

Public Comment Proposal

Liver Review Board Guidance Documents

OPTN/UNOS Liver and Intestinal Organ Transplantation Committee

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Liver Review Board Guidance Documents

Affected Policies: None
Sponsoring Committee: Liver and Intestinal Organ Transplantation
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Executive Summary

Medical urgency for liver allocation is determined either by the MELD¹ or PELD² score, or by the assignment of a status (1A or 1B). The scores are intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant, and the scores and statuses are good discriminators of death for many candidates with chronic liver disease. However, for some the risk of death without access to liver transplant or the complications of the liver disease are not accurately predicted by the statuses or the MELD or PELD score. In these instances, the liver transplant program may request exceptions.

Hepatocellular carcinoma (HCC) is the most common diagnosis requiring a MELD or PELD score exception. The ability to request an exception for HCC has existed since the implementation of the MELD/PELD allocation system. In 2009, the OPTN Board of Directors adopted additional common diagnoses that often required MELD/PELD exceptions. All of these exceptions in policy are called standardized exceptions, and transplant programs can request a standardized exception for their candidates if the candidates meet the criteria contained within policy.³ For HCC, transplant programs can submit exception requests for candidates meeting standard criteria directly into UNetSM. For the remaining diagnoses, transplant programs complete standard templates and submit them to the Chair of their respective Regional Review Board (RRB), who verifies that the candidate meets the policy criteria and approves them. If a standardized exception is approved, the exception scores are determined by policy and increase every 3 months until transplant as long as the candidates continue to meet criteria. Transplant programs are also permitted to request exceptions from the RRB for candidates who do not meet the criteria for the standardized MELD/PELD exceptions, but who may have complications of their liver disease not accounted for by the MELD score which increase their waitlist mortality.

Many OPTN/UNOS regions have adopted independent criteria used to request and approve non-standardized exceptions, commonly referred to as "regional agreements." These regional agreements may contribute to regional differences in exception submission and award practices, even among regions with similar organ availability and candidate demographics.^{4,5}

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, the Committee) is pursuing the establishment of a National Liver Review Board (NLRB) to promote consistent, evidence-based review of exception requests and award of exception points. In support of this project, the Committee has developed guidance for specific clinical situations for use by the NLRB to evaluate common exceptional case requests for adult candidates, pediatric candidates, and candidates with hepatocellular carcinoma (HCC). However, the guidance contained in this proposal can be used by existing review boards upon adoption, independent of the implementation of the NLRB. This supplements

¹ Model for End-Stage Liver Disease

² Pediatric End-Stage Liver Disease

³ Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁴ Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. "Regional Variability in Symptom-Based MELD Exceptions: A Response to Organ Shortage?" *Am J Transplant*, 11(2011): 2353-2361.

⁵ Rodriguez-Luna, H., H.E. Vargas, A. Moss, et al. "Regional variations in peer reviewed liver allocation under the MELD system." *Am J Transplant*, 5(2005): 2244-2247.

existing national guidance and replaces the regional agreements. If adopted, review board members and transplant programs would consult this resource when considering submitting exception requests.

What problem will this proposal solve?

Current liver policy includes standardized exceptions for nine diagnoses in which waitlist mortality is not accurately predicted by the MELD or PELD.⁶ A candidate that meets the criteria for one of these diagnoses is approved for a standardized MELD or PELD exception. If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board. In June 2015, the Board of Directors approved guidance to promote consistent standards for review boards when reviewing four of the most common types of exceptions: Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), and Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH).⁷

For non-standardized diagnoses, most OPTN/UNOS regions have adopted independent criteria used to request and approve exceptions, commonly referred to as “regional agreements.” These regional agreements may contribute to regional differences in exception submission and award practices, even among regions with similar organ availability and candidate demographics.^{8,9} Nationally, exception candidates drop off the waitlist at lower rates, and are transplanted at higher rates, than their peers with the equivalent calculated MELD.¹⁰ In addition, there are differences in the proportion of exception requests that are approved and the proportion of transplants that occur under exception among the various regions. On average, 88.4% of initial, appeal, and extension requests submitted between July 1, 2014 and June 30, 2015 were approved; however, individual regions approved as few as 75.8% and as many as 93.5% of requests during this timeframe.¹¹ Excluding Status 1 recipients, the proportion of recipients transplanted with an exception score ranged from 32.0% to 56.5% among the regions, and non-standardized exceptions ranged from 3.1% to over 21.0% (see **Table 1** below).¹²

Table 1. Deceased donor adult liver transplants in 2015, by exception type at time of transplant and OPTN/UNOS region.*

Region	No Exception (N)	No Exception (%)	Standard Exception (N)	Standard Exception (%)	Non-Standard Exception (N)	Non-Standard Exception (%)	Total Transplants (N)
1	117	52.7	90	40.5	15	6.8	222
2	421	57.8	216	29.7	91	12.5	728
3	784	66.2	333	28.1	68	5.7	1185
4	358	60.0	207	34.7	32	5.3	597
5	509	59.1	283	32.9	69	8.0	861
6	81	43.5	66	35.5	39	21.0	186
7	279	57.9	188	39.0	15	3.1	482
8	237	58.7	135	33.4	32	7.9	404
9	128	50.4	96	37.8	30	11.8	254

⁶ Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁷ Organ Procurement and Transplantation Network. *Guidance to Liver Transplant Programs and Regional Review Boards for MELD/PELD Exceptions Submitted for Neuroendocrine Tumors (NET), Polycystic Liver Disease (PLD), Primary Sclerosing Cholangitis (PSC), and Portopulmonary Hypertension (POPH)*. Richmond, VA, 2015, available at <https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/>.

⁸ Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. “Regional Variability in Symptom-Based MELD Exceptions: A Response to Organ Shortage?” *Am J Transplant*, 11(2011): 2353-2361.

⁹ Rodriguez-Luna, H., H.E. Vargas, A. Moss, et al. “Regional variations in peer reviewed liver allocation under the MELD system.” *Am J Transplant*, 5(2005): 2244-2247.

¹⁰ Massie, A.B., B. Caffo, S.E. Gentry, et al. “MELD exceptions and rates of waiting list outcomes.” *Am J Transplant*, 11(2011): 2362-2371.

¹¹ Based on OPTN data presented to the Committee on October 20, 2015

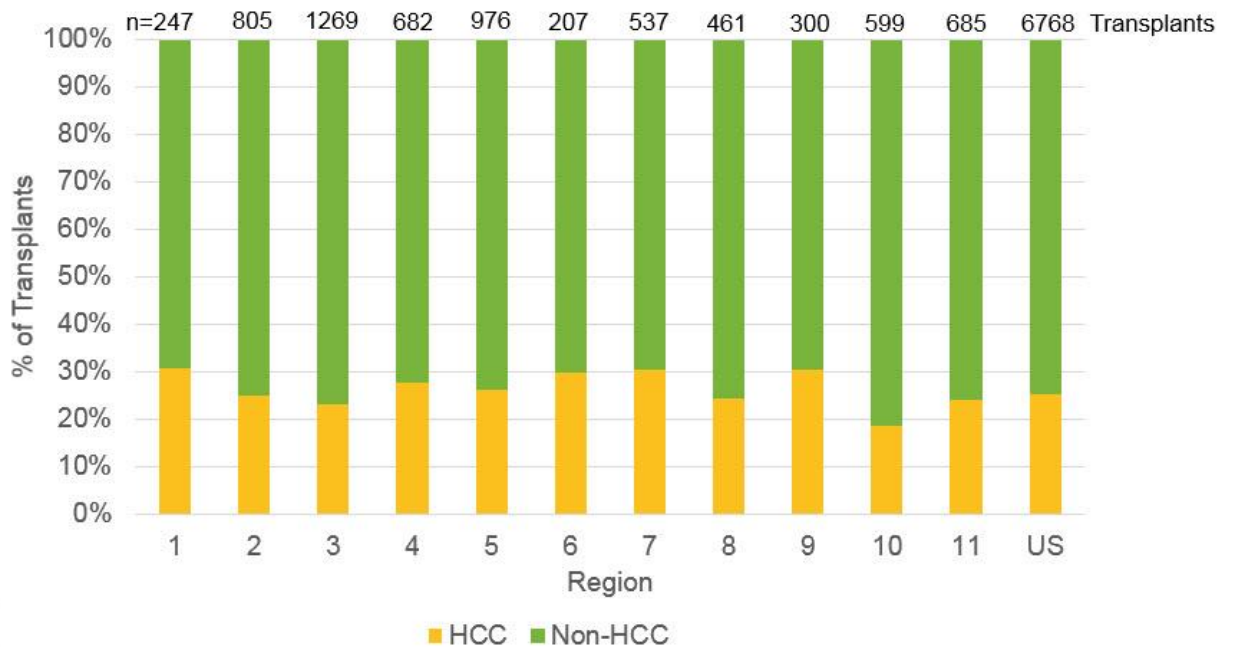
¹² Based on OPTN data as of July 8, 2016

Region	No Exception (N)	No Exception (%)	Standard Exception (N)	Standard Exception (%)	Non-Standard Exception (N)	Non-Standard Exception (%)	Total Transplants (N)
10	363	68.0	121	22.7	50	9.3	534
11	395	62.4	187	29.5	51	8.1	633
US	3672	60.3	1922	31.6	492	8.1	6086

*Status 1 recipients excluded from analysis.

