Liver Transplant

Policy # 00411  
Original Effective Date: 05/21/2014  
Current Effective Date: 03/15/2017

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 in Background/Overview 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.
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 in Background/Overview 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

**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 hepatocellular carcinoma (HCC) that has extended beyond the liver*

**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 cholangiocarcinoma (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.*

**Background/Overview**
Liver transplantation is currently performed routinely as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS). The severity of illness is determined by the model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) scores.

**Recipients**
The original liver allocation system was based on assignment to Status 1, 2A, 2B, or 3. Status 2A, 2B, and 3 were based on the Child-Turcotte-Pugh score, which included a subjective assessment of symptoms as...
part of the scoring system. In February 2002, Status 2A, 2B, and 3 were replaced with 2 disease severity scales: the MELD and PELD for patients younger than age 12 years scoring systems. In June 2013, OPTN/UNOS published its most recent allocation system, which previously expanded Status1 to Status 1A and 1B in September 2012. Status 1A patients have acute liver failure with a life expectancy of less than 7 days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis and acute Wilson’s disease. Status 1A patients must be recertified as Status 1A every 7 days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease listed as: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute decompensated Wilson’s disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to Status 1A upon age18 but still qualify for pediatric indications.

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

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

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
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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 MELD and PELD scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during the course of 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.

Patients with polycystic disease of the liver do not develop liver failure but may require transplantation due to the anatomic complications of a hugely enlarged liver. The MELD/PELD score may not apply to these cases. One of the following complications should be present:
- Enlargement of liver impinging on respiratory function
- Extremely painful enlargement of liver
- Enlargement of liver significantly compressing and interfering with function of other abdominal organs

Patients with familial amyloid polyneuropathy do not experience liver disease, per se, but develop polyneuropathy and cardiac amyloidosis due to the production of a variant transthyretin molecule by the liver. The MELD/PELD 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.

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 (UCSF) expanded criteria, and UNOS criteria.

**Milan criteria:** a single tumor 5 cm or less in diameter or 2 to 3 tumors 3 cm or less

**UCSF expanded criteria:** a single tumor 6.5 cm or less or up to 3 tumors 4.5 cm or less, and a total tumor size of 8 cm or less

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

Patients with HCC are appropriate candidates for liver transplant only if the disease remains confined to the liver. Therefore, the patient should be periodically monitored while on the waiting list, and if metastatic
disease develops, the patient should be removed from the transplant waiting list. In addition, at the time of transplant, a backup candidate should be scheduled. If locally extensive or metastatic cancer is discovered at the time of exploration prior to hepatectomy, the transplant should be aborted, and the backup candidate scheduled for transplant.

Note that liver transplantation for those with T3 HCC is not prohibited by UNOS guidelines, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at 3-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given a Class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent loco-regional treatment after being automatically approved on initial application or extension. A single Class 5A nodule (greater than 1 cm and less than 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 loco-regional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list.

**Cholangiocarcinoma**

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

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

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

- If cross-sectional imaging studies (computed tomography [CT] scan, ultrasound, magnetic resonance imaging [MRI]) 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.
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.

- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

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

- Should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure
- Should undergo evaluation to assure that they fully understand the procedure and associated risks
- Should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- Should be emotionally related to the recipients
- Must be excluded if the donor is felt or known to be coerced
- Needs to have the ability and willingness to comply with long-term follow-up

**Other Governmental Regulatory Approval**
Centers for Medicare and Medicaid Services (CMS)
Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility which is approved by the CMS 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 June 21, 2012, on review of this national coverage decision for new evidence, Medicare began offering coverage for adult liver transplantation, at Medicare administrative contractor discretion, for extrahepatic unresectable 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 (younger than age 18 years) when performed in a CMS-approved pediatric hospital for extrahepatic biliary atresia or any other form of end-stage liver disease, except that coverage is not provided for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.
Rationale/Source

Overview

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. The most controversial etiologies include viral hepatitis and primary hepatocellular cancer. In particular, 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 indicate 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. 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. Similarly, the long-term outcome in patients with primary hepatocellular malignancies was poor (19%) in the past compared to the overall survival of liver transplant recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or smaller and without extrahepatic spread or macrovascular invasion), has dramatically improved overall survival rates. In a systematic review of liver transplant for HCC in 2012, Maggs et al found 5-year overall survival rates ranged from 65% to 94.7% in reported studies. Nevertheless, transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease, and expansion of patient selection criteria, bridging to transplant or downstaging of disease to qualify for liver transplantation is frequently studied. Liver transplant cannot be considered curative in patients with locally extensive or metastatic liver cancer or in patients with isolated liver metastases with extrahepatic primaries or in CCA.

