Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Liver Transplant

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Policy

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

When Policy Topic is covered

A liver transplant, using a cadaver or living donor, is **medically necessary** for carefully selected patients with end-stage liver failure due to irreversibly damaged livers.

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

A. Hepatocellular diseases
- Alcoholic cirrhosis
- Viral hepatitis (either A, B, C, or non-A, non-B)
- Autoimmune hepatitis
- Alpha-1 antitrypsin deficiency
- Hemochromatosis
- Non-alcoholic steatohepatitis
- Protoporphyria
- Wilson's disease
- Cryptogenic cirrhosis
- Epithelioid hemangioendothelioma

B. Cholestatic liver diseases
- Primary biliary cirrhosis
- Primary sclerosing cholangitis with development of secondary biliary cirrhosis
- Biliary atresia

C. Vascular disease
- Budd-Chiari syndrome

D. Primary hepatocellular carcinoma

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
- Familial amyloid polyneuropathy

Liver transplantation may be considered **medically necessary** in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.

Liver transplantation may be considered **medically necessary** in patients with unresectable hilar cholangiocarcinoma (see Considerations for patient selection criteria).

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

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Liver *retransplantation* may be considered **medically necessary** in patients with:

- primary graft non-function
- hepatic artery thrombosis
- chronic rejection
- ischemic type biliary lesions after donation after cardiac death
- recurrent non-neoplastic disease causing late graft failure

When Policy Topic is not covered

Liver transplantation is considered **investigational** in the following situations:

- Patients with intrahepatic cholangiocarcinoma
- Patients with neuroendocrine tumors metastatic to the liver

Liver transplantation is considered **not medically necessary** in the following situations:

- Patients with hepatocellular carcinoma that has extended beyond the liver
- Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.)

Liver transplantation is considered **investigational** in all other situations not described above.

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Considerations

General

Potential contraindications subject to the judgment of the transplant center:

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

Liver Specific

The 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 score may apply to these cases. Candidacy for liver transplant is an individual consideration based on the morbidity of the polyneuropathy. Many patients may not be candidates for liver transplant alone due to coexisting cardiac disease.

Patients with hepatocellular carcinoma 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.

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

Cholangiocarcinoma
(Available online at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf)
According to the OPTN policy on liver allocation, candidates with cholangiocarcinoma (CCA) meeting the following criteria will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase every 3 months:

- Centers must submit a written protocol for patient care to the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee.
- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and one of the following: carbohydrate antigen 19-9 100 U/mL, or and biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (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. 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.

Coverage will **not** be provided for:

- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient.
- An artificial organ

Liver transplants should be considered for coverage under the Transplant Benefit:

Transplant Benefit

The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (**Note:** The member's benefits must be verified with regard to the **potential** donor who does not turn out to be the **actual** donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:

- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Candidates for all liver transplants should meet the following criteria:

- Adequate cardiopulmonary status
- Absence of active infection
- No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
- Documentation of patient compliance with medical management.

The specific member contract should be reviewed for coverage related to donors and recipients, out of network treatment, drugs and other possible limitations or exclusions.

Clinical trials related to liver transplantation may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: there are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Refer to Clinical Trials - MO in Contracts and Compliance for more information.

Description of Procedure or Service

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.

Background

Recipients

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS). The original liver allocation system was based on assignment to Status 1, 2A, 2B, or 3. Status 2A, 2B, and 3 were based on the Child-Turcotte-Pugh score, which included a subjective assessment of symptoms as part of the scoring system. In February 2002, Status 2A, 2B, and 3 were replaced with 2 disease severity scales: the model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) for patients younger than age 12 years scoring systems. In September 2012, OPTN/UNOS published its most recent allocation system, which expanded Status1 to Status 1A and 1B. (1) 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 non-function, 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 (ages 0-17 years) with chronic liver disease. Following Status 1, donor livers will be prioritized to those with the highest scores on MELD or PELD. With this allocation system, the highest priority for liver transplantation is given to patients receiving the highest number of points. The scoring system for MELD and PELD is a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (i.e., international normalized ratio [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, since 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. (2) Status 7 describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation.

Donors

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, split graft refers to dividing a donor liver into 2 segments that can be used for 2 recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe or the left lateral segment can be used for LDLT. In addition to addressing the problem of

donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

Rationale

This policy was originally created in 1995 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period of December 2012 through December 18, 2013. The following is a summary of the key findings to date.

