OPTN

Notice of OPTN Policy, Guidance, and Data Collection Changes

Review of National Liver Review Board (NLRB) Diagnoses and Update to Alcohol Associated Diagnoses

Sponsoring Committee:	**OPTN Liver and Intestinal Organ Transplantation Committee**
Policies Affected:	**Policy 9.5.I.i: Initial Assessment and Requirements for HCC Exception Requests;** **Policy 9.5.I.vii: Extensions of HCC Exceptions**
Guidance Affected:	**Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC);** **Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review**
Public Comment:	**August 3, 2021 – September 30, 2021**
Board Approved:	**December 6, 2021**
Effective Date:	**February 1, 2022: Policy 9.5.I.i: Initial Assessment and Requirements for HCC Exception Requests; Policy 9.5.I.vii: Extensions of HCC Exceptions; Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma (HCC); Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review** **Pending implementation and notice to OPTN members: Changes to the diagnosis field on the Transplant Candidate Registration Form and Transplant Recipient Registration Form**

Purpose of Policy, Guidance, and Data Collection Changes

This proposal includes two distinct aspects intended to improve the liver allocation system. The two parts of the proposal are improvements to the National Liver Review Board (NLRB) and updates to the diagnoses on the transplant candidate registration form (TCR) and transplant recipient registration form (TRR) to better capture alcohol-associated liver diseases (ALD).

The NLRB was implemented on May 14, 2019.[1] The purpose of the NLRB is to provide equitable access to transplant for liver candidates whose calculated model for end-stage liver disease (MELD) score or pediatric end-stage liver disease (PELD) score does not accurately reflect the candidate's medical urgency for transplant. Since the implementation of the NLRB, the OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) has continued to evaluate the effectiveness of the system and has identified a number of ways in which the NLRB could be improved. The purpose of this proposal is to continue to improve the NLRB by creating a more efficient and equitable system for reviewing MELD and PELD exception requests. The included changes ensure that guidance and policy language remain clear and aligned with current research so that the appropriate candidates receive MELD or PELD exceptions.

In 2016, ALD overtook chronic hepatitis C virus (HCV) as the leading indication for liver transplantation.[2] Despite ALD being the leading indication for liver transplantation, recent research has shown that there is significant inconsistency when entering the diagnosis for candidates with ALD.[3] The purpose for updating the alcohol-associated diagnoses on the TCR and TRR is to allow for more accurate data collection and analysis in the future. By updating the diagnoses on the TCR and TRR, more candidates will be categorized with the correct diagnosis, leading to a more complete and reliable OPTN dataset.

Proposal History

Prior to the implementation of the NLRB, MELD and PELD exception requests were reviewed by regional review boards (RRBs). The implementation of the NLRB was a significant change in the process for reviewing MELD or PELD exception requests and because of the significance and complexity of the change, the Committee has continued to receive feedback on areas for improvement to the NLRB guidance and policy. This proposal represents the Committee's commitment to continue to improve the NLRB.

Separately, the proposed changes to ALD diagnoses were developed by the Committee based on their subject matter expertise and clinical experience.

Summary of Changes

The proposal includes the following changes to the NLRB:

- **HCC Policy**: Clarify that a chest CT is only required for an initial HCC exception.
- **HCC Guidance**:
    - Add guidance so that candidates treated with immunotherapy are able to access an exception score.
    - Update guidance for candidates with history of resected HCC that recurs to make it clear these candidates do not need to wait six months to receive an exception score equal to median MELD at transplant (MMaT) minus three.
- **Encephalopathy Guidance**: Non-substantive change to include updated references.

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[1] Proposal to Establish a National Liver Review Board, OPTN Liver and Intestinal Organ Transplantation Committee, June 2017, Available at https://optn.transplant.hrsa.gov/

[2] George Cholankeril and Aijaz Ahmed, "Alcoholic Liver Disease Replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States," *Clinical Gastroenterology and Hepatology* 16, no. 8 (2018): pp. 1356-1358, https://doi.org/10.1016/j.cgh.2017.11.045.

[3] Brian P. Lee et al., "Underestimation of Liver Transplantation for Alcoholic Hepatitis in the National Transplant Database," *Liver Transplantation* 25, no. 5 (2019): pp. 706-711, https://doi.org/10.1002/lt.25448.

