Clinical Policy Title: Liver transplantation

Clinical Policy Number: 08.02.05

Effective Date: January 1, 2016
Initial Review Date: November 18, 2015
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:
None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of liver transplants to be clinically proven and, therefore, medically necessary when the patient has been diagnosed with end-stage liver disease (ESLD). Indications for liver transplant include, but are not limited to:

Acute liver failure complications of cirrhosis:
- Ascites.
- Chronic gastrointestinal blood loss due to portal hypertensive gastrostopy.
- Encephalopathy.
- Liver cancer.
- Refractory variceal hemorrhage.
- Synthetic dysfunction.

Liver-based metabolic conditions with systemic manifestations:
- a1 antitrypsin deficiency.
- Familial amyloidosis.
- Glycogen storage disease.
- Hemochromatosis.
- Primary oxaluria.
- Wilson disease.

Systemic complications of chronic liver disease:
- Hepatopulmonary syndrome.
- Portopulmonary hypertension.

In addition, re-transplantation following one or more failed liver transplant(s) is considered medically necessary if the initial transplant was performed for one of the criteria above.

Limitations:

Liver transplants are contraindicated for any of (but not limited to) the following:
- MELD score <15.
- Severe cardiac or pulmonary disease.
- AIDS. (patients that have active current AIDS defining illness or meet definition for AIDS while still on appropriate active antiretroviral therapy. NOTE: HIV+ recipients that are adherent to antiretroviral therapy with either a non detected viral load or adequate sustained viral response would be eligible for transplantation under current federal and AASLD, UNOS. Per federal regulations, HIV+ patients can receive organs from HIV+ donors)
- Ongoing alcohol or illicit substance abuse.
- Hepatocellular carcinoma with metastatic spread.
- Uncontrolled sepsis.
- Anatomic abnormality that precludes liver transplantation.
- Intrahepatic cholangiocarcinoma.
- Extrahepatic malignancy.
- Fulminant hepatic failure with sustained intracranial pressure >50 mm/Hg or cerebral perfusion pressure <40 mm/Hg.
- Hemangiosarcoma.
- Persistent noncompliance.
- Lack of adequate social support system.

Keystone First also considers other criteria as medically necessary or contraindicated, according to the recommendations for the American Association for the Study of Liver Disease, for adolescents and adults (Martin, 2013) and children (Squires, 2014).

Alternative covered services:

None.
Background

Liver transplants are only performed in patients with End Stage Liver Disease (ESLD) marked by extreme liver dysfunction. Liver transplants were first performed in 1963. Throughout the 1960s and 1970s, the technique was largely experimental, and about 75 percent of patients did not survive one year. After rising to a peak of 6,650 such procedures performed in the United States in 2006, the number slightly declined to 6,256 in 2012 (NOPTN, 2015) at 144 hospitals throughout the nation (STR, 2016).

The efficacy of liver transplants has increased in the past several decades. The survival rate has jumped to 85 – 90 percent after one year, and 75 – 85 percent after five years (UNOS, 2016). About 16,000 patients await a donated liver at any given time, and about 1,500 die waiting for a transplant in the United States each year (UNOS, 2016). The estimated cost of care for a liver transplant, including pre- and post-operative treatment over 180 days, is $735,000 (NFT, 2016).

The scoring system known as the MELD (model for ESLD) is used to determine whether a liver transplantation is required, and is a reliable predictor of mortality. The MELD scale ranges from 6 to 40 points, with higher scores representing sicker patients. There is also a PELD scale (pediatric ESLD) that uses the same scoring system. In general, any patient with a MELD or PELD score under 10 is not likely to need liver transplantation.