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%). (6) Recurrence of HCV infection in transplant recipients has been nearly universal, and 10%-20% of patients will develop cirrhosis within 5 years. (7) 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 hepatocellular carcinoma (HCC) in 2012, Maggs et al. found 5-year overall survival rates ranged from 65%-94.7% in reported studies. (8) 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 cholangiocarcinoma. (6)

Living Donor Liver Transplantation Donor Outcomes

Due to the scarcity of donor organs and the success of living donation, living donor liver transplantation has become accepted practice. The living donor undergoes hepatectomy of the right lobe, the left lobe, or the left lateral segment, which is then transplanted into the recipient. 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 living donor liver transplantations, performed between June 1998 and October 1999. (9) There were an equal number of related and unrelated donors. Minor complications occurred in 7 donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, 4 of the 5 deaths occurred in recipients who were classified as 2A (see Description section). In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living-donor transplant. Other case series have reported similar success rates. (10-12) Reports of several donor deaths re-emphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team. (13-15) In December 2000, the National Institutes of Health (NIH) convened a workshop focusing on living-donor liver transplantation. A summary of this workshop was published in 2002. (16) According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2%–0.5%.

Based on survey results, the workshop reported that donor morbidity was common; 7% required re-exploration, 10% had to be re-hospitalized, 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. (16)

In 2000, the American Society of Transplant Surgeons issued the following statement (17):

“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 living donor liver transplantation has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult living donor liver transplantation 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 and colleagues reported on the results of a survey focusing on adult living-related recipients in the United States. (18) The following statistics were reported:

- The survey encompasses 449 adult-to-adult transplantations.
- Half of the responding programs already had performed at least one 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.
- There was 1 death among the donors, but complications were relatively common, i.e., biliary complications in 6% and reoperation in 4.5%.

In 2002, NIH sponsored a conference on living-donor liver transplantation. (10) 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. (19) For disease-free survival after living donor liver transplantation, the combined hazard ratio (HR) was 1.59 (95% confidence interval [CI], 1.02-2.49) compared with deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI, 0.73-1.27). 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.

HIV-Positive Patients
This subgroup of recipients has long been controversial, due to the long-term prognosis for human immunodeficiency virus (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 co-infected with hepatitis B or C, and viral co-infection 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 United Network of Organ Sharing (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.” (20) 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. (21) These criteria may be extrapolated to other organs:

- CD4 count >200 cells/mm-3 for >6 months
- HIV-1 RNA undetectable
- On stable anti-retroviral therapy >3 months
- No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm).
- Meeting all other criteria for transplantation.

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

In 2011, Cooper and colleagues conducted a systematic review to evaluate liver transplantation in patients co-infected with HIV and hepatitis. (22) 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%-87.8%) at 12 months. Patients were 2.89 (95% CI, 1.41-5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared with those with detectable HIV viremia.

Terrault and colleagues 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. (23) Patient and graft survival reductions were significantly associated with only one factor: HIV infection. At 3 years, in the HCV only group, patient and graft survival rates were significantly better at 79% (95% CI, 72%-84%) and 74% (95% CI, 66%-79%), respectively, than the group with both HIV and HCV infection at 60% (95% CI, 47%-71%) and 53% (95% CI, 40%-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.

Hepatocellular Carcinoma Selection Criteria

Patient selection criteria for liver transplantation for hepatocellular carcinoma (HCC has 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. (3) 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 up to 3 tumors ≤3 cm. An editorial by Llovet (4) 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. UNOS adopted the Milan criteria, combined with one 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 University of California, San Francisco (UCSF), (5) proposed expanded criteria to include patients with a single tumor ≤6.5 cm in diameter, 3 or fewer tumors ≤4.5 cm, and a total tumor size of ≤8 cm. 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%– 30%, and 5-year survival rates not reported by intention-to-treat should be adjusted down by 10%–15%.

A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see following table). The largest series was conducted in 14 centers in France, (24) 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 6–12 months in North America. Dropouts comprised 11.4% of total. Post-transplant 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 (25) included 10 patients beyond pathologic Milan criteria but within UCSF criteria. Two-year survival post-transplant 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, (26) 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, (5) and the French study meets this by post-transplant pathologic staging results (63.6%) and falls short by preoperative intention-to-treat results (45.5%).

