OPTN

Briefing to the OPTN Board of Directors on

National Liver Review Board (NLRB) Updates Related to Transplant Oncology

OPTN Liver & Intestinal Organ Transplantation Committee

Prepared by: Meghan McDermott
UNOS Policy Department

Contents

Executive Summary	2
Purpose	3
Background	3
Proposal for Board Consideration	5
Overall Sentiment from Public Comment	14
Compliance Analysis	17
Implementation Considerations	17
Post-implementation Monitoring	20
Conclusion	20
Policy Language	21
Guidance Language	23
Operational Guidelines Language	36
Appendix A: Post-Public Comment Changes	38

National Liver Review Board (NLRB) Updates Related to Transplant Oncology

Affected Policy: *9.5.A: Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions*
Affected Guidance: *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma; Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review; National Liver Review Board Operational Guidelines*
Sponsoring Committee: *Liver & Intestinal Organ Transplantation*
Public Comment Period: *January 23, 2024 – March 19, 2024*
Board of Directors Meeting: *June 17-18, 2024*

Executive Summary

The purpose of the National Liver Review Board (NLRB) is to provide equitable access to transplant for liver transplant 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 recommends the addition of OPTN guidance specific to colorectal liver metastases and intrahepatic cholangiocarcinoma for the NLRB. This proposal also expands the purview of the Adult Hepatocellular Carcinoma (HCC) Review Board to review non-standard exception cases related to liver cancers and tumors. As such, the scope of the Adult HCC Review Board is proposed to be broadened and renamed as the Adult Transplant Oncology Review Board. The proposed Adult Transplant Oncology guidance document includes guidance for HCC, intrahepatic cholangiocarcinoma, neuroendocrine tumors, colorectal liver metastases, hepatic epithelioid hemangioendothelioma, and hepatic adenomas. The Adult Transplant Oncology Review Board will review non-standard exception cases for these diagnoses as well as any non-standard exception requests for hilar cholangiocarcinoma (CCA), and any other liver cancer or tumor-related request.

Additionally, this proposal recommends two clarifications to Policy 9.5.A: *Requirements for CCA MELD or PELD Score Exceptions* to ensure consistency and accuracy of the policy.

The Committee made minor clarifications post-public comment to the NLRB guidance document. No post-public comment changes were proposed that changed the substance or intent of the original proposals.

[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 of updates related to the NLRB is to continue to improve the NLRB by creating a more efficient and equitable system for reviewing MELD and PELD exception requests. This proposal has several changes related to liver oncology as an indication for liver transplant. The first of these changes is the creation of new guidance that seeks to increase access to transplant for candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma through non-standard exceptions. Additionally, the Committee is proposing for the Adult HCC Review Board to become an Adult Transplant Oncology Review Board to ensure that non-standard exception cases specific to liver cancers and tumors are reviewed by specialists in the field. Lastly, a policy clarification is included in this proposal to ensure the current practice for reviewing and approving hilar CCA protocols aligns with language in Policy *9.5.A: Requirements for CCA MELD or PELD Score Exceptions*.

Background

National Liver Review Board

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 non-standard exception requests and either approving or denying the requested score.

The NLRB was approved by the OPTN Board of Directors (the Board) during a June 2017 meeting and was implemented on May 14, 2019.[3] The NLRB was designed to create an efficient and equitable system for reviewing non-standard exception requests for liver 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] If a candidate does not meet the standardized criteria in OPTN policy or is seeking an exception outside of one of the nine diagnoses in policy, a non-standard exception request can be submitted to the NLRB.

There are three specialty review boards, Pediatric, Adult - HCC, and Adult - Other Diagnosis (**Figure 1**) and each specialty review board has an associated guidance document.[6] The guidance documents contain information for review board members and transplant programs on diagnoses and clinical

---

[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] OPTN Policy 9.5: Specific Standardized MELD or PELD Exceptions, as of December 2023. Available at https://optn.transplant.hrsa.gov/.
[6] NLRB Guidance Documents are available at https://optn.transplant.hrsa.gov/.

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 non-standard exception cases and are not OPTN policy.

Figure 1: National Liver Review Board: Specialty Review Boards

Pediatrics

- Reviews requests made on behalf of:
  - Candidates registered prior to turning 18 years old
  - Adult candidates with certain pediatric diagnoses

Adult Other Diagnosis

- Reviews requests made on behalf of:
  - Adult candidates whose calculated scores do not reflect their medical urgency
  - Adult candidates that do not meet the standard criteria for one of the nine diagnoses in Policy 9.5: *Specific Standardized MELD or PELD Score Exceptions* (excluding HCC cases)

Adult Hepatocellular Carcinoma (HCC)

- Reviews requests made on behalf of:
  - Adult candidates that do not meet the standard criteria in Policy 9.5.I*: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions*

Because the guidance documents are consulted by transplant programs and NLRB reviewers when applying for and reviewing non-standard exception requests, they impact which liver candidates are approved for a MELD or PELD exception. Therefore, it is necessary for the Committee to update the guidance documents to ensure they continue to align with current clinical consensus and updated data. This proposal modifies and renames the Adult HCC guidance document by broadening its scope to encompass additional indications for transplant related to liver cancers or tumors.

Transplant Oncology

Transplant oncology is an emerging approach to cancer treatment used to improve patients' likelihood of survival and quality of life. The field of transplant oncology combines oncologic, transplant medicine, and surgical expertise to manage and treat diagnoses. Transplant oncology can potentially contribute to the treatment and research of liver cancers in innovative ways.[7,8] By removing the cancerous organ entirely and replacing it with a non-cancerous organ, liver transplantation may be used as a curative approach for malignancy.

Using liver transplantation as an effective therapy for HCC has been widely accepted by the community for years. With this, it has been proven that liver transplantation is an effective treatment for those with

[7] Abdelrahim M, Esmail A, Abudayyeh A, Murakami N, Saharia A, McMillan R, Victor D, Kodali S, Shetty A, Nolte Fong JV, Moore LW, Heyne K, Gaber AO, Ghobrial RM. Transplant Oncology: An Evolving Field in Cancer Care. Cancers (Basel). 2021 Sep 29;13(19):4911. doi: 10.3390/cancers13194911. PMID: 34638395; PMCID: PMC8508383.
[8] Abdelrahim M, Esmail A, Abudayyeh A, Murakami N, Victor D, Kodali S, Cheah YL, Simon CJ, Noureddin M, Connor A, et al. Transplant Oncology: An Emerging Discipline of Cancer Treatment. *Cancers*. 2023; 15(22):5337. https://doi.org/10.3390/cancers15225337.

small, unresectable HCC lesions. Liver transplantation has extended the quality and quantity of years of life for these individuals. [9]

More recently, liver transplantation has been expanded to patients with other liver malignancies such as neuroendocrine tumors and hepatic epithelioid hemangioendotheliomas. NLRB guidance has already been developed for the aforementioned diagnoses, and with the evolution of the liver transplantation field, the Committee proposes the creation of guidance for colorectal liver metastases and intrahepatic cholangiocarcinoma based on literature.

Proposal for Board Consideration

The Committee proposes the creation of NLRB guidance for colorectal liver metastases and intrahepatic cholangiocarcinoma. While liver transplantation has been observed to be beneficial for these populations[10,11] calculated MELD scores remain low resulting in a lack of access to liver transplant. Therefore, transplant rates for candidates with these diagnoses remain low. The Committee recognizes the small population sizes for each diagnosis as well as the need for additional literature to establish more robust outcomes analyses. For those reasons, the Committee is recommending creating specific NLRB guidance for each diagnosis for liver candidates to access exception scores rather than developing standardized criteria for policy. The Committee determined it is necessary to establish score recommendations for each diagnosis that would not interfere with transplant access for other medically urgent liver candidates. More information on the proposed guidance, score recommendations, and public comment feedback is provided in each relevant section.

To ensure that the appropriate reviewers with expertise are reviewing these cases, the Committee proposes broadening the current Adult HCC Review Board to become an Adult Transplant Oncology Review Board.

Additionally, the Committee proposes a clarification of Policy 9.5.A in order to align the policy language to current practice and original intent.

The Committee made minor clarification modifications post-public comment to the NLRB guidance document. No post-public comment changes were proposed that changed the substance or intent of the original proposal. The modifications to the language in the NLRB guidance document, detailed below, were made for the purposes of clarity.

- Modified “MMaT score” to “exception score” for use of accurate and consistent terminology.
- Separated two criteria within the intrahepatic cholangiocarcinoma guidance to become distinct criterion.

---

[9] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334(11):693-9. doi: 10.1056/NEJM199603143341104. PMID: 8594428.

[10] Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, Clavien PA, Furtado E, Barroso E, Bismuth H; Compagnons Hépato-Biliaires Group. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. Liver Transpl. 2017 Aug;23(8):1073-1076. doi: 10.1002/lt.24791. PMID: 28544246.

[11] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucchetti A, Pinna A, Hwang S, Lee SG, Agopian VG, Busuttil RW, Rizvi S, Heimbach JK, Montenovo M, Reyes J, Cesaretti M, Soubrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferro V, Dutkowski P, Clavien PA, Toso C, Majno P, Kneteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016 Oct;64(4):1178-88. doi: 10.1002/hep.28744. Epub 2016 Aug 24. PMID: 27481548.

- Provided clarity around the criterion related to tumor stability for the intrahepatic cholangiocarcinoma guidance.

The Committee unanimously approved this proposal to be submitted to the OPTN Board of Directors of consideration.[12]

Colorectal Liver Metastases

Colorectal liver metastases are malignant growths in the liver that develop from colorectal cancer, and studies have shown that around 25% of patients diagnosed with colorectal cancer develop liver metastases during the course of their disease.[13] Surgical resection of the metastases is a treatment option that can offer a chance of cure and long-term survival; however, only a minority of patients are suitable candidates for resection.[14] Colorectal liver metastases that are deemed unresectable are due to the location within the liver which prevents complete resection. Therefore, interest has remained in liver transplantation as a potential treatment option for unresectable colorectal liver metastases.

While unresectable colorectal liver metastases historically have been considered absolute contraindications by transplant programs for a liver transplant, literature has demonstrated the potential benefit of a liver transplant for individuals with this diagnosis.[15,16,17] Studies have indicated that liver transplant for unresectable colorectal liver metastases results in higher overall survival when compared to other treatment options such as chemotherapy or portal vein embolization with resection.[18,19]

However, candidates listed for transplant with colorectal liver metastases have low MELD scores, and as a result access to transplant also remains low. Therefore, the Committee is proposing to add guidance for this diagnosis in order for specific candidates with unresectable colorectal liver metastases to access MELD non-standard exception scores. The drafted guidance is based on protocol developed and studied

---

[12] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 15, 2024. Available at https://optn.transplant.hrsa.gov/.