Living Donor Liver Transplantation Donor 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. Since hepatectomy involves the resection of up to 70% of the total volume of the donor liver, the safety of the donor has been the major concern. For example, the surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia reported the results of their first 40 adult-to-adult LDLTs, performed between June 1998 and October 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 of time. However, in the initial series of 20 patients, 4 of the 5 deaths occurred in recipients who were classified as 2A (see Background/Overview section). In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living-donor transplant. Other case series have reported similar success rates. 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 (NIH) convened a workshop focusing on living-donor liver transplantation. A summary of
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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%. Based on survey results, the workshop reported that donor morbidity was common; 7% required reexploration, 10% had to be rehospitalized, and biliary tract complications occurred in 7%. 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. According to the workshop summary, “At the present time, nearly all centers strive to identify donors who are entirely healthy and at minimal risk during right hepatectomy. As a result, only approximately one third of persons originally interested in becoming a living liver donor complete the evaluation process and are accepted as candidates for this procedure.”

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

In 2000, the American Society of Transplant Surgeons issued the following statement:

Living donor transplantation in children has proven to be safe and effective for both donors and recipients and has helped to make death on the waiting list a less common event. Since its introduction in 1990, many of the technical and ethical issues have been addressed and the procedure is generally applied.

The development of left or right hepatectomy for adult-to-adult LDLT has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult LDLT has been undertaken at a number of centers. While early results appear encouraging, sufficient data are not available to ascertain donor morbidity and mortality rates. There is general consensus that the health and safety of the donor is and must remain central to living organ donation.

Brown et al reported on the results of a survey focusing on adult living-related recipients in the United States. The following statistics were reported:

- The survey encompasses 449 adult-to-adult transplantations.
- Half of the responding programs already had performed at least 1 adult-to-adult living-donor liver transplantation, and 32 of the remaining 41 centers were planning to initiate such surgery.
- 14 centers had performed more than 10 such transplantations, and these centers accounted for 80% of these transplants.
- A total of 45% of those evaluated for living donation subsequently donated a liver lobe; 99% were genetically or emotionally related to the recipient.
- Complications in the donor were more frequent in the centers that performed the fewest living-related donor transplantations.
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

- There was 1 death among the donors, but complications were relatively common, ie, biliary complications in 6% and reoperation in 4.5%.

In 2002, NIH sponsored a conference on living-donor liver transplantation. This report offered the following observations:
- The incidence and type of complications encountered and mortality associated with living-donor liver transplant in both donors and recipients need to be determined and compared with those for patients undergoing cadaveric transplantation.
- The question of whether all U.S. transplant programs should perform this operation or this complex procedure should be limited to only a few select centers needs to be addressed.

Living Donor versus Deceased Donor Liver Transplant Recipient Outcomes
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 hazard ratio (HR) was 1.59 (95% confidence interval [CI], 1.02 to 2.49) compared with deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Further study is needed to determine any differences between living and deceased liver transplantation outcomes.

Human Immunodeficiency Virus (HIV)-Positive Patients
This subgroup of recipients has long been controversial, due to the long-term prognosis for HIV positivity, the impact of immunosuppression on HIV disease, and the interactions of immunosuppressive therapy with antiretroviral therapy in the setting of a transplanted liver. For example, most antiretroviral agents are metabolized through the liver and can cause varying degrees of hepatotoxicity. HIV candidates for liver transplantation are frequently coinfected with hepatitis B or C, and viral coinfection can further exacerbate drug-related hepatotoxicities. Nevertheless, HIV positivity is not an absolute contraindication to liver transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease and the increasing experience with liver transplant in HIV-positive patients. Furthermore, the UNOS states that asymptomatic HIV-positive patients should not necessarily be excluded for candidacy for organ transplantation, stating "A potential candidate for organ transplantation whose test for HIV is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality because of immunosuppressive therapy." In 2001, the Clinical Practice Committee of the American Society of Transplantation proposed that the presence of AIDS [acquired immune deficiency syndrome] could be considered a contraindication to kidney transplant unless the following criteria were present. These criteria may be extrapolated to other organs:
- CD4 count greater than 200 cells/mm³ for more than 6 months
- HIV-1 (ribonucleic acid) RNA undetectable
- On stable antiretroviral therapy more than 3 months
- No other complications from AIDS (eg, opportunistic infection, including aspergillus, tuberculosis, coccidiodes mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm).
- Meeting all other criteria for transplantation.

