OPTN

Briefing to the OPTN Board of Directors on

Continued Review of National Liver Review Board (NLRB) Guidance

OPTN Liver and Intestinal Organ Transplantation Committee

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Continued Review of National Liver Review Board (NLRB) Guidance

Affected Guidance:	*Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review* *Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review*
Sponsoring Committee:	*Liver and Intestinal Organ Transplantation*
Public Comment Period:	*August 3, 2022-September 28, 2022*
Board of Directors Meeting:	*December 5, 2022*

Executive Summary

This proposal includes three updates to OPTN guidance related to the National Liver Review Board (NLRB).

The purpose of the NLRB, which was implemented on May 14, 2019, 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.[1] Since implementation, the OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) has regularly evaluated the NLRB to identify opportunities for improvement. This proposal seeks to make improvements to the NLRB guidance documents, including creating guidance for pediatric liver transplant candidates with cystic fibrosis and updating guidance for adult liver transplant candidates with hepatic adenomas and Budd Chiari syndrome.

The proposal was widely supported throughout public comment and the Committee is proposing only minor post-public comment changes.

[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/

Purpose

The purpose for updating NLRB guidance documents is to continue to improve the NLRB by creating a more efficient and equitable system for reviewing MELD and PELD exception requests. These changes ensure that guidance language remains clear and aligned with current clinical consensus and updated data so the NLRB approves MELD or PELD exception requests for the appropriate candidates.

Background

When being listed for a liver transplant, candidates receive a calculated MELD or PELD score, which is based on a combination of the candidate's clinical lab values.[2] These scores are designed to reflect the probability of death on the waitlist within a 90 day period, with higher scores indicating a higher probability of mortality and increased urgency for transplant. Candidates who are less than 12 years old receive a PELD score, while candidates who are at least 12 years old receive a MELD score. Candidates that are particularly urgent are assigned status 1A or 1B.

When a transplant program believes that a candidate's calculated MELD or PELD score does not accurately reflect a candidate's medical urgency, they can request a score exception. The NLRB is responsible for reviewing exception requests and either approving or denying the requested score.

The NLRB was approved by the OPTN Board of Directors (the Board) at their June 2017 meeting and was implemented on May 14, 2019.[3] The NLRB was designed to create an efficient and equitable system for reviewing exception requests for candidates across the country.[4]

Under the NLRB, candidates who meet the criteria outlined in OPTN policy for one of the nine standardized diagnoses are eligible to have their exception automatically approved.[5] In addition, each of the three specialty review boards (Pediatric, Adult - Hepatocellular Carcinoma (HCC), and Adult - Other Diagnosis) has an associated guidance document.[6] The guidance documents contain information for review board members and transplant programs on diagnoses and clinical situations not included as one of the standardized diagnoses in policy. They provide recommendations on which candidates should be considered for a MELD or PELD exception and are based on published research, clinical guidelines, medical experience, and data. The documents are intended to help ensure consistent and equitable review of exception cases, and are not OPTN policy.

Because these documents are consulted by transplant programs and NLRB reviewers when applying for and reviewing exception requests, they have the ability to impact which candidates are approved for a MELD or PELD exception. Therefore, it is necessary for the Committee to systematically and proactively review the documents to ensure they continue to align with current clinical consensus and updated data. This proposal was developed using a systematic and proactive review process. Rather than waiting

[2] The calculations for the MELD and PELD scores can be found in OPTN Policy, Available at https://optn.transplant.hrsa.gov/.
[3] *Proposal to Establish a National Liver Review Board*, OPTN Liver and Intestinal Organ Transplantation Committee, June 2017, Available at https://optn.transplant.hrsa.gov/
[4] Ibid.
[5] See OPTN Policy 9.5: Specific Standardized MELD or PELD Exceptions, Available at https://optn.transplant.hrsa.gov/
[6] NLRB Guidance Documents are available at https://optn.transplant.hrsa.gov/

to consider a change once an issue was identified, the Committee is continuing to examine current guidance and policy for a subset of NLRB diagnoses using a set schedule and review process.

As a result of this process, the Committee is proposing updates to OPTN guidance related to pediatric candidates with cystic fibrosis, and adult candidates with multiple hepatic adenomas and Budd Chiari syndrome. The review process included reviewing recent literature, consulting with subject matter experts, and analyzing updated data, as needed. In addition to the changes included in this proposal, the Committee reviewed current guidance for hepatic epithelioid hemangioendothelioma, hereditary hemorrhagic telangiectasia, and pruritus, as well as the policy for hepatopulmonary syndrome, and is not recommending any changes to these diagnoses.