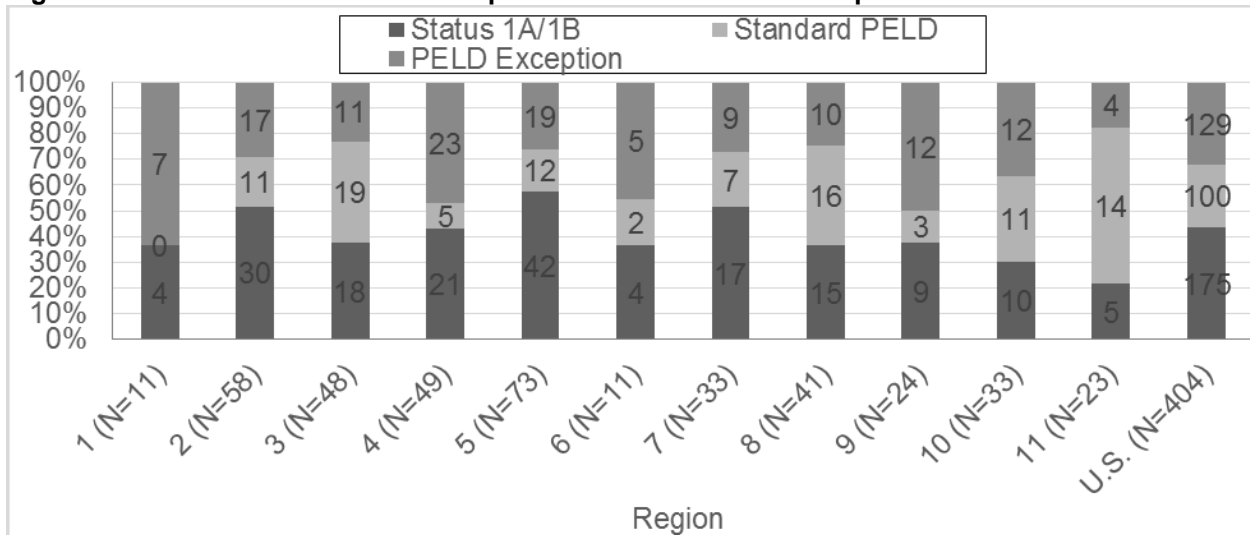
There is also evidence of regional variability in the awarding of HCC exception requests for candidates who do not meet criteria for a standardized exception. In nearly all regions, review boards grant MELD exceptions to patients with lesions beyond T2 though the criteria are not consistently applied across the regions.

Figure 1. Deceased Donor Liver Transplants in 2015: Percentage with Approved HCC Exception at Transplant, by Region.



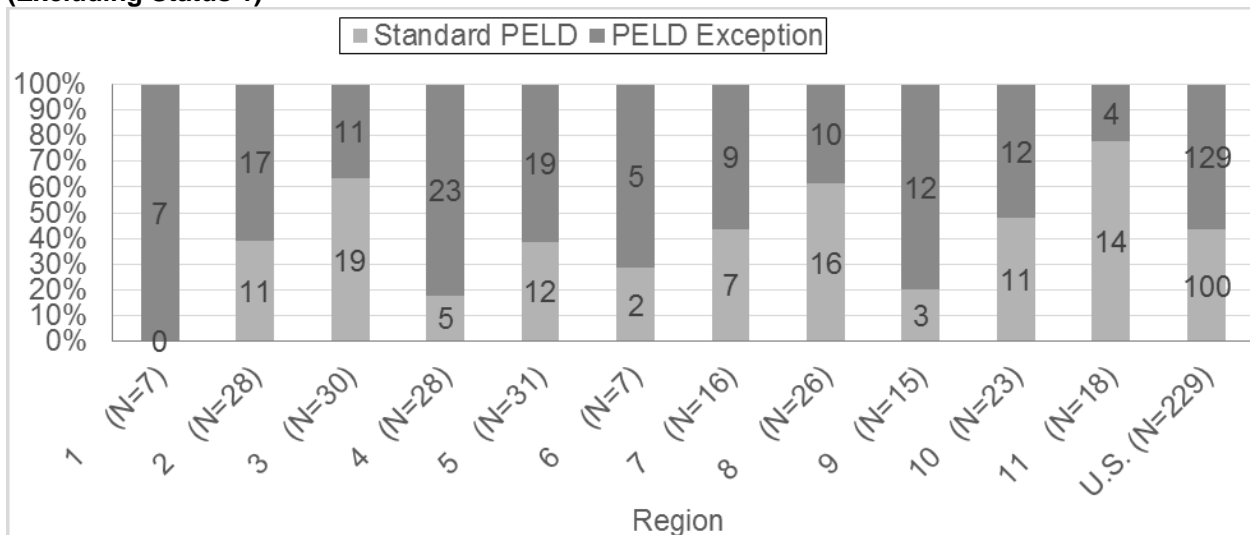
Regional variability exists among young pediatric liver transplant candidates as well. The percentage of pediatric candidates age 0 to 11 years old transplanted while listed with an exception varies widely across regions, from as low as 17% to as high as 64%.

Figure 2: Deceased Donor Liver Transplants in 0-11 Years Old Recipients 7/1/2014-6/30/2015



After excluding any status 1A candidates, the percent of 0 to 11 year old recipients who received PELD exceptions across all regions is 56%, ranging from as low as 22% to as high as 100%.

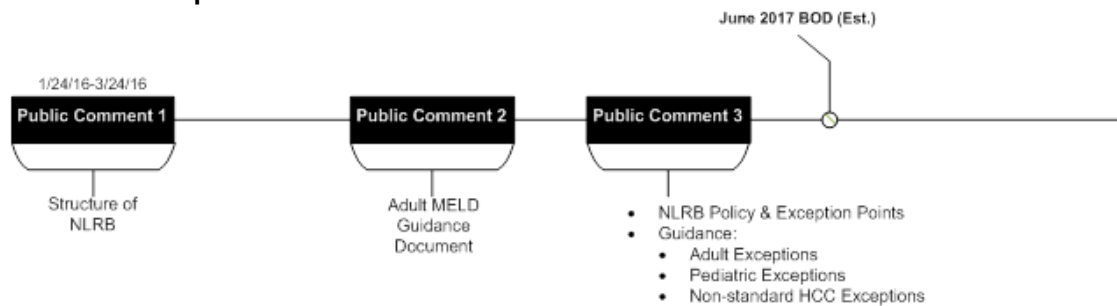
Figure 3: Deceased Donor Liver Transplants in 0-11 Years Old Recipients 7/1/2014-6/30/2015 (Excluding Status 1)



Why should you support this proposal?

This proposal is a companion to the proposal to establish a National Liver Review Board (NLRB). In November 2013, the OPTN/UNOS Board of Directors charged the Liver and Intestinal Organ Transplantation Committee (hereafter, the Committee) with developing a conceptual plan and timeline for the implementation of an NLRB to promote consistent, evidence-based review of exception requests. In January 2016, the Committee distributed for public comment the proposed structure of the NLRB and operational guidelines to govern it.¹³ The Committee sought feedback from the community on the method for assigning MELD exception points and is currently gathering evidence to support the proposed change. The updated proposal is also currently out for public comment during the January to March 2017 public comment cycle.