©2017 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Page 9 of 25
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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

In 2011, Cooper et al conducted a systematic review to evaluate liver transplantation in patients coinfected with HIV and hepatitis. The review 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 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 both HIV and HCV infection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.

HCC Selection Criteria

Patient selection criteria for liver transplantation for HCC have focused mainly on the number and size of tumors. In 1996 Mazzafaro et al identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis. This patient selection criteria became known as the Milan criteria and specifies patients may have either a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or less. An editorial by Llovet noted that the Milan criteria is considered the criterion standard for selecting transplant candidates. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. United Network of Organ Sharing adopted the Milan criteria, combined with 1 additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. Interest in expanding liver transplant selection criteria for HCC and other indications is ongoing. A 2001 paper from the UCSF, proposed expanded criteria to include patients with a single tumor 6.5 cm or less in diameter, 3 or fewer tumors 4.5 cm or less, and a total tumor size of 8 cm or less. It should be noted that either set of criteria can be applied preoperatively (with imaging) or with pathology of the explanted liver at the time of intended transplant. Preoperative staging often underestimates what is seen on surgical pathology. To apply pathologic criteria, a backup candidate must be available in case preoperative staging is inaccurate. Given donor organ scarcity, any expansion of liver transplant selection criteria has the potential to prolong waiting times for all candidates. Important outcomes in assessing expanded criteria include waiting time duration, death, or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence (or related outcomes such as disease-free survival). Survival time can be estimated beginning when the patient is placed on the waiting list, using the intention-to-treat principal, or at the time of transplantation. Llovet stated that 1-year dropout rates for patients meeting Milan criteria are 15% to 30%, and 5-year survival rates not reported by intention-to-treat should be adjusted down by 10% to 15%.
A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see Table 1). The largest series was conducted in 14 centers in France, including an intention-to-treat total of 44 patients based on preoperative imaging at the time of listing and a subset of 39 patients meeting pathologic UCSF criteria. The median waiting time was 4.5 months, shorter than the typical 6 to 12 months in North America. Dropouts comprised 11.4% of total. Postransplant overall patient 5-year survival at 63.6%, was more favorable than the intention-to-treat probability (45.5%) but less favorable than among larger numbers of patients meeting Milan criteria. Similar findings were seen for disease-free survival and cumulative incidence of recurrence. Three centers in Massachusetts included 10 patients beyond pathologic Milan criteria but within UCSF criteria. Two-year survival postransplant was 77.1%, with 2 patients dying and 8 alive after a median of 32 months. A group of 74 patients meeting preoperative Milan criteria had a 2-year survival probability of about 73%, but it is inadvisable to compare different preoperative and pathologic staging criteria. From the series of patients who developed the expanded UCSF criteria, 14 satisfied those criteria on pathology but exceeded the Milan criteria. UCSF investigators did not provide survival duration data for this subgroup, but noted that 2 patients died. A center in Essen, Germany reported on 4 patients. Although the French series suggests that outcomes among patients exceeding Milan criteria and meeting UCSF criteria are worse than for patients meeting Milan criteria, it is unclear whether the latter group still achieves acceptable results. A benchmark of 50% 5-year survival has been established in the liver transplant community, and the French study meets this by postransplant pathologic staging results (63.6%) and falls short by preoperative intention-to-treat results (45.5%).

In their 2008 review, Schwartz et al argue that selection based exclusively on the Milan criteria risks prognostic inaccuracy due to the diagnostic limitations of imaging procedures and the surrogate nature of size and number of tumors. They predict that evolution of allocation policy will involve the following: (1) the development of a reliable prognostic staging system to help with allocation of therapeutic alternatives; (2) new molecular markers that might improve prognostic accuracy; (3) aggressive multimodality neoadjuvant therapy to downstage and limit tumor progression before transplant and possibly provide information about tumor biology based on response to therapy; and (4) prioritization for transplantation should consider response to neoadjuvant therapy, time on waiting list, suitability of alternative donor sources. Two papers describe work on identifying predictors of survival and recurrence of disease. Ioannou et al analyzed UNOS data pre- and postadoption of the MELD allocation system finding a 6-fold increase in recipients with HCC and that survival in the MELD era was similar to survival in patients without HCC. The subgroup of patients with larger (3-5 cm) tumors, serum alpha-fetoprotein level equal to or greater than 455 mg/mL, or a MELD score equal to or greater than 20, however, had poor transplantation survival. A predicting cancer recurrence scoring system was developed by Chan et al based on a retrospective review and analysis of liver transplants at 2 centers to determine factors associated with recurrence of HCC. Of 116 patients with findings of HCC in their explanted livers, 12 developed recurrent HCC. Four independent significant explant factors were identified by stepwise logistic regression: size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio (OR). The accuracy of the method was confirmed in 2 validation cohorts.
In 2010, Guiteau et al reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4. On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of 1 lesion less than 6 cm, equal to or less than 3 lesions, none greater than 5 cm and total diameter less than 9 cm. Patient allograft and recurrence-free survival at 3 years did not differ significantly between patients meeting Milan criteria versus patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2% and 90.5% and 86.9%, all respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in Region 4 and that similar outcomes may be different in other regions with different waiting times. Additionally, the authors noted that a report from a 2010 national HCC consensus conference on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement. The report addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early-stage HCC on the transplant waiting list in the U.S. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF or other criteria.