[13] Martin J, Petrillo A, Smyth EC, Shaida N, Khwaja S, Cheow HK, Duckworth A, Heister P, Praseedom R, Jah A, Balakrishnan A, Harper S, Liau S, Kosmoliaptsis V, Huguet E. Colorectal liver metastases: Current management and future perspectives. World J Clin Oncol. 2020 Oct 24;11(10):761-808. doi: 10.5306/wjco.v11.i10.761. PMID: 33200074; PMCID: PMC7643190.

[14] Chow FC, Chok KS. Colorectal liver metastases: An update on multidisciplinary approach. World J Hepatol. 2019 Feb 27;11(2):150-172. doi: 10.4254/wjh.v11.i2.150. PMID: 30820266; PMCID: PMC6393711.

[15] Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013 May;257(5):800-6. doi: 10.1097/SLA.0b013e3182823957. PMID: 23360920.

[16] Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, Clavien PA, Furtado E, Barroso E, Bismuth H; Compagnons Hépato-Biliaires Group. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. Liver Transpl. 2017 Aug;23(8):1073-1076. doi: 10.1002/lt.24791. PMID: 28544246.

[17] Sasaki K, Ruffolo LI, Kim MH, Fujiki M, Hashimoto K, Imaoka Y, Melcher ML, Aucejo FN, Tomiyama K, Hernandez-Alejandro R. The Current State of Liver Transplantation for Colorectal Liver Metastases in the United States: A Call for Standardized Reporting. Ann Surg Oncol. 2023 May;30(5):2769-2777. doi: 10.1245/s10434-023-13147-6. Epub 2023 Jan 31. PMID: 36719568; PMCID: PMC9888331.

[18] Dueland S, Yaqub S, Syversveen T, Carling U, Hagness M, Brudvik KW, Line PD. Survival Outcomes After Portal Vein Embolization and Liver Resection Compared With Liver Transplant for Patients With Extensive Colorectal Cancer Liver Metastases. JAMA Surg. 2021 Jun 1;156(6):550-557. doi: 10.1001/jamasurg.2021.0267. PMID: 33787838; PMCID: PMC8014205.

[19] Quillin RC 3rd, Shah SA. Liver Transplant for Extensive Colorectal Liver Cancer Metastases: Another Tool in the Arsenal? JAMA Surg. 2021 Jun 1;156(6):558. doi: 10.1001/jamasurg.2021.0269. PMID: 33787855.

by the Oslo University Hospital in Norway.[20] The proposed guidance outlines several criteria suggested for initial exception requests, extension exception requests, as well as exclusion criteria.

The proposed criteria in the guidance states that candidates can be considered for a non-standard exception if the colorectal liver metastases are unresectable. Additional criteria proposed in the guidance for an initial MELD exception relate to the primary diagnosis of colon/rectal adenocarcinoma, treatment of the primary colorectal cancer, and evaluation of extrahepatic and hepatic disease. If the candidate has synchronous colon lesions, there are additional proposed criteria.

The guidance outlines exclusion criteria to specify which candidates should not be considered for an initial MELD exception. This includes candidates with extra-hepatic disease after primary tumor resection, local relapse of the primary disease, or carcinoembryonic antigen (CEA) levels greater than 80 µg/L.

Regarding the criteria for extending an exception, the Committee proposes that the candidates should continue to have computed tomography (CT) or magnetic resonance imaging (MRI) performed every three months, CEA testing performed every three months, no progression of hepatic disease, no development of extrahepatic disease, and that CEA levels remain less than 80 µg/L.

The Committee proposes that candidates meeting the criteria in guidance should be awarded median MELD at transplant (MMaT) minus 20. Per Policy *9.4.E: MELD or PELD Exception Scores Relative to Median MELD or PELD at Transplant*, if a candidate's exception score relative to MMaT or median PELD at transplant (MPaT) is lower than 15, the candidate's exception score will automatically be set to 15. As an example, if a candidate has an approved non-standard exception for colorectal metastases (MMaT minus 20) and receives a liver offer from a donor hospital whose MMaT is 27, that candidate will appear on the match run with an allocation MELD score of 15 due to the requirements in Policy 9.4.E.

The Committee reviewed the current MMaT scores around the donor hospital and determined that the highest MMaT in the most recent calculation was 35.[21] With the knowledge that a candidate's allocation score will automatically be set to 15 if their exception score relative to MMaT is lower than 15 and the highest MMaT for a donor hospital was 35, the Committee determined MMaT minus 20 would put most, if not all, candidates with these exceptions on match runs with allocation scores of 15. The Committee aimed for a score recommendation to place candidates meeting the criteria in guidance to have MELD scores around 15 because it would increase access to transplant for those candidates while not having them compete with candidates who are more medically urgent. The Committee reasoned that most transplants for this candidate population are likely to occur with a medically complex liver and MELD scores around 15 give access to these types of liver offers.[22]

Public comment feedback on colorectal liver metastases guidance

Public comment was supportive of the proposed NLRB guidance for colorectal liver metastases. Some public comment feedback stated that MMaT – 20 was too low of a score recommendation to provide

[20] Solheim JM, Dueland S, Line PD, Hagness M. Transplantation for Nonresectable Colorectal Liver Metastases: Long-Term Follow-Up of the First Prospective Pilot Study. Ann Surg. 2023 Aug 1;278(2):239-245. doi: 10.1097/SLA.0000000000005703. Epub 2022 Sep 9. PMID: 36082986.
[21] Median MELD at Transplant Around Liver Donor Hospitals and Median PELD at Transplant Within the Nation available at https://optn.transplant.hrsa.gov/.
[22] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, October 16, 2023. Available at https://optn.transplant.hrsa.gov/.

meaningful access to transplant while other public comment feedback stated that exceptions should not be granted for colorectal liver metastases. While discussing public comment feedback, the Committee considered adjusting the score recommendation based on community suggestions. Ultimately, the Committee reaffirmed their initial recommendation of MMaT – 20.[23] As noted in the Committee's initial rationale, a MMaT – 20 will place most, if not all, candidates with this exception with allocation scores of 15 meaning that it will not result in this population competing with more medically urgent candidates. The Committee reasoned that, if implemented, the impact will be monitored, and if a change to the score recommendation is indicated at that time, then they will reconsider and adjust as appropriate. But for the time being, the Committee considers MMaT – 20 to be the most appropriate score recommendation.

There was some feedback from the community that offered clarifying suggestions for parts of the proposed guidance language. This feedback included suggestions such as defining the term unresectable or including all of the guidance from the International Hepato-Pancreato Biliary Association's (IHBPA) guidance on colorectal liver metastases. The Committee concluded that NLRB guidance should not be overly prescriptive and decided to maintain the proposed criteria.

Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma is a type of cancer that forms in the bile ducts and is categorized according to anatomical location.[24,25] Surgical resection remains the main treatment option for intrahepatic cholangiocarcinoma.[26] However, surgical resection is not a treatment option for all patients due to the progression of disease, location of the tumor, or underlying liver disease.[27] Therefore, liver transplantation offers an alternative treatment option for patients with unresectable intrahepatic cholangiocarcinoma.

Historically, very early transplant for liver candidates with intrahepatic cholangiocarcinoma has been rare. However, literature has shown that transplant outcomes for early intrahepatic cholangiocarcinoma (tumor size less than two centimeters) have high recurrence-free survival, as well as overall

---

[23] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 5, 2024. Available at https://optn.transplant.hrsa.gov/.

[24] "Cholangiocarcinoma (bile duct cancer)", Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/cholangiocarcinoma/symptoms-causes/syc-20352408.

[25] Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018 Feb;15(2):95-111. doi: 10.1038/nrclinonc.2017.157. Epub 2017 Oct 10. PMID: 28994423; PMCID: PMC5819599.

[26] Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018 Feb;15(2):95-111. doi: 10.1038/nrclinonc.2017.157. Epub 2017 Oct 10. PMID: 28994423; PMCID: PMC5819599.

[27] Sapisochín G, Fernández de Sevilla E, Echeverri J, Charco R. Liver transplantation for cholangiocarcinoma: Current status and new insights. World J Hepatol. 2015 Oct 8;7(22):2396-403. doi: 10.4254/wjh.v7.i22.2396. PMID: 26464755; PMCID: PMC4598610.

survival.[28,29,30,31] This indicates that transplant for liver candidates with small unresectable intrahepatic cholangiocarcinoma may be beneficial.

However, MELD scores for candidates with intrahepatic cholangiocarcinoma are low[32], so access to transplant for this population remains lacking. The Committee proposes the creation of NLRB guidance for unresectable intrahepatic cholangiocarcinoma to increase transplant access for a select population of candidates meeting criteria.

Guidance indicates that the intrahepatic cholangiocarcinoma must be biopsy-proven in order to understand whether the tumor is intrahepatic cholangiocarcinoma, HCC, or mixed HCC-intrahepatic cholangiocarcinoma.[33] The Committee recommends that mixed HCC-intrahepatic cholangiocarcinoma cases be included in the proposed guidance in order to create a pathway to access non-standard exceptions for these candidates.[34]

While the Committee acknowledges that there is more robust evidence to support transplantation for intrahepatic cholangiocarcinoma tumors that are less than or equal to two centimeters in size, the Committee proposes a less than or equal to three centimeters tumor size threshold in guidance. The Committee believes this tumor size threshold is more appropriate for several reasons including literature that has shown good 5-year survival outcomes.[35] The Committee recommends less than or equal to three centimeters tumor size criterion in guidance because transplant programs may not pursue tumors that are less than or equal to two centimeters in size and a less than or equal to three centimeters size threshold aligns with HCC criteria.[36] Additionally, the population of candidates with this

[28] Sapisochin G, Rodríguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, Castroagudín JF, Varo E, López-Andujar R, Palacios F, Sanchez Antolín G, Perez B, Guiberteau A, Blanco G, González-Diéguez ML, Rodriguez M, Varona MA, Barrera MA, Fundora Y, Ferron JA, Ramos E, Fabregat J, Ciria R, Rufian S, Otero A, Vazquez MA, Pons JA, Parrilla P, Zozaya G, Herrero JI, Charco R, Bruix J. "Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? Am J Transplant. 2014 Mar;14(3):660-7. doi: 10.1111/ajt.12591. Epub 2014 Jan 10. PMID: 24410861.

[29] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucchetti A, Pinna A, Hwang S, Lee SG, Agopian VG, Busuttil RW, Rizvi S, Heimbach JK, Montenovo M, Reyes J, Cesaretti M, Soubrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferro V, Dutkowski P, Clavien PA, Toso C, Majno P, Kneteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016 Oct;64(4):1178-88. doi: 10.1002/hep.28744. Epub 2016 Aug 24. PMID: 27481548.