In their 2008 review, Schwartz and colleagues 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. (27) 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 and colleagues analyzed UNOS data pre- and post-adoption of the

Model for End-stage Liver Disease (MELD) allocation system finding a 6-fold increase in recipients with HCC and that survival in the MELD era was similar to survival in patients without HCC. (28) 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. (29) 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 one 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. The accuracy of the method was confirmed in 2 validation cohorts.

In 2010, Guiteau and colleagues reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4. (30) On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of one 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. (31) 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.

Outcomes Among Patients with Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

Study	Probability (%) Outcome Group n 1yr 2yr 5yr
Decaens et al. 2006 (24) 14 centers in France Meeting Milan criteria (Milan+) Exceeding Milan criteria, meeting UCSF criteria (Milan-/UCSF+)	Intention-to-treat, preoperative Overall patient survival Milan+ 279 60.1 Milan-/UCSF+ 44 45.5 Cumulative incidence of recurrence Milan+ 20.2 Milan-/UCSF+ 27.1 Disease-free survival Milan+ 60.4 Milan-/UCSF+ 47.8 Post-transplant, pathologic (p) Overall patient survival pMilan+ 184 70.4 pMilan-/pUCSF+ 39 63.6 Cumulative incidence of recurrence pMilan+ 9.4 pMilan-p/UCSF+ 16.5 Disease-free survival pMilan+ 7.02 pMilan-/pUCSF+ 62.7 Milan-/UCSF+ median waiting time 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)
Leung et al. 2004 (25) 3 centers in Massachusetts	Post-transplant overall patient survival Milan+ 74 85.9 ~73 50.9 pMilan-/pUCSF+ 10 77.1 2 patients died at 3 and 22 months, 8 patients alive after median 32-mo follow-up (6.6-73.5)

Meeting preoperative Milan criteria (Milan+)	
Yao et al. 2002 (26) UCSF	Post-transplant overall patient survival pMilan+ 46 91 81 72 pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant
Sotiropoulos et al. 2006 (32) Essen, Germany	Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo
Unclear if criteria preoperative or pathologic	

Liver Transplantation versus Liver Resection for Hepatocellular Carcinoma

Liver transplantation is the criterian 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. (33) Additionally; current UNOS criteria indicate a liver transplant candidate must not be eligible for resection. (1) 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. (34) Overall 1-year survival was similar between procedures (odds ratio [OR] =1.08; 95% CI, 0.81- 1.43; p=0.61). However, overall 3- and 5-year survival significantly favored liver transplantation over resection (OR=1.47; 95% CI, 1.18-1.84; p<0.001, and OR=1.77; 95% CI, 1.45-2.16; 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; CI, 0.15-0.28; 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. (1)

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 non-randomized comparative studies by Zhu et al, (n=1272 for primary transplant and n=236 for salvage), (35) 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, 0.42-0.92; 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. (36) 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, 0.01-4.94, p=0.37; 3-year OR=0.41, 95% CI, 0.01-24.54, p=0.67; and 5-year OR=0.55, 95% CI, 0.07-4.48, p=0.57).

In 2013, Chan et al. systematically reviewed 16 non-randomized studies (n=319) on salvage liver transplantation after primary hepatic resection for HCC. (37) 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%-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%-89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. 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 nonalcoholic steatohepatitis (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. (38) 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, 0.05-0.89; p=0.03). However, NASH liver transplant patients had a greater risk of death related to cardiovascular disease (OR=1.65; 95% CI, 1.01-2.70; p=0.05) and sepsis (OR=1.71; 95% CI, 1.17-2.50; p=0.006) than non-NASH liver transplant patients.

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

In 2012, Gu et al. reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma. (39) Overall 1-, 3-, and 5-year pooled survival rates from 605 study patients were 0.73 (95% CI, 0.65-0.80), 0.42 (95% CI, 0.33-0.51), and 0.39 (95% CI, 0.28-0.51), respectively. When patients received adjuvant therapies preoperatively, 1-, 3-, and 5-year pooled survival rates improved and were 0.83 (95% CI, 0.57-0.98), 0.57 (95% CI, 0.18-0.92), and 0.65 (95% CI, 0.40-0.87), respectively.

In 2012, Darwish Murad et al. reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar cholangiocarcinoma followed by liver transplantation. (40) 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 post-transplant were 78% at 2 years and 65% at 5 years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria 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. (41) Among 186 patients with intrahepatic cholangiocarcinoma, 1-year survival was 58%, and 5-year survival was 29%. In 169 patients with extrahepatic cholangiocarcinoma, the probabilities were 63% and 29%, respectively. The Cincinnati Transplant Registry (42) reported on 207 patients with either intrahepatic or extrahepatic cholangiocarcinoma, finding a 1-year survival of 72% and a 5-year rate of 23%. The multicenter Spanish report (43) 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.