¹³ <https://optn.transplant.hrsa.gov/governance/public-comment/national-liver-review-board/>

Figure 4: NLRB Proposal Timeline

An important aspect of the NLRB proposal is the establishment of specialty boards, which will ensure that exception requests are assigned to reviewers with relevant expertise. There will be three specialty boards: a board to review adult MELD exception requests for all non-HCC diagnoses; a board to review pediatric exceptions requests for candidates less than 18 years old; and a board to review HCC exception requests.

The guidance documents contained in this proposal will help the specialty boards make more consistent decisions by providing the reviewers with up-to-date information about the most common conditions for which exceptions are most likely to be submitted. The proposal contains a guidance document for each of the three specialty boards. If supported by the community and approved by the Board of Directors, this guidance would replace any independent criteria that OPTN/UNOS regions used to request and approve exceptions, commonly referred to as “regional agreements.” Review board members and transplant centers would consult this resource when considering MELD exception requests for adult candidates with these diagnoses, recognizing that this resource is not exhaustive of all clinical scenarios.

Consistent with the NLRB policy proposal currently out for public comment, the Committee recommends that the NLRB award exception points for non-standardized exceptions in a uniform manner. The Committee recommends that the NLRB award adult candidates exception scores equal to three points below the median MELD at transplant in the DSA, and pediatric exception scores equal to the median MELD at transplant in the DSA. The NLRB can use its discretion to assign more or less points depending on the candidate’s medical urgency.

Importantly, the guidance contained in this proposal can be used immediately, independent of the implementation of the NLRB.

How was this proposal developed?

The three guidance documents were developed separately. The MELD/NLRB Subcommittee of the Liver Committee developed the adult MELD exception guidance document and the HCC guidance document, while a group of pediatric liver transplantation experts, including members of the Liver Committee and the OPTN/UNOS Pediatric Committee, formed a work group to develop the pediatric exception guidance document. The groups performed extensive literature searches to find evidence in peer-reviewed journals to support their positions. They also met via teleconference on multiple occasions to reach clinical consensus on questions that may not be explicitly answered by data or literature alone.

Adult MELD Exception Guidance Document

The MELD/NLRB Subcommittee proposed some modifications to the adult MELD exception guidance in response to feedback received during the first round of public comment in January 2016. The Board previously approved guidance for four standardized exceptions: Neuroendocrine Tumors (NET); Polycystic Liver Disease (PLD); Primary Sclerosing Cholangitis (PSC); and Portopulmonary Hypertension.¹⁴ Because this guidance was approved in June 2015, the Committee did not include those sections in the proposed guidance in the August 2016 version. However, that may have led to some

¹⁴ <https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/>

confusion, particularly for people concerned about PSC, because it may have created the impression that the Committee was proposing removing guidance for PSC. That was not the intent. Therefore, in this version of the proposal, guidance for all conditions, including the guidance previously approved, are combined into one document. The Committee also proposes clerical and grammatical changes to the existing PLD section to make it more understandable.

The Committee proposes a few changes based on feedback received during public comment. It proposes clarifying that the exception is for *chronic* Budd Chiari, and included that transplant programs should submit the etiology for the hypercoagulable state in the exception request, as well as documentation ruling out extrahepatic malignancy. The Committee disagreed with some commenters who suggested that Budd Chiari should not be eligible for exception points because Budd Chiari patients already have a MELD that reflects their severity of illness, because MELD sometimes does not reflect the severity of illness for Budd Chiari and therefore an exception may be needed.

Similar to Budd Chiari, the Committee disagreed with comments that said hepatic adenoma exceptions were not needed because MELD accurately reflects the severity of illness. However, the Committee proposes minor changes to the criteria in the guidance document based on public comment, specifically, that the tumor must be unresectable with two of the following characteristics:

- Malignant transformation proven by biopsy
- Presence of beta-catenin gene mutation
- Presence of glycogen storage disease

Finally, the Committee discussed feedback regarding diffuse ischemic cholangiopathy. Some commenters suggested that the guidance should not be limited to candidates that previously received a donation after cardiac death (DCD) liver transplant. However, as discussed in the previous public comment proposal, the Committee believes the data supports limiting the guidance to those candidates that are re-listed for a liver transplant with diffuse ischemic cholangiopathy that previously received a DCD liver transplant. Those candidates have waitlist outcomes that have a similar or improved waitlist survival compared to donation after brain death (DBD) candidates who are relisted with similar MELD scores.¹⁵ Though evidence is not conclusive, the Committee supported limiting the guidance to candidates that previously received a DCD liver transplant, and noted that this guidance document does not preclude a transplant program from applying for an exception for candidates with diffuse ischemic cholangiopathy after receiving a donation after DBD liver transplant.

Pediatric Exception Guidance Document

The Liver Committee convened a joint working group with the OPTN/UNOS Pediatric Transplantation Committee to develop guidance for assessing exceptions for pediatric liver candidates (less than 18 years old) to promote consistent, evidence-based review of pediatric MELD/PELD exception requests and status 1B requests. The working group categorized the proposed guidance into different sections:

- Status 1B
- Neoplasms
- Chronic Liver Disease
- Congenital Portosystemic Shunts
- Post-Transplant Complications

The working group systematically evaluated the clinical criteria that a transplant program should provide as evidence to the review board when requesting an exception for all of the conditions under each category. When clinically appropriate, the working group agreed that the adult MELD guidance and pediatric exception guidance should be consistent. The working group largely relied on literature to

¹⁵ 7Allen, A.M., W.R. Kim, H. Xiong, et al "Survival of recipients of livers from donation after circulatory death who are relisted and undergo retransplant for graft failure." Am J Transplant 15 (2014): 1120-8.

support its proposal, but also evaluated OPTN data and SRTR analyses^{16,17} to inform its decisions when relevant. Finally, absent conclusive evidence in literature or in data, the working group reached clinical consensus to determine its final recommendations.

HCC Exception Guidance Document

In December 2016, the OPTN/UNOS Board of Directors approved policy changes to the criteria for standardized HCC exceptions. In the development of this proposal, the Committee identified the need for a subsequent guidance document to the NLRB for HCC exception candidates falling outside of standard criteria. The Committee addressed specific scenarios in which guidance on a decision would be helpful to NLRB reviewers. These include:

- Contraindications for HCC exception score
- History of HCC in candidates
- HCC progression while undergoing local-regional treatment
- Alpha-fetoprotein (AFP) level in candidates
- Candidates beyond standard down-staging criteria

The guidance also includes recommendations for dynamic contrast-enhanced CT or MRI of the liver. These recommendations previously existed in policy, but recommendations, rather than rules, are not appropriate for policy. In the development of the HCC proposal in 2016, the Committee agreed to remove these two tables from policy that describe the recommended CT and MRI characteristics, and put them in the guidance document instead.

Which populations are impacted by this proposal?

This proposal promotes equitable access to transplant for all liver candidates whose status or MELD or PELD scores do not accurately reflect the severity of their disease. The proposal may also benefit liver candidates without exceptions, as the guidance in some instances is more conservative than current review board practices and some candidates currently receiving exceptions may not in the future.

How does this proposal impact the OPTN Strategic Plan?

Increase the number of transplants: There is no impact to this goal.

Improve equity in access to transplants: The primary goal for this proposal is to improve equity in access to transplant. Nationally, exception candidates are less likely to die while waiting for a liver transplant or be removed from the waitlist because they are too sick to transplant, and more likely to be transplanted, than their peers with the equivalent calculated MELD.¹⁸ There are also regional differences in whether similar candidates are awarded exception points.^{19,20} This guidance replaces any independent criteria OPTN regions used to request and approve exceptions, commonly referred to as “regional agreements,” and promotes national standards for review.

¹⁶ Analysis Report: Data request from the OPTN Liver and Intestinal Organ Transplantation Committee, July 29, 2016. Presented to the Pediatric Liver Working Group on September 29, 2016. Data Request ID# LI2016_02 (Data Request 1).

¹⁷ Analysis Report: Data request from the OPTN Liver and Intestinal Organ Transplantation Committee, August 31, 2016. Presented to the Pediatric Liver Working Group on September 29, 2016. Data Request ID# LI2016_02 (Data Request 2).

¹⁸ Massie, A.B., B. Caffo, S.E. Gentry, et al. “MELD exceptions and rates of waiting list outcomes.” *A J Transplant*, 11(2011): 2362- 2371

¹⁹ Argo, C.K., G.J. Stukenborg, T.M. Schmitt, et al. “Regional variability in symptom-based MELD exceptions: A response to organ shortage?” *Am J Transplant*, 11(2011): 2353-2361.

²⁰ Rodriguez-Luna, H., H. E. Vargas, A. Moss, et al. “Regional variations in peer reviewed liver allocation under the MELD system.” *Am J Transplant*, 5(2005): 2244-2247.

Improve waitlisted patient, living donor, and transplant recipient outcomes: Decisions made using this guidance will contribute to better waitlist and post-transplant outcomes for exception candidates, as well as those who will be transplanted on the basis of the calculated MELD score.

Promote living donor and transplant recipient safety: There is no impact to this goal.

Promote the efficient management of the OPTN: There is no impact to this goal.

How will the OPTN implement this proposal?

If public comment is favorable, the Committee plans to bring this guidance with the final NLRB proposal to the Board of Directors in 2017. Upon Board approval, the OPTN/UNOS will publish this guidance to the resources section of both the OPTN and other websites.

The OPTN/UNOS will work with the Committee to develop the orientation training all NLRB representatives and alternates must complete before beginning their term of service. The content of this guidance will be included as part of that training.

This proposal will not require programming in UNetSM.

How will members implement this proposal?

Review board members should consult this resource when assessing exception requests.

Transplant Hospitals

Liver programs should also consider this guidance when submitting exception requests for their adult and pediatric liver transplant candidates with these diagnoses. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice.

Will this proposal require members to submit additional data?

This proposal does not require additional data collection; however, the OPTN/UNOS will provide exception templates upon implementation to encourage programs to include the recommended information for the candidate's diagnosis.

How will members be evaluated for compliance with this proposal?

This resource is not OPTN/UNOS Policy, so it does not carry the monitoring or enforcement implications of policy. It will not change the current routine monitoring of OPTN/UNOS members. 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 is a resource intended to provide guidance to transplant programs and the NLRB, and is for voluntary use by members. Any data entered by members on exception forms is still subject to OPTN/UNOS review, and members are still required to provide documentation as requested.

How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

The OPTN/UNOS will assess the impact of these policy changes using a pre versus post analysis at 6-month intervals, up to 24 months after implementation. At the Committee's request, analyses beyond 24 months may be performed. The Committee will monitor several metrics, including, but not limited to, the following:

- Waiting List o Number of non-standardized exception requests
 - i. Number of non-standardized exception requests approved
 - ii. Distribution of MELD/PELD scores among approved requests
 - iii. Outcomes (probability of removals for transplant, death, too sick) for approved requests
- Transplant
 - i. Number of approved non-standardized exceptions
 - ii. Distribution of MELD/PELD scores among approved non-standardized exceptions
 - iii. Variance in the median MELD/PELD score among approved non-standardized exceptions
 - iv. Outcomes (graft/patient survival) for non-standardized approved exceptions compared to recipients with standardized exceptions and no exceptions

Results will be presented for the US and where applicable, by region.

Guidance Documents

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.²¹ 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
- Multiple Hepatic Adenomas
- Neuroendocrine Tumors (NET)
- Polycystic Liver Disease (PLD)
- Portopulmonary Hypertension
- Primary Sclerosing Cholangitis (PSC)
- 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/UNOS 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.

²¹ Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

36 **Guidance to Liver Transplant Programs and the**
37 **National Liver Review Board for Adult MELD**
38 **Exception Review**

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1 Background

2 A liver candidate receives a MELD²² or, if less than 12 years old, a PELD²³ score that is used for
3 liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-
4 month mortality without access to liver transplant. When the calculated score does not reflect
5 the candidate's medical urgency, a liver transplant program may request an exception score. A
6 candidate that meets the criteria for one of nine diagnoses in policy is approved for a
7 standardized MELD exception.²⁴ If the candidate does not meet criteria for standardized
8 exception, the request is considered by the Review Board.

9 The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee (hereafter, "the
10 Committee") has developed guidance for adult MELD exception candidates. The MELD
11 Exceptions and Enhancements Subcommittee proposed these recommendations after
12 reviewing the 2006 MELD Exception Study Group (MESSAGE) Conference, a descriptive
13 analysis of recent MELD exception requests submitted to the OPTN, and available peer-
14 reviewed literature. To support a recommendation for approving additional MELD exception
15 points, there must have been adequate evidence of increased risk of mortality associated with
16 the complication of liver disease.

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

21 Recommendation

22 Ascites

23 **There is inadequate evidence to support granting a MELD exception for ascites in adult**
24 **candidates with the typical clinical symptoms associated with this diagnosis.** Ascites is a
25 common clinical finding in liver transplant candidates. Refractory ascites, as defined by the
26 International Ascites Club, occurs in 5-10% of patients with portal hypertension and has a 1-
27 year mortality rate of approximately 50%.^{25,26,27,28} Hyponatremia is common in patients with
28 cirrhosis and refractory ascites from portal hypertension.^{29,30,31} In January 2016, the OPTN

²²Model for End-Stage Liver Disease

²³Pediatric End-Stage Liver Disease

²⁴Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

²⁵Moore, K.P., F. Wong, P. Gines, et al. "The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club." *Hepatology* 38 (2003): 258-66.

²⁶Runyon, B.A., AASLD. "Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012." *Hepatology* 57 (2013): 1651-3.

²⁷Runyon, B.A., Committee APG. "Management of adult patients with ascites due to cirrhosis: an update." *Hepatology* 49 (2009): 2087-107.

²⁸Gines P., A. Cardenas, V. Arroyo, et al. "Management of cirrhosis and ascites." *N Engl J Med* 350 (2004):1646-54.

²⁹Biggins, S.W., W.R. Kim, N.A. Terrault, et al. "Evidence-based incorporation of serum sodium concentration into MELD." *Gastroenterology* 130 (2006):1652-60.

³⁰Porcel, A., F. Diaz, P. Rendon, et al. "Dilutional hyponatremia in patients with cirrhosis and ascites." *Arch Intern Med* 162 (2002):323-8.

³¹Gines, A., A. Escorsell, P. Gines, et al. "Incidence, predictive factors, and prognosis of the hepatorenal

29 implemented a modification to the MELD score to incorporate serum sodium for candidates with
30 a calculated MELD greater than 11.³² Much of the excess mortality risk related to ascites is
31 similar to portal hypertension and hepatorenal syndrome and will be accurately reflected in the
32 lab values used to calculate the MELD score, specifically the serum creatinine and serum
33 sodium. Therefore, MELD exception for ascites is not recommended.

34 Budd Chiari

35 **Approval of MELD exception points for adult candidates with Budd Chiari may be**
36 **appropriate in some instances.** Budd Chiari syndrome is an uncommon manifestation of
37 hepatic vein thrombosis and patients might present with evidence of decompensated portal
38 hypertension (ascites and hepatic hydrothorax) among others.³³ Medical management may
39 include diuresis and anticoagulation; or more aggressive management with Transjugular
40 Intrahepatic Portosystemic Shunt (TIPS), portosystemic shunting, or liver transplant.³⁴
41 Anticoagulation and pharmacologic management is the cornerstone treatment.^{35,36} Patients with
42 severe portal hypertension not controlled with the standard of care might have evidence of
43 hyponatremia or renal impairment, but these will be accurately reflected by the calculated MELD
44 score.

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

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

55

56 Gastrointestinal Bleeding

57 **There is inadequate evidence to support granting a specific MELD exception for**
58 **gastrointestinal bleeding in adult candidates who experience acute or chronic blood loss**

syndrome in cirrhosis with ascites." *Gastroenterology* 105 (1993):229-36.