The changes to ALD diagnoses are outlined in **Table 1** below:

Table 1: Updating Diagnoses on TCR/TRR

Current Diagnosis	New Diagnosis
Alcoholic Cirrhosis	Alcohol-associated cirrhosis without acute alcohol-associated hepatitis
Alcoholic Cirrhosis with Hepatitis C	N/A: diagnosis will be inactivated
Acute Alcoholic Hepatitis	Acute alcohol-associated hepatitis with or without cirrhosis

Implementation

Liver transplant programs and NLRB reviewers will need to be familiar with the changes to NLRB policy and guidance when submitting and reviewing MELD or PELD exception requests. Liver transplant programs will also need to be familiar with the updated diagnoses when providing candidate information.

The OPTN will implement information technology changes for the updated ALD diagnoses. All changes will be communicated and published.

Affected Policy and Guidance Language

Proposed new language is underlined (<u>example</u>) and language that is proposed for removal is struck through (~~example~~). […] signifies language in current Policy that is not presented here for the purposes of brevity and will not be affected by this proposal. Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

9.5 Specific Standardized MELD or PELD Score Exceptions

[…]

9.5.I Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions

Upon submission of the first exception request, a candidate with hepatocellular carcinoma (HCC) will receive a score according to Policy *9.5.I.vii: Extensions of HCC Exceptions* if the candidate meets the criteria according to *Policies 9.5.I.i through 9.5.I.vi.*

9.5.I.i Initial Assessment and Requirements for HCC Exception Requests

Prior to applying for a standardized MELD or PELD exception, the candidate must undergo a thorough assessment that includes *all* of the following:

1. An evaluation of the number and size of lesions before local-regional therapy that meet Class 5 criteria using a dynamic contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI)

2. A CT of the chest to rule out metastatic disease. This is only required prior to applying for an initial exception. A CT of the chest is not required for exception extensions.
3. A CT or MRI to rule out any other sites of extrahepatic spread or macrovascular involvement
4. An indication that the candidate is not eligible for resection
5. An indication whether the candidate has undergone local-regional therapy
6. The candidate's alpha-fetoprotein (AFP) level

The transplant hospital must maintain documentation of the radiologic images and assessments of all OPTN Class 5 lesions in the candidate's medical record. If growth criteria are used to classify a lesion as HCC, the radiology report must contain the prior and current dates of imaging, type of imaging, and measurements of the lesion.

For those candidates who receive a liver transplant while receiving additional priority under the HCC exception criteria, the transplant hospital must submit the *Post-Transplant Explant Pathology Form* to the OPTN within 60 days of transplant. If the *Post-Transplant Explant Pathology Form* does not show evidence of HCC or liver-directed therapy for HCC, the transplant program must also submit documentation or imaging studies confirming HCC at the time of assignment.

The Liver and Intestinal Organ Transplantation Committee will review the submitted documentation or imaging studies when more than 10 percent of the *Post-Transplant Explant Pathology Forms* submitted by a transplant program in a one-year period do not show evidence of HCC or liver-directed therapy for HCC.

9.5.I.vii Extensions of HCC Exceptions

A candidate with an approved exception for HCC is eligible for automatic approval of an extension if the transplant program enters a MELD or PELD Exception Score Extension Request that contains the following:

1. Documentation of the tumor using a CT or MRI
2. The type of treatment if the number of tumors decreased since the last request
3. The candidate's alpha-fetoprotein (AFP) level

A CT of the chest to rule out metastatic disease is not required after the initial exception request.

The candidate's exception extension will then be automatically approved unless *any* of the following occurs:

- The candidate's lesions progress beyond T2 criteria, according to *9.5.I.ii: Eligible Candidates Definition of T2 Lesions*
- The candidate's alpha-fetoprotein (AFP) level was less than or equal to 1,000 ng/mL on the initial request but subsequently rises above 1,000 ng/mL

- The candidate's AFP level was greater than 1,000 ng/mL, the AFP level falls below 500 ng/mL after treatment but before the initial request, then the AFP level subsequently rises to greater than or equal to 500 ng/mL
- The candidate's tumors have been resected since the previous request
- The program requests a score different from the scores assigned in Table 9-10.

When a transplant program submits either an initial exception request or the first extension request for a liver candidate at least 18 years old at the time of registration that meets the requirements for a standardized MELD score exception, the candidate appear on the match run according to the calculated MELD score.

A candidate who meets these requirements for a MELD or PELD score exception for HCC will receive a score according to *Table 9-10* below.