Among the individual centers, the Mayo Clinic in Minnesota has the most experience and most favorable results (44, 45). Between 1993 and 2006, 65 patients underwent liver transplantation for unresectable perihilar cholangiocarcinoma or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and 5-year survival was 76%. The University of California, Los Angeles (UCLA)/Cedars-Sinai, (46) reported on 25 cases of both intrahepatic and extrahepatic cholangiocarcinoma. 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 cholangiocarcinoma. (47) A German study of 24 patients reported the poorest results. (48) In 2011, Friman and colleagues reported on 53 patients who received liver transplants for cholangiocarcinoma during the period of 1984-2005, in Norway, Sweden, and Finland. (49) The 5-year survival rate was 25% overall, 36% in patients with TNM stage equal to or less than 2, and 10% in patients with TNM greater than 2. Upon 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.

Outcomes Among Patients with Cholangiocarcinoma

Outcomes Among Patients with Cholangiocarcinoma Study	Probability (%) Outcome Group n 1yr 2yr 3yr 5yr
Pascher et al. 2003, review (41) European Liver Transplant Registry	Overall patient survival IH-CCA 186 58 38 29 EH-CCA 169 63 38 29
Meyer et al. 2000 (42) Cincinnati Transplant Registry unresectable CCA, cholangiohepatoma, incidental median follow-up 23 mo (<1-96)	Overall patient survival IH/EH-CCA 207 72 48 23
Robles et al. 2004 (43) Multiple centers in Spain 03/88-09/01; hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental	Overall patient survival Hilar CCA 36 82 53 30 Peripheral CCA 23 77 65 23 Crude recurrence rate: EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)
Heimbach et al. 2006 (44); Rea et al. 2006 (45) Mayo Clinic, Rochester MN 01/93-01/06, aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis mean follow-up 32 mo (2 d–13 yr)	Overall patient survival Perihilar CCA 65 91 76 Cumulative recurrence 38 0 5 13 Crude recurrence rate: 11/65 (17%) median onset 22 mo (7-65)
Shimoda et al. 2001 (46) UCLA/Cedars-Sinai, Los Angeles, CA 1984-2000; IH or EH CCA median follow-up 22.3 mo	Overall patient survival All 25 71 35 IH-CCA 16 62 39 EH-CCA 9 86 31 Disease-free survival All 25 67 42 IH-CCA 16 70 35 EH-CCA 9 57 57
Casavilla et al. 1997 (47) University of Pittsburgh, PA	Overall patient survival IH-CCA 20 70 29 18 Tumor-free survival 20 67 31 31

1981-1994	
Weimann et al. 2000 (48)	Overall patient survival IH-CCA 24 21 8 4 0
Hannover, Germany	Crude recurrence rate: 15/24 (63%)
1978-1996; unresectable CCA	
Friman et al. 2011 (49)	Actual patient survival All 53 25
Norway, Sweden, and Finland	TNM stage >2 21 10
1984-2005; unresectable CCA	TNM stage ≤2 32 36

CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic

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. (45) The series of 20 patients from the University of Pittsburgh experienced 67% 1-year tumor-free survival and a 31% 5-year rate. (46) The multicenter Spanish series reported crude recurrence rates of 53% and 36% for extrahepatic and intrahepatic cholangiocarcinoma, respectively. (43) The German center at Hannover found a crude recurrence rate of 63%. (48)

Mayo Clinic has reported promising results after liver transplantation for cholangiocarcinoma. 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 cholangiocarcinoma.

In a 2008 review, Heimbach considers the published outcomes of the combined protocol in the context of data on outcomes for surgical resection and concludes that outcomes of neoadjuvant chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar cholangiocarcinoma, which is unresectable, or arising in the setting of primary sclerosing cholangitis are comparable to transplantation for patients with HCC and other chronic liver diseases and superior to resection. (50) 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. (51) They retrospectively review their experience with surveillance and early detection of cholangiocarcinoma and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of patients with early-stage cholangiocarcinoma complicating primary sclerosing cholangitis. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with cholangiocarcinoma 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 5.7–10.1 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. (52) Challenges of treatment post-transplantation 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 >10mg/dL, creatinine level >2 mg/dL, age >55 years, development of cirrhosis in the first post-transplant year, and donor age >40 years.