Table 1. Outcomes Among Patients With Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>1 Y Probability, %</th>
<th>2 Y</th>
<th>5 Y</th>
<th>Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 centers in Franceb</td>
<td>Overall patient survival</td>
<td>Milan-/UCSF+</td>
<td>44</td>
<td>45.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>Milan+</td>
<td>20.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>Milan-/UCSF+</td>
<td>27.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posttransplant, pathologic (p)</td>
<td>Milan+</td>
<td>60.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall patient survival</td>
<td>Milan-/UCSF+</td>
<td>47.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>pMilan+</td>
<td>70.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>pMilan-/pUCSF+</td>
<td>63.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posttransplant, pathologic (p)</td>
<td>pMilan+</td>
<td>9.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall patient survival</td>
<td>pMilan-/pUCSF+</td>
<td>16.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>pMilan+</td>
<td>70.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>pMilan-/pUCSF+</td>
<td>62.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 centers in Massachusettsb</td>
<td>pMilan-/pUCSF+</td>
<td>74</td>
<td>50.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milan-/UCSF+ median waiting time, 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)</td>
<td>74</td>
<td>50.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCSF</td>
<td>pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant</td>
<td>46</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotiropoulos et al (2006)c</td>
<td>Posttransplant overall patient survival</td>
<td>Milan-/UCSF+</td>
<td>91</td>
<td>81</td>
<td></td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>Essen, Germanyc</td>
<td>pMilan-/pUCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo</td>
<td>46</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

UCSF: University of California, San Francisco; Y: year.
a Milan+: meeting Milan criteria; Milan-/UCSF+: exceeding Milan criteria/meeting UCSF criteria.
b Milan+: meeting preoperative Milan criteria.
c Unclear if criteria preoperative or pathologic.

Liver Transplantation Versus Liver Resection for Hepatocellular Carcinoma

Liver transplantation is the criterion standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A. Additionally, current UNOS criteria indicate a liver transplant candidate must not be eligible for resection. However, the best treatment approach for early HCC in well-compensated livers is controversial. In 2013, Zheng et al reported on a meta-analysis of 62 cohort studies (n = 10,170 total patients) comparing liver transplantation to 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 over resection (OR = 1.47; 95% CI, 1.18 to 1.84; p < 0.001; OR = 1.77; 95% CI, 1.45 to 2.16; p < 0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than in liver resection patients at 1, 3, and 5 years, all respectively (p < 0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR = 0.20; 95% CI, 0.15 to 0.28; p < 0.001). While liver transplantation outcomes appear favorable compared to liver resection, a shortage of donor organs may necessitate liver resection as an alternative to liver transplantation.

In patients who have a recurrence of HCC after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection, chemotherapy, or other local therapies such as radiofrequency ablation, transarterial chemoembolization, percutaneous ethanol ablation, or cryoablation.

Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared with primary transplant. In a 2013 meta-analysis of 14 nonrandomized comparative studies by Zhu et al, (n = 1272 for primary transplant and n = 236 for salvage), overall survival at 1, 3, and 5 years and disease-free survival at 1 and 3 years was not significantly different between groups. Disease-free survival, however, was significantly lower at 5 years in salvage liver transplantation compared with primary transplantation (OR = 0.62; 95% CI, 0.42 to 0.92; p = 0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria, but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting salvage liver transplantation may be a viable option in these patients.

In a 2012 meta-analysis, Li et al, compared primary liver transplantation to salvage liver transplantation (liver transplantation after liver resection) for HCC. Included in the meta-analysis were 11 case-controlled or cohort studies totaling 872 primary liver transplants and 141 salvage liver transplants.