Proposal for Board Consideration

Pediatric Cystic Fibrosis Guidance

Cystic fibrosis (CF) is a genetic disorder that can lead to chronic damage in several organs including the lungs, pancreas, and liver. CF-related liver disease (CFLD) is now the third leading cause of death amongst people with CF. [7] For people with CF who have complications of CF-related cirrhosis or portal hypertension, liver transplant can be life-saving.[8,9] *OPTN Policy 9.5.B: Requirements for Cystic Fibrosis (CF) MELD or PELD Score Exceptions* outlines the standardized criteria a candidate must meet in order to automatically be approved for a MELD or PELD score exception for CF-related liver disease.

The Committee reviewed this policy as part of the current round of NLRB diagnosis review. Because a large portion of patients with CFLD are under the age of 18, the Committee sought input from the OPTN Pediatric Transplantation Committee on the current policy. The current policy for a CF exception requires a transplant program to submit that a candidate's CF diagnosis has been confirmed by genetic analysis and that the candidate has a forced expiratory volume at 1 second (FEV_1) below 40%. Adult candidates meeting these criteria are provided a MELD exception equal to median MELD at transplant (MMaT) minus three; adolescent candidates meeting the criteria are assigned a score equal to MMaT; pediatric candidates meeting the criteria are provided a PELD exception equal to median PELD at transplant (MPaT).[10]

The Committee, in collaboration with the OPTN Pediatric Transplantation Committee and subject matter experts, agreed that the current policy does not apply to many pediatric candidates and is therefore proposing the addition of guidance specific to pediatric candidates with CFLD. Such guidance does not currently exist and the creation of guidance for CFLD will make it more likely this population of candidates is able to appropriately access MELD or PELD exception scores.

The proposed guidance states that the calculated MELD or PELD score may underestimate mortality risk for pediatric candidates with CFLD who meet one of the following three criteria:

[7] See Cystic Fibrosis Foundation Liver Disease Clinical Care Guidelines; Available at https://www.cff.org/medical-professionals/liver-disease-clinical-care-guidelines
[8] Ibid.
[9] Sokol, Ronald J.; Durie, Peter R. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group Recommendations for Management of Liver and Biliary Tract Disease in Cystic Fibrosis, Journal of Pediatric Gastroenterology & Nutrition: Volume 28 - Issue - p S1-S13
[10] OPTN Policy 9.5.B: Requirements for Cystic Fibrosis (CF) MELD or PELD Score Exceptions

- Candidates who have portal hypertension with complications and have failed or are not candidates for medical, endoscopic or surgical interventions to prevent or treat these complications.
- Candidates who have growth failure as a result of their liver disease, defined by age and sex-specific weight, length/height, weight-for-length, and/or body mass index (BMI) percentiles or have moderate to severe malnutrition.[11]
- Candidates who have a forced expiratory volume at 1 second (FEV_1) less than 70% or evidence of decline in FEV_1 of greater than or equal to 5% per year.[12]

The Committee is recommending these three criteria based on published literature and the expertise of clinical subject matter experts.

Approximately 5-10% of all patients with CF develop liver disease with portal hypertension.[13,14] Furthermore, CFLD develops primarily in pediatric patients and is an independent risk factor for mortality.[15,16] In fact, portal hypertension complications are the leading indication for liver transplant in patients with CF.[17,18,19] As a result, the first group of CFLD candidates covered by the new guidance are those who have portal hypertension with associated complications who are not able to receive medical, surgical, or endoscopic interventions to treat these complications. The Committee agreed that pediatric candidates with CFLD who are unable to receive treatment for their portal hypertension complications are at increased risk of liver-related mortality and should be able to access a MELD or PELD exception, pending review from the NLRB.

Second, the proposed guidance covers CFLD candidates with growth failure or moderate to severe malnutrition. According to recent research, almost one-third (31.8%) of pediatric liver transplant candidates with CF met the criteria for growth failure at the time of registration for liver transplant.[20] Young children (age under 2) and adolescents (age 12-17) listed for liver transplant with CF were significantly more likely to have growth failure than candidates with other diagnoses.[21] Most importantly, in multivariate analysis, the presence of CF and growth failure increased waitlist mortality risk by nearly four times in the pediatric liver transplant population.[22] Despite this, pediatric candidates