[30] Ziogas IA, Giannis D, Economopoulos KP, Hayat MH, Montenovo MI, Matsuoka LK, Alexopoulos SP. Liver Transplantation for Intrahepatic Cholangiocarcinoma: A Meta-analysis and Meta-regression of Survival Rates. Transplantation. 2021 Oct 1;105(10):2263-2271. doi: 10.1097/TP.0000000000003539. PMID: 33196623.

[31] McMillan RR, Javle M, Kodali S, Saharia A, Mobley C, Heyne K, Hobeika MJ, Lunsford KE, Victor DW 3rd, Shetty A, McFadden RS, Abdelrahim M, Kaseb A, Divatia M, Yu N, Nolte Fong J, Moore LW, Nguyen DT, Graviss EA, Gaber AO, Vauthey JN, Ghobrial RM. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. Am J Transplant. 2022 Mar;22(3):823-832. doi: 10.1111/ajt.16906. Epub 2021 Dec 27. PMID: 34856069.

[32] McMillan RR, Javle M, Kodali S, Saharia A, Mobley C, Heyne K, Hobeika MJ, Lunsford KE, Victor DW 3rd, Shetty A, McFadden RS, Abdelrahim M, Kaseb A, Divatia M, Yu N, Nolte Fong J, Moore LW, Nguyen DT, Graviss EA, Gaber AO, Vauthey JN, Ghobrial RM. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. Am J Transplant. 2022 Mar;22(3):823-832. doi: 10.1111/ajt.16906. Epub 2021 Dec 27. PMID: 34856069.

[33] OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, April 13, 2023. Available at https://optn.transplant.hrsa.gov/.

[34] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, October 16, 2023. Available at https://optn.transplant.hrsa.gov/.

[35] Ziogas IA, Giannis D, Economopoulos KP, Hayat MH, Montenovo MI, Matsuoka LK, Alexopoulos SP. Liver Transplantation for Intrahepatic Cholangiocarcinoma: A Meta-analysis and Meta-regression of Survival Rates. Transplantation. 2021 Oct 1;105(10):2263-2271. doi: 10.1097/TP.0000000000003539. PMID: 33196623.

[36] OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, October 10, 2023. Available at https://optn.transplant.hrsa.gov/.

diagnosis is small, and having a size threshold that is less than or equal to two centimeters will limit the population eligible to receive a non-standard exception even further. There is evidence to support consideration of intrahepatic cholangiocarcinoma less than or equal to three centimeters on a case-by-case basis and it would allow more research to occur on outcomes.[37,38]

Additional criteria that the Committee proposed in the guidance for intrahepatic cholangiocarcinoma include that the tumor is unresectable. The candidate should have presence of cirrhosis as well as have been treated for cancer and stable for six months. The Committee recommends that for exception extensions, imaging should be performed every three months to ensure the tumor remains less than or equal to three centimeters and that there is no extrahepatic disease.

The Committee proposes that candidates meeting the criteria in the guidance document should be awarded MMaT minus three. The Committee reasons that MMaT minus three is an acceptable score recommendation due to the small population size, evidence of good outcomes which are similar to HCC outcomes, and the specific criteria in guidance for the candidate to have undergone therapy and a six-month wait before applying for an initial exception.[39]

Public comment feedback on intrahepatic cholangiocarcinoma guidance

Public comment was supportive of the proposed NLRB guidance for intrahepatic cholangiocarcinoma. Most of the feedback provided offered suggestions for clarifications or modifications to parts of the proposed guidance. The Committee again determined that NLRB guidance should not be too prescriptive and as such opted to not incorporate all clarification suggestions in order to allow for clinical variation.[40] The one post-public comment change the Committee did incorporate was clarifying the criteria related to treatment and six-months of stability.[41] This clarification separates the criteria into two distinct criterion, and adds language to explain the meaning of tumor stability.

A couple of public comments offered alternative suggestions for a score recommendation, but the Committee ultimately agreed to move forward with their proposed score recommendation of MMaT – 3 due to the broad support of the score recommendation.[42]

Adult Transplant Oncology Guidance Document & Review Board

Due to the addition of two new diagnoses specific to oncological indications for transplant, the Committee believes that reviewers on the Adult HCC Review Board would be best suited to review these new cases.[43] Reviewers on the Adult HCC Review Board have more expertise in the field of cancer than those on the Adult Other Diagnosis Review Board. As such, the Committee is proposing to expand the

---

[37] OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, September 12, 2023. Available at https://optn.transplant.hrsa.gov/.

[38] OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, October 10, 2023. Available at https://optn.transplant.hrsa.gov/.

[39] OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, September 12, 2023. Available at https://optn.transplant.hrsa.gov/.

[40] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 5, 2024. Available at https://optn.transplant.hrsa.gov/.

OPTN Liver & Intestinal Organ Transplantation Committee, NLRB Subcommittee, Meeting Summary, April 9, 2024. Available at https://optn.transplant.hrsa.gov/.

[42] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 5, 2024. Available at https://optn.transplant.hrsa.gov/.

[43] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, October 16, 2023. Available at https://optn.transplant.hrsa.gov/.

purview of the Adult HCC Review Board to include the review of non-standard exception requests related to all liver cancers and tumors. The Committee proposes for this review board to be renamed as the Adult Transplant Oncology Review Board.

Since the scope of the review board has broadened, the Committee reviewed the current guidance in the Adult Other Diagnosis guidance document to ensure proper alignment. The Committee proposes that some of the diagnoses that are currently reviewed by the Adult Other Diagnosis Review Board should be reviewed by an Adult Transplant Oncology Review Board These diagnoses include neuroendocrine tumors, hepatic epithelioid hemangioendotheliomas, and hepatic adenomas.[44] Thus, modifications to the Adult Other Diagnosis guidance were made to remove the guidance for these three diagnoses and add them to the Adult Transplant Oncology guidance document. **Figure 2** details the current diagnoses in the Adult Other Diagnosis guidance document and highlights the diagnoses that are being proposed to be moved to the Adult Transplant Oncology guidance document.

Figure 2: Shift from Adult Other Diagnosis and Adult Transplant Oncology Guidance Documents

Adult Other Diagnosis	Adult Transplant Oncology
•Ascites	•Hepatocellular Carcinoma
•Budd Chiari	**•Neuroendocrine Tumors**
•Gastrointestinal Bleeding	**•Hepatic Epithelioid Hemangioendothelioma**
~~**•Hepatic Epithelioid Hemangioendothelioma**~~	**•Hepatic Adenomas**
•Hepatic Hydrothorax	•Colorectal Liver Metastases (*new*)
•Hereditary Hemorrhagic Telangiectasia	•Intrahepatic Cholangiocarcinoma (new)
~~**•Hepatic Adenomas**~~	
~~**•Neuroendocrine Tumors**~~	
•Polycystic Liver Disease	
•Portopulmonary Hypertension	
•Primary Sclerosing Cholangitis or Secondary Sclerosing Cholangitis	
•Metabolic Disease	
•Multivisceral Transplant Candidates	
•Post-Transplant Complications	

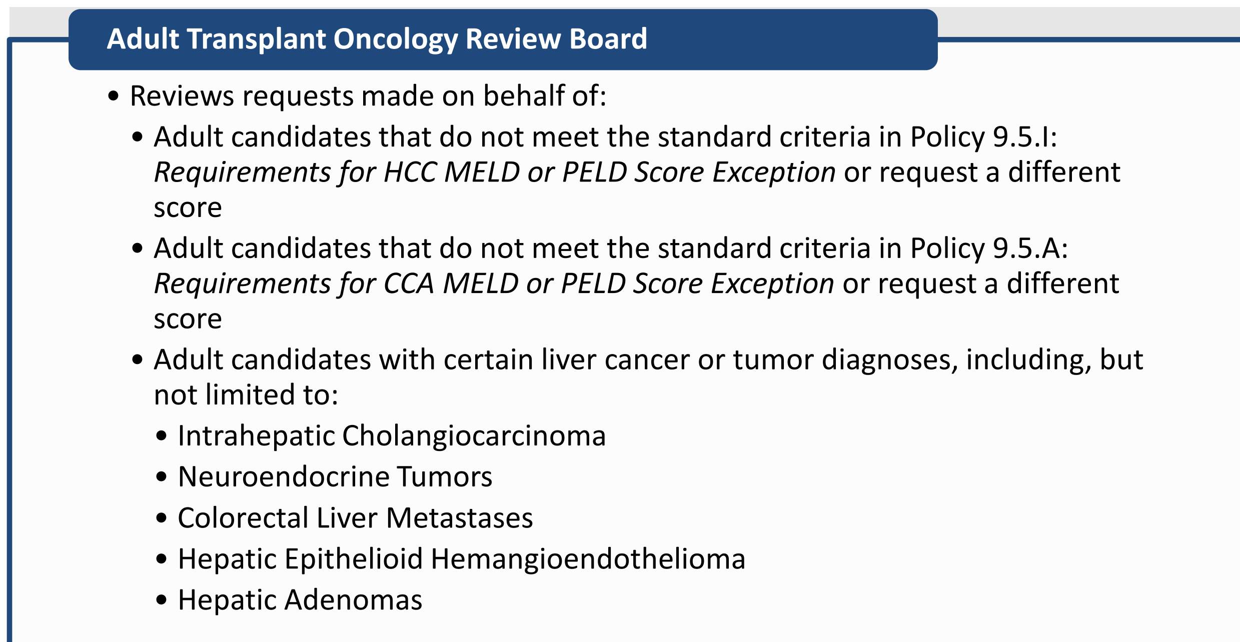
The Committee proposes that any new non-standard exception requests for CCA be reviewed by the new Adult Transplant Oncology Review Board, including hilar CCA. Currently, if a candidate does not meet standard criteria for hilar CCA in Policy 9.5.A, the case would be reviewed by the Adult Other Diagnosis Review Board. Under this proposal, non-standard hilar CCA exception requests would be reviewed by the Adult Transplant Oncology Review Board. There is not currently guidance for candidates with hilar CCA who do not meet the standardized criteria in Policy 9.5.A, however, the Committee may develop guidance in the future for non-standard hilar CCA exception requests should it be indicated.

Figure 3 details the scope of the proposed Adult Transplant Oncology Review Board. To summarize the proposed modifications, the Adult Transplant Oncology Review Board will review exception requests for

[44] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, November 3, 2023. Available at https://optn.transplant.hrsa.gov/.

candidates who do not meet the standard criteria for HCC and hilar CCA or if a different exception score is requested. The Adult Transplant Oncology Review Board will also review non-standard exception requests for neuroendocrine tumors, hepatic epithelioid hemangioendotheliomas, and hepatic adenomas, which were previously reviewed by the Adult Other Diagnosis Review Board. Any exception request relative to the new guidance for colorectal liver metastases and intrahepatic cholangiocarcinoma will also be reviewed by the Adult Transplant Oncology Review Board. Finally, any non-standard liver cancer or tumor exception requests that are not covered by the previously mentioned diagnoses can be entered in an *other specify* field that is specific to liver cancers and tumors, and these will be routed to the Adult Transplant Oncology Review Board for review.

Figure 3: Purview of Transplant Oncology Review Board



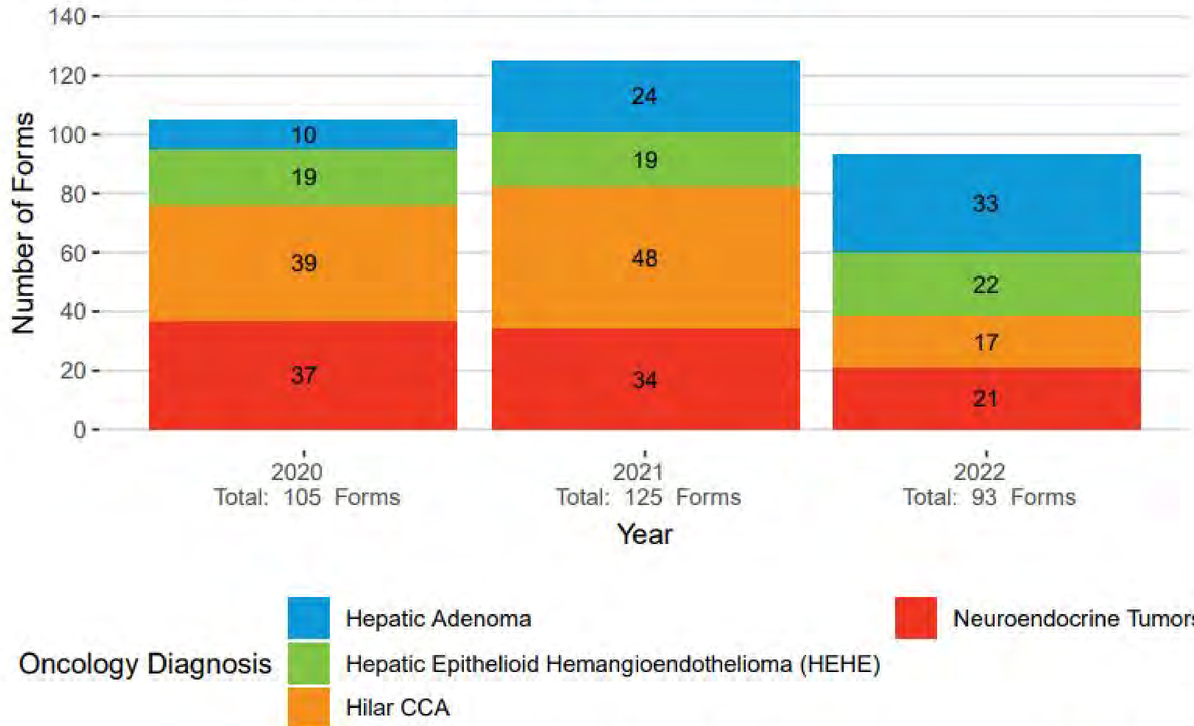
As noted in **Figure 1**, the Pediatric specialty board reviews non-standard exception requests for candidates registered prior to turning 18 years old and cases for adult candidates with certain pediatric diagnoses. Currently, if a non-standard exception is submitted for a pediatric candidate related to transplant oncology, it will be reviewed by the Pediatric Review Board. The Committee affirmed upholding this same process as they believe the experts in the pediatric liver transplant field would be best suited to review and take action on pediatric transplant oncology-related cases.[45]

The Committee discussed whether the broadened scope for the Adult HCC Review Board to encompass all cases related to transplant oncology would burden the reviewers on the specialty board.[46] The Committee reviewed data on the number of non-standard exception requests relative to the four diagnoses that are proposed to be rerouted to the Adult Transplant Oncology Review Board (**Figure 4**). Based on the data, the Committee estimated that rerouting these diagnoses could potentially add an additional 2 to 3 cases a week for review by the Adult Transplant Oncology specialty board. This estimation does not account for non-standard exceptions related to colorectal liver metastases or intrahepatic cholangiocarcinoma. The Committee acknowledged the number of cases that will be

[45] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, November 3, 2023. Available at https://optn.transplant.hrsa.gov/.
[46] Ibid.

submitted for review for these two diagnoses is unknown at this time but is not expecting a significant addition of cases.[47]

Figure 4: Oncology Exception Requests Reviewed by the NLRB by Year Submitted and Diagnosis



Currently, 93 of 144 liver transplant programs have a representative appointed to the Adult HCC Review Board. Additional outreach could be performed to increase the number of liver transplant programs with a representative. Alternatively, the operational guidelines could be modified to either require or allow a voluntary secondary appointment for each liver transplant program. At this time, the Committee is proposing neither as they believe the case review load will be manageable for the reviewers of the proposed Adult Transplant Oncology Review Board. The Committee will be monitoring the impact of the proposal if implemented and will address any unintended consequences should there be an influx of cases.

Public comment feedback on Adult Transplant Oncology Review Board

Public comment was supportive of the expanded scope of the Adult HCC Review Board to become an Adult Transplant Oncology Review Board. While some feedback noted concern about ensuring appropriate expertise and potential overburden of case review, the Committee does not propose any post-public comment changes. In regard to the concern about reviewers on an Adult Transplant

[47] Ibid.

Oncology Review Board having necessary expertise, the Committee emphasizes the purpose of the guidance document.[48] The Committee does not expect all reviewers to be experts on every diagnosis, which is why the clarity and relevancy of the guidance documents are imperative. Additionally, the Committee reiterated that they would monitor the impact of the expanded scope of the Adult Transplant Oncology Review Board and if an influx of cases become routed and submitted to the new Adult Transplant Oncology Review Board, the Committee will develop modifications at that time. [49]

Clarifications to Policy 9.5.A: Requirements for CCA MELD or PELD Score Exceptions

One of the criteria necessary for a liver candidate to be approved for a standardized exception for hilar CCA is that the transplant program must develop a written protocol for patient care and submit it to the Committee. Currently, the Committee reviews these protocols and either approves or denies them. The Committee will offer feedback to the transplant program if denied, and transplant programs are allowed to resubmit.

The Committee proposes to clarify Policy 9.5.A that Committee approval of the protocol is necessary as this is part of the current practice. Additionally, the Committee proposes clarifying that the criteria in Policy 9.5.A are specific to standard exceptions for hilar CCA. The purposes of these clarifications are to ensure clarity that the Committee reviews and approves protocols as part of the standard criteria for hilar CAA.

Public Comment Feedback on Policy 9.5.A Clarifications

This portion of the proposal received support from the community as it was recognized that this policy clarification intended to ensure consistency and clarity. The Committee proposed no post-public comment modifications.[50]

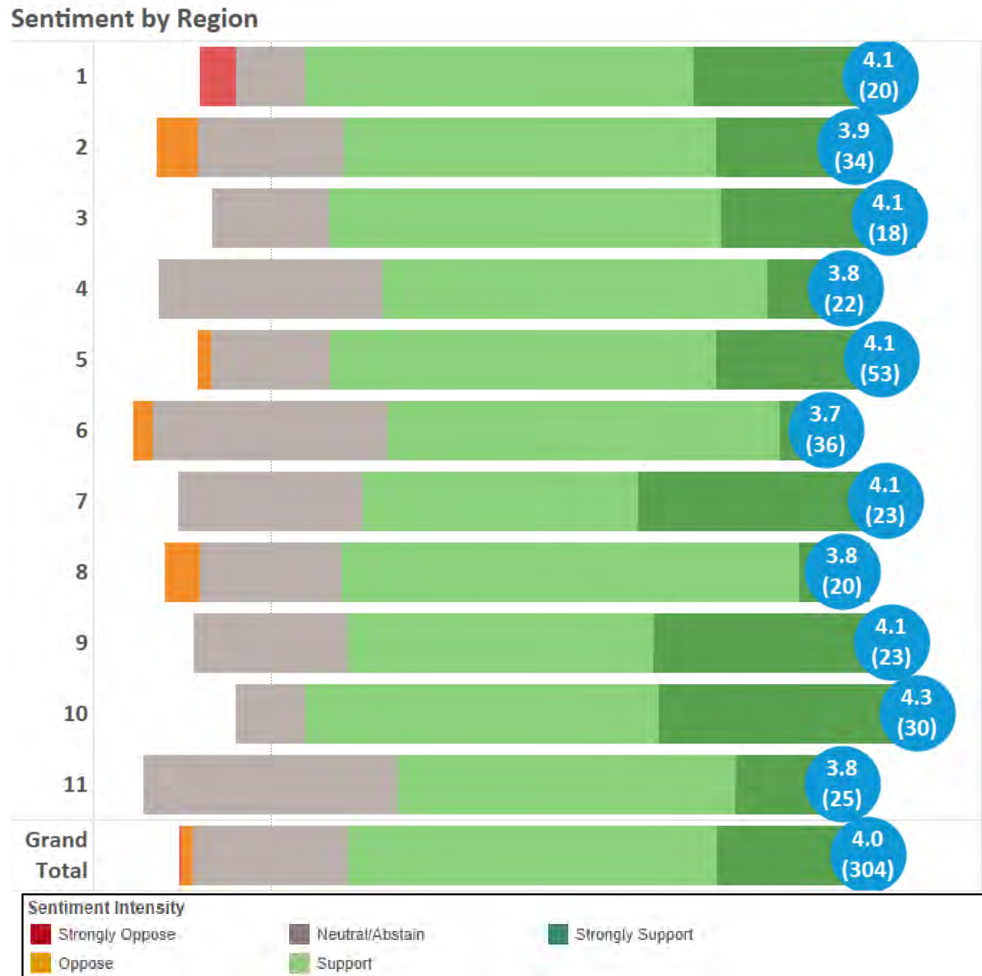
Overall Sentiment from Public Comment

The proposal was released for public comment from January 23, 2024 to March 19, 2024. The proposal was presented during 11 OPTN regional meetings and received feedback via the OPTN website. Two transplant stakeholder organizations, American Society of Transplantation (AST) and American Society of Transplant Surgeons (ASTS), submitted written public comments. Additional public comment feedback was received from transplant programs, organ procurement organizations, and individuals of the community.

Sentiment is collected from participants who submit an individual public comment and from regional meeting participants. Participants are asked to provide their feedback on “What is your opinion of this proposal?”. There are five Likert scale response choices with 1 representing strongly oppose up to 5 representing strongly support. Most public comments expressed support for the proposed changes, and some offered suggestions for Committee consideration as detailed above. As seen in **Figure 5**, sentiment of support or strong support was indicated across regions.

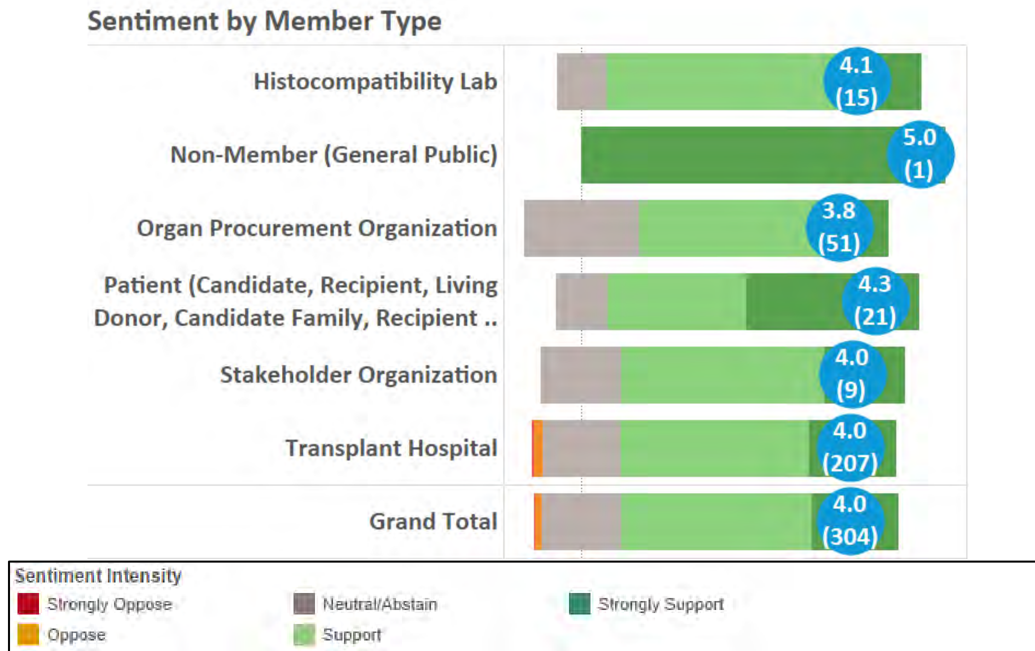
[48] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 5, 2024. Available at https://optn.transplant.hrsa.gov/.
[49] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 5, 2024. Available at https://optn.transplant.hrsa.gov/.
[50] Ibid.

Figure 5: Sentiment by Region, *NLRB Updates Related to Transplant Oncology* (Winter 2024 Public Comment)



Public comment sentiment by stakeholder, as seen in **Figure 6**, also indicated sentiment of support or strong support for the Committee's *NLRB Updates Related to Transplant Oncology* proposal.

Figure 6: Sentiment by Member Type, *NLRB Updates Related to Transplant Oncology* (Winter 2024 Public Comment)



Overall, the transplant community is supportive of the initiative to create an Adult Transplant Oncology Review Board and new guidance for candidates with intrahepatic cholangiocarcinoma or colorectal liver metastases to access non-standard exceptions. The majority of public comment was supportive of the proposed score recommendations for both intrahepatic cholangiocarcinoma and colorectal liver metastases, but some opposition offered additional suggestions for colorectal liver metastases due to concern of the score recommendation being potentially too low. Notably, the ASTS did not endorse the proposed guidance and score recommendation for colorectal liver metastases because of a lack of evidence to support liver transplant for this diagnosis. However, as detailed in the section above, the Committee affirms their decision to create a pathway for certain candidates with colorectal liver metastases to receive non-standard exceptions. The Committee had also previously considered various score recommendations and affirms that the current score recommendation is the most apt solution.[51]

In addition to feedback on the proposed score recommendations, the Committee received general feedback regarding areas of clarification within the new NLRB guidance. Ultimately, the Committee agreed that most of the clarifications suggested would create NLRB guidance that was too prescriptive, and the Committee agrees that NLRB guidance should allow for some clinical variation. [52]

Additional public comment feedback emphasized the need for monitoring these changes and the Committee agrees and intends to review the impact of the proposal and adjust as necessary.

[51] OPTN Liver & Intestinal Organ Transplantation Committee, Meeting Summary, April 15, 2024. Available at https://optn.transplant.hrsa.gov/.
[52] Ibid.

Compliance Analysis

NOTA and OPTN Final Rule

The Committee submits this proposal for consideration under the authority of the National Organ Transplant Act of 1984 (NOTA) and the OPTN Final Rule. NOTA requires the OPTN to establish "medical criteria for allocating organs and provide to members of the public an opportunity to comment with respect to such criteria".[53] The potential changes included in this project will ensure that transplant programs and NLRB reviewers have updated and accurate clinical guidance regarding medical criteria when submitting and reviewing exception requests.

The OPTN Final Rule requires the Board to establish performance goals for allocation policies, including "reducing the inter-transplant program variance" in performance indicators.[54] While this proposal does not address a specific performance goal, the updated guidance will assist in reducing the inter-transplant program variance by facilitating a more consistent review of exception cases. The purpose of NLRB guidance is to provide reference documents for transplant programs and NLRB reviewers to utilize when applying for and reviewing non-standard exception cases. The NLRB guidance may act as a guiding document to ensure more consistent application by submitting transplant programs and review by review board members, thereby reducing variance in the non-standard exception processes for liver allocation. By facilitating a more consistent review of exception cases, the proposal will, in turn, help ensure the equitable allocation of deceased donor organs by providing similar priority for candidates in similar clinical situations and allowing the appropriate candidates to receive a MELD or PELD exception.

OPTN Strategic Plan

This proposal supports the strategic goal of improving equity in access to transplants. Adding guidance for candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma will improve access to transplant for these select populations thereby increasing equity in access for candidates with oncological indications for liver transplant. Additionally, the expanded scope of an Adult Transplant Oncology Review Board improves equity by having reviewers with the appropriate expertise reviewing cases within their subject area.

Implementation Considerations

Member and OPTN Operations

The proposed changes to the Adult HCC Review Board to become an Adult Transplant Oncology Review Board will need to be updated in the OPTN computer system. This will include adding diagnosis options specific to the diagnoses in the proposed Adult Transplant Oncology guidance document for liver exception request forms. It will also include ensuring transplant oncology-related diagnoses are routed appropriately to the Adult Transplant Oncology Review Board. The Adult HCC Review Board will be named Adult Transplant Oncology Review Board upon implementation; This includes historical data, which means that any non-standard HCC exception requests that were reviewed by the Adult HCC Review Board will be indicated to have been reviewed by the Adult Transplant Oncology Review Board.

[53] 42 U.S.C. §274(b)(2)(B).
[54] 42 C.F.R. §121.8(b)(4).

There are no modifications to the structure of the review board, the review process, or the appeal process. Modifications to the operational guidelines are nomenclature changes to reflect that the Adult HCC Review Board will become the Adult Transplant Oncology Review Board.

Any case that is up for extension or is currently in the appeal process that was based upon a decision from the Adult Other Diagnosis Review Board will continue to be reviewed by the Adult Other Diagnosis Review Board. This will ensure consistency in decision-making. Transplant programs can re-submit an initial exception should they wish for the Adult Transplant Oncology specialty board to review their case.

Relevant guidance documents, NLRB operational guidelines, and policy language will need to be updated. All changes and educational offerings will be communicated to the community prior to implementation. Transplant programs and NLRB reviewers will need to be aware of the changes.

Histocompatibility Laboratories

Operational Considerations

This proposal will have no operational impact on histocompatibility laboratories.

Fiscal Impact

No impact.

Organ Procurement Organizations

Operational Considerations

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

Fiscal Impact

No impact.

Transplant Programs

Operational Considerations

Transplant programs will need to be familiar with the proposed changes to NLRB guidance documents when submitting exception requests for liver candidates. Transplant programs will also need to be aware of updated diagnoses to ensure accurate data entry when submitting exception requests for liver candidates. Representatives on the Adult Transplant Oncology Review Board may have additional cases to review during their term.

Fiscal Impact

No impact.

OPTN

Operational Considerations

Relevant guidance documents will need to be updated. The OPTN computer system will need to be updated to reflect changes to the Adult Transplant Oncology Review Board and route liver cancer and tumor cases accordingly. The OPTN will communicate any changes prior to implementation and will provide educational resources as appropriate.

Resource Estimates

It is estimated that 690 hours would be needed to implement this proposal. Implementation would involve updates to the OPTN Computer System, the Adult HCC Review Board, and relevant documents. In addition, implementation would include communication and education to the community regarding these changes. It is estimated that 120 hours will be required for ongoing support. Ongoing support will include member monitoring process updates, research post implementation monitoring reports, and answering member questions, as necessary.

Potential Impact on Select Patient Populations

The proposed changes to NLRB guidance may impact candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma. The expansion of guidance should increase access to transplant for certain candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma through non-standard exceptions. The Committee determined it necessary to establish a score recommendations that would not interfere with transplant access for other medically urgent liver candidates.

Since the proposed Adult Transplant Oncology Review Board will be expanded to review liver cancer and tumor-related non-standard exception requests, reviewers will be more equipped to analyze these cases and make decisions based on their clinical expertise in the transplant oncology field. Because of this, individual candidates with neuroendocrine tumors, hepatic epithelioid hemangioendothelioma, hepatic adenomas, colorectal liver metastases, and intrahepatic cholangiocarcinoma, HCC, and CCA will have their exception cases evaluated by this review board.

None of the proposed changes to guidance for candidates with these diagnoses are more limiting than the current criteria 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 impact individual candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma. Candidates meeting the new criteria will be more likely to be approved for a MELD exception and therefore may experience improved 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. Any data entered in the OPTN Computer System may be reviewed by the OPTN, and members are required to provide documentation as requested.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate." This guidance will be formally evaluated at approximately 6-months and 1-year post-implementation. The following metrics, and any subsequently requested by the Committee, will be evaluated as data becomes available (appropriate lags will be applied, per typical OPTN conventions, to account for time delay in institution reporting of data) and compared to an appropriate pre-guidance cohort to assess performance before and after implementation of this guidance:

- The number of exception forms submitted overall and by review board
- The number of exception forms submitted to the oncology review board by diagnosis and case outcome (approved, withdrawn, denied, etc.)