The federal Organ Procurement and Transplantation Network (OPTN) serves as the basis for the priority for transplant according to mortality risk and severity of illness. Patients are assigned to categories status 1A (1A and 1B for children), calculated or exception MELD/PELD score, and inactive status with status 1A representing most urgent, i.e., the patient has liver failure with life expectancy under seven days. Previously, waiting time was a factor in assigning priority to potential liver recipients, but this factor is no longer considered, as it is a poor predictor of mortality (OPTN/UNOS, 2016). Types of liver transplantations include:

- Transplantations performed using a liver from either a living or deceased donor.
- Auxiliary live transplantations, which occur when a second liver is implanted ectopically, while the patient’s original liver remains.
- Split-liver transplantations, which occur when a donor’s liver is broken into smaller parts and implanted into the patient. This technique is often used for pediatric patients.
- Xenotransplantations, which use a liver donated from primates. Transmission of diseases remains a concern for this approach.
- Bioartificial liver transplantations, which use an artificial liver. Results to date show that this method is generally not recommended for use.
- Retransplantations of livers, which can take place when a liver transplant recipient again experiences ESLD.

Searches
Keystone First searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on October 13, 2016. Search terms were: “liver transplantation,” “survival” and “mortality.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The American Association for the Study of Liver Disease (AASLD) recently published detailed practice guidelines for the evaluation of adult and child patients for liver transplants (Martin, 2016, and Squires, 2014). These guidelines include 56 and 89 recommendations for adults and children, respectively, according to the patient’s condition and severity. The AASLD also addressed contraindications for liver transplantation in these guidelines.

Mortality outcomes for liver transplant recipients have improved markedly. In an early study, the one-year and three-year survival rates were only 26 and 12 percent, respectively (Scharschmidt, 1984). Current survival has risen to 93 and 76 percent for one-year and five-year periods (Stepanova, 2015). In two decades, improvements have been observed in average length of hospital stay (42 to 20 days), percent acute post-transplant rejections (33 to 4 percent), and discharges from the hospital alive (78 to 91 percent) (Stepanova, 2015).

Mortality after liver transplant using living donors and deceased donors was studied in 672 patients with MELD scores over 35. The percent of recipients of a liver from a living versus a deceased donor were similar after one year (88.9 versus 94.7 percent), three years (87.0 versus 86.9 percent), and five years (84.8 versus 83.3 percent). Similar rates between the two groups were observed for postoperative complication, hospital mortality, and graft survival (Chok, 2016). Another study found that recipients from live donors had higher perioperative complications, but those from deceased donors tended to have more serious complications (Reichman, 2013).
Partial liver transplants (which use a portion of an adolescent or adult donated liver), introduced for young children requiring a new liver, initially had a mortality rate higher than whole liver donations. More recently, mortality for partial and whole-liver transplants is relatively similar (Cauley, 2013).

Age is another mortality factor in liver transplantation. One study of 2,938 patients found that mortality increased with patient age, probably because older patients are more often on dialysis and have more medical comorbidities (Chen, 2016). A comparison of adult and child liver recipients found that after surgery, child survival rates exceeded that of adults after five years (89 versus 73 percent), and after 20 years (77 versus 50 percent) (Petrowsky, 2013).

Infections are not uncommon in liver transplant recipients. One study of 201 patients found no difference in infection rates between those with a MELD score of 6 – 20, 21 – 30, and 31 – 40, even though survival declines as MELD score increases (Juntermanns, 2015).