[11] Katherine Cheng et al., "Liver Transplant in Children and Adults with Cystic Fibrosis: Impact of Growth Failure and Nutritional Status," *American Journal of Transplantation* 22, no. 1 (September 2, 2021): pp. 177-186, https://doi.org/10.1111/ajt.16791.
[12] A. Jay Freeman et al., "A Multidisciplinary Approach to Pretransplant and Posttransplant Management of Cystic Fibrosis–Associated Liver Disease," *Liver Transplantation* 25, no. 4 (2019): pp. 640-657, https://doi.org/10.1002/lt.25421.
[13] Jaclyn R. Bartlett et al., "Genetic Modifiers of Liver Disease in Cystic Fibrosis," *JAMA* 302, no. 10 (September 2009): p. 1076, https://doi.org/10.1001/jama.2009.1295.
[14] Thomas Flass and Michael R. Narkewicz, "Cirrhosis and Other Liver Disease in Cystic Fibrosis," *Journal of Cystic Fibrosis* 12, no. 2 (2013): pp. 116-124, https://doi.org/10.1016/j.jcf.2012.11.010.
[15] Dominique Debray et al., "Outcome of Cystic Fibrosis-Associated Liver Cirrhosis: Management of Portal Hypertension," *Journal of Hepatology* 31, no. 1 (1999): pp. 77-83, https://doi.org/10.1016/s0168-8278(99)80166-4.
[16] Marion Rowland et al., "Outcome in Patients with Cystic Fibrosis Liver Disease," *Journal of Cystic Fibrosis* 14, no. 1 (2015): pp. 120-126, https://doi.org/10.1016/j.jcf.2014.05.013.
[17] PIOTR MILKIEWICZ et al., "Transplantation for Cystic Fibrosis: Outcome Following Early Liver Transplantation," *Journal of Gastroenterology and Hepatology* 17, no. 2 (2002): pp. 208-213, https://doi.org/10.1046/j.1440-1746.2002.02671.x.
[18] Peter Witters et al., "Liver Disease in Cystic Fibrosis Presents as Non-Cirrhotic Portal Hypertension," *Journal of Cystic Fibrosis* 16, no. 5 (2017), https://doi.org/10.1016/j.jcf.2017.03.006.
[19] Dominique Debray et al., "Best Practice Guidance for the Diagnosis and Management of Cystic Fibrosis-Associated Liver Disease," *Journal of Cystic Fibrosis* 10 (2011), https://doi.org/10.1016/s1569-1993(11)60006-4.
[20] Katherine Cheng et al., "Liver Transplant in Children and Adults with Cystic Fibrosis: Impact of Growth Failure and Nutritional Status," *American Journal of Transplantation* 22, no. 1 (September 2, 2021): pp. 177-186, https://doi.org/10.1111/ajt.16791.
[21] Ibid.
[22] Ibid.

with CF typically waited on the list more than three times longer than non-CF candidates.[23,24] This same research found that pediatric candidates with CF tend to have low MELD or PELD scores because CFLD-related mortality is more often related to portal hypertension complications, which may not be captured in MELD or PELD.[25,26] This research clearly demonstrates that pediatric candidates with a combination of CF and growth failure and/or malnutrition are at increased risk of waitlist mortality, which is not being captured in their calculated MELD or PELD scores. Therefore, the Committee is recommending that these candidates be considered for MELD or PELD score exceptions by the NLRB.

Finally, the new guidance also recommends that candidates with an FEV_1 less than 70% or evidence of decline in FEV_1 of greater than or equal to 5% per year be considered for a MELD or PELD exception. FEV_1 is a pulmonary function test that measures the amount of air an individual can force from his or her lungs in one second. The current policy for a CF exception requires candidates to have an FEV_1 less than 40% in order to be approved for a standard exception. However, the 40% FEV_1 criterion was included in the policy because it is the threshold at which CFLD candidates are likely to require a lung-liver transplant, not an isolated liver.[27] With the increasing availability of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies, which treat the underlying causes of CF and can relieve pulmonary-associated symptoms, more CFLD candidates are requiring an isolated liver transplant, as opposed to combined lung-liver transplant. Therefore, the proposed guidance includes a different threshold set at an FEV_1 of 70%, which captures candidates who still have significant pulmonary disease but who will be able to withstand a liver transplant procedure. An FEV_1 above 70% is considered normal for pediatric patients with CF, whereas anything below 70% is abnormal.[28]

The proposed guidance also covers candidates with declining lung function as measured by an annual decline in FEV_1 of greater than or equal to 5%. FEV_1 typically declines about 1-2% per year in people without pulmonary injury. The Committee felt that providing a pathway for a MELD or PELD exception for candidates with pulmonary function declining more rapidly was appropriate. These thresholds are based on the clinical input of the Committee and subject matter experts. Providing access to MELD or PELD exception points for this group of CFLD candidates will allow them to access liver transplant before their lung function declines to the point where liver transplantation is no longer a viable option.

