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 according to length of time on the waiting list and severity of illness criteria developed by 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. Patients are prioritized for transplant according to length of time on the waiting list and severity of illness criteria developed by the United Network of Organ Sharing (UNOS). On February 27, 2002, UNOS eliminated the original liver allocation system, which was based on assignment to Status 1, 2A, 2B, or 3. The new system retains Status 1, which is intended to describe patients with acute liver failure who have a life expectancy of less than 7 days, and Status 7, which describes patients who are temporarily inactive due to intercurrent medical problems. Status 2A, 2B, and 3 were replaced with a new scoring system: model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) for patients younger than age 12 years. 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. MELD and PELD are 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 1 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Aside from Status 1, donor livers will be prioritized...
to those with the highest MELD or PELD number; 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 new MELD/PELD allocation system, patients with higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer. (1)

**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 transplantation of the left lateral segment is now commonly performed between parent and child. Recently, adult-to-adult living-donor transplantation has been investigated, using the right lobe of the liver from a related or unrelated donor. In addition to addressing the problem of donor organ scarcity, living donation allows the procedure to be scheduled electively, shortens the preservation time for the donor liver, and allows time to optimize the recipient’s condition pretransplant.

**II. Policy**

A liver transplant, using a cadaver or living donor, is covered (subject to Administrative Guidelines) 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
   1. Alcoholic cirrhosis
   2. Viral hepatitis (either A, B, C, or non-A, non-B)
   3. Autoimmune hepatitis
   4. Alpha-1 antitrypsin deficiency
   5. Hemochromatosis
   6. Protoporphyria
   7. Wilson’s disease

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

C. Vascular disease
   1. Budd-Chiari syndrome

D. Primary hepatocellular carcinoma

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
1. Polycystic disease of the liver
2. Familial amyloid polyneuropathy

Liver transplantation is not covered for the following patients:

1. Patients with an extrahepatic malignancy including cholangiocarcinoma
2. Patients with neuroendocrine tumors metastatic to the liver
3. Patients with hepatocellular carcinoma that has extended beyond the liver
4. 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.)

Policy Guidelines:

General

Potential contraindications subject to the judgment of the transplant center:

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

In addition, HMSA has the following requirements:

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

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 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:

1. Enlargement of liver impinging on respiratory function
2. Extremely painful enlargement of liver
3. 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-Related Adult-to-Adult Transplant

Donor morbidity and mortality are prime concerns in adult donors undergoing right donor hepatectomy as part of an adult-to-adult living-donor liver transplantation. Right 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:

1. 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
2. Should undergo evaluation to assure that they fully understand the procedure and associated risks
3. Should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
4. Should be emotionally related to the recipients
5. Must be excluded if the donor is felt or known to be coerced
6. Needs to have the ability and willingness to comply with long-term follow-up

III. Administrative Guidelines

Precertification is required for this service as well as for any transplant evaluations. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>47133</td>
<td>Donor hepatectomy (including cold preservation); from cadaver donor</td>
</tr>
<tr>
<td>47135</td>
<td>Liver allotransplantation; orthotopic; partial or whole, from cadaver or</td>
</tr>
</tbody>
</table>
Liver Transplant

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>47136</td>
<td>living donor, any age</td>
</tr>
<tr>
<td>47140-47142</td>
<td>heterotopic, partial or whole, from cadaver or living donor, any age</td>
</tr>
<tr>
<td>47143-47145</td>
<td>Donor hepatectomy from living donor, code range</td>
</tr>
<tr>
<td>47146-47147</td>
<td>Backbench standard preparation of cadaver liver graft, code range</td>
</tr>
<tr>
<td></td>
<td>Backbench reconstruction of cadaver or living donor liver graft, code range</td>
</tr>
</tbody>
</table>

**IV. Rationale**

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) has been a controversial indication 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%). Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rate of 45% is significant in a group of patients who have no other treatment options. Similarly, the long-term outcome in patients with primary hepatocellular malignancies (19%) is poor compared to the overall survival of liver transplant recipients. Nevertheless, transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease. However, 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. (2)

Due to the scarcity of donor organs and the success of living donation between parent and child, adult-to-adult living-donor liver transplantation has been investigated and is now performed at several transplant centers. Specifically, the living donor undergoes hepatectomy of the right lobe, which is then transplanted into the recipient. Since right hepatectomy involves the resection of 60–70% 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 has reported the results of their first 40 adult-to-adult living-donor liver transplantations, performed between June 1998 and October 1999. (3) 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. (4-6) Reports of several donor deaths re-emphasize the importance of careful patient
Liver Transplant

selection based in part on a comprehensive consent process and an experienced surgical team. (7-9) 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. (10) 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. (10)

In 2000, the American Society of Transplant Surgeons issued the following statement (11):

“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. (12) 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.