³²Biggins, S.W. "Use of serum sodium for liver transplant graft allocation: a decade in the making, now is it ready for primetime?" *Liver Transpl* 21 (2015):279-81.

³³Janssen, H.L., J.C. Garcia-Pagan, E. Elias, et al. "Budd-Chiari syndrome: a review by an expert panel." *Hepatology* 38 (2003): 364-371.

³⁴Seijo, S., A. Plessier, J. Hoekstra, et al. "Good long-term outcome of Budd-Chiari syndrome with a step-wise management." *Hepatology* 57 (2013): 571962-8.

³⁵Plessier, A., A. Sibert, Y. Consigny, et al. "Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome." *Hepatology* 44 (2006):1308-16.

³⁶DeLeve, L.D., D.C. Valla, G. Garcia-Tsao. "Vascular disorders of the liver AASLD practice guidelines." *Hepatology* 49 (2009): 1729-64.

59 **independent of their calculated MELD.** There is also inadequate evidence to support a MELD
60 exception for transfusion dependence independent of MELD with one exception, spur cell
61 hemolytic anemia (SCHA).³⁷ However, due to the infrequent occurrence of SCHA in a transplant
62 candidate, and its common association with recent alcohol use or active infection, MELD
63 exception is not recommended. Similarly there is no evidence to support that candidates with
64 transfusion dependence who develop antibodies while waiting warrant a MELD exception.^{38,39}

65 Hepatic Encephalopathy

66 Hepatic encephalopathy (HE) is a complication of chronic liver disease associated with
67 significant morbidity. There is an absence of evidence of sufficient quality to support MELD
68 exception for complications of HE.^{40,41,42,43}

69 Hepatic Epithelioid Hemangioendothelioma

70 **Approval of MELD exception points for adult candidates with unresectable Hepatic**
71 **Epithelioid Hemangioendothelioma (HEHE) may be appropriate in some instances.** Biopsy
72 must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma.

73 HEHE is a rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity
74 of the diagnosis, as well as the variability in presentation, the optimal treatment strategies are
75 not fully established. However, for lesions which cannot be resected, liver transplant is
76 associated with 1, 5, and 10-year patient survival rates of 97%, 83%, and 74%; with more
77 favorable results occurring in patients without microvascular invasion. The presence of extra-
78 hepatic disease has not been associated with decreased survival post liver transplant and
79 therefore should not be an absolute contraindication. Controversy regarding the role of liver
80 transplant in treating HEHE relates to the variable course of disease in the absence of liver
81 transplant, with some patients demonstrating regression or stabilization of disease and
82 prolonged survival.^{44,45}

³⁷Alexopoulou, A., L. Vasilieva, T. Kanellopoulou, et al. "Presence of spur cells as a highly predictive factor of mortality in patients with cirrhosis." *J Gastroenterol Hepatol.* 4 (2014):830-4.

³⁸Lyles, T., A. Elliott, D.C. Rockey. "A risk scoring system to predict in-hospital mortality in patients with cirrhosis presenting with upper gastrointestinal bleeding." *J Clin Gastroenterol* 48 (2014):712-20.

³⁹Flores-Rendón, A.R., J.A. González-González, D. García-Compean, et al. "Model for end stage of liver disease (MELD) is better than the Child-Pugh score for predicting in-hospital mortality related to esophageal variceal bleeding." *Ann Hepatol* 7 (2008):230-4.

⁴⁰Cordoba J., M. Ventura-Cots, M. Simón-Talero, et al. "Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF)." *Hepatology* 60 (2014): 275-81.

⁴¹García-Martínez, R., M. Simón-Talero, J. Córdoba. "Prognostic assessment in patients with hepatic encephalopathy." *Dis Markers* 31 (2011): 171-9.

⁴²D'Amico, G., G. Garcia-Tsao, L. Pagliaro. "Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies." *Hepatology* 44 (2006): 217-31.

⁴³Brandman, D., S.W. Biggins, B. Hameed, et al. "Pretransplant severe hepatic encephalopathy, peritransplant sodium and post-liver transplantation morbidity and mortality." *Liver Int* 32 (2012): 158-64.

⁴⁴Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry." *Ann Surg* 246 (2007): 949-57.

⁴⁵Nudo, 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.

83 Hepatic Hydrothorax

84 **There is inadequate evidence to support granting a MELD exception for hepatic**
 85 **hydrothorax in adult candidates with the typical clinical symptoms associated with this**
 86 **diagnosis. Liver transplant candidates with chronic, recurrent, confirmed hepatic**
 87 **hydrothorax could be considered on individual basis for a non-standard MELD**
 88 **exception.**

89 Hepatic hydrothorax is a relatively uncommon complication of endstage liver disease occurring
 90 in only 5-10% of patients with cirrhosis and portal hypertension.^{46,47,48} Hepatic hydrothorax can
 91 occur in either or both pleural spaces and can occur with or without portal hypertensive
 92 ascites.⁴⁹ By definition, hepatic hydrothorax is a transudative pleural effusion due to portal
 93 hypertension without a cardiopulmonary source. Infectious and malignant pleural effusions must
 94 be excluded. In this context, a serum pleural fluid albumin gradient (SPAG) of at least 1.1 g/dL
 95 may be more accurate in identifying hepatic hydrothorax than the more traditional Light's criteria
 96 for a transudative pleural effusion.^{22,50} The mostly like explanation for hepatic hydrothorax is
 97 passage of fluid from the peritoneal space to the pleural space through diaphragmatic defects
 98 which can be documented by intraperitoneal injection of 99mTc-tagged nannocolloids followed
 99 by scintigraphy.⁵¹ Unlike ascites, relatively small amounts of fluid in the pleural space (1 to 2 L)
 100 lead to severe symptoms such as shortness of breath and hypoxia. Initial management with
 101 dietary sodium restriction, diuretics, intravenous albumin, and therapeutic thoracentesis can be
 102 successful. Hepatic hydrothorax can be complicated by spontaneous bacterial empyema or
 103 iatrogenic complication of thoracentesis (infections, pneumothorax, or hemothorax). For chronic,
 104 recurrent, confirmed hepatic hydrothorax, transjugular intrahepatic portosystemic shunt,
 105 indwelling pleural catheter, and surgical repair of diaphragmatic defects can be effective in
 106 some patients yet risk additional complications. Like ascites, hepatic hydrothorax is similar to
 107 portal hypertension and hepatorenal syndrome and will be accurately reflected in the lab values
 108 used to calculate the MELD score, specifically the serum creatinine and serum sodium.
 109 Therefore, MELD exception for hepatic hydrothorax is not recommended in the majority of
 110 circumstances.

111 Adult liver transplant candidates with chronic, recurrent, confirmed hepatic hydrothorax could be
 112 considered on an individual basis for a MELD exception provided that infectious and malignant
 113 causes have been ruled out. Documentation submitted for case review should include the
 114 following:

- 115 • At least 1 thoracentesis over 1 L weekly in last 4 weeks; report date and volume of each
 116 thoracentesis

⁴⁶Norvell, J.P., J.R. Spivey. "Hepatic hydrothorax." *Clin Liver Dis* 18 (2014): 439-49.

⁴⁷Baikati, K., D.L. Le, I.I. Jabbour, et al. "Hepatic hydrothorax." *Am J Ther* 21 (2014): 43-51.

⁴⁸Cardenas, A., T. Kelleher, S. Chopra. "Review article: hepatic hydrothorax." *Aliment Pharmacol Ther* 20 (2004): 271-9.

⁴⁹Badillo, R., D.C. Rockey. "Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature." *Medicine (Baltimore)* 93 (2014): 135-42.

⁵⁰Porcel, J.M. "Identifying transudates misclassified by Light's criteria." *Current Opinion Pulmonary Medicine* 19 (2013): 362-7.

⁵¹Hewett, L.J., M.L. Bradshaw, L.L. Gordon, et al. "Diagnosis of isolated hepatic hydrothorax using peritoneal scintigraphy." *Hepatology* (2016).