As noted above, Terrault and colleagues 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. (23) HCV status was not significantly associated with reduced patient and graft survival. In the HCV-only group, patient and graft survival rates were significantly better at 79% (95% CI, 72%-84%) and 74% (95% CI, 66%-79%), respectively, than the group with HIV and HCV at 60% (95% CI, 47%-71%) and 53% (95% CI, 40%-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 (NETs) are relatively rare neoplasms that are generally slow-growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In select patients with non-resectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms. In 2011, Mathe and colleagues conducted a systematic review of the literature to evaluate patient survival after liver transplant for pancreatic NETs. (53) 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, 22–76 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. (54) UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation. (1) In 2011, Barrena et al. reported on 15 children with hepatoblastoma requiring liver transplantation. (55) 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. (56) Tumor recurrence occurred in one 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). (57) While studies on liver transplantation for pediatric hepatoblastoma are limited, case series have demonstrated good outcomes and high rates of long-term survival. Additionally, non-metastatic pediatric hepatoblastoma is included in UNOS criteria for patients eligible for liver transplantation. Therefore, liver transplantation for non-metastatic pediatric hepatoblastoma may be considered medically necessary.

Retransplantation
In 2012, Bellido and colleagues reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data. (58) 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. (59) When compared to primary liver transplanation patients, retransplantation patients had significantly lower 6-year survival rates (80% vs. 58%, respectively; p=0.0001). 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 and colleagues, in 2011, reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation. (60) Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than one 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

A search of online site ClinicalTrials.gov on December 21, 2013 identified many ongoing clinical trials on liver transplant. There is an ongoing multi-institutional prospective study of liver and kidney transplantation in HIV-positive recipients (NCT00074386). This study is no longer recruiting and was expected to be completed in August 2013. The target enrollment was 150 kidney transplant recipients and 125 liver transplant recipients. The goals of the trial are described as follows (20):

Washington State University is conducting a prospective registry study of neoadjuvant chemoradiation in conjunction with liver transplantation for cholangiocarcinoma (NCT00301379). 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.

Liver transplantation for metastatic neuroendocrine tumors 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.

A study on liver transplantation after downstaging hepatocellular carcinoma exceeding the Milan Criteria is ongoing in Italy (NCT01387503). This study is evaluating 260 patients and is expected to be completed in January 2014.

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 non-function, ischemic type biliary injury after donation after cardiac death, 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 cholangiocarcinoma for patients who meet strict eligibility criteria. In general, there was not support for the use of liver transplantation for neuroendocrine tumors 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 United Network of Organ Sharing (UNOS) criteria. Liver transplantation is investigational in patients in whom the procedure is expected to be futile due to comorbid disease or in whom post-transplantation care is expected to significantly worsen comorbid conditions. Case series and case-control data indicate that human immunodeficiency virus (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 hepatocellular carcinoma (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 cholangiocarcinoma is performed at some transplant centers, and long-term survival has been reported in select patients with unresectable disease. For metastatic neuroendocrine tumors, 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 cholangiocarcinoma who meet strict eligibility criteria may be considered medically necessary; transplantation for neuroendocrine tumors 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, non-metastatic pediatric hepatoblastoma is included in UNOS criteria for patients eligible for liver transplantation. Therefore, liver transplantation for non-metastatic 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 non-function, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent non-neoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.

Practice Guidelines and Position Statements
In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for HCC. (61) Consensus criteria for selecting candidates for liver transplantation were developed at the conference. Milan criteria was recommended for use as the benchmark for patient selection, although it is noted the Milan criteria may be modestly expanded based on data from expansion studies that demonstrate outcomes that are comparable to outcomes from studies using the Milan criteria. Candidates for liver transplantation should also have a

predicted survival of 5 years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

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

In 2005, the American Association for the Study of Liver Diseases (AASLD) issued guidelines on evaluating patients for liver transplant. (62) These guidelines state liver transplantation is indicated for acute or chronic liver failure from any cause after all effective medical treatments have been attempted. Furthermore, the AASLD guidelines indicate patients should be assessed by a transplantation center to determine whether liver transplantation is appropriate. While the AASLD guidelines indicate liver transplant may be appropriate in patients with cholangiocarcinoma and metastatic neuroendocrine tumors, these recommendations and many of the recommendations in the AASLD guidelines are based on opinion.