Conclusion

This proposal creates guidance for transplant programs to submit exceptions for colorectal liver metastases candidates and intrahepatic cholangiocarcinoma candidates. The Committee is also proposing to broaden the scope of the Adult HCC Review Board to encompass reviewing non-standard exception requests for other liver cancers and tumors. As such, the Committee is proposing the Adult HCC Review Board to become the Adult Transplant Oncology Review Board and the associated guidance documents will reflect these changes. The proposed modifications will ensure that reviewers with more relevant expertise in the field of liver cancer and tumors are reviewing appropriate exception requests. Additionally, new NLRB guidance for colorectal liver metastases and intrahepatic cholangiocarcinoma creates a pathway for certain candidates to receive a non-standard exception which may increase access to liver transplant. Finally, this proposal recommends two clarifications to Policy 9.5.A: *Requirements for CCA MELD or PELD Score Exceptions* to ensure consistency and accuracy of the policy.

The Committee made minor clarifications post-public comment to the NLRB guidance document. No post-public comment changes were proposed that changed the substance or intent of the original proposals.

Policy Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (example). Heading numbers, table and figure captions, cross-references, and footnotes affected by the numbering will be updated as necessary.[1]

9.5 Specific Standardized MELD or PELD Score Exceptions

Candidates are eligible for MELD or PELD score exceptions or extensions that do not require evaluation by the NLRB if they meet *any* of the following requirements for a specific diagnosis of *any* of the following:

- Hilar Cholangiocarcinoma (CCA), according to *Policy 9.5.A: Requirements for Hilar Cholangiocarcinoma MELD or PELD Score Exceptions*
- Cystic fibrosis, according to *Policy 9.5.B: Requirements for Cystic Fibrosis MELD or PELD Score Exceptions*
- Familial amyloid polyneuropathy, according to *Policy 9.5.C: Requirements for Familial Amyloid Polyneuropathy (FAP) MELD or PELD Score Exceptions*
- Hepatic artery thrombosis, according to *Policy 9.5.D: Requirements for Hepatic Artery Thrombosis (HAT) MELD Score Exceptions*
- Hepatopulmonary syndrome, according to *Policy 9.5.E: Requirements for Hepatopulmonary Syndrome (HPS) MELD or PELD Score Exceptions*
- Metabolic disease, according to *Policy 9.5.F: Requirements for Metabolic Disease MELD or PELD Score Exceptions*
- Portopulmonary hypertension, according to *Policy 9.5.G: Requirements for Portopulmonary Hypertension MELD or PELD Score Exceptions*
- Primary hyperoxaluria, according to *Policy 9.5.H: Requirements for Primary Hyperoxaluria MELD or PELD Score Exceptions*
- Hepatocellular carcinoma, according to *Policy 9.5.I: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exception*

9.5.A Requirements for Hilar Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions

A candidate will receive a MELD or PELD score exception for hilar CCA, if the candidate's transplant program meets *all* the following qualifications:

1. Submits a written protocol for patient care to the Liver and Intestinal Organ Transplantation Committee for review and approval. The written protocol ~~that~~ must include *all* of the following:
   i. Candidate selection criteria
   ii. Administration of neoadjuvant therapy before transplantation
   iii. Operative staging to exclude any patient with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease
   iv. Any data requested by the Liver and Intestinal Organ Transplantation Committee

[1] Briefing paper update: Line 33 (bullet point iv) was inadvertently left out of the original proposal document. Line 33 was added into the finalized briefing paper and does not affect the proposed changes.

34 2. Documents that the candidate meets the diagnostic criteria for hilar CCA with a malignant
35 appearing stricture on cholangiography and at least *one* of the following:
36 - Biopsy or cytology results demonstrating malignancy
37 - Carbohydrate antigen 19-9 greater than 100 U/mL in absence of cholangitis
38 - Aneuploidy
39 - Hilar mass, which is less than 3 cm in radial diameter.

40 The tumor must be considered un-resectable because of technical considerations or
41 underlying liver disease.

42 3. Submits cross-sectional imaging studies. If cross-sectional imaging studies demonstrate a
43 mass, the mass must be single and less than three cm in radial (perpendicular to the duct)
44 diameter. The longitudinal extension of the stricture along the bile duct is not considered in
45 the measurement of a mass.

46 4. Documents the exclusion of intrahepatic and extrahepatic metastases by cross-sectional
47 imaging studies of the chest and abdomen within 90 days prior to submission of the initial
48 exception request.

49 5. Assesses regional hepatic lymph node involvement and peritoneal metastases by operative
50 staging after completion of neoadjuvant therapy and before liver transplantation.
51 Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable
52 to exclude patients with obvious metastases before neo-adjuvant therapy is initiated.

53 6. Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound,
54 operative or percutaneous approaches) must be avoided because of the high risk of tumor
55 seeding associated with these procedures.

56 A candidate who meets the requirements for a standardized MELD or PELD score exception will receive
57 a score according to *Table 9-2*.

58 **Table 9-2: Hilar CCA Exception Scores**

Age	Age at registration	Score
At least 18 years old	At least 18 years old	3 points below MMaT
At least 12 years old	Less than 18 years old	Equal to MMaT
Less than 12 years old	Less than 12 years old	Equal to MPaT

59 In order to be approved for an extension of this MELD or PELD score exception, transplant programs
60 must submit an exception extension request according to *Policy 9.4.C: MELD or PELD Exception*
61 *Extensions,* and provide cross-sectional imaging studies of the chest and abdomen that exclude
62 intrahepatic and extrahepatic metastases. These required imaging studies must have been completed
63 within 30 days prior to the submission of the extension request.

#

OPTN

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, cross-references, and footnotes affected by the numbering will be updated as necessary.

Guidance to Liver Transplant Programs and the National Liver Review Board for: Adult MELD Exceptions for ~~Hepatocellular Carcinoma (HCC)~~ Transplant Oncology

Summary and Goals

For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score, which is used to prioritize candidates on the waiting list. However, for some patients the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[1] This document summarizes available evidence to assist clinical reviewers in approving candidates for MELD exceptions in the specific setting of hepatic neoplasms. It contains guidance for specific clinical situations for use by the review board to evaluate common exception case requests for adult candidates with the following diagnoses:

- Hepatocellular Carcinoma (HCC)
- Hepatic Epithelioid Hemangioendothelioma (HEHE)
- Hepatic Adenomas
- Neuroendocrine Tumors (NET)
- Colorectal Liver Metastases (CRLM)
- Intrahepatic Cholangiocarcinoma (iCCA)

These guidelines are intended to promote consistent review of these diagnoses and summarize the Committee's recommendations to the OPTN Board of Directors.

This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the review board.

[1] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

Background

A liver candidate receives a MELD[2] or, if less than 12 years old, a PELD[3] 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.[4] 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 Transplant Oncology ~~Hepatocellular Carcinoma (HCC)~~. This guidance document is intended to provide recommendations for the review board considering hepatic neoplasm ~~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.

Instructions for Submitting a Non-Standard Exception Request

Instructions for how to submit a non-standard exception request can be found in each relevant diagnosis section. For any other diagnosis that should be reviewed by the Adult Transplant Oncology review board, select "other liver cancer or tumor specify", indicate the diagnosis, and submit a written justification narrative.

Recommendations

Hepatocellular Carcinoma (HCC)

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

[2]Model for End-Stage Liver Disease
[3]Pediatric End-Stage Liver Disease
[4]See OPTN *Policy 9.5: Specific Standardized MELD or PELD Exceptions*, Available at https://optn.transplant.hrsa.gov/.

Evidence for the use of immunotherapy as a downstaging 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.[5]

- Patients beyond standard criteria who have continued progression while waiting despite locoregional 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~~ Adult Transplant Oncology 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 who presented with stage T2 HCC (LI-RADS 5 or biopsy proven; one lesion >2 cm and <5 cm in size, two or three lesions >1 cm and <3 cm in size) which was treated by locoregional therapy or resected but developed T1 or T2 HCC (LI-RADS 5 or biopsy proven) recurrence and the transplant program is requesting an initial HCC exception more than 6 months but less than 60 months following initial treatment or resection are eligible for a MELD score exception without a six month delay period.

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 or T2 HCC (LI-RADS 5 or biopsy proven) recurrence may also be considered for MELD score exception for HCC. Because of the larger tumor size, the 6-month delay is appropriate to ensure favorable tumor biology.

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

[5] 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.

Feature:	CT scans should meet the below specifications:
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

149 **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.

150 To submit an HCC exception request, select *Hepatocellular carcinoma (HCC)* and fill out the associated
151 form. If the candidate does not meet the standardized criteria per Policy 9.5. I or seeks a different
152 exception score, the system will direct the transplant program to write and submit a justification
153 narrative that will be reviewed by the Adult Transplant Oncology Review Board.

154 Intrahepatic Cholangiocarcinoma

155 Candidates with biopsy proven unresectable solitary intrahepatic cholangiocarcinoma (iCCA) or mixed
156 hepatocellular carcinoma/intrahepatic cholangiocarcinoma (mixed HCC-iCCA) less than or equal to 3 cm
157 with 6 months of tumor stability after locoregional or systemic therapy should be considered for MELD
158 exception points based on existing data supporting the role of liver transplantation in this setting.[6, 7, 8, 9]

[6] Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, Lopez-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a Spanish matched cohort multicenter study. Ann Surg; 2014. p. 944-52.
[7] Fu BS, Zhang T, Li H, Yi SH, Wang GS, Xu C. The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. European Surgical; 2011.
[8] Hayashi A, Misumi K, Shibahara J, Arita J, Sakamoto Y, Hasegawa K, et al. Distinct Clinicopathologic and Genetic Features of 2 Histologic Subtypes of Intrahepatic Cholangiocarcinoma. The American Journal of Surgical Pathology. 2016;40(8):1021-30.
[9] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016;64(4):1178-88.

159 Based on current evidence-based medicine, transplant programs should provide the following elements
160 when submitting an initial MELD exception for iCCA:
161 - Biopsy proven iCCA or mixed HCC-iCCA[10]
162 - Presence of cirrhosis
163 - Unresectable
164 - Locoregional or systemic therapy for iCCA
165 - 6 months from time of diagnosis or last treatment of tumor stability meaning less than or
166 equal to 3 cm, no new lesions, or extrahepatic disease before applying for exception

167 Candidates with iCCA should be considered for a MELD exception extension if they continue to meet *all*
168 *of* the following criteria:
169 - Imaging every 3 months to ensure tumor less than or equal to 3 cm
170 - No extrahepatic disease prior to extending the MELD exception

171 Candidates meeting the criteria described above should be considered for a MELD exception score equal
172 to MMaT-3.

173 To submit an iCCA exception request, select *Cholangiocarcinoma (CCA)* and fill out the associated form.
174 The transplant program will then be directed to submit a justification narrative that will be reviewed by
175 the Adult Transplant Oncology Review Board. Utilize this same process if submitting an exception
176 request for mixed HCC-iCCA.