The proposed guidance for pediatric candidates with CF was largely supported throughout public comment with some comments requesting clarification on a few areas. First, NATCO and the OPTN Pediatric Transplantation Committee commented that it was not particularly clear if the guidance is aimed at lung-liver transplant candidates or liver-alone candidates. The Committee agreed to add language to the proposed guidance making it more clear that the guidance is specific to liver-alone transplant candidates. In addition, the American Society of Transplant Surgeons (ASTS) noted concern that malnutrition in pediatric candidates can be measured subjectively and may be related to pancreas disease. The Committee noted that there are no objective ways to measure malnutrition in the pediatric population and agreed no changes were needed in response to this feedback.[29]

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[23] Ibid.
[24] The median waiting time for candidates with CF in the study population was 242 days, compared to 71 days for non-CF candidates.
[25] Katherine Cheng et al., "Liver Transplant in Children and Adults with Cystic Fibrosis: Impact of Growth Failure and Nutritional Status," *American Journal of Transplantation* 22, no. 1 (September 2, 2021): pp. 177-186, https://doi.org/10.1111/ajt.16791.
[26] The median calculated MELD or PELD at listing in the study population was 9 for CF candidates compared to 13 for non-CF candidates.
[27] Simon Horslen et al., "Model for End-Stage Liver Disease (MELD) Exception for Cystic Fibrosis," *Liver Transplantation* 12, no. S3 (2006), https://doi.org/10.1002/lt.20967.
[28] Peter D. Sly and Claire E. Wainwright, "Preserving Lung Function: The Holy Grail in Managing Cystic Fibrosis," *Annals of the American Thoracic Society* 14, no. 6 (2017): pp. 833-835, https://doi.org/10.1513/annalsats.201703-254ed.
[29] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 11, 2022. Available at https://optn.transplant.hrsa.gov/

Hepatic Adenomas Guidance

Hepatic adenomas (HA) are rare benign nodules occurring principally in women taking oral contraceptives.[30] Current NLRB guidance for multiple hepatic adenomas recommends candidates with HA and malignant transformation proven by biopsy or glycogen storage disease (GSD) be considered for a MELD exception. The Committee is proposing a number of updates to make this guidance more succinct, clear, and specific to the candidate population who should receive a MELD exception.
First, the proposed guidance removes the lengthy introductory paragraph that provides background information on HA. This paragraph does not contain any information that is pertinent to the actual criteria candidates must meet in order to be considered for an exception and the Committee felt it was unnecessary detail that all transplant physicians, surgeons, and NLRB reviewers would already know. More so, they found the information confusing and distracting from the exception recommendation. Therefore, the Committee elected to remove this paragraph from the guidance document.[31]

The Committee also proposes to update the criteria for a MELD exception for candidates with HA. The Committee noted that there are three general indications for liver transplant for candidates with HA:

- Candidates with adenoma in the presence of Glycogen Storage Disease (GSD)
- Candidates with unresectable β Catenin (+) adenoma
- Candidates with adenoma(s) that are unresponsive to medical or surgical management (resection) and continue to progress in size or are at risk of further complication such as hemorrhage or malignant transformation

The updated requirements are intended to provide a pathway for candidates meeting these criteria to receive a MELD exception.

First, patients with GSD or β Catenin (+) mutations are at increased risk of developing hepatic adenomas with malignant transformation.[32,33,34,35] While liver transplant is indicated for HA only in rare circumstances, it is indicated for patients at risk of malignant transformation.[36] The proposed guidance is intended to provide MELD exceptions for these candidates so they are able to access transplant before their HA develops into a malignant state.

Furthermore, there are generally accepted surgical and medical management options for hepatic adenomas, including the cessation of oral contraceptive intake in females or resection to reduce risk of more severe complications including malignant transformation or bleeding. However, when these surgical and medical options have been exhausted or if the patient is not a candidate for such interventions, and the HA continues to grow or is at risk for further complications, liver transplantation

[30] Jean-Charles Nault et al., "Molecular Classification of Hepatocellular Adenoma in Clinical Practice," *Journal of Hepatology* 67, no. 5 (2017): pp. 1074-1083, https://doi.org/10.1016/j.jhep.2017.07.009.
[31] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, June 10, 2022. Available at https://optn.transplant.hrsa.gov/
[32] Jean-Charles Nault et al., "Molecular Classification of Hepatocellular Adenoma in Clinical Practice," *Journal of Hepatology* 67, no. 5 (2017): pp. 1074-1083, https://doi.org/10.1016/j.jhep.2017.07.009.
[33] Laurence Chiche et al., "Liver Transplantation for Adenomatosis: European Experience," *Liver Transplantation* 22, no. 4 (2016): pp. 516-526, https://doi.org/10.1002/lt.24417.
[34] Julien Calderaro et al., "Molecular Characterization of Hepatocellular Adenomas Developed in Patients with Glycogen Storage Disease Type I," *Journal of Hepatology* 58, no. 2 (2013): pp. 350-357, https://doi.org/10.1016/j.jhep.2012.09.030.
[35] Jean-Charles Nault et al., "Molecular Classification of Hepatocellular Adenoma Associates with Risk Factors, Bleeding, and Malignant Transformation," *Gastroenterology* 152, no. 4 (2017), https://doi.org/10.1053/j.gastro.2016.11.042.
[36] Laurence Chiche et al., "Liver Transplantation for Adenomatosis: European Experience," *Liver Transplantation* 22, no. 4 (2016): pp. 516-526, https://doi.org/10.1002/lt.24417.