**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. (13) 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. (14) These criteria may be extrapolated to other organs: CD4 count >200 cells/mm-3 for >6 months

• CD4 count >200 cells/mm-3 for >6 months
• HIV-1 RNA undetectable
• On stable anti-retroviral therapy >3 months
Liver Transplant

- 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. (15) The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% confidence interval [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 to those with detectable HIV viremia.

**Hepatocellular Carcinoma**

Interest in expanding liver transplant selection criteria for hepatocellular carcinoma (HCC) and other indications is ongoing. Patient selection questions have focused mainly on the number and size of tumors. An editorial by Llovet (15) noted that the Milan criteria are considered the gold standard and specify that patients may either have a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or smaller. A 2001 paper from the University of California, San Francisco (UCSF), (16) proposed expanded criteria to include patients with a single tumor up to 6.5 cm in diameter, 3 or fewer tumors with maximum size 4.5 cm, 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 15–30%, 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, (17) 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 (18) 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, (19) 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, (16) 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. (20) 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 MELD allocation system finding a 6-fold increase in recipients with hepatocellular carcinoma and that survival in the MELD era was similar to survival to patients without hepatocellular carcinoma (HCC). (21) 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 hepatocellular carcinoma. (22) Of 116 patients with findings of hepatocellular carcinoma in their explanted livers, 12 developed recurrent hepatocellular carcinoma. 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. 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. (23) 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%, 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 an HCC consensus conference report does not recommend expanding Milan criteria nationally and encourages regional agreement. (24)

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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decaens et al. 2006 (17) 14 centers in France Meeting Milan criteria (Milan+)</td>
<td>Intention-to-treat, preoperative</td>
<td>Milan+</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milan-/UCSF+</td>
<td>44</td>
</tr>
<tr>
<td>Exceeding Milan criteria, meeting UCSF criteria (Milan-/UCSF+)</td>
<td>Overall patient survival</td>
<td>Milan+</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milan-/UCSF+</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>Milan+</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milan-/UCSF+</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>Milan+</td>
<td>60.4</td>
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<tr>
<td></td>
<td></td>
<td>Milan-/UCSF+</td>
<td>47.8</td>
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<tr>
<td></td>
<td>Post-transplant, pathologic (p)</td>
<td>pMilan+</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Overall patient survival</td>
<td>pMilan+</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>pMilan+</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>16.5</td>
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<tr>
<td></td>
<td>Disease-free survival</td>
<td>pMilan+</td>
<td>7.02</td>
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<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>62.7</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>Milan+</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>10</td>
</tr>
<tr>
<td>Leung et al. 2004 (18) 3 centers in Massachusetts Meeting preoperative Milan criteria (Milan+)</td>
<td>Post-transplant overall patient survival</td>
<td>Milan+</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2 patients died at 3 and 22 months, 8 patients alive after median 32 mo follow-up (6.6-73.5)</td>
<td>Milan+</td>
<td>74</td>
</tr>
</tbody>
</table>
Yao et al. 2002 (19) 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 (25) Essen, Germany Unclear if criteria preoperative or pathologic  
Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo.  

**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.  

The European Liver Transplant Registry was cited by a review article. (26) 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 (27) 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 (28) 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 (29, 30). 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, (31) 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. (32) A German study of 24 patients reported the poorest results. (33) 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. (34) 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.
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pascher et al. 2003, review (26) European Liver Transplant Registry</td>
<td>Overall patient survival</td>
<td>IH-CCA</td>
<td>186</td>
<td>58 78 38 29</td>
</tr>
<tr>
<td>Meyer et al. 2000 (27) Cincinnati Transplant Registry unrectable CCA</td>
<td>Overall patient survival</td>
<td>IH/EH-CCA</td>
<td>207</td>
<td>72 48 23</td>
</tr>
<tr>
<td>Meyer et al. 2000 (27) Cincinnati Transplant Registry</td>
<td>Crude recurrence rate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robles et al. 2004 (28) Multiple centers in Spain</td>
<td>overall patient survival</td>
<td>Hilar CCA</td>
<td>36</td>
<td>82 53 30</td>
</tr>
<tr>
<td>Heimbach et al. 2006 (29); Rea et al. 2006 (30) Mayo Clinic, Rochester MN</td>
<td>overall patient survival</td>
<td>Peripheral CCA</td>
<td>23</td>
<td>77 65 23</td>
</tr>
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<td>Shimoda et al. 2001 (31) UCLA/Cedars-Sinai, Los Angeles, CA</td>
<td>overall patient survival</td>
<td>All</td>
<td>25</td>
<td>71 35</td>
</tr>
<tr>
<td>Casavilla et al. 1997 (32) University of Pittsburgh, PA</td>
<td>overall patient survival</td>
<td>IH-CCA</td>
<td>16</td>
<td>62 39</td>
</tr>
<tr>
<td>Casavilla et al. 1997 (32) University of Pittsburgh, PA</td>
<td>overall patient survival</td>
<td>EH-CCA</td>
<td>9</td>
<td>86 31</td>
</tr>
<tr>
<td>Weimann et al. 2000 (33) Hannover, Germany 07/78-12/96; unrectable CCA</td>
<td>overall patient survival</td>
<td>IH-CCA</td>
<td>24</td>
<td>21 8 4 0</td>
</tr>
<tr>
<td>Friman et al. 2011 (34) Norway, Sweden, and Finland</td>
<td>Actual patient survival</td>
<td>All</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>1984-2005; unresectable CCA</td>
<td>TNM stage &gt;2</td>
<td>21</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>TNM stage ≤2</td>
<td>32</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