Overall survival and disease-free survival rates between primary liver transplantation and salvage liver transplantation were not statistically significant at 1, 3, and 5 years (p > 0.05). Survival rates of patients who exceeded the Milan criteria at 1, 3, and 5 years were also not significantly different between the 2 groups (1-year OR = 0.26; 95% CI, 0.01 to 4.94; p = 0.37; 3-year OR = 0.41; 95% CI, 0.01 to 24.54; p = 0.67; 5-year OR = 0.55; 95% CI, 0.07 to 4.48; p = 0.57).
Liver Transplant
Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

In 2013, Chan et al systematically reviewed 16 nonrandomized studies (n = 319) on salvage liver transplantation after primary hepatic resection for HCC. The authors found that overall and disease-free survival outcomes with salvage liver transplantation were similar to reported primary liver transplantation outcomes. The median overall survival for salvage liver transplantation patients was 89%, 80% and 62% at 1, 3, and 5 years, respectively. Disease-free survival was 86%, 68% and 67% at 1, 3, and 5 years, respectively. Salvage liver transplantation studies had median overall survival rates of 62% (range, 41%-89%) compared with a range of 61% to 80% in the literature for primary liver transplantation. Median disease-free survival rates for salvage liver transplantation were 67% (range, 29%-100%) compared with a range of 58% to 89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. The UNOS criteria indicate liver transplant candidates with HCC who subsequently undergo tumor resection must be prospectively reviewed by a regional review board for the extension application.

Nonalcoholic Steatohepatitis
Liver transplantation is a treatment option for patients with NASH who progress to liver cirrhosis and failure. In a 2013 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 = 0.21; 95% CI, 0.05 to 0.89; p = 0.03). However, NASH liver transplant patients had a greater risk of death related to cardiovascular disease (OR = 1.65; 95% CI, 1.01 to 2.70; p = 0.05) and sepsis (OR = 1.71; 95% CI, 1.17 to 2.50; p = 0.006) than non-NASH liver transplant patients.

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

In 2012, Gu et al reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for CCA. Overall 1-, 3-, and 5-year pooled survival rates from 605 study patients were 0.73 (95% CI, 0.65 to 0.80), 0.42 (95% CI, 0.33 to 0.51), and 0.39 (95% CI, 0.28 to 0.51), respectively. When patients received adjuvant therapies preoperatively, 1-, 3-, and 5-year pooled survival rates improved and were 0.83 (95% CI, 0.57 to 0.98), 0.57 (95% CI, 0.18 to 0.92), and 0.65 (95% CI, 0.40 to 0.87), respectively.

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. Intent-to-treat survival (after a loss of 71 patients before liver transplantation) was 68% at 2 years and 53% at 5 years, and recurrence-free survival rates posttransplant were 78% at 2 years and 65% at 5 years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy (p < 0.001).

The European Liver Transplant Registry was cited by a review article. Among 186 patients with intrahepatic CCA, 1-year survival was 58%, and 5-year survival was 29%. In 169 patients with extrahepatic CCA, the
probabilities were 63% and 29%, respectively. The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic CCA, finding a 1-year survival of 72% and a 5-year rate of 23%. The 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% in the 2 groups, respectively.

With Table 2 displaying all values discussed in this paragraph, among the individual centers, the Mayo Clinic in Minnesota has the most experience and most favorable results. Between 1993 and 2006, 65 patients underwent liver transplantation for unresectable perihilar CCA or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and 5-year survival was 76%. The University of California, Los Angeles (UCLA)/Cedars-Sinai, reported on 25 cases of both intrahepatic and extrahepatic CCA. One-year survival was 71% and 3-year survival was 35%. The University of Pittsburgh found 1-year survival of 70% and 5-year survival of 18% among 20 patients with intrahepatic CCA. A German study of 24 patients reported the poorest results. In 2011, Friman et al reported on 53 patients who received liver transplants for CCA during the period of 1984-2005, in Norway, Sweden, and Finland. The 5-year survival rate was 25% overall, 36% in patients with Tumor Node Metastases (TNM) stage equal to or less than 2, and 10% in patients with TNM greater than 2. On further analysis using only data from those patients transplanted after 1995, the 5-year survival rate increased to 38% versus 0% for those transplanted before 1995. Additionally, the 5-year survival rate increased to 58% in those patients transplanted after 1995 with TNM stage equal to or less than 2 and a CA-19-9 equal to or less than 100. The authors suggest transplantation may have acceptable outcomes in select patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Y</td>
<td>2 Y</td>
<td>3 Y</td>
</tr>
<tr>
<td>Pascher et al (2003) review European Liver Transplant Registry</td>
<td>Overall patient survival</td>
<td>IH-CCA</td>
<td>186</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral CCA</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crude recurrence rate, EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative recurrence</td>
<td>38</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Crude recurrence rate, 11/65 (17%); median onset, 22 mo (7-65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimoda et al (2001) UCLA/Cedars-Sinai, Los Angeles, CA, 1984-2000⁷</td>
<td>Overall patient survival</td>
<td>All</td>
<td>25</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>IH-CCA</td>
<td>16</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>EH-CCA</td>
<td>9</td>
<td>86</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>25</td>
<td>67</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>IH-CCA</td>
<td>16</td>
<td>70</td>
</tr>
</tbody>
</table>
Liver Transplant