177 Neuroendocrine Tumors (NET)

178 A review of the literature supports that candidates with NET are expected to have a low risk of waiting
179 list drop-out.

180 **Transplant programs should be aware of the following criteria when submitting exceptions for NET.**
181 **The review board should consider the following criteria when reviewing exception applications for**
182 **candidates with NET.**

183 - Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence
184 for at least six months prior to MELD exception request.
185 - Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.

186 Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:
187 1. If CT Scan:
188 a. Triple phase contrast Lesions may be seen on only one of the three phases
189 b. Arterial phase: may demonstrate a strong enhancement
190 c. Large lesions can become necrotic/calcified
191 2. If MRI Appearance:
192 a. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
193 b. Diffusion restriction

[10] There may be worse survival outcomes with poor differentiation of tumor on biopsy.

194 c. Majority of lesions are hypervascular on arterial phase with wash –out during portal
195 venous phase
196 d. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are
197 characteristics of NET

198 1. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors
199 with portal system drainage. Note: Neuroendocrine tumors with the primary located in the
200 lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic
201 MELD exception.
202 2. Lower - intermediate grade following the WHO classification. Only well differentiated (Low
203 grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20 per 10 HPF
204 with less than 20% ki 67 positive markers.
205 3. Tumor metastatic replacement should not exceed 50% of the total liver volume.
206 4. Negative metastatic workup should include one of the following:
207 a. Positron emission tomography (PET scan)
208 b. Somatostatin receptor scintigraphy
209 c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane-N,
210 N′, N″,N‴-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other
211 scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

212 **Note:** Exploratory laparotomy and or laparoscopy is not required prior to MELD exception request.

213 1. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3
214 months prior to MELD exception request (submit date).
215 2. Recheck metastatic workup every 3 months for MELD exception increase consideration by the
216 review board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive
217 locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease
218 is zeroed and remained so for at least 6 months.
219 3. Presence of extra-hepatic solid organ metastases (i.e., lungs, bones) should be a permanent
220 exclusion criteria

221 To submit an exception request for NET, select the *Neuroendocrine Tumor (NET)* option. Transplant
222 programs will be directed to write and submit a justification narrative that will be reviewed by the Adult
223 Transplant Oncology Review Board.

224 Colorectal Liver Metastases

225 The diagnosis of unresectable colorectal liver metastases (CRLM) has a poor prognosis despite improved
226 local and systemic treatments. Published studies support liver transplantation in highly selected patients
227 and has demonstrated a survival benefit in initial prospective clinical trials.[11, 12, 13, 14]

[11] Hagness, M., et al., *Liver transplantation for nonresectable liver metastases from colorectal cancer.* Ann Surg, 2013. **257**(5): p. 800-6.
[12] Dueland, S., et al., *Survival Outcomes After Portal Vein Embolization and Liver Resection Compared With Liver Transplant for Patients With Extensive Colorectal Cancer Liver Metastases.* JAMA Surgery, 2021. **156**(6): p. 550-557.
[13] Line, P.-D. and S. Dueland, *Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence.* Journal of Hepatology, 2020. **73**(6): p. 1557-1562.
[14] Dueland, S., et al., *Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases.* Annals of Surgery, 2020. **271**(2).

228 Based on currently available published studies, transplant programs should provide the following
229 elements when submitting an initial MELD exception for CRLM:

230 **Initial MELD Exception Criteria**
231 Candidates can be considered for MELD exception points for CRLM if all of the following criteria are met:
232 **Primary diagnosis:**
233 - Histological diagnosis of colon/rectal adenocarcinoma
234 - BRAF wild type, microsatellite stable[15]
235 - At least 12 months from time of CRLM diagnosis to time of initial exception request

236 **Treatment of primary colorectal cancer**
237 - Standard resection of the primary tumor with negative resection margins
238 - No evidence of local recurrence by colonoscopy within 12 months prior to time of initial
239 exception request

240 **Evaluation of extrahepatic disease**
241 - No signs of extrahepatic disease or local recurrence, based on CT/MRI (chest, abdomen
242 and pelvis) and PET scan within one month of initial exception request.[16]

243 **Evaluation of hepatic disease and prior systemic/liver directed treatment**
244 - Received or receiving first-line chemotherapy/immunotherapy
245 - Relapse of liver metastases after liver resection or liver metastases not eligible for
246 curative resection
247 - No hepatic lesion should be greater than 10 cm before start of treatment
248 - Must have stability or regression of disease with systemic and/or locoregional therapy
249 for at least 6 months.[17]

250 In cases of synchronous colon lesions, in addition to above criteria, all of the following are required:
251 - Resection of the primary tumor is performed more than 6 months after initial diagnosis
252 - Minimum of 6 months of chemotherapy after primary tumor resection before exception
253 request with stability of disease for a total of at least 12 months after initial diagnosis.[18]

254 Candidates meeting the criteria described should be considered for a MELD exception score equal to
255 MMaT-20. If MMaT-20 results in an exception score below 15, the candidate's exception score **will**
256 **automatically be set to a MELD score of 15** per OPTN Policy 9.4.E: *MELD or PELD Exception Scores*
257 *Relative to Median MELD or PELD at Transplant*.

258 **Exclusion Criteria**
259 Candidates should not be considered for an initial MELD exception for CRLM if any of the following
260 criteria are met:

---

[15] Insufficient data to include KRAS as exclusionary factor but should be considered as a negative prognostic factor.
[16] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.
[17] Progression is defined as more than 10% increase in diameter of existing lesions (according to RECIST 1.1) OR any new lesions detected on imaging.
[18] Progression is defined as more than 10% increase in diameter of existing lesions (according to RECIST 1.1) OR any new lesions detected on imaging

261 - Extra-hepatic disease after primary tumor resection (including lymphadenopathy
262 outside of the primary lymph node resection)
263 - Local relapse of primary disease
264 - Carcinoembryonic antigen (CEA) >80 µg/L with or without radiographic evidence of
265 disease progression or new lesion.

266 **MELD Exception Extension Criteria**
267 Candidates with CRLM should be considered for a MELD exception extension if they continue to meet *all*
268 *of* the following criteria:
269 - Every 3 months from initial MELD exception:
270 - Perform CT or MRI (chest, abdomen and pelvis)
271 - Perform CEA testing
272 - No progression of hepatic disease[19]
273 - No development of extrahepatic disease
274 - CEA < 80 µg/L

275 To submit an exception request for CRLM, select the *Colorectal liver metastases* option. Transplant
276 programs will be directed to write and submit a justification narrative that will be reviewed by the Adult
277 Transplant Oncology Review Board.

278 Hepatic Epithelioid Hemangioendothelioma

279 **Approval of MELD exception points for adult candidates with unresectable Hepatic Epithelioid**
280 **Hemangioendothelioma (HEHE) may be appropriate in some instances.**

281 Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma. HEHE is a
282 rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity of the diagnosis, as
283 well as the variability in presentation, the optimal treatment strategies are not fully established.
284 However, for lesions which cannot be resected, liver transplant is associated with 1, 5, and 10-year
285 patient survival rates of 97%, 83%, and 74%; with more favorable results occurring in patients without
286 microvascular invasion. The presence of extra-hepatic disease has not been associated with decreased
287 survival post liver transplant and therefore should not be an absolute contraindication. Controversy
288 regarding the role of liver transplant in treating HEHE relates to the variable course of disease in the
289 absence of liver transplant, with some patients demonstrating regression or stabilization of disease and
290 prolonged survival.[20,21]

291 To submit an exception request for HEHE, select the *Hepatic Epithelioid Hemangioendothelioma (HEHE)*
292 option. Transplant programs will be directed to write and submit a justification narrative that will be
293 reviewed by the Adult Transplant Oncology Review Board.

---

[19] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.
[20] Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry." Ann Surg 246 (2007): 949-57.
[21] Nudo, C.G., E.M. Yoshida, V.G. Bain, et al. "Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience." Can J Gastroenterol 22 (2008):821-4.

294 ## Hepatic Adenomas

295 Orthotopic liver transplantation for hepatic adenomas (HA) remains an extremely rare indication;
296 however, it is a valid therapeutic option in select patients with adenoma meeting one of the following
297 categories:

298 - Adenoma in the presence of Glycogen Storage Disease
299 - Unresectable β Catenin (+) Adenoma
300 - Adenoma(s) with all three below:
301   - Unresponsive to medical management
302   - Unresectable
303   - Progressive or with complication such as hemorrhage or malignant transformation
304   (must specify)

305 The identification of these criteria is mandatory to aid in the decision-making process.[22,23,24,25]

306 To submit an exception request for HA, select the *Hepatic Adenomas* option. Transplant programs will
307 be directed to write and submit a justification narrative that will be reviewed by the Adult Transplant
308 Oncology Review Board.

[22] Blanc, J.F., N. Frulio, L. Chiche, et al. “Hepatocellular adenoma management: call for shared guidelines and multidisciplinary approach.” Clinics and research in hepatology and gastroenterology 39 (2015): 180-187.
[23] Chiche, L., A. David, R. Adam, et al. “Liver transplantation for adenomatosis: European experience.” Liver Transplantation 22 (2016): 516-526.
[24] Alagusundaramoorthy, S. S., V. Vilchez, A. Zanni, et al. “Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set.” JAMA Surgery 150 (2015): 337-342.
[25] Dokmak, S., V. Paradis, V. Vilgrain, et al. “A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas.” Gastroenterology 137 (2009): 1698-1705.

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

Summary and Goals

For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score, which is used to prioritize candidates on the waiting list. However, for some patients the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[1] This document summarizes available evidence to assist clinical reviewers in approving candidates for MELD exceptions. It contains guidance for specific clinical situations for use by the review board to evaluate common exceptional case requests for adult candidates with the following diagnoses, not all of which are appropriate for MELD exception:

- Ascites
- Budd Chiari
- GI Bleeding
- Hepatic Encephalopathy
- ~~Hepatic Epithelioid Hemangioendothelioma~~
- Hepatic Hydrothorax
- Hereditary Hemorrhagic Telangiectasia
- ~~Hepatic Adenomas~~
- ~~Neuroendocrine Tumors (NET)~~
- Polycystic Liver Disease (PLD)
- Portopulmonary Hypertension
- Primary Sclerosing Cholangitis (PSC) or Secondary Sclerosing Cholangitis (SSC)
- Metabolic Disease
- Multivisceral Transplant Candidates
- Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection, Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- Pruritus

These guidelines are intended to promote consistent review of these diagnoses and summarize the Committee's recommendations to the OPTN Board of Directors.