is a valid therapeutic option. As such, the final criterion in the updated guidance recommends candidates with adenomas that are unresponsive to medical or surgical management and are continuing to progress with risk of further complication should be considered for a MELD exception. Because these patients are not candidates for or have progressed despite other available therapies, liver transplantation is the remaining treatment option and typically require a MELD exception to align with their urgency for transplant.

Finally, the Committee is recommending that the guidance be updated to account for the fact that there can be rare instances where a candidate presents with a single, large, unresectable HA. The previous guidance required the presence of *multiple* hepatic adenomas. The updated guidance instead refers more generally to hepatic adenoma(s), thereby no longer implying there must be multiple adenomas in order to qualify for an exception.

This aspect of the proposal was supported throughout public comment and the Committee is not recommending any post-public comment changes.

Budd Chiari Guidance

Budd Chiari syndrome is a medical condition characterized by hepatic vein thrombosis. Patients with Budd Chiari may present with evidence of decompensated portal hypertension (ascites and hepatic hydrothorax), among other symptoms.[37]

The current MELD exception guidance for Budd Chiari asks transplant programs to submit the following information for review by the NLRB:

- Failed medical management
- Etiology of hypercoagulable state
- Any contraindications to transjugular intrahepatic portosystemic shunt (TIPS) or TIPS failure
- Decompensated portal hypertension in the form of hepatic hydrothorax requiring thoracentesis more than 1 liter per week for at least 4 weeks (transudate, no evidence of empyema, and negative cytology or any evidence of infection).
- Documentation that extrahepatic malignancy has been ruled out

The Committee is proposing four changes to this guidance.

First, similar to HA, the guidance for Budd Chiari includes a wordy introductory paragraph that explains the clinical condition but does not provide any actual information related to the criteria needed for a MELD exception. The Committee agreed that this information was distracting and confusing and is therefore proposing to remove the paragraph from guidance.

Second, the Committee is proposing the addition of failed *surgical* management alongside failed *medical* management. As listed above, transplant programs are required to provide documentation of failed medical management when submitting a MELD exception for a candidate with Budd Chiari. Members of the Committee, however, noted that some programs may attempt to treat these candidates via surgical

[37] Laura Iliescu et al., "Budd-Chiari Syndrome - Various Etiologies and Imagistic Findings. A Pictorial Review," *Medical Ultrasonography* 21, no. 3 (2019): p. 344, https://doi.org/10.11152/mu-1921.

interventions, such as shunts, and such therapeutic options should similarly be ruled out before candidates can be considered for a MELD exception.[38]

Third, the Committee is recommending that the "etiology of the hypercoagulable state" criterion be removed from the list of exception criteria. The Committee agreed that the etiology of this state is irrelevant to the candidate's need for a MELD or PELD exception and therefore is recommending the criterion be removed.[39]

And finally, the updated guidance removes the criterion related to decompensated hepatic hydrothorax requiring thoracentesis. This same criterion is covered by the guidance specific to hepatic hydrothorax, which is included elsewhere in the guidance document. Candidates with hepatic hydrothorax would be considered under that guidance and its inclusion here is redundant and unnecessary.

The proposed changes to guidance for candidates with Budd Chiari syndrome were supported throughout the public comment period and the Committee is not recommending any post-public comment changes.

Overall Sentiment from Public Comment

This proposal was released for public comment from August 3, 2022 to September 28, 2022. The proposal was on the non-discussion agenda during regional meetings. Feedback on the proposal was received via the OPTN website and sentiment polling during regional meetings.[40] Most public comment expressed support for the proposed changes to NLRB guidance. As seen in **Figure 1**, most of the regions indicated sentiment of support for the Committee's *Continued Review of NLRB Guidance* proposal.[41]