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. (30) The series of 20 patients from the University of Pittsburgh experienced 67% 1-year tumor-free survival and a 31% 5-year rate. (31) The multicenter Spanish series reported crude recurrence rates of 53% and 36% for extrahepatic and intrahepatic cholangiocarcinoma, respectively. (28) The German center at Hannover found a crude recurrence rate of 63%. (33)

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 hepatocellular carcinoma and other chronic liver diseases and superior to resection. (35) 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. (36) They retrospectively review their experience with surveillance and early detection of cholangiocarcinoma and en bloc total hepatectomy-pancreatectoduodenectomy-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 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 hepatitis C virus (HCV) eradication is pretransplant before hepatic decompensation. (37) 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.

**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. (38) 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.

**Ongoing Clinical Trials**

There is an ongoing multi-institutional prospective study of liver and kidney transplantation in HIV-positive recipients. The target enrollment is 150 kidney transplant recipients and 125 liver transplant recipients. The goals of the trial are described as follows (20):

“Primary aims of the study are to assess the impact of iatrogenic immunosuppression on patient survival and to assess the impact of HIV infection and antiretroviral treatment on graft survival, including in the setting of HBV or HCV coinfection and HIV-associated nephropathy. Secondary aims include assessment of the effect of immunosuppressant therapy on CD 4+ cell counts, HIV RNA levels, and opportunistic complications; exploration of the relationships among disease development, the host immune response and viral evolution with regard to HBC, HCV, CMV, herpes virus-8 and HPV; assessment of the impact of HIV infection on alloimmune response and graft
rejection rates; and analysis of pharmacokinetic interactions between immunosuppressant drugs and hepatically metabolized antiretroviral agents."

The participating institutions are as follows:

**Kidney and Liver**

Beth Israel Deaconess Medical Center, Boston, MA
Georgetown Medical Center, Washington, DC
Mount Sinai School of Medicine, New York
University of California, San Francisco
University of Chicago
University of Cincinnati
University of Minnesota
University of Pennsylvania
University of Pittsburgh
University of Virginia

**Kidney**

Drexel University, Philadelphia
University of Maryland
University of Miami
Washington Hospital Center, Washington, DC

**Liver**

Cedars-Sinai Medical Center, Los Angeles
Columbia University, NY, NY

In clinical trial NCT00708877, the University of Utah is evaluating the effectiveness of liver transplantation for cholangiocarcinoma in 50 patients. The study is expected to be completed in March 2012. At Stanford University, in a Phase II study that began in January 2011, researchers will evaluate whether neoadjuvant stereotactic body radiotherapy and chemotherapy for unresectable cholangiocarcinoma can lead to successful liver transplantation (NCT01151761). Washington State University is conducting a prospective registry study of neoadjuvant chemoradiation in conjunction with liver transplantation for cholangiocarcinoma (NCT00301379).

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 177lutetium about 9 months prior to liver transplantation.

**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
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 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 hepatocellular carcinoma, predictors of recurrence, the role of neoadjuvant therapy in patients with hepatocellular carcinoma, expanded donor criteria, transplantation and retransplantation for hepatitis C, and living donor transplantation. For metastatic neuroendocrine tumors, cure of disease is not achieved and 5-year survival is not high. As a result, there is a lack of consensus concerning whether transplantation should be offered to this population. Further study is needed before liver transplant selection criteria can be expanded for hepatocellular carcinoma, and/or extended to other indications such as cholangiocarcinoma and metastatic neuroendocrine tumors.

Practice Guidelines and Position Statements
In 2005, the American Association for the Study of Liver Diseases (AASLD) issued guidelines on evaluating patients for liver transplant. (39) 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. (40) 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 liver transplant in patients with hepatocellular carcinoma meeting UNOS criteria equal to or less than 5 cm, or 2-3 lesions equal to or less than 3cm. (41) In patients with Child-Pugh Class A liver function with tumors that are resectable and meet UNOS criteria, NCCN indicates resection or transplant may be considered. The NCCN guidelines on hepatobiliary cancers also indicate liver transplant is appropriate in select patients with extrahepatic cholangiocarcinoma. These are level 2A recommendations based on lower-level evidence and uniform consensus.

Medicare National Coverage
Medicare covers adult liver transplantation for end-stage liver disease and hepatocellular carcinoma 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. (42) Adult liver transplantation is excluded for other malignancies. The following conditions must be met for coverage of hepatocellular carcinoma:

- 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.

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.

V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References:
