This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

Centers for Medicare and Medicaid Services (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a National Coverage Determination (NCD) #260.1 for adult liver transplantation and covers liver transplantation and follow-up care that is medically necessary for adults who have:

- End-stage liver disease when performed in a facility which is approved by CMS as meeting institutional coverage criteria
- Hepatocellular carcinoma (HCC) that meets the following criteria:
  - Tumor diameter must be ≤ 5 cm
  - Presence of nodule confirmed by testing done within the last 3 months in the following order:
    1. Abdominal ultrasound
    2. If nodule is < 1 cm:
      - liver biopsy to confirm HCC diagnosis
    3. If nodule > 1 cm on ultrasound:
      - test with 4-phase multidetector computed tomography (CT) scan and if inconclusive
      - test with contrast enhanced magnetic resonance imaging (MRI)
- Subtotal liver resection not feasible;
- No macrovascular involvement;
- No identifiable extrahepatic tumor spread to lymph nodes, bone, or other organs; and
- Transplant facility has met CMS institutional coverage criteria and received CMS approval for liver transplants.

- Effective June 21, 2012 CMS covers the following malignancies:
  - extrahepatic unresectable cholangiocarcinoma (CCA)
  - liver metastases due to a neuroendocrine tumor (NET)
  - hemangioendothelioma (HAE)

- Adult liver transplantation for other malignancies is not covered.

CMS does have a National Coverage Determination \(^2\) (NCD) \#260.2 for pediatric liver transplantation and covers liver transplantation for children (under age 18) who have:
1. Extrahepatic biliary atresia or any form of end stage liver disease.
2. Liver transplantation is not covered when a malignancy extends beyond the margins of the liver or
3. In persistent viremia.
4. Liver transplantation is covered when performed in a pediatric hospital that performs pediatric liver transplants if the hospital submits an application which CMS approves documenting that:
   - The hospital’s pediatric liver transplant program is operated jointly by the hospital and another facility that has been found by CMS to meet the institutional coverage criteria in the "Federal Register" notice of April 12, 1991;
   - The unified program shares the same transplant surgeons and quality assurance program (including oversight committee, patient protocol, and patient selection criteria); and
   - The hospital is able to provide the specialized facilities, services, and personnel that are required by pediatric liver transplant patients.

**INITIAL COVERAGE CRITERIA**

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCG policies the Corporate Senior Medical Director’s designee can approve the requested transplant.

Members must meet the United Network Organ Sharing (UNOS) guidelines for MELD and PELD scores and the diagnosis of liver disease must be made by a Hepatologist and/or Transplant Surgeon.
Pre-Transplant Evaluation:

General requirements for pre-transplant evaluation include all of the following:

- History and physical examination
- **Psychosocial evaluation and clearance**: This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.
- Dietary consult
- EKG
- Chest X-ray
- Coronary artery disease screening: [ONE]
  - Chronic smokers
  - > 50 years age
  - Those with a clinical or family history of heart disease or diabetes should be evaluated with testing in the following order:
    1. Dobutamine stress echocardiography and if these results are positive,
    2. Cardiac catheterization
- Carotid doppler scanning: [ONE]
  - For age > 50 years
  - History of cardiovascular disease
- For diagnosis of HCC:
  - Presence of nodule confirmed by testing within the last 3 months done in the following order:
    1. Abdominal ultrasound
    2. If nodule is < 1 cm:
      - Liver biopsy to confirm HCC diagnosis
    3. If nodule > 1 cm on ultrasound:
      - Test with 4-phase multidetector computed tomography (CT) scan and if inconclusive
      - Test with contrast enhanced magnetic resonance imaging (MRI)
- Pulmonary Function Testing in patients with history of pulmonary disease, smoking
- Pulmonary hypertension screening for end stage liver disease to determine presence of pulmonary artery hypertension (PAH) – (pulmonary artery pressure should be <60 mm hg or per transplant facility criteria) in the following order:
  1. Transthoracic echocardiography and if measurements are positive for PAH
  2. Right heart catheterization
- Lab studies:
  - Complete blood cell count, liver chemistry, kidney profile, coagulation profile (prothrombin time, partial thromboplastin time)
  - HIV testing.
Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D, Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology, syphilis, toxoplasmosis, herpes simplex virus

- Antinuclear antibody, smooth muscle antibody, antimitochondrial antibody
- Iron studies, ceruloplasmin, α1-antitrypsin phenotype
- Alpha-fetoprotein
- Blood type

Within the last 12 months the following is required:

- Colonoscopy (indicated > age 50 with removal of any polyps if applicable)
- Dental examination (contact plan for coverage criteria)
- GYN examination with Pap smear (indicated > age 18) with complete workup and treatment of abnormal results as indicated
- Immunizations up to date when indicated: Hepatitis A and Hepatitis B, pneumococcal vaccine, influenza vaccine, tetanus booster
- Mammogram (indicated > age 40) with complete workup and treatment of abnormal results as indicated
- Osteoporosis screening with DEXA scan: [ONE]
  - indicated for cholestatic disorders
  - prolonged corticosteroid therapy
  - postmenopausal women
  - > age 65
- Peripheral artery disease (PAD) screening with doppler-recorded ankle-brachial index: [ONE]
  - age > 50
  - history of diabetes or smoking
- Testicular examination > age 50

Adult Criteria for Transplantation:

1. Molina Healthcare considers cadaver or live donor liver transplantation medically necessary in adults over the age of 18 years when ALL of the following criteria are met:

   - Documentation that all medical, pharmacological and surgical alternatives to liver transplant have been utilized that include but are not limited to:
     - ablation or surgical resection of tumors in patients who have hepatocellular carcinoma
     - biliary reconstruction procedures such as biliary tract diversion and/or dilatation by endoscopic retrograde cholangiopancreatography (ERCP) in patients with primary sclerosing cholangitis
     - immunosuppressive and corticosteroid therapy for patients who have severe autoimmune hepatitis
     - chelation therapy for patients with severe chronic Wilson’s disease
     - antiviral therapy for patients with decompensated cirrhosis secondary to chronic hepatitis B
     - vasoactive agents, sclerotherapy and band ligation, transjugular intrahepatic portosystemic shunt (TIPS), in patients who have had variceal bleeding
     - low sodium diet, aldosterone antagonists [e.g., spironolactone], loop diuretics [furosemide], and paracenteses in patients who have ascites
     - vasoconstrictor agents, α-adrenergic agonists, TIPS in patients with hepatic encephalopathy
- hepatopancreaticoenterostomy (Kasai procedure or anastomosis of bile duct remnants in the porta hepatis to a loop of bowel) in patients with **biliary atresia**
- special formulas, antihistamines in patients with **Alagille syndrome**
- specialized diets in patients with **metabolic disorders**
- anticoagulation, portal venous decompression in patients with **Budd-Chiari syndrome**

- **Age < 70 years** \(^{30,31}\)

- **Must have either of the following:**
  - End-Stage Liver Disease (ESLD) with a life expectancy < 12 – 24 months; or
  - Hepatocellular Carcinoma HCC that meets the Milan criteria \(^{3,17}\):
    - Tumor diameter ≤ 5 cm; or
    - Multiple tumors: maximum number 3, largest tumor ≤3.0 cm; and
    - Not a candidate for subtotal hepatic resection; and
    - No macrovascular involvement; and
    - No identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone
    - Presence of nodule confirmed by testing done within the last 3 months in the following order \(^{5,27,28}\):
      1. Abdominal ultrasound
      2. If nodule is < 1 cm:
         - liver biopsy to confirm HCC diagnosis
      3. If nodule > 1 cm on ultrasound:
         - test with 4-phase multidetector computed tomography (CT) scan and if inconclusive
         - test with contrast enhanced magnetic resonance imaging (MRI)

- **Presence of any life-threatening complications interfering with quality of life:**
  - Intractable acites
  - Progressive hepatic encephalopathy (with or without bacterial peritonitis)
  - Recurrent portal hypertension bleeding
  - Hepato-pulmonary syndrome requiring oxygen therapy \(^{18}\)
  - Hepatic hydrothorax requiring recurrent thoracentesis \(^{19}\)

- **Severe hepatic dysfunction:**
  - Model of End-stage Liver Disease (MELD used for age >12 years) score ≥ 15*; **OR**
  - Child-Turcotte-Pugh (CTP) Classification score > 7 (Child's class B or C)**

- **No active alcohol or substance abuse for a minimum of 6 months prior to transplant**
- No behavioral health disorder by history or psychosocial issues: [One]³⁸
  - if history of behavioral health disorder, no severe psychosis or personality disorder
  - mood/anxiety disorder must be excluded or treated
  - member has understanding of surgical risk and post procedure compliance and follow-up required

  **Note:** Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

- Adequate social/family support

- If HIV positive all of the following are met:
  - 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, coccidiose mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm)
  - Meeting all other criteria for transplantation

- None of the following absolute contraindications are present:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignancy outside of the liver within 5 years of the evaluation not including skin cancers
  - Systemic and/or uncontrolled infection
  - Active alcohol and/or other substance abuse (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
  - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
  - Irreversible brain damage
  - AIDS (CD4 count < 200cells/mm3)
  - Anatomic abnormality that would preclude the transplant (requires statement from surgeon that such an abnormality is not present)
  - Compensated cirrhosis without complications (Child-Turcotte-Pugh score, 5–6) unless the patient has hepatocellular carcinoma and is not a candidate for alternative curative therapy.

**Pediatric Criteria for Transplantation:**

2. Molina Healthcare considers cadaver or live donor liver transplantation medically necessary in infants and children between the ages of < one month to 18 years when ALL of the following criteria are met³

- Documentation that all medical and surgical alternatives to liver transplant have been utilized that includes but is not limited to the following:
  - ablation or surgical resection of tumors in patients who have hepatocellular carcinoma
  - biliary reconstruction procedures such as biliary tract diversion and/or dilatation by endoscopic retrograde cholangiopancreatography (ERCP) in patients with primary sclerosing cholangitis
immunosuppressive and corticosteroid therapy for patients who have severe autoimmune hepatitis

- chelation therapy for patients with severe chronic Wilson’s disease
- antiviral therapy for patients with decompensated cirrhosis secondary to chronic hepatitis B
- vasoactive agents, sclerotherapy and band ligation, transjugular intrahepatic portosystemic shunt (TIPS), in patients who have variceal bleeding
- low sodium diet, aldosterone antagonists [e.g., spironolactone], loop diuretics [furosemide], and paracenteses in patients who have acities
- vasoconstrictor agents, α-adrenergic agonists, TIPS in patients with hepatic encephalopathy
- hepatoperoenterostomy (Kasai procedure or anastamosis of bile duct remnants in the porta hepatitis to a loop of bowel) in patients with biliary atresia (usually done prior to 3 months of age)
- special formulas, antihistamines in patients with Alagille syndrome
- specialized diets in patients with metabolic disorders
- anticoagulation, portal venous decompression in patients with Budd-Chiari syndrome

- Life expectancy <18 months because of liver disease

- Severe hepatic dysfunction:
  - Model of End-stage Liver Disease (MELD) (used for age >12 years or PELD used for age <12 years) score ≥ 15*; OR
  - Child-Turcotte-Pugh (CTP) Classification score > 7 (Child's class B or C)**

- Probability of irreversible end organ damage (which may be renal, respiratory or cardiovascular depending on underlying disorder)

- If HIV positive all of the following are met:
  - 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

- No behavioral health disorder by history or psychosocial issues: [One]
  - if history of behavioral health disorder, no severe psychosis or personality disorder
  - mood/anxiety disorder must be excluded or treated
  - member has understanding of surgical risk and post procedure compliance and follow-up required

  Note: Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

- None of the following absolute contraindications are present:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery

Note:
Malignancy outside of the liver within 5 years of the evaluation not including skin cancers

- Systemic and/or uncontrolled infection
- Active alcohol and/or other substance abuse (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
- Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
- Irreversible brain damage
- AIDS (CD4 count < 200cells/mm3)
- Anatomic abnormality that would preclude the transplant
- Compensated cirrhosis without complications (Child-Turcotte-Pugh score, 5–6) unless the patient has hepatocellular carcinoma and is not a candidate for alternative curative therapy.

Retransplantation for Adult and Pediatric: When retransplantation is being considered, a number of factors need to be considered that include the timing and indication for retransplant, the presence of other comorbidities, immunosuppressive management, infection prophylaxis, and the likelihood of success.

- The member must meet all of the other requirements for transplantation outlined above AND have:
  - Intractable, acute, or chronic rejection
  - Retransplantation is not covered for the following conditions because of high mortality and poor outcomes:
    - recurrent hepatitis C in members who have not been successfully treated and achieved sustained virologic response (SVR) after the initial transplant
    - fibrosing cholestatic hepatitis (FCH)
    - recurrent hepatocellular carcinoma (HCC)
    - chronic rejection associated with non-compliance with medical regime
    - cirrhosis in members with relapsing alcoholism
  - Requests for a third or subsequent liver transplant are not covered

Simultaneous Liver-Kidney Transplantation: Molina Healthcare considers a simultaneous liver and kidney transplant medically necessary when any of the following criteria are met:

- End stage renal disease (ESRD) with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ≥10 mmHg
- Hepatic failure and GFR ≤30 mL/min due to chronic kidney disease
- Acute kidney injury (AKI) or hepatorenal syndrome with serum creatinine ≥2 mg/dL (177 µmol/L) and dialysis ≥8 weeks
- Hepatic failure and chronic kidney disease with a kidney biopsy showing >30 percent glomerulosclerosis or >30 percent fibrosis
*The MELD score is a disease severity scoring system for adults with liver disease to determine the prognosis of patients at various stages of disease in order to improve organ allocation. It is based on the severity of liver disease using only laboratory data in order to be as objective as possible. The laboratory values used are a patient's serum creatinine, serum bilirubin, and international normalized ratio (INR), which has been shown to be highly predictive of 3-month mortality and postoperative mortality in patients with chronic liver disease. For children up to age 12, a similar model has been developed for pediatric endstage liver disease (PELD) that includes: age younger than 1 year; serum albumin level; serum bilirubin; INR and growth failure (<2 SD below the age based mean). A higher PELD score directly corresponds to a lower probability rate of a 3 month survival without transplantation.

**The Child-Turcote-Pugh (CPT) score determines short-term prognosis among groups of patients awaiting liver transplantation and has been widely adopted for risk-stratifying patients before transplantation.

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>1 – 2</td>
<td>3 – 4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2 – 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>For PBC/PSC, Bilirubin</td>
<td>&lt; 4</td>
<td>4 – 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>INR*</td>
<td>&lt; 1.7</td>
<td>1.7 – 2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td>PT (seconds prolonged)</td>
<td>&lt; 4</td>
<td>4 - 6</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

The individual scores are summed and then grouped as a classification:

- < 7 = A
- 7-9 = B
- > 9 = C (forecasts a survival of less than 12 months)

*INR = International Normalized Ratio; PT = prothrombin time.

**CONTINUATION OF THERAPY**

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindications as listed above;
  - History and physical within the last 6 months;
o Liver chemistries within the last 6 months;
o Stress test within the last 2 years (≥ 50 years of age);
o Psychosocial evaluation or update within the last 12 months;
o Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
o Authorization letter/documentation from previous insurer;
o Presence of no absolute contraindications as listed above;
o History and physical within the last 6 months;
o Liver chemistries within the last 6 months;
o Stress test within the last 2 years (≥ 50 years of age);
o Psychosocial evaluation or update within the last 12 months;
o Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

<table>
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<th>COVERAGE EXCLUSIONS</th>
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Absolute contraindications to liver transplantation include any of the following:

- Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
- Malignancy outside of the liver within 5 years of the evaluation not including skin cancers
- Systemic and/or uncontrolled infection
- Active alcohol and/or other substance abuse requires 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing
- Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
- Irreversible brain damage
- AIDS (CD4 count < 200cells/mm3)
- Anatomic abnormality that would preclude the transplant (requires statement from surgeon that such an abnormality is not present)
- Compensated cirrhosis without complications (Child-Turcotte-Pugh score, 5–6) unless the patient has hepatocellular carcinoma and is not a candidate for alternative curative therapy.

Relative contraindications to liver transplantation include any of the following:

- Advanced age > 70 years
- Cholangiocarcinoma
- Moderate pulmonary hypertension defined as mean pulmonary artery pressure >35 mm hg
- Obesity BMI > 40kg/m^2 (if BMI >40kg/m^2) (to remove as a relative contraindication the summary must contain a more detailed history & physical description, including an estimate of ascites present)
DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Liver transplantation is performed to replace a diseased liver in patients with end-stage liver disease with a healthy liver graft from a donor. The engrafted liver may be all or part of a liver removed from a brain-dead donor (cadaveric) or a portion of a liver from a healthy living donor. Liver transplantation is 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) referred to as MELD (model for end-stage liver disease) for adults and PELD (pediatric end-stage liver disease) for children under age 12 years. 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., 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 are prioritized to those with the highest MELD or PELD number; waiting time is only 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. The only priority exceptions to MELD are the categories known as Status 1A and 1B. Status 1A patients have acute (sudden and severe onset) liver failure and a life expectancy of hours to a few days without a transplant. Status 1B is reserved for very sick, chronically ill pediatric patients (age less than 18). All other liver candidates age 12 and older are prioritized by the MELD system.