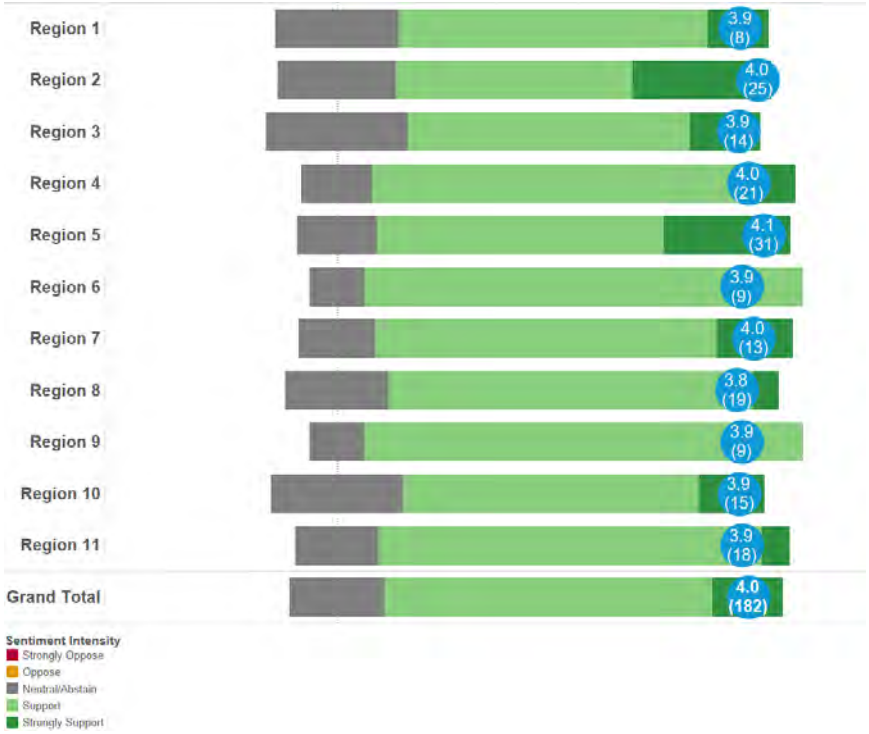
[38] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 4, 2022. Available at https://optn.transplant.hrsa.gov/

[39] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, June 10, 2022. Available at https://optn.transplant.hrsa.gov/

[40] All public comments submitted on the proposal are available at https://optn.transplant.hrsa.gov/.

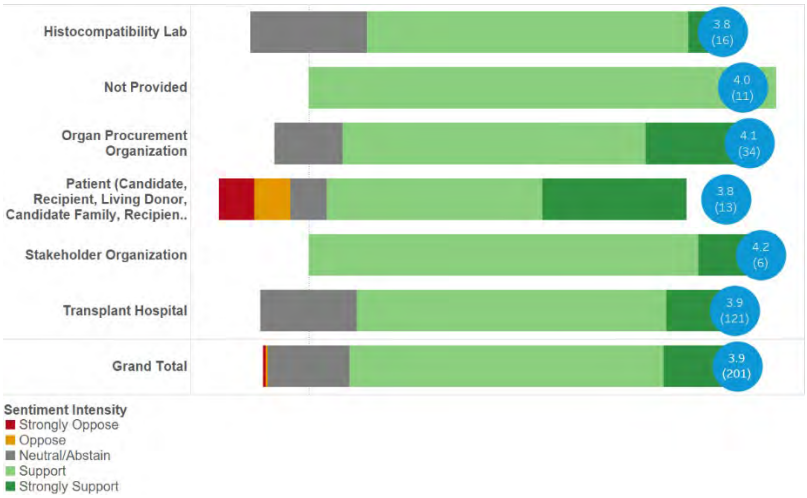
[41] This chart shows the sentiment for the public comment proposal. Sentiment is reported by the participant using a 5-point Likert scale (1-5 representing Strongly Oppose to Strongly Support). Sentiment for regional meetings only includes attendees at that regional meeting. Region 6 uses the average score for each institution. The circles after each bar indicate the average sentiment score and the number of participants is in the parentheses

Figure 1: Sentiment by Region



Public comment by member type is below in **Figure 2**.[42]

Figure 2: Sentiment by Member Type



The transplant community was largely supportive of the proposed changes to NLRB guidance. The OPTN Pediatric Transplantation Committee and the OPTN Transplant Coordinators Committee both supported

[42] This chart shows the sentiment for the public comment proposal. Sentiment is reported by the participant using a 5-point Likert scale (1-5 representing Strongly Oppose to Strongly Support). Sentiment by member type includes all comments. The circles after each bar indicate the average sentiment score and the number of participants is in the parentheses.

the proposal, with the OPTN Pediatric Transplantation Committee asking for further clarification on the pediatric CF guidance, which the Committee addressed as a post-public comment change.

The ASTS, NATCO, American Society of Transplant (AST), Society for Pediatric Liver Transplant (SPLIT) all supported the proposal. As previously noted, NATCO asked for more clarity on the target population for the pediatric CF guidance, which the Committee addressed. The ASTS noted concern that malnutrition can be difficult to objectively measure in children; the Committee discussed these concerns but elected not to make any changes to the proposed guidance. Sentiment from regional meetings was also supportive.