Table 9-10: HCC Exception Scores

Age	Age at registration	Exception Request	Score
At least 18 years old	At least 18 years old	Initial and first extension	Calculated MELD
At least 18 years old	At least 18 years old	Any extension after the first extension	3 points below MMaT
At least 12 years old	Less than 18 years old	Any	40
Less than 12 years old	Less than 12 years old	Any	40

Guidance Language

Proposed new language is underlined (<u>example</u>) and language that is proposed for removal is struck through (~~example~~). Heading numbers, table and figure captions, and cross-references affected by the numbering of these policies will be updated as necessary.

Guidance to Liver Transplant Programs and the National Liver Review Board for:

Adult MELD Exceptions for Hepatocellular Carcinoma (HCC)

Background

A liver candidate receives a MELD[4] or, if less than 12 years old, a PELD[5] score that is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. When the calculated score does not reflect the candidate's medical urgency, a liver transplant program may request an exception score. A candidate that meets the criteria for one of nine diagnoses in policy is approved for a standardized MELD exception.[6] If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board.

The OPTN Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exceptions for Hepatocellular Carcinoma (HCC). This guidance document is intended to provide recommendations for the review board considering HCC cases which are outside standard policy.

This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements." Review board members and transplant centers should consult this resource when considering MELD exception requests for adult candidates with the following diagnoses.

Recommendation

- Patients with the following are contraindications for HCC exception score:
  - Macro-vascular invasion of main portal vein or hepatic vein
  - Extra-hepatic metastatic disease
  - Ruptured HCC
  - T1 stage HCC

While in most cases, ruptured HCC and primary portal vein branch invasion of HCC would be contraindications, some patients who remain stable for a prolonged (minimum of 12 months) interval

[4]Model for End-Stage Liver Disease
[5]Pediatric End-Stage Liver Disease
[6]Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

after treatment for primary portal vein branch invasion or after ruptured HCC may be suitable for consideration.

Evidence for the use of immunotherapy as a down-staging or bridging therapy is preliminary. However, based on the published data in transplant and non-transplant setting, the use of immunotherapy does not preclude consideration for an HCC exception.[7]

- Patients who have a history of prior unresectable HCC more than 2 years ago which was completely treated with no evidence of recurrence, who develop new or recurrent lesions after 2 years should generally be considered the same as those with no prior HCC, in order to determine the current stage suitability for an initial MELD exception, and initial MELD exception score assignment.

- Patients beyond standard criteria who have continued progression while waiting despite LRT are generally not acceptable candidates for HCC MELD exception.

- Patients with AFP>1000 who do not respond to treatment to achieve an AFP below 500 are not eligible for standard MELD exception, and must be reviewed by the HCC review board to be considered. In general, these patients are not suitable for HCC MELD exception but may be appropriate in some cases.

- Patients with HCC beyond standard down-staging criteria who are able to be successfully downstaged to T2 may be appropriate for MELD exception, as long as there is no evidence of metastasis outside the liver, or macrovascular invasion, or AFP >1,000. Imaging should be performed at least 4 weeks after last down-staging treatment. Patients must still wait for 6 months from the time of the first request to be eligible for an HCC exception score.

- Patients with cirrhosis who presented with stage T2 resectable HCC (one lesion >2 cm and <5 cm in size, or two or three lesions >1 cm and <3 cm in size, based on resection specimen pathology) who underwent complete resection but developed T1 (biopsy proven), or T2 HCC (LI-RADS 5) following complete resection should be considered for MELD score exception, without a six month delay period. This includes candidates who initially presented with T2 resectable HCC and who underwent complete resection more than 2 years ago.

Patients with cirrhosis and HCC beyond T2 but within generally accepted criteria for down-staging (such as up to 5 lesions, total tumor volume <8 cm based on resection pathology) who underwent complete resection with negative margins and developed T1 (biopsy proven) or T2 recurrence (LI-RADS 5) may also be considered for MELD score exception for HCC. Because the larger tumor size, the 6 month delay is appropriate to ensure favorable tumor biology.

[7] Parissa Tabrizian, Sander S. Florman, and Myron E. Schwartz, "PD-1 Inhibitor as Bridge Therapy to Liver Transplantation?," *American Journal of Transplantation* 21, no. 5 (February 2021): pp. 1979-1980, https://doi.org/10.1111/ajt.16448.