This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the review board.

[…]

[1] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

346 ## ~~Hepatic Epithelioid Hemangioendothelioma~~

347 **~~Approval of MELD exception points for adult candidates with unresectable Hepatic Epithelioid~~**
348 **~~Hemangioendothelioma (HEHE) may be appropriate in some instances.~~**
349 ~~Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma. HEHE is a~~
350 ~~rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity of the diagnosis, as~~
351 ~~well as the variability in presentation, the optimal treatment strategies are not fully established.~~
352 ~~However, for lesions which cannot be resected, liver transplant is associated with 1, 5, and 10-year~~
353 ~~patient survival rates of 97%, 83%, and 74%; with more favorable results occurring in patients without~~
354 ~~microvascular invasion. The presence of extra-hepatic disease has not been associated with decreased~~
355 ~~survival post liver transplant and therefore should not be an absolute contraindication. Controversy~~
356 ~~regarding the role of liver transplant in treating HEHE relates to the variable course of disease in the~~
357 ~~absence of liver transplant, with some patients demonstrating regression or stabilization of disease and~~
358 ~~prolonged survival.~~[101,102]
359 […]

360 ## ~~Hepatic Adenomas~~

361 ~~Orthotopic liver transplantation for hepatic adenomas (HA) remains an extremely rare indication;~~
362 ~~however, it is a valid therapeutic option in select patients with adenoma meeting one of the following~~
363 ~~categories:~~
364 - ~~Adenoma in the presence of Glycogen Storage Disease~~
365 - ~~Unresectable β Catenin (+) Adenoma~~
366 - ~~Adenoma(s) with all three below:~~
367   - ~~Unresponsive to medical management~~
368   - ~~Unresectable~~
369   - ~~Progressive or with complication such as hemorrhage or malignant transformation~~
370 ~~(must specify)~~
371 ~~1.~~
372 ~~The identification of these criteria is mandatory to aid in the decision-making process.~~[84,85,86,87]

373 ## ~~Neuroendocrine Tumors (NET)~~

374 ~~A review of the literature supports that candidates with NET are expected to have a low risk of waiting~~
375 ~~list drop-out.~~

~~[101] Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry." Ann Surg 246 (2007): 949-57.~~

~~[102] Nudo, C.G., E.M. Yoshida, V.G. Bain, et al. "Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience." Can J Gastroenterol 22 (2008):821-4.~~

~~[84] Blanc, J.F., N. Frulio, L. Chiche, et al. "Hepatocellular adenoma management: call for shared guidelines and multidisciplinary approach." Clinics and research in hepatology and gastroenterology 39 (2015): 180-187.~~

~~[85] Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." Liver Transplantation 22 (2016): 516-526.~~

~~[86] Alagusundaramoorthy, S. S., V. Vilchez, A. Zanni, et al. "Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set." JAMA Surgery 150 (2015): 337-342.~~

~~[87] Dokmak, S., V. Paradis, V. Vilgrain, et al. "A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas." Gastroenterology 137 (2009): 1698-1705.~~

~~**Transplant programs should be aware of the following criteria when submitting exceptions for NET. The review board should consider the following criteria when reviewing exception applications for candidates with NET.**~~

- ~~Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.~~
- ~~Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection. Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:~~
  3. ~~If CT Scan:~~
     a. ~~Triple phase contrast Lesions may be seen on only one of the three phases~~
     b. ~~Arterial phase: may demonstrate a strong enhancement~~
     c. ~~Large lesions can become necrotic/calcified~~
  4. ~~If MRI Appearance:~~
     e. ~~Liver metastasis are hypodense on T1 and hypervascular in T2 wave images~~
     f. ~~Diffusion restriction~~
     g. ~~Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase~~
     h. ~~Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET~~
     2.

5. ~~Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.~~
6. ~~Lower - intermediate grade following the WHO classification. Only well differentiated (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20 per 10 HPF with less than 20% ki 67 positive markers.~~
7. ~~Tumor metastatic replacement should not exceed 50% of the total liver volume.~~
8. ~~Negative metastatic workup should include one of the following:~~
   d. ~~Positron emission tomography (PET scan)~~
   e. ~~Somatostatin receptor scintigraphy~~
   f. ~~Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane-N, N′, N″,N‴-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.~~
   3.

   ~~**Note:**~~ ~~Exploratory laparotomy and or laparoscopy is not required prior to MELD exception request.~~

4. ~~No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD exception request (submit date).~~
5. ~~Recheck metastatic workup every 3 months for MELD exception increase consideration by the review board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.~~
6. ~~Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion criteria~~

Operational Guidelines Language

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

National Liver Review Board Operational Guidelines

1. Overview

The purpose of the National Liver Review Board (NLRB) is to provide fair, equitable, and prompt peer review of exceptional candidates whose medical urgency is not accurately reflected by the calculated MELD/PELD score. The NLRB will base decisions on policy, the guidance documents, and in cases which lack specific guidance, the medical urgency of the candidate as compared to other candidates with the same MELD or PELD score adjustment or specific MELD or PELD score.

The NLRB is comprised of specialty boards, including:

- Adult ~~Hepatocellular Carcinoma (HCC)~~ Transplant Oncology
- Adult Other Diagnosis
- Pediatrics, which reviews requests made on behalf of any candidate registered prior to turning 18 years old and adults with certain pediatric diagnoses

The immediate past-Chair of the Liver and Intestinal Organ Transplantation Committee serves as the Chair of the NLRB for a two year term.

2. Representation

[…]

6. Appeals Review Team (ART)

At the beginning of each new service term, nine NLRB members from the Adult Other Diagnosis and Adult ~~HCC~~ Transplant Oncology specialty boards are assigned to serve each month of the year on the Adult ART and nine NLRB members from the Pediatric specialty board are assigned to serve each month of the year on the Pediatric ART. There may be multiple ARTs, depending on the volume of cases. Each ART will be scheduled to meet via conference call according to a predetermined schedule.

ART appeals from the Adult Other Diagnosis and Adult ~~HCC~~ Transplant Oncology specialty boards will be reviewed by the Adult ART. ART appeals from the Pediatric specialty board will be reviewed by the Pediatric ART.

In the event of a planned absence, the ART member may designate their alternate to serve. The representative must notify the OPTN of this in the OPTN Computer System.

Five members of the ART must participate in the call. If at least five members do not attend the call, the appeal will be rescheduled for the following regularly scheduled conference call. If at least five members

30 do not attend the second attempt to review the appeal, the candidate's exception request is
31 automatically approved.

32 The appeal must achieve a majority plus one affirmative votes in order to be approved.

33 A representative at the petitioning program may serve as the candidate's advocate. If a representative is
34 unable to attend the conference call, the program may ask for the appeal to be scheduled for the
35 following regularly scheduled conference call. If after two attempts a representative is unable to attend
36 the call, the ART will review the appeal without the program's participation. In the absence of a
37 representative on the conference call, the program may submit written information for the ART's
38 consideration.

39 A current member of the Liver Committee serving on either the Adult Other Diagnosis specialty board or
40 Adult ~~HCC~~ Transplant Oncology specialty board will be appointed to serve as the ART leader for the
41 Adult ART prior to each service term. A current member of the Liver Committee or current member of
42 the OPTN Pediatric Transplantation Committee (Pediatric Committee) serving on the Pediatric specialty
43 board will be appointed to serve as the ART leader for the Pediatric ART prior to each service term. If no
44 current member of either the Liver Committee or the Pediatric Committee is available to serve as the
45 ART leader, prior members of each Committee or other members of the NLRB may be appointed to
46 serve as ART leader. The ART leader will be prepared to lead ART discussion and provide feedback to the
47 Liver Committee.

48 The ART will work with the OPTN to document the content of the discussion and final decision in the
49 OPTN Computer System.

50 **7. Liver Committee Review**

51 […]

#

Appendix A: Post-Public Comment Changes

New language that was proposed following public comment is underlined and highlighted (example); language that is proposed for removal following public comment is struck through and highlighted (~~example~~).

Guidance to Liver Transplant Programs and the National Liver Review Board for: Adult MELD Exceptions for Transplant Oncology

[…]

Recommendations

Hepatocellular Carcinoma (HCC)

[…]

To submit an HCC exception request, select *Hepatocellular carcinoma (HCC)* and fill out the associated form. If the candidate does not meet the standardized criteria per Policy 9.5. I or seeks a different MMaT ~~exception~~ score, the system will direct the transplant program to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

Intrahepatic Cholangiocarcinoma

Candidates with biopsy proven unresectable solitary intrahepatic cholangiocarcinoma (iCCA) or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma (mixed HCC-iCCA) less than or equal to 3 cm with 6 months of tumor stability after locoregional or systemic therapy should be considered for MELD exception points based on existing data supporting the role of liver transplantation in this setting.[88, 89, 90, 91]

Based on current evidence-based medicine, transplant programs should provide the following elements when submitting an initial MELD exception for iCCA:

- Biopsy proven iCCA or mixed HCC-iCCA[92]
- Presence of cirrhosis
- Unresectable
- Locoregional or systemic therapy for iCCA ~~with~~

---

[88] Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, Lopez-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a Spanish matched cohort multicenter study. Ann Surg; 2014. p. 944-52.
[89] Fu BS, Zhang T, Li H, Yi SH, Wang GS, Xu C. The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. European Surgical; 2011.
[90] Hayashi A, Misumi K, Shibahara J, Arita J, Sakamoto Y, Hasegawa K, et al. Distinct Clinicopathologic and Genetic Features of 2 Histologic Subtypes of Intrahepatic Cholangiocarcinoma. The American Journal of Surgical Pathology. 2016;40(8):1021-30.
[91] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016;64(4):1178-88.
[92] There may be worse survival outcomes with poor differentiation of tumor on biopsy.

- 6 months from time of diagnosis or last treatment of tumor stability meaning less than or equal to 3 cm, no new lesions, or extrahepatic disease before applying for exception

Candidates with iCCA should be considered for a MELD exception extension if they continue to meet *all of* the following criteria:

- Imaging every 3 months to ensure tumor less than or equal to 3 cm
- No extrahepatic disease prior to extending the MELD exception

Candidates meeting the criteria described above should be considered for a MELD exception score equal to MMaT-3.

To submit an iCCA exception request, select *Cholangiocarcinoma (CCA)* and fill out the associated form. The transplant program will then be directed to submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board. Utilize this same process if submitting an exception request for mixed HCC-iCCA.

#