**Policy updates**

The policy now contains two new guidelines and seven new peer-reviewed references, and has removed eight guidelines and six peer-reviewed references, each of which are not current or judged to be too narrow for a policy on a topic with a large amount of available literature.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreyzin (2015)</td>
<td><strong>Key points:</strong> 9% – 29% of pediatric liver transplant patients required retransplant. Analysis of all retransplants 1991 – 2013 at Children’s Hospital of Pittsburgh. Since 2002, one- and five-year survival has risen to 98% and 87%.</td>
</tr>
<tr>
<td>Wan (2015)</td>
<td><strong>Key points:</strong> 17 studies, 48,457 patients, split- versus whole-liver transplants. Survival rates were similar. Group with split transplants had higher rates of 1) biliary complications, 2) bile leaks, 3) vascular complications, 4) hepatic artery thromboses and 5) outflow tract obstructions.</td>
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<td>Evans (2014)</td>
<td><strong>Key points:</strong> 14 studies of liver transplant patients. Antifungal prophylaxis patients had fewer invasive fungal infections (actual and suspected), and lower mortality from fungal infections.</td>
</tr>
<tr>
<td>Wan (2014)</td>
<td><strong>Key points:</strong> 19 studies, 5,450 patients, outcomes of living versus deceased donor liver transplantation. Living donor cases have higher rate of surgical complications after transplant, but they still offer greater access to transplants. Improvement is possible with greater experience.</td>
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<tr>
<td>Zhang (2013)</td>
<td><strong>Key points:</strong></td>
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<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<tr>
<td></td>
<td>• 62 studies.</td>
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<td></td>
<td>• Liver transplant versus resection, patients with hepatocellular carcinoma.</td>
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<td></td>
<td>• Transplant group had higher survival and lower recurrence rate.</td>
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<tr>
<td>Petrowsky (2013)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Difference in survival</td>
<td>• Review of 5- and 20-year survival of liver transplants, n=152.</td>
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<tr>
<td>between child and adult</td>
<td>• After 5 years, children had a higher survival (89% versus 73%).</td>
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<tr>
<td>liver recipients</td>
<td>• After 20 years, children had a higher survival (77% versus 50%).</td>
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<td></td>
<td>• Without transplants, fewer than 5% would survive.</td>
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<tr>
<td>Gu (2012)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• 14 studies, 605 patients with bile duct cancers, 1995 – 2009.</td>
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<td></td>
<td>• One-, three- and five-year survival rates were 73%, 42% and 39%</td>
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<td></td>
<td>• Pre-operative adjuvant therapies raised survival.</td>
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**Glossary**

**Cirrhosis** — A late-stage scarring of the liver with many causes.

**End-stage liver disease (ESLD)** — A state of terminal illness due to various causes leading to liver failure.

**Liver transplantation** — A procedure in which a new liver replaces a diseased liver in patients with ESLD.

**Model for end-stage liver disease (MELD)** — A system for evaluating severity of liver illness.

**Model for pediatric end-stage liver disease (PELD)** — A system for evaluating severity of liver illness in children.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Scharschmidt BF. Human liver transplantation: analysis of data on 540 patients from four centers. *Hepatology.* 1984; 4(1 suppl.):95S — 101S.


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.
Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>47135</td>
<td>Liver allotransplantation; orthotopic, partial or whole, from cadaver or</td>
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<tr>
<td></td>
<td>living donor, any age</td>
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<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
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<tr>
<td>C22.2</td>
<td>Hepatoblastoma</td>
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<tr>
<td>E72.53</td>
<td>Hyperoxaluria</td>
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<td>E74.00</td>
<td>Glycogen storage disease</td>
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<td>E83.01</td>
<td>Wilson's disease</td>
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<td>E83.110 - E83.119</td>
<td>Hemochromatosis</td>
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<td>E85.2</td>
<td>Heredofamilialamyloidosis</td>
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<tr>
<td>E88.01</td>
<td>Alpha-1-antitrypsin deficiency</td>
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<tr>
<td>I85.11</td>
<td>Secondary esophageal varices</td>
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<tr>
<td>K70.11</td>
<td>Alcoholic hepatitis with ascites</td>
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<tr>
<td>K70.31</td>
<td>Alcoholic cirrhosis of the liver with ascites</td>
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<tr>
<td>K71.51</td>
<td>Toxic liver disease with with chronic active hepatitis with ascites</td>
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<tr>
<td>K72.00-11</td>
<td>Chronic hepatic failure</td>
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<tr>
<td>K72.90-91</td>
<td>Hepatic failure</td>
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<td>K74.3</td>
<td>Primary biliary cirrhosis</td>
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<td>K74.4</td>
<td>Secondary biliary cirrhosis</td>
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<td>K74.69</td>
<td>Other cirrhosis of liver</td>
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<tr>
<td>K75.81 - K75.9</td>
<td>Other and unspecified inflammatory liver diseases</td>
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<tr>
<td>K76.81</td>
<td>Hepatopulmonary syndrome</td>
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<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
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