Policy #  00411
Original Effective Date:  05/21/2014
Current Effective Date:  03/15/2017

Some articles have reported recurrence data using survival analysis techniques. In a series of 38 patients from the Mayo Clinic, cumulative recurrence was 0% at 1 year, 5% at 3 years, and 13% at 5 years. The series of 20 patients from the University of Pittsburgh experienced 67% 1-year tumor-free survival and a 31% 5-year rate. The multicenter Spanish series reported crude recurrence rates of 53% and 36% for extrahepatic and intrahepatic CCA, respectively. The German center at Hannover found a crude recurrence rate of 63%.

Mayo Clinic has reported promising results after liver transplantation for CCA. Five-year patient survival among 65 patients who received neoadjuvant radiochemotherapy was 76%. No other center or group of centers reported 5-year survival above 30%. The Mayo Clinic found a 5-year cumulative recurrence rate of 13% among 38 patients and additional recurrence data are quite limited. While a single center’s results are encouraging, it is important to see if other centers can produce similar findings before forming conclusions about outcomes after liver transplantation for CCA.

In a 2008 review, Heimbach considers the published outcomes of the combined protocol in the context of data on outcomes for surgical resection and concludes that outcomes of neoadjuvant chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar CCA, which is unresectable, or arising in the setting of primary sclerosing cholangitis are comparable to transplantation for patients with HCC and other chronic liver diseases and superior to resection. The author describes intraoperative challenges attributable to the neoadjuvant therapy including severe inflammatory changes and dense fibrosis and suggests that key principles to be considered by centers considering use of the combined protocol include a multidisciplinary approach, pretransplant staging, inclusion of only patients without lymph node metastasis, replacement of irradiated vessels (when possible), and monitoring for postoperative vascular complications. Wu et al describe an extensive surgical procedure combined with radiotherapy. They retrospectively review their experience with surveillance and early detection of CCA and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of

### Study Outcome Group n Probability, %

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor-free survival</td>
<td>IH-CCA</td>
<td>20</td>
<td>67 31</td>
</tr>
<tr>
<td></td>
<td>Crude recurrence rate, 15/24 (63%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor stage &gt;2</td>
<td>TNM stage &gt;2</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Tumor stage ≤2</td>
<td>TNM stage ≤2</td>
<td>32</td>
<td>36</td>
</tr>
</tbody>
</table>

CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic; UCLA: University of California, Los Angeles; Y: year.

a Unresectable CCA, cholangiohepatoma; incidental median follow-up, 23 mo (<1-96).

b Hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental.

c Aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis; mean follow-up, 32 mo (2 d to 13 y).

d IH or EH CCA; median follow-up, 22.3 mo.

e Unresectable CCA.
patients with early-stage CCA complicating primary sclerosing cholangitis. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with CCA were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. Cholangiocarcinoma was detected in 8 of the 42 patients followed up according to the surveillance protocol between 1988 and 2001, and 6 patients underwent OLT-Whipple. One died at 55 months after transplant of an unrelated cause without tumor recurrence, and 5 are without recurrence at 5.7 to 10.1 years.

Hepatitis C
Mukherjee and Sorrell, reviewing controversies in liver transplantation for hepatitis C, indicate 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 list the following factors associated with poor outcomes in liver transplantation for recurrent HCV: high HCV-RNA level pretransplant, non-Caucasian ethnicity, advanced donor age, T cell-depleting therapies, inappropriate treatment of Banff A1 acute cellular rejection (ACR) with steroid boluses, cytomegalovirus disease, and year of transplantation (worse with recent transplants). They cite the International Liver Transplantation Society Consensus on Retransplantation, which states that the following are associated with worse outcomes of retransplantation: total bilirubin level greater than 10mg/dL, creatinine level greater than 2 mg/dL, age greater than 55 years, development of cirrhosis in the first posttransplant year, and donor age greater than 40 years.