According to the American Association for the Study of Liver Diseases (AASLD) common indications for liver transplantation include any of the following:

- Chronic noncholestatic & cholestatic disorders caused by: Alagille syndrome, alcoholic liver disease, autoimmune hepatitis, biliary atresia, chronic hepatitis B & C virus infection, cystic fibrosis, primary biliary cirrhosis, primary sclerosing cholangitis, progressive familiar intrahepatic cholestasis and secondary biliary cirrhosis
- Metabolic disorders caused by: Alpha-1 antitrypsin deficiency, amyloidosis if the amyloid protein is produced by the liver, branch chain, amino acid disorders, familial homozygous hypercholesterolemia, glycogen-storage disorders, hereditary hemochromatosis, neonatal hemochromatosis, nonalcoholic steatohepatitis (NASH), Type 1 hyperoxaluria, tyrosinemia, urea cycle defects, fulminant liver failure secondary to Wilson's disease
- Malignancy caused by hepatocellular carcinoma (HCC)
- Miscellaneous conditions such as Budd-Chiari syndrome, neuroendocrine tumors, polycystic liver disease and trauma
Indications for liver transplantation in infants and children include acute liver failure (ALF), chronic liver failure with pruritus, complications of cholestasis. In young children, the most common liver disease leading to transplantation is biliary atresia. 50 percent of all liver transplants in children are for biliary atresia which is characterized by the failure of the bile ducts to develop normally and drain bile from the liver. Acute liver failure from hemochromatosis, leading to a histologic diagnosis of giant-cell hepatitis, is the primary indication for liver transplantation in the neonatal population. Other disease states that progress to end-stage liver disease among pediatric patients and require liver transplantation include metabolic disorders and progressive intrahepatic cholestasis. 32 33

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. The cardiopulmonary evaluation is intended to evaluate for any significant coronary artery or valvular disease, cardiomyopathy, obstructive or restrictive lung disease, and pulmonary hypertension. Some positive results during initial testing may permanently preclude transplant, whereas others may need to be corrected or simply noted prior to surgery. In patients with coronary artery disease or those with severe hypoxemia and elevated mean pulmonary artery pressure measurements morbidity and mortality of liver transplantation are increased. Although neither are absolute contraindications for transplant a detailed evaluation for both is critical. The ideal evaluation of coronary artery disease prior to liver transplantation remains controversial. The reported sensitivity of dobutamine stress echocardiography and myocardial perfusion scintigraphy varies. The limitations of the studies in this population are potentially related to minimal coronary artery reserve, low resting systolic blood pressure, and the use of beta blockers. The current American Association for the Study of Liver Disease practice guidelines recommend that dobutamine stress echocardiography is an effective initial screening tool but that abnormal results should be followed with angiography. Some cardiologists recommend that in patients with known coronary artery disease, diabetes mellitus, or more than two cardiovascular risk factors; coronary angiography is preferred to assess the extent and severity of coronary artery disease. Therefore, ideal testing is still under investigation, and transplant centers vary in their approach. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

Cadaveric Donor Selection and Operation: In a standard cadaveric liver transplantation, the diseased liver is surgically replaced with a healthy, whole liver. The donor organ is harvested from a brain-dead donor who has been sustained on cardiopulmonary ventilation. To minimize trauma, the donor liver is manipulated as little as
possible during removal. The donor’s iliac artery and vein are removed for possible reconstruction of the recipient’s hepatic vessels and portal vein. Preservation time of the liver can be extended up to 30 hours, but preferably no more than 15 hours, using the University of Wisconsin (UW) cold preservation solution. The potential for bleeding problems is great due to coagulation abnormalities common in patients with liver disease. It takes approximately 2 hours to prepare the donor liver in the operating room; this usually takes place while a different surgical team prepares the recipient’s body. Cadaver liver donors should meet the following criteria:

- Established brain death
- ABO compatibility of donor and recipient. Although ABO incompatibility may not be of disadvantage in children, it may be in adults. Significantly fewer graft failures were observed in adults who received ABO identical grafts when compared with those who received ABO incompatible or no identical grafts.
- Donor size comparable with recipient size
- Normal liver function tests
- Prothrombin time normal or correcting.
- No active or ongoing disseminated intravascular coagulopathy

Standard Recipient Procedure: Hepatectomy is performed in the recipient by isolating the liver from blood circulation. A veno-venous bypass, in which blood from the portal vein and the inferior vena cava flows through an extracorporeal bypass into the superior vena cava system, may be used to reduce bowel congestion and renal function impairment during the anhepatic phase. Incisions are made in the axilla and left groin for placement of cannulas for the bypass. The cadaveric allograft is implanted by vascular anastomoses and cholangioenterostomy, which involves anastomosis of the common bile duct and the jejunum, or end-to-end anastomosis of the common bile ducts. The procedure can take from 3 to 12 hours.

