrome</td>
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<td>K75.81 - K75.9</td>
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<td>K76.81</td>
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<td>K83.0</td>
<td>Cholangitis [primary sclerosing cholangitis with development of secondary biliary cirrhosis]</td>
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<tr>
<td>K83.1</td>
<td>Obstruction of bile duct</td>
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<tr>
<td>Q44.2</td>
<td>Atresia of bile duct</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:

9. Reding R, de Goyet J, Delbeke I, et al. Pediatric liver transplantation with cadaveric or living related donors: Comparative results in 90 elective recipients of primary


34. Turrion VS, Salas C, Alvira LG, et al. Carcinoid tumour of the


82. National Horizon Scanning Centre (NHSC). MARS: A liver assist device - horizon scanning review. Birmingham, UK:
NHSC; 2003.


103. Elsharkawi M, Staib L, Henne-Bruns D, Mayer J. Complete remission of postransplant lung metastases from


114. Clavien PA, Lesurtel M, Bossuyt PM, et al; OLT for HCC


Amendment to
Aetna Clinical Policy Bulletin Number: 0596 Liver Transplantation

There are no amendments for Medicaid.