As noted above, Terrault et al reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HIV and HCV infection (n = 89), patients with only HCV (n = 235), and all transplant patients age 65 and older. Hepatitis C virus 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%). While HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.

Metastatic Neuroendocrine Tumors
Neuroendocrine tumors are relatively rare neoplasms that are generally slow-growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In 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.

In 2014, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin.52 A total of 706 patients were included in the studies reviewed. Reported overall 5-year survival rates ranged from 0 to 100%, while 5-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the 5-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after liver transplantation were reported in most studies.
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

In 2011 Mathe et al conducted a systematic review of the literature to evaluate patient survival after liver transplant for pancreatic NETs. Data from 89 transplanted patients from 20 clinical studies were included in the review. Sixty-nine patients had primary endocrine pancreatic tumors, 9 patients were carcinoids, and 11 patients were not further classified. Survival rates at 1, 3, and 5 years were 71%, 55%, and 44%, respectively. The mean calculated survival rate was 54.45 (6.31) months, and the median calculated survival rate was 41 months (95% CI, 22 to 76 months). While there may be centers that perform liver transplantation on select patients with NETs, further studies are needed to determine appropriate selection criteria. The quality of available studies is currently limited by their retrospective nature and heterogeneous populations.

Pediatric Hepatoblastoma
Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, often tumors are not discovered until they are unresectable. In cases of unresectable tumors, liver transplantation with pre- and/or postchemotherapy is a treatment option with reports of good outcomes and high rates of survival. The UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation. In 2011, Barrena et al reported on 15 children with hepatoblastoma requiring liver transplantation. Overall survival after liver transplant was 93.3% (6.4%) at 1, 5, and 10 years. In 2010, Malek et al reported on liver transplantation results for 27 patients with primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007. Tumor recurrence occurred in 1 patient after liver transplantation, and overall survival was 93%. In 2008 Browne et al reported on 14 hepatoblastoma patients treated with liver transplantation. Mean follow-up was 46 months, with overall survival in 10 of 14 patients (71%). Tumor recurrence caused all 4 deaths. In the 10 patients receiving primary liver transplantation, 9 survived while only 1 of 4 patients transplanted after primary resection survived (90% vs 25%, p = 0.02). While studies on liver transplantation for pediatric hepatoblastoma are limited, 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. Therefore, liver transplantation for nonmetastatic pediatric hepatoblastoma may be considered medically necessary.

Retransplantation
In 2012, Bellido et al reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data. Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent versus 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%), which were mostly related to chronic rejection. In 2011, Remiszewski et al examined factors influencing survival outcomes in 43 liver retransplantation patients. When compared to 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, in 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 age of recipient, MELD score greater than 27, more than 1 prior liver transplant, need for mechanical ventilation, serum albumin of less than 2.5 g/dL, donor age older than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful in patient selection.

Ongoing Clinical Trials
An online search of ClinicalTrials.gov on November 19, 2014, identified many ongoing clinical trials on liver transplant. Study (NCT000743860 is a multi-institutional prospective study of liver and kidney transplantation in HIV-positive recipients). This study has been completed; results have not been published. The enrollment was 150 kidney transplant recipients and 125 liver transplant recipients.

Washington State University is conducting a prospective registry study of neoadjuvant chemoradiation in conjunction with liver transplantation for cholangiocarcinoma (NCT00301379). There is an estimated enrollment of 20 and an estimated completion date of November 2015.

A study on liver transplantation for hilar cholangiocarcinoma began in March 2012 in Italy (NCT01549795). This study will enroll 33 patients, is still recruiting and had a primary completion date of July 2013. Status of this study is unknown, last verified in July 2012.

Liver transplantation for metastatic NET is being evaluated in a German study (NCT 01201096). In this observational study, patients will receive neoadjuvant peptide receptor-mediated radiotherapy with 177 lutetium about 9 months prior to liver transplantation. This study is expected to enroll 50 patients and is scheduled for completion in September 2018. This study was last verified in September 2010.

A study on liver transplantation after downstaging HCC exceeding the Milan Criteria is ongoing in Italy (NCT01387503). This study is evaluating 260 patients and is expected to be completed in January 2014. The status of this study is unknown, last verified in June 2011.

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

2012
In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review. There was consensus of agreement by the reviewers that liver transplantation may be medically necessary for end-stage liver failure due to irreversibly damaged livers from various disease states such as those listed in the above policy statement. There was also consensus of agreement by the reviewers that liver retransplantation is appropriate in patients with acute or chronic liver failure such as primary graft nonfunction, ischemic type biliary injury after donation after cardiac death,
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

hepatic artery thrombosis, chronic rejection or recurrent diseases such as primary sclerosing cholangitis (PSC), autoimmune hepatitis, and hepatitis C resulting in end-stage liver failure. There was general support for the use of liver transplantation for the treatment of CCA for patients who meet strict eligibility criteria. In general, there was not support for the use of liver transplantation for NET metastatic to the liver.