Split Liver Transplantation: In split liver transplantation an adult cadaver liver is split into two grafts; each lobe maintains its vascular and biliary pedicles, which are transplanted along with the graft. Generally, the left lobe is given to a pediatric recipient and the right lobe to an adult patient. The donor organ harvesting procedure is modified accordingly; more preparation time is required since the process of preparing portions of the liver for transplantation is more complex than the process for transplanting the entire organ into a single recipient.

Living Donor Liver Transplantation: Both left- and right-lobe liver grafts have been used for living donor liver transplantation. The surgical technique is similar to that used for split-liver donations from beating heart donors. Although there is risk to the donor, this procedure allows for optimal preparation of the recipient and an ideally tailored graft.

Management of patients who have end-stage liver failure and who are waiting for a suitable donor depends on the cause of liver disease. General medical management strategies may include the following:

- avoidance of alcohol and hepatotoxic drugs,
- vaccination against hepatitis A and hepatitis B to avoid further liver damage,
- use of beta-blockers to prevent or limit variceal bleeding,
- manipulation of diet to avoid encephalopathy and prevent complications in patients who have ascites,
• prompt recognition and treatment of bacterial peritonitis, and
• ablation or resection of tumors in patients who have hepatocellular carcinoma

**GENERAL INFORMATION**

**Summary of Medical Evidence**

The medical evidence for liver transplantation consists of individual case series obtained from transplant centers that perform adult and pediatric transplantation and registry data and is summarized below.

A case series analysis to evaluate the long-term survival outcomes of a large cohort of liver transplant recipients and to identify factors that influenced these outcomes over time was published. Four thousand consecutive patients who underwent liver transplantation between February 1981 and April 1998 were included in this analysis and were followed up until March 2000. The effect of donor and recipient age at the time of transplantation, recipient gender, diagnosis, and year of transplantation were compared. Rates of retransplantation, causes of retransplantation, and cause of death were also reviewed. The overall patient survival for the entire cohort was 59%; the actuarial 18-year survival was 48%. Patient survival was significantly better in children, in female recipients, and in patients who received transplants after 1990. The rates of retransplantation for acute or chronic rejection were significantly lower with tacrolimus-based immunosuppression. The risk of graft failure and death was relatively stable after the first year, with recurrence of disease, malignancies, and age-related complications being the major factors for loss. The authors concluded that significantly improved patient and graft survival has been observed over time, and graft loss from acute or chronic rejection has emerged as a rarity. Age-related and disease-related causes of graft loss represent the greatest threat to long-term survival.  

Another single centers experience with pediatric liver transplantation is reported in terms of patient survival; graft survival in relation to age, gender, and immunosuppressive protocols; causes of death; and indications for retransplantation. From March 1981 to April 1998, 808 children received liver transplants at Children's Hospital of Pittsburgh. All patients were followed until March 2001, with a mean follow-up of 12.2 +/- 3.9 years. There were 405 female (50.2%) and 403 male (49.8%) pediatric recipients. Mean age at transplant was 5.3 +/- 4.9 years (mean=3.3; range 0.04-17.95), with 285 children (25.3%) being less than 2 years of age at transplant. Overall patient survival at 1, 5, 10, 15, and 20 years was 77.1%, 72.6%, 69.4%, 65.8%, and 64.4%, respectively. There was no difference in survival for male or female patients at any time point. At up to 10 years post-transplant, the survival for children greater than 2 years of age (79.5%, 75.7%, and 71.6% at 1, 5, and 10 years, respectively) was slightly higher than those at less than 2 years of age (72.6%, 66.9%, and 65.3% at 1, 5, and 10 years, respectively). However, at 15 and 20 years post-transplant, survival rates were similar (>2 years=67.3% and 65.8%; <2 years=64.1% and 64.1%). The authors concluded that the overall 20-year actuarial survival for pediatric liver transplantation is 64%. Survival has increased by 20% in the last 12 years with tacrolimus-based immunosuppression. Although this improvement may be the result of several factors, re-transplantation as a result of acute or chronic rejection has been completely eliminated in patients treated with tacrolimus.
A consensus conference sponsored by the American Society of Transplant Surgeons (ASTS), American Society of Transplantation (AST), United Network for Organ Sharing (UNOS) and American Society of Nephrology (ASN) convened to examine simultaneous liver-kidney transplantation (SLK). Directors from the 25 largest liver transplant programs along with speakers with recognized expertise attended. The purposes of this conference were to propose indications for SLK, to establish a prospective data registry and, most importantly, to recommend standard listing criteria for these patients. Scientific registry of transplant recipients data, and single center data regarding chronic kidney disease (CKD) and acute kidney injury (AKI) in conjunction with liver failure as a basis for SLK was presented and discussed. The consensus was that Regional Review Boards (RRB) should determine listing for SLK, as with other MELD exceptions, with automatic approval for: (i) End-stage renal disease with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient $\geq 10$ mm Hg (ii) Liver failure and CKD with GFR $\leq 30$ mL/min (iii) AKI or hepatorenal syndrome with creatinine $\geq 2.0$ mg/dL and dialysis $\geq 8$ weeks (iv) Liver failure and CKD and biopsy demonstrating $\geq 30\%$ glomerulosclerosis or $30\%$ fibrosis. The RRB would evaluate all other requests to determine appropriateness. $^{39}$