Compliance Analysis

NOTA and OPTN Final Rule

The OPTN issues the *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review* and *Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review* to support the operation of the NLRB by assisting the reviewers with evaluating exception requests. The OPTN Final Rule requires the Board to establish performance goals for allocation policies, including "reducing inter-transplant program variance" in performance indicators.[43] The changes to these guidance documents will assist in reducing inter-transplant program variance in the types of cases reviewed and approved by the NLRB by facilitating more consistent review of exception cases.

OPTN Strategic Plan

Per alignment with the OPTN Strategic Plan, this proposal seeks to increase equity in access to transplants.

Implementation Considerations

Histocompatibility Laboratories

Operational Considerations

This proposal will have no operational impact on histocompatibility laboratories.

Fiscal Impact

There is no expected fiscal impact for histocompatibility laboratories.

Organ Procurement Organizations

Operational Considerations

This proposal will have no operational impact on organ procurement organizations.

[43] 42 C.F.R. §121.8(b)(4)

Fiscal Impact

There is no expected fiscal impact for organ procurement organizations.

Transplant Programs

Operational Considerations

Transplant programs will need to be familiar with the proposed changes to NLRB guidance documents when submitting exception requests for candidates.

Fiscal Impact

Transplant hospitals will need to train staff on updated guidance documents for MELD and PELD exceptions.

OPTN

The OPTN contractor estimates 110 hours for implementation. Implementation will involve updates to guidance documents on the OPTN website, as well as education and training on the changes, and communication efforts about the changes. The OPTN contractor estimates 90 hours for ongoing support. Ongoing support will involve answering member questions and monitoring as part of the ongoing NLRB review effort.

Potential Impact on Select Patient Populations

The proposed changes to NLRB guidance documents may impact candidates with CF, hepatic adenomas, and Budd Chiari syndrome. The creation of guidance for pediatric candidates with CF should increase the number of such candidates receiving a MELD or PELD exception. The number of pediatric CF candidates is small and the creation of this guidance is not anticipated to drastically shift which candidates are being transplanted. It will, however, ensure that pediatric CF candidates are able to access the appropriate MELD or PELD score.

None of the proposed changes to guidance for candidates with HA or Budd Chiari are more limiting than the current criteria in guidance. As such, while the proposed changes are unlikely to create a large change in any population's ability to access transplant, the updated guidance will certainly impact individual candidates with HA or Budd Chiari. Candidates meeting the updated criteria will be more likely to be approved for a MELD exception and therefore will experience increased access to transplant.

No exception candidates will lose a current exception at the time of implementation of the updated guidance. However, NLRB reviewers and transplant programs will need to consult the updated guidance for initial exceptions and extension requests submitted after implementation.

Post-implementation Monitoring

Member Compliance

This proposal will not change current routine monitoring of OPTN members. At transplant hospitals, the OPTN will continue to review a sample of medical records, and any material incorporated into the medical record by reference, to verify that data reported in the OPTN Computer System are consistent with source documentation, including qualifying criteria for standardized MELD or PELD exceptions or exception extensions.

Policy Evaluation

Changes made to guidance will be monitored as requested by the NLRB subcommittee as part of the ongoing NLRB review.

Conclusion

This proposal includes the creation of guidance for pediatric candidates with CF and updates to guidance for adult candidates with Budd Chiari syndrome or hepatic adenomas. The Committee is proposing the creation of the new CF guidance, as such guidance does not currently exist and the exception criteria in policy are not applicable to pediatric candidates. The proposed guidance will make it more likely that these candidates are able to access liver transplant in a timely and equitable manner.

The proposal also includes a number of updates to NLRB guidance for adult candidates with Budd Chiari syndrome and hepatic adenomas. The changes to the guidance for these diagnoses include the removal of unnecessary information and the alignment of the exception criteria with the Committee's clinical consensus.

Together, these changes will create a more efficient and equitable system for reviewing MELD and PELD exception requests.

Guidance Language

Proposed new language is underlined (example) 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 Exception Review

~~Multiple~~ Hepatic Adenoma~~s~~

~~Hepatic adenomas (HA) are rare benign nodules occurring principally in women taking oral contraceptives, are solitary or multiple, and highly variable in size; there is no consensus for their management except that once their size exceeds 5 cm nodules are resected to prevent 2 major complications: bleeding and malignant transformation. An exception to this is in men where it is recommended to remove smaller nodules. The presence of HCC in HA is a well-documented observation, the risk ranging from 5 to 9%; gene coding for β-catenin mutations (15-18% of cases) are associated with a high risk of malignant transformation (together with cytologic atypia). HA are a frequent mode of presentation in some genetic diseases, particularly Glycogen Storage Disease (GSD) and congenital or acquired vascular anomalies.~~