The European Neuroendocrine Society (ENETS) issued consensus guidelines in 2008 for the management of patients with liver metastases from neuroendocrine tumors. (63) The ENETS guidelines indicate, in a “minimal consensus” statement, that liver transplantation may be considered for diffuse unresectable neuroendocrine tumor metastases or when hormonal disturbances that are refractory to medical therapy are life-threatening.

The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers recommends referral to a liver transplant center or bridge therapy for patients with HCC meeting UNOS criteria of a single tumor ≤ 5 cm, or 2-3 tumors ≤ 3 cm with no macrovascular involvement or extrahepatic disease. (33) Patients should be referred to the transplant center before biopsy. In patients meeting UNOS criteria who are ineligible for transplant and in select patients with Child-Pugh Class A or B liver function with tumors that are resectable, NCCN indicates resection is the preferred treatment option or locoregional therapy may be considered. Patients with unresectable HCC should be evaluated for liver transplantation and if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. The NCCN guidelines on hepatobiliary cancers also indicate liver transplant is appropriate in select patients with extrahepatic cholangiocarcinoma, which is unresectable, but biliary and hepatic function is otherwise normal or when underlying chronic liver disease precludes surgery. These are level 2A recommendations based on lower-level evidence and uniform consensus.

Liver transplantation guidelines for non-alcoholic steatohepatitis (NASH) were developed by the Council of the British Transplant Society and approved by the British Society of Gastroenterology, the British Association for the Study of Liver and NHS Blood and Transplant in 2012. These guidelines indicate liver transplantation may be considered for the treatment of NASH cirrhosis with end-stage liver disease or HCC. (64) These guidelines are based primarily on consensus of expert opinion.

Medicare National Coverage

Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility which is approved by the Centers for Medicare and Medicaid Services (CMS) as meeting institutional coverage criteria for liver transplants. (65) 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, upon review of this National Coverage Decision for new evidence, Medicare began offering coverage for adult liver transplantation, at Medicare Administrative Contractor discretion, for extrahepatic unresectable cholangiocarcinoma, liver metastases due to a neuroendocrine tumor and hemangioendothelioma. Adult liver transplantation is excluded for other malignancies.

Pediatric liver transplantation is covered for children (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.

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Billing Coding/Physician Documentation Information

47133 Donor hepatectomy (including cold preservation), from cadaver donor
47135 Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
47136 Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor, any age
47140 Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
47141 Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
47142 Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
47143 Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
47144 Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into 2 partial liver grafts (ie, left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
47145 Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into 2 partial liver grafts (ie, left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
47146 Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
47147 Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/01 New policy. Added to Surgery section
12/1/02 Added cryptogenic cirrhosis as a medically necessary indication, added 2002 scoring system.
12/1/03 No policy statement changes
12/1/04 No policy statement changes. Added new codes for living donor hepatectomy; added to Transplant section;
12/1/05 Removed HIV positivity as an investigational indication.
2/1/06 Policy statement updated to include epithelioid hemangioendothelioma as medically necessary.
4/1/06 Added general criteria to the Considerations section.
12/1/06 No policy statement changes.
12/1/07 No policy statement changes.
12/1/08 No policy statement changes.
12/1/09 No policy statement changes.
12/1/10 No policy statement changes.
12/1/11 Policy statements for medically necessary indications unchanged; neuroendocrine tumor metastases added to investigational statement. Policy statements on hepatocellular carcinoma that has extended beyond the liver and ongoing alcohol and/or drug abuse moved from investigational to not medically necessary. Removed “Patients with an active infection” from the investigational policy statement.
12/1/12 No policy statement changes.

3/1/13	Policy statements revised as follows: non-alcoholic steatohepatitis cirrhosis added to the medically necessary policy statement; a statement added that retransplantation may be considered medically necessary; a statement added that extrahepatic peri-hilar or hilar cholangiocarcinoma may be considered medically necessary. Other intrahepatic or extrahepatic malignancies including non-peri-hilar or non-hilar cholangiocarcinoma and recurrent hepatocellular carcinoma salvage treatment added to the investigational policy statement
3/1/14	Policy statement on polycystic liver disease moved to a separate policy statement. Pediatric non-metastatic hepatoblastoma added as may be medically necessary. Policy statement added that liver transplantation is considered investigational in all other situations not described.