- 117 • Pleural fluid is transudative by pleural albumin-serum albumin gradient of at least 1.1
- 118 and by cell count
- 119 • No evidence of heart failure; provide objective evidence excluding heart failure
- 120 • Pleural fluid culture negative on 2 separate occasions
- 121 • Pleural fluid cytology is benign on 2 separate occasions
- 122 • There is contraindications to TIPS; specify specific contraindication
- 123 • Diuretic refractory

124 Hereditary Hemorrhagic Telangiectasia

125 **Approval of MELD exception points for adult candidates with high output cardiac failure**

126 **due to multiple arteriovenous (AV) malformations may be appropriate in some instances.**

127 Hereditary hemorrhagic telangiectasia is an uncommon, autosomal dominant genetic disorder
128 characterized by mucocutaneous telangiectasias, as well as arteriovenous malformations in the
129 brain, spine, lungs, gastrointestinal tract, and liver. The AV malformations can progress to high
130 output cardiac failure, which eventually may be irreversible. In the future, there may be effective
131 non-transplant options, and if such agents become widely available, the recommendation to
132 offer MELD score exception will need to be revisited. ^{52,53}

133 Documentation submitted for case review should include both of the following:

- 134 • Documentation of high output cardiac failure by echocardiography
- 135 • Imaging supporting intra-hepatic AV malformations or severe diffuse bilobar hepatic
- 136 necrosis in the setting of hepatic AV malformation

⁵²Lee, M., D.Y. Sze, C.A. Bonham, et al. "Hepatic arteriovenous malformations from hereditary hemorrhagic telangiectasia: treatment with liver transplantation." *Dig Dis Sci* 55 (2010): 3059-62.

⁵³Boillot, O., F. Bianco, J.P. Viale, et al. "Liver transplantation resolves the hyperdynamic circulation in hereditary hemorrhagic telangiectasia with hepatic involvement." *Gastroenterology* 116 (1999): 187-92.

137 Multiple Hepatic Adenomas

138 Hepatic adenomas (HA) are rare benign nodules occurring principally in women taking oral
 139 contraceptives, are solitary or multiple, and highly variable in size; there is no consensus for
 140 their management except that once their size exceeds 5 cm nodules are resected to prevent 2
 141 major complications: bleeding and malignant transformation. An exception to this is in men
 142 where it is recommended to remove smaller nodules. The presence of HCC in HA is a well-
 143 documented observation, the risk ranging from 5 to 9%; gene coding for β -catenin mutations
 144 (15-18% of cases) are associated with a high risk of malignant transformation (together with
 145 cytologic atypia). HA are a frequent mode of presentation in some genetic diseases, particularly
 146 Glycogen Storage Disease (GSD) and congenital or acquired vascular anomalies. **Orthotopic
 147 liver transplantation for HA remains an extremely rare indication; however, it is a valid
 148 therapeutic option in select patients with adenoma with risk of malignant transformation,
 149 not amenable to resection (the reason must be provided), and one or more of the
 150 following:**

- 151 • Malignant transformation proven by biopsy
- 152 • Presence of glycogen storage disease which increases the risk for malignant
 153 transformation

154 The identification of these criteria is mandatory to aid in the decision-making process. ^{54,55,56,57}

155 Neuroendocrine Tumors (NET)

156 A review of the literature supports that candidates with NET are expected to have a low risk of
 157 waiting list drop-out. Initial recommendations included age less than 60. Older patients with a lot
 158 of disease burden may be referred to transplant as a last resort, leading to poor outcomes, while
 159 data presented at the AASLD show that very young patients with NET and early stage disease
 160 do well. Committee members believed that these initial guidelines could include strict criteria
 161 that could be expanded based upon the experience of the Review Board.

162 **Transplant programs should also be aware of these criteria when submitting exceptions
 163 for NET. The Review Board should consider the following criteria when reviewing
 164 exception applications for candidates with NET.**

- 165 1. Recipient age <60 years.
- 166 2. Resection of primary malignancy and extra-hepatic disease without any evidence of
 167 recurrence at least six months prior to MELD exception request.
- 168 3. Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to
 169 resection.
- 170 4. Tumors in the liver should meet the following radiographic characteristics on *either* CT or

⁵⁴Blanc, 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.

⁵⁵Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." *Liver Transplantation* 22 (2016): 516-526.

⁵⁶Alagusundaramoorthy, 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.

⁵⁷Dokmak, 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.

- 171 MRI:
- 172 ▪ a. If CT Scan: Triple phase contrast
- 173 ○ i. Lesions may be seen on only one of the three phases
- 174 ○ ii. Arterial phase: may demonstrate a strong enhancement
- 175 ○ iii. Large lesions can become necrotic/calcified
- 176 ▪ b. If MRI Appearance:
- 177 ○ i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave
- 178 images
- 179 ○ ii. Diffusion restriction
- 180 ○ iii. Majority of lesions are hypervascular on arterial phase with wash –out
- 181 during portal venous phase
- 182 ○ iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense
- 183 lesions are characteristics of NET
- 184 5. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin
- 185 tumors with portal system drainage. Note: Neuroendocrine tumors with the primary
- 186 located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not
- 187 candidates for automatic MELD exception.
- 188 6. Lower - intermediate grade following the WHO classification. Only well differentiated
- 189 (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20
- 190 per 10 HPF with less than 20% ki 67 positive markers.
- 191 7. Tumor metastatic replacement should not exceed 50% of the total liver volume.
- 192 8. Negative metastatic workup should include one of the following:
- 193 ▪ a. Positron emission tomography (PET scan)
- 194 ▪ b. Somatostatin receptor scintigraphy
- 195 ▪ c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-
- 196 tetraazacyclododecane-N, N', N'',N'''-tetraacetic acid (DOTA)-D-Phe1-Try3–
- 197 octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease,
- 198 especially bone metastasis.
- 199
- 200 **Note:** Exploratory laparotomy and or laparoscopy is not required prior to MELD
- 201 exception request.
- 202 9. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup
- 203 at least 3 months prior to MELD exception request (submit date).

204 10. Recheck metastatic workup every 3 months for MELD exception increase consideration
 205 by the Review Board. Occurrence of extra-hepatic progression – for instance lymph-
 206 nodal Ga68 positive locations – should indicate de-listing. Patients may come back to
 207 the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.

208 11. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a
 209 permanent exclusion criteria

210

211 **Polycystic Liver Disease (PLD)**

212 Certain patients with PLD may benefit from MELD exception points. Indication for an exception
 213 include those with PCLKD (Mayo type D or C) with severe symptoms plus *any* of the following:

- 214 • Hepatic decompensation
- 215 • Concurrent hemodialysis
- 216 • GFR less than 20 ml/min

217

218 **Transplant programs should provide the following criteria when submitting**
 219 **exceptions for PLD. The Review Board should consider the following criteria**
 220 **when reviewing exception applications for candidates with PLD.**

221 1) Management of PLD

PLD Classification – Mayo Modification

Types	A	B	C	D
Symptoms	0 - +	++/+++	++/+++	++/+++
Cyst Findings	Focal	Focal	Diffuse	Diffuse
Spared Remnant Volume	≥ 3	≥ 2	≥ 1	< 1
PV/HV Occlusion	No	No	No	Yes

222

223 2) Surgical Management of PLD

- 224 ▪ Indications
 - 225 • Types C* and D **and** at least 2 of the following:
 - 226 • Hepatic decompensation
 - 227 • Concurrent renal failure (dialysis)
 - 228 • Compensated comorbidities

229 * Note: Prior resection/fenestration, alternative therapy precluded.

230 Patients who meet the criteria above should be considered for MELD exception points such that
 231 transplantation may be expected within the year.

232 **Portopulmonary Hypertension**

233 Candidates meeting the criteria in *Policy 9.3.C: Specific MELD/PELD Exceptions, Table 9-2* are
 234 eligible for MELD or PELD score exceptions that do not require evaluation by the full Review
 235 Board. The transplant program must submit a request for a specific MELD or PELD score
 236 exception with a written narrative that supports the requested score. Templates were developed

237 for these exceptions to aid the transplant programs in the process of submitting the required
238 information to justify the exception.