Recommendations for Dynamic Contrast-enhanced CT or MRI of the Liver

Table 1: Recommendations for Dynamic Contrast-enhanced CT of the Liver

Feature:	CT scans should meet the below specifications:
Scanner type	Multidetector row scanner
Detector type	Minimum of 8 detector rows and must be able to image the entire liver during brief late arterial phase time window
Slice thickness	Minimum of 5 mm reconstructed slice thickness; thinner slices are preferable especially if multiplanar reconstructions are performed
Injector	Power injector, preferably dual chamber injector with saline flush and bolus tracking recommended
Contrast injection rate	3 mL/sec minimum, better 4-6 mL/sec with minimum of 300 mg I/mL or higher, for dose of 1.5 mL/kg body weight
Mandatory dynamic phases on contrast-enhanced MDCT	1. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein 2. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins 3. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast
Dynamic phases (Timing)	Use the bolus tracking or timing bolus

Table 2: Recommendations for Dynamic Contrast-enhanced MRI of the Liver

Feature	MRIs should meet the below specifications:
Scanner type	1.5T Tesla or greater main magnetic field strength. Low field magnets are not suitable.
Coil type	Phased array multichannel torso coil, unless patient-related factors precludes its use.
Minimum sequences	Pre-contrast and dynamic post gadolinium T1-weighted gradient echo sequence (3D preferable), T2 (with and without fat saturation), T1-weighted in and out of phase imaging.
Injector	Dual chamber power injector with bolus tracking recommended.
Contrast injection rate	2-3 mL/sec of extracellular gadolinium chelate that does not have dominant biliary excretion, preferably resulting in vendor-recommended total dose.

Feature	MRIs should meet the below specifications:
Mandatory dynamic phases on contrast- enhanced MRI	1. Pre-contrast T1W: do not change scan parameters for post contrast imaging. 2. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein. 3. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins. 4. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast.
Dynamic phases (Timing)	The use of the bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal vein phase images should be acquired 35 to 55 seconds after initiation of late arterial phase. Delayed phase images should be acquired 120 to 180 seconds after the initial contrast injection.
Slice thickness	5 mm or less for dynamic series, 8 mm or less for other imaging.
Breath-holding	Maximum length of series requiring breath-holding should be about 20-seconds with a minimum matrix of 128 x 256. Technologists must understand the importance of patient instruction about breath-holding before and during scan.

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Guidance to Liver Transplant Programs and the National Liver Review Board for:

Adult MELD Exception Review

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complication of chronic liver disease ~~associated with significant morbidity. There is an absence of evidence of sufficient quality to support MELD exception for complications of HE.[8,9,10,11]~~ with an associated mortality independent of MELD scoring. Presently, no additional MELD priority for HE is recommended in the absence of a widely available, reliable, objective assessment of its severity. [12, 13,14,15]

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~~[8] Cordoba J., M. Ventura-Cots, M. Simón-Talero, et al. "Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF)." Hepatology 60 (2014): 275-81.~~

~~[9] García-Martínez, R., M. Simón-Talero, J. Córdoba. "Prognostic assessment in patients with hepatic encephalopathy." Dis Markers 31 (2011): 171-9.~~

~~[10] D'Amico, G., G. Garcia-Tsao, L. Pagliaro. "Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies." Hepatology 44 (2006): 217-31.~~

~~[11] Brandman, D., S.W. Biggins, B. Hameed, et al. "Pretransplant severe hepatic encephalopathy, peritransplant sodium and post-liver transplantation morbidity and mortality." Liver Int 32 (2012): 158-64.~~

[12] Kerbert, Annarein J., Enric Reverter, Lara Verbruggen, Madelon Tieleman, Miguel Navasa, Bart J. Mertens, Sergio Rodríguez-Tajes, et al. "Impact of Hepatic Encephalopathy on Liver Transplant Waiting List Mortality in Regions with Different Transplantation Rates." *Clinical Transplantation* 32, no. 11 (2018). https://doi.org/10.1111/ctr.13412.

[13] Chiranjeevi Gadiparthi et al., "Waitlist Outcomes in Liver Transplant Candidates with High MELD and Severe Hepatic Encephalopathy," *Digestive Diseases and Sciences* 63, no. 6 (February 2018): pp. 1647-1653, https://doi.org/10.1007/s10620-018-5032-5.

[14] Cristina Lucidi et al., "Hepatic Encephalopathy Expands the Predictivity of Model for End-Stage Liver Disease in Liver Transplant Setting: Evidence by Means of 2 Independent Cohorts," *Liver Transplantation* 22, no. 10 (2016): pp. 1333-1342, https://doi.org/10.1002/lt.24517.

[15] Robert J. Wong, Robert G. Gish, and Aijaz Ahmed, "Hepatic Encephalopathy Is Associated with Significantly Increased Mortality among Patients Awaiting Liver Transplantation," *Liver Transplantation*, 2014, https://doi.org/10.1002/lt.23981.