According to the Organ Procurement and Transplantation Network Scientific Registry of Transplant Recipients OPTN/SRTR 2010 data report shows the survival rate for liver transplantation was 94.6% at 3 months, 89.1% at one year, 73.7% at 5 years and 59.9% at ten years. $^{36}$

Hayes, Cochrane, UpToDate, MD Consult etc.

The Hayes Medical Technology Directory report for pediatric liver transplantation $^{10}$ indicates that most published studies are retrospective case series documenting the experience of individual transplant centers including the evolution of both surgical technique and medical management. Some are case series establishing the safety of liver transplantation in very young children and for the treatment of particular disorders and some evaluated groups of sufficient size and analyzed long-term outcomes. Comparison of outcomes in patients receiving different types of transplants, such as cadaveric whole and split-liver or living donor grafts were hindered by differences in clinical status of the recipients and the relatively small number of patients who have received living donor grafts.

Liver transplantation is a feasible alternative for pediatric patients with end-stage liver disease, with outcomes comparable to those seen in adult populations. Most of the available data are from cadaver organ transplants and are insufficient to provide a definitive conclusion regarding which specific type of liver transplant provides the best long-term outcome. The primary indications for liver transplantation in children include acute or chronic end-stage liver disease or failure, life-threatening complication of chronic liver disease, decompensation of previously stable liver disease, or the severe impairment of quality of life related to liver disease. Liver transplantation is not indicated in children with hepatocellular carcinoma who are candidates for subtotal liver resection, or whose tumor is greater than 5 cm in diameter, or have macrovascular involvement or extrahepatic spread of tumor. Liver transplantation is contraindicated in children with active HIV infection, nonhepatic malignancy other than skin cancer, severe pulmonary or cardiovascular disease, and in those unwilling or unable to adhere to post-transplant lifestyle restrictions and medical regimen. This report was archived in 2008.
The Hayes Medical Technology Directory Report for liver transplantation in adults indicates that the majority of the available studies reviewed were retrospective of a transplant center’s experience with adult liver transplantation. The only prospective studies were those that evaluated different immunosuppressive or antiviral drugs. The reviewed studies provided evidence that there has been continuous improvement in the management of end-stage liver disease with liver transplantation, advancements in surgical technique, improved preoperative and postoperative management of patients, more effective immuno- and antiviral therapies, and less toxic immunosuppressive regimens.

Liver transplantation is indicated in adults who experience life-threatening complications of chronic liver disease, a decompensation of previously stable liver disease, or severe impairment of quality of life directly related to liver disease caused by primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic cirrhosis, alpha-1 antitrypsin deficiency disease, or Wilson’s disease. Liver transplantation is indicated in adults who experience life-threatening complications caused by hepatitis and who receive adequate immuno- and antiviral therapy following transplantation and for selected patients diagnosed with hepatocellular carcinoma. Liver transplantation is not indicated for patients with hepatocellular carcinoma who are candidates for subtotal liver resection, or whose tumor is greater than 5 cm in diameter, or have macrovascular involvement or extrahepatic spread of tumor; and for any type of liver transplantation in patients with absolute contraindications. This report was archived in 2008.