Orthotopic liver transplantation for hepatic adenoma (HA) remains an extremely rare indication; however, it is a valid therapeutic option in select patients with adenoma meeting one of the following categories: ~~with risk of malignant transformation, not amenable to resection (the reason must be provided), and one or more of the following~~:

- ~~Malignant transformation proven by biopsy~~
- ~~Presence of glycogen storage disease which increases the risk for malignant transformation~~
- Adenoma in the presence of Glycogen Storage Disease
- Unresectable β Catenin (+) Adenoma
- Adenoma(s) with all three below:
  - Unresponsive to medical management
  - Unresectable
  - Progressive or with complication such as hemorrhage or malignant transformation (must specify)

The identification of these criteria is mandatory to aid in the decision-making process.

Budd Chiari

Approval of MELD exception points for adult candidates with Budd Chiari may be appropriate in some instances.

~~Budd Chiari syndrome is an uncommon manifestation of hepatic vein thrombosis and patients might present with evidence of decompensated portal hypertension (ascites and hepatic hydrothorax) among others. Medical management may include diuresis and anticoagulation; or more aggressive management with Transjugular Intrahepatic Portosystemic Shunt (TIPS), portosystemic shunting, or liver transplant. Anticoagulation and pharmacologic management is the cornerstone treatment. Patients with severe portal hypertension not controlled with the standard of care might have evidence of hyponatremia or renal impairment, but these will be accurately reflected by the calculated MELD score.~~

Liver transplant candidates with Budd Chiari syndrome ~~could~~ can be considered ~~on an individual basis~~ for a MELD exception based on severity of liver dysfunction and failure of standard management. Documentation submitted for case review should include all of the following:

- Failed medical or surgical management (please specify)
- ~~Etiology of hypercoagulable state~~
- Any contraindications to TIPS or TIPS failure; specify specific contraindication
- ~~Decompensated portal hypertension in the form of hepatic hydrothorax requiring thoracentesis more than 1 liter per week for at least 4 weeks (transudate, no evidence of empyema, and negative cytology or any evidence of infection).~~
- Documentation that extrahepatic malignancy has been ruled out

Guidance to Liver Transplant Programs and the National Liver Review Board for: Pediatric MELD/PELD Exception Review

Cystic Fibrosis

The current criteria for a standard exception for cystic fibrosis (CF) outlined in *OPTN Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* often do not apply to children and adolescents with CF-related liver disease (CFLD) who are listed for liver-only transplant. The major causes of liver-related morbidity and mortality in children with CFLD include cirrhosis with hepatic dysfunction and microscopic portal venopathy, leading to portal hypertension without hepatic dysfunction. CF-related comorbidities, including lung disease, sinusitis, CF-related diabetes, multi-drug resistant organisms and pancreatic insufficiency, may impact survival as well.

Calculated MELD or PELD score may underestimate the risk of waitlist mortality for pediatric liver candidates with CFLD, particularly in those with complications of portal hypertension or with other CF-related morbidities. **Evidence currently supports that pediatric liver transplant candidates with CFLD should be considered for additional MELD or PELD exception points when any of the following criteria are met:**

- Candidate has portal hypertension with complications and the transplant program demonstrates that the patient has failed or is not a candidate for medical, endoscopic or surgical interventions to prevent or treat these complications.
- Candidate has growth failure as a result of liver disease, defined by age and sex-specific weight, length/height, weight-for-length, and/or BMI percentiles or has moderate to severe malnutrition. Children and adolescents with CF and growth failure have a higher risk of waitlist mortality than children with non-CF related liver disease and therefore calculated MELD or PELD may not fully capture their risk of mortality.[44]
- Candidate has an FEV_1 <70% or evidence of decline in FEV_1 of ≥5% per year, as these children may be expected to move toward advanced lung disease, reducing the opportunity for liver transplant.[45]

Since CFLD is an uncommon indication for liver transplant, there is minimal direct evidence on mortality risk conferred by other CF-related morbidities in CF liver transplant candidates. Other CF-related morbidities should thus be considered as justification for MELD or PELD exceptions on a case-by-case basis.

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[44] Katherine Cheng et al., "Liver Transplant in Children and Adults with Cystic Fibrosis: Impact of Growth Failure and Nutritional Status," *American Journal of Transplantation* 22, no. 1 (September 2, 2021): pp. 177-186, https://doi.org/10.1111/ajt.16791.
[45] A. Jay Freeman et al., "A Multidisciplinary Approach to Pretransplant and Posttransplant Management of Cystic Fibrosis–Associated Liver Disease," *Liver Transplantation* 25, no. 4 (2019): pp. 640-657, https://doi.org/10.1002/lt.25421.