239 The Committee recommends that the following three elements be considered in reviewing the
240 exception application in addition to the requirements listed in policy for the purposes of policy
241 research:

242 1) Although policy only requires reporting of the MPAP and PVR, complete Hemodynamics
243 should be reported, including MPAP, PVR, PWAP and CO.

244 2) To be considered abnormal, the initial mean pulmonary artery pressure (MPAP) should
245 be >35 mmHg and pulmonary vascular resistance (PVR) levels should be > 240
246 dynes.s.cm-5.

247 3) The initial transpulmonary gradient (MPAP-PVR) to correct for volume overload should be
248 > 12 mmHg

249 As noted in policy, these candidates will receive a MELD score of 22/ PELD score of 28. In
250 order to qualify for MELD/PELD extensions and a 10% mortality equivalent increase in points,
251 the required documentation must be resubmit every three months and the mean pulmonary
252 arterial pressure (MPAP) must remain below 35 mmHg, confirmed by repeat heart
253 catheterization.

254 Primary Sclerosing Cholangitis

255 Candidates with PSC historically have low mortality rates, and therefore do not need exception
256 scores. Based on clinical experience and a review of the available literature, the Committee
257 recommends that four specific elements be considered.

258 **Transplant programs should provide the following criteria when submitting exceptions for**
259 **PSC. The Review Board should consider the following criteria when reviewing exception**
260 **applications for candidates with PSC.** The candidate must meet both of the following two
261 criteria:

- 262 1. The candidate has been admitted to the intensive care unit (ICU) two or more times
263 over a three month period for hemodynamic instability requiring vasopressors
264 2. The candidate has cirrhosis

265 In addition the candidate must have one of the following criteria:

- 266 1. The candidate has biliary tract stricture which are not responsive to treatment by
267 interventional radiology (PTC) or therapeutic endoscopy (ERCP) or
268 2. The candidate has been diagnosed with a highly-resistant infectious organism (e.g.
269 Vancomycin Resistant Enterococcus (VRE), Extended Spectrum Beta-Lactamase
270 (ESBL) producing gram negative organisms, Carbapenem-resistant
271 Enterobacteriaceae (CRE), and Multidrug-resistant Acinetobacter.)

272

273 Post-Transplant Complications

274 Small for Size Syndrome

275 Small for size syndrome refers to graft dysfunction of varying severity occurring in the early
276 post-operative period, less than 30 days, following transplantation of a size-reduced liver

277 allograft, with no other identified cause of graft dysfunction such as vascular thrombosis,
278 prolonged ischemia, or other etiology.⁵⁸ Typical findings include worsening cholestasis and
279 ascites. With optimal care, some patients may recover while others may require re-
280 transplantation. **In many cases, the calculated MELD score will provide adequate priority.**
281 **However, mortality risk may not be adequately reflected by the calculated MELD score in**
282 **cases of severe dysfunction, and an exception may be appropriate.**

283 Documentation submitted for case review should include all of the following:

- 284 • Risk factor for small for size syndrome
- 285 • Interventions used to treat small for size syndrome
- 286 • Clinical status of the patient (hospitalized, requiring ICU care, intubated)

287

288 Chronic Rejection

289 **There is inadequate evidence to support granting a MELD exception for chronic rejection**
290 **in adult candidates with the typical clinical symptoms associated with this diagnosis.** In
291 cases where re-transplantation is being considered, it is anticipated that progressive injury of
292 the allograft due to rejection will be reflected in the development of liver dysfunction, and
293 prioritization by MELD score may be appropriate. Cases with atypical clinical scenarios in which
294 the degree of liver dysfunction and risk of waitlist mortality are not reflected by the MELD score
295 may be considered on an individual basis.

296 Diffuse Ischemic Cholangiopathy

297 Diffuse ischemic cholangiopathy is a complication associated with donation after cardiac death
298 (DCD) donors. Analysis of waitlist outcomes for patients re-listed after undergoing liver
299 transplant from a DCD donor demonstrates that these patients have a similar or improved
300 waitlist survival compared to donation after brain death (DBD) candidates who are re-listed with
301 similar MELD scores.⁵⁹ However, patients with ischemic cholangiopathy may have significant
302 morbidity and require multiple repeat biliary interventions and repeat hospitalizations for
303 cholangitis. Despite similar waitlist outcomes as DBD donor liver recipients who are listed for
304 retransplant, the Committee supports increased priority for prior DCD donor liver recipients to
305 encourage use of DCD livers when appropriate.

306 In addition, analyses has shown that patients with a prior DCD transplant and an approved
307 MELD score exception had an improved survival compared to those who never had an
308 exception approved.⁶⁰ Patients with biliary injuries and need for biliary interventions also have
309 been demonstrated to have an increased risk of graft loss and death.⁶¹ **Therefore, patients**
310 **with a prior DCD transplant that demonstrated two or more of the following criteria within**
311 **12 months of transplant should be considered for MELD exception:**

- 312 • Persistent cholestasis as defined by abnormal bilirubin (greater than 2 mg/dl)

⁵⁸Uemura, T., S. Wada, T. Kaido, et al. "How far can we lower graft-to-recipient weight ratio for living donor liver transplantation under modulation of portal venous pressure?" *Surgery* 159 (2016): 1623-30.

⁵⁹Allen, A.M., W.R. Kim, H. Xiong, et al "Survival of recipients of livers from donation after circulatory death who are re-listed and undergo retransplant for graft failure." *Am J Transplant* 15 (2014): 1120-8.

⁶⁰Makuda, R.C., P.L. Abt, D.S. Goldberg. "Use of Model for End-Stage Liver Disease exceptions for donation after cardiac death graft recipients re-listed for liver transplantation." *Liver Transpl* 21 (2015):554-60.

⁶¹Axelrod, D.A., K.L. Lentine, H. Xiao, et al. "National assessment of early biliary complications following liver transplantation: incidence and outcomes." *Liver Transpl.* 20 (2014): 446-56.

- 313 • Two or more episodes of cholangitis with an associated bacteremia requiring hospital
314 admission
- 315 • Evidence of non-anastomotic biliary strictures not responsive to further treatment

316 Late Vascular Complications

317 Patients with hepatic artery thrombosis occurring within 7 days of transplant with associated
318 severe graft dysfunction may be eligible for Status 1A, or occurring within 14 days of
319 transplantation without severe graft dysfunction may be eligible for a standard exception of
320 40.⁶²⁶³ Cases of late hepatic artery thrombosis which do not meet these criteria are not eligible
321 for standard MELD exception. **Due to the highly variable outcomes associated with late
322 hepatic artery thrombosis, there is inadequate evidence to support granting a MELD
323 exception in adult candidates with the typical clinical symptoms, including hepatic
324 abscess and intrahepatic biliary strictures that may be associated with late HAT.
325 However, patients with atypical severe complications may be considered for MELD
326 exception on an individual basis.** Complications that warrant consideration of MELD
327 exception are similar to those criteria noted for DCD cholangiopathy (with 2 or more episodes of
328 cholangitis requiring hospital admission over a 3 months period plus biliary strictures not
329 responsive to further treatment or bacteremia with highly resistant organisms). Patients with
330 early HAT just beyond 7 or 14 day cut off with evidence of severe graft dysfunction may be
331 considered for MELD exception, depending on the clinical scenario.

332 Pruritus

333 **There is inadequate evidence to support granting a MELD exception for pruritus in adult
334 candidates with the typical clinical symptoms associated with this diagnosis.** Pruritus is a
335 manifestation of predominantly cholestatic liver diseases. It had been reported that chronic
336 pruritus may lead to a decreased quality of life, prolonged wound healing, skin infections, and
337 sleep disturbance.⁶⁴ The frequency ranges from 80-100% for patients suffering from Primary
338 Biliary Cirrhosis; 20-40% for patients with primary Sclerosing Cholangitis and Chronic Viral
339 Hepatitis among other diseases.⁶⁵ The pruritus increases as the disease progresses. So far
340 data have failed to support an endpoint related to quantity but rather of quality of life and were
341 considered inappropriate for additional MELD points.⁶⁶ Due to inadequate evidence of increased
342 risk of pre-transplant mortality, or a widely-accepted threshold for access to liver transplant,
343 MELD score exception for isolated clinical finding of pruritus are not recommended.