The Hayes Health Technology Brief for liver transplantation in obese adults indicates that the results of three large retrospective studies suggest that there is a complex relationship between pretransplant obesity and post-transplant survival. The largest available study found that patients who are obese (body mass index > 35 kg/m²) have shorter post-transplant survival than patients who have a lower body mass index and that the influence of obesity was relatively small and less significant than cause of disease, bilirubin level, serum creatinine level, ethnicity, and United Network for Organ Sharing status. A second study found that transplant survival was reduced for patients who had a body mass index ≥ 40 kg/m² or a body mass index < 19 kg/m² and was not affected by a body mass index of 35 to 39 kg/m². This study found that a body mass index of 25 to 34 kg/m² was favorable and improved post-transplant survival. The smallest of the 3 studies found that body mass index did not have any major impact on post-transplant survival but did affect waiting-list mortality and that decreased pretransplant survival was seen for underweight patients (body mass index < 20 kg/m²). In comparison, patients with a body mass index of 35.0 to 39.9 kg/m² had lower waiting-list mortality. The Hayes report concluded that liver transplantation is standard of care for patients with end stage liver failure.

UpToDate recommends that any patient with documented acute liver failure, decompensated cirrhosis, or hepatocellular carcinoma within defined criteria is a potential candidate for liver transplantation and that early referral to a transplant center should be the standard of care. The first step in deciding the timing of referral is to determine if there has been a complication of end-stage liver disease. This is followed by a determination of severity of illness using the MELD score and Child-Pugh score. Any patient with one of the defined complications of end-stage liver disease (e.g., ascites, variceal bleeding, encephalopathy, or hepatocellular carcinoma), a Child-Pugh score greater than 7, and/or a MELD score of 10 should be considered for referral to a transplant center.
Professional Organizations

American Association for the Study of Liver Disease⁵ (AASLD): The Practice Guidelines Committee of the AASLD has published several Position Papers and Practice Guidelines regarding the management of liver disease and liver transplantation. These include guidelines for the evaluation of the patient for liver transplantation, management of acute liver failure, diagnosis, management and treatment of hepatitis C, hepatocellular carcinoma, chronic hepatitis B, biliary cirrhosis, primary sclerosing cholangitis, and alcoholic liver disease.

National Comprehensive Cancer Network⁸ (NCCN) Guidelines indicate that patients eligible for liver transplantation should not be eligible for liver resection therefore transplantation can be considered for patients with early HCC and those with moderate to severe cirrhosis (Child-Pugh class B-C score) who fit UNOS criteria for organ distribution: radiologic evidence of a single tumor ≤ 5.0 cm in diameter or 2-3 tumors ≤ 3.0 cm and no evidence of macrovascular or extrahepatic disease.

The Clinical Practice Committee of the American Society of Transplantation proposed that the presence of AIDS could be considered a contraindication to kidney transplant unless the following criteria were present. These criteria may be extrapolated to other solid organs such as the liver¹¹:

- 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

**CODING INFORMATION**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<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 living donor, any age</td>
</tr>
<tr>
<td>47136</td>
<td>Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor, any age</td>
</tr>
<tr>
<td>47140</td>
<td>Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)</td>
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<tr>
<td>47141</td>
<td>Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)</td>
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<td>47142</td>
<td>Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)</td>
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<tr>
<td>47143</td>
<td>Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation,</td>
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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

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<tr>
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<tr>
<td>47144</td>
<td>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 two partial liver grafts (ie, left lateral segment (segments II and III) and right trisegment (segments I and IV through VIII))</td>
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<td>47145</td>
<td>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 two partial liver grafts (ie, left lobe (segments II, III, and IV) and right lobe (segments I and V-VIII))</td>
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<tr>
<td>47146</td>
<td>Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each</td>
</tr>
<tr>
<td>47147</td>
<td>Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each</td>
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<tr>
<td>S2152</td>
<td>Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor (s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and Rehabilitative services, and the number of days of pre- and post-transplant care in the global definition</td>
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<tr>
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<td>Transplant from donor, cadaver</td>
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<tr>
<td>070-070.9</td>
<td>Hepatitis</td>
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<td>50.5-50.59</td>
<td>Liver transplant</td>
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<td>155.2</td>
<td>Malignant neoplasm of liver, not specified as primary or secondary</td>
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<td>273.4</td>
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<tr>
<td>K70-K77</td>
<td>Diseases of the Liver</td>
</tr>
</tbody>
</table>

**Resource References**


18. UpToDate. Lange P. Hepato-pulmonary syndrome requiring oxygen therapy. May 2012.


42. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Surgery, Transplant. June 18, 2012