Summary

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and thus, may be considered medically necessary for the above indications listed in the policy statement and in those otherwise meeting UNOS criteria. Liver transplantation is investigational in patients in whom the procedure is expected to be futile due to comorbid disease or in whom posttransplantation care is expected to significantly worsen comorbid conditions. Case series and case-control data indicate that HIV-infection is not an absolute contraindication to liver transplant; for patients who meet selection criteria, these studies have demonstrated patient and graft survival rates are similar to those in the general population of kidney transplant recipients.

Recent literature continues to address expanded criteria for transplantation for HCC, predictors of recurrence, the role of neoadjuvant therapy in patients with HCC, expanded donor criteria, transplantation and retransplantation for hepatitis C, and living donor transplantation. Further study is needed before liver transplant selection criteria can be expanded for HCC. Additionally, further study is needed to address salvage liver transplantation for HCC recurrence after primary liver resection.

Liver transplantation for hilar CCA is performed at some transplant centers, and long-term survival has been reported in select patients with unresectable disease. For metastatic NET, cure of disease is not achieved, and 5-year survival is generally not high. However, there have been reports of survival benefit in patients receiving liver transplantation for unresectable neuroendocrine tumor metastasis confined to the liver. Based on survival data and clinical vetting input, transplantation in patients with hilar CCA who meet strict eligibility criteria may be considered medically necessary; transplantation for NET metastatic to the liver is considered investigational.

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. Therefore, liver transplantation for nonmetastatic pediatric hepatoblastoma may be considered medically necessary.

Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for an original liver transplantation are met for retransplantation. While some evidence suggests outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. There was support from clinical vetting for retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent nonneoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

References

Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

Liver Transplant Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017


Policy History
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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 “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.)” requirement.
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.

Next Scheduled Review Date: 03/2018

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 2016 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

©2017 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147, 47399</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
</tbody>
</table>

ICD-10 Diagnosis

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>A52.15</td>
<td>B15.0</td>
</tr>
<tr>
<td>B17.10-B17.11</td>
<td>B17.8-B17.9</td>
</tr>
<tr>
<td>B19.9</td>
<td>B25.1</td>
</tr>
<tr>
<td>D64.0-D64.3</td>
<td>D81.810</td>
</tr>
<tr>
<td>E70.21-E70.29</td>
<td>E70.30</td>
</tr>
<tr>
<td>E70.330-E70.339</td>
<td>E70.039</td>
</tr>
<tr>
<td>E70.5</td>
<td>E70.8-E70.9</td>
</tr>
<tr>
<td>E71.118</td>
<td>E71.120-E71.121</td>
</tr>
<tr>
<td>E71.2</td>
<td>E71.30</td>
</tr>
<tr>
<td>E72.20-E72.29</td>
<td>E72.3-E72.4</td>
</tr>
<tr>
<td>E73.0-E73.9</td>
<td>E74.00-E74.39</td>
</tr>
<tr>
<td>E75.21-E75.22</td>
<td>E75.240-E75.249</td>
</tr>
<tr>
<td>E77.0-E77.9</td>
<td>E78.0-E78.6</td>
</tr>
<tr>
<td>E78.9</td>
<td>E80.0-E80.1</td>
</tr>
<tr>
<td>E85.0-E85.9</td>
<td>E88.1-E88.2</td>
</tr>
<tr>
<td>G63</td>
<td>G65.0-G65.2</td>
</tr>
<tr>
<td>G82.0</td>
<td>G87.9</td>
</tr>
<tr>
<td>K71.10-K71.11</td>
<td>K71.2-K71.4</td>
</tr>
<tr>
<td>K74.3-K74.5</td>
<td>K75.2-K75.3</td>
</tr>
<tr>
<td>K75.9</td>
<td>K76.0</td>
</tr>
<tr>
<td>K77</td>
<td>K80.30-K80.37</td>
</tr>
<tr>
<td>K83.8</td>
<td>K87</td>
</tr>
<tr>
<td>S31.609A</td>
<td>S36.112A-S36.119A</td>
</tr>
</tbody>
</table>

*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. 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);
Liver Transplant

Policy # 00411
Original Effective Date: 05/21/2014
Current Effective Date: 03/15/2017

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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.