344 Conclusion

345 Review Board members should consult this resource when assessing adult MELD exception
346 requests. Liver programs should also consider this guidance when submitting exception
347 requests for adult candidates with these diagnoses. However, these guidelines are not

⁶²Policy 9.1.A: Adult Status 1A Requirements, Organ Procurement and Transplantation Network Policies.

⁶³Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁶⁴Pruritus in chronic cholestatic liver disease. Bunchorntavakul C, Reddy KR Clin Liver Dis. 2012 May;16(2):331-46.

⁶⁵Elman, S., L.S. Hynan, V. Gabriel, et al. "The 5-D itch scale: a new measure of pruritus." Br J Dermatol 162 (2010): 587-93

⁶⁶Martin, P., A. DiMartini, S. Feng, et al. "Evaluation for liver transplantation in adults: 2013 practice guideline by the AASLD and the American Society of Transplantation." (2013): 61.

348 prescriptive of clinical practice.

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

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Summary and Goals

The MELD⁶⁷ or PELD⁶⁸ score and status (1A or 1B) are used to prioritize candidates on the waiting list, and are good discriminators of death without a transplant for many pediatric patients with chronic liver disease. However, for some patients, complications of the liver disease and not the degree of liver dysfunction determine the need for liver transplant. Statuses and MELD or PELD scores do not reflect these complications, which have an increased risk of mortality or waitlist dropout without access to timely transplant.⁶⁹ This document summarizes available evidence to assist clinical reviewers in approving candidates for status 1B exceptions and MELD or PELD exceptions. It contains guidance for use by the Review Board or the OPTN/UNOS Liver & Intestinal Organ Committee (hereafter, “the Committee”) to evaluate common exceptional case requests for pediatric candidates with the following diagnoses, not all of which are appropriate for an exception:

- Status 1B exceptions (including neoplasms)
- Neoplasms
 - Metastatic Neuroendocrine Tumor (NET)
 - Hepatocellular Carcinoma (HCC)
 - Hilar Cholangiocarcinoma
- Complications of Liver Disease
 - Growth failure or nutritional insufficiency
 - Infections

⁶⁷ Model for End-Stage Liver Disease

⁶⁸ Pediatric End-Stage Liver Disease

⁶⁹ Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

- 35 ○ Complications of portal hypertension, including ascites
- 36 ○ Encephalopathy
- 37 ○ Hepatopulmonary syndrome
- 38 ○ Developmental delay
- 39 ○ Pruritus
- 40 ○ Metabolic bone disease
- 41 ● Congenital Portosystemic Shunts
- 42 ● Post-transplant complications
 - 43 ○ Chronic Rejection
 - 44 ○ Cholangiopathy
 - 45 ○ Vascular Complications

46
47 These guidelines promote consistent review of these diagnoses and summarize the
48 Committee's recommendations to the OPTN/UNOS Board of Directors. This resource is not
49 OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not
50 an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define
51 a standard of care. This resource is intended to provide guidance to transplant programs and
52 the Review Board.

53

54 Background

55 For allocation purposes, a liver candidate is either registered in a status or receives a MELD or,
56 if less than 12 years old, a PELD score. Candidates are registered in either status 1A or 1B if
57 the candidate meets certain clinical criteria defined by policy, and transplant programs may
58 request to register a candidate in a status if the candidate does not meet the policy
59 requirements. The Committee retrospectively reviews candidates registered in a status by
60 exception.

61 The MELD and PELD scores are intended to reflect the candidate's disease severity, based on
62 the risk of 3-month mortality without access to liver transplant. When the calculated score does
63 not reflect the candidate's medical urgency, a liver transplant program may request an
64 exception for a higher score. A candidate that meets the criteria for one of the diagnoses in
65 policy is approved for a standardized MELD or PELD exception.⁷⁰ If the candidate does not
66 meet criteria for standardized exception, the Review Board considers the request. Pediatric
67 candidates with approved exceptions who turn 18 while still waiting with an approved exception
68 continue to be eligible to receive pediatric exceptions unless or until the candidate is removed
69 from the waiting list.⁷¹

70 The Committee has developed guidance for pediatric status and MELD or PELD exception
71 candidates. To support a recommendation for approving an exceptional status registration or
72 additional MELD or PELD exception points, there must have been adequate evidence of
73 increased risk of mortality associated with the complication of liver disease.

74 This guidance replaces any independent criteria that OPTN regions use to request and approve

⁷⁰ Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁷¹ Policy 9.1: Status and Score Exceptions, Organ Procurement and Transplantation Network Policies.

75 exceptions, commonly referred to as “regional agreements.” Review Board members, transplant
76 centers, and the Committee should consult this resource when considering status or
77 MELD/PELD exception requests for pediatric candidates less than 18 years old. Any guidance
78 contained within this document that differs from the guidance offered for adult MELD exceptions
79 is intentional, and is based on peer-review literature and/or clinical practice.

80 Recommendation

81 Status 1B

82 Status 1B - Chronic liver disease

83 Generally candidates that do not meet criteria in *Policy 9.1.C: Pediatric Status 1B Requirements*
84 should not receive a status 1B exception. Candidates that meet criteria in *Policy 9.1.C.2.c* or
85 *9.1.C.2.d* but without a PELD score of at least 25 may be considered for status 1B exception if
86 the candidate is critically ill and admitted in the Intensive Care Unit (ICU). Candidates without
87 renal replacement therapy may be considered for a status 1B exception if they meet all other
88 criteria in policy and require a liver support device (such as Molecular Adsorbent Recirculating
89 System (MARS), albumin dialysis, plasmapheresis).

90 Status 1B – Neoplasm

91 Under *Policy 9.1.C.2*, candidates with biopsy-proven hepatoblastoma without evidence of
92 metastatic disease qualify for status 1B. In some instances, it may also be appropriate to
93 consider the following pediatric candidates with hepatoblastoma for a status 1B exception:
94

- 95 • Candidates less than 8 years old with hepatoblastoma⁷² but not biopsied with
96 radiographic criteria consistent with unresectable hepatoblastoma, and all of the
97 following:
 - 98 ○ No evidence of metastasis at time of listing
 - 99 ○ AFP greater than 100
- 100 • Candidates with a biopsy-confirmed embryonal sarcoma that has not
101 metastasized^{73,74,75}
- 102 • Candidates with vascular malformation (congenital, infantile, or other) and
103 hospitalized with presence of Kasabach-Merritt syndrome or presence of high output
104 cardiac failure requiring pressor or ventilatory support
105

106 There is inadequate evidence to support approving Status 1B exception for pediatric candidates

⁷² Meyers et al, in press, *Lancet Oncology*, 2016

⁷³ Ismail H, Dembowska-Baginska B, Broniszczak D, et al. Treatment of undifferentiated embryonal sarcoma of the liver in children--single center experience. *J Pediatr Surg* 2013;48:2202-6.

⁷⁴ Plant AS, Busuttil RW, Rana A, Nelson SD, Auerbach M, Federman NC. A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. *J Pediatr Hematol Oncol* 2013;35:451-5.

⁷⁵ Walther A, Geller J, Coots A, et al. Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. *Liver Transpl* 2014;20:191-9.

107 with rhabdoid tumors.^{76,77,78,79} There is also inadequate evidence to support approving Status 1B
108 exception for pediatric candidates with angiosarcoma.⁸⁰

109 **Neoplasms**

110 **Hepatoblastoma**

111 Candidates with non-metastatic hepatoblastoma are eligible for status 1B under *Policy 9.1.C*
112 *Pediatric Status 1B*.

113 **Epithelioid Hemangioendothelioma (HEHE)**

114 Candidates with (HEHE) with unresectable lesions unresponsive to therapy may be considered
115 for exceptions.⁸¹

116

117 **Metastatic Neuroendocrine Tumor (NET)**

118 A review of the literature supports that candidates with NET are expected to have a low risk of
119 waiting list drop-out, though they benefit from transplantation.⁸²

120 The Review Board should consider the following criteria when reviewing exception applications
121 for candidates with NET:

- 122 1) Resection of primary malignancy and extra-hepatic disease without any evidence of
123 recurrence at least six months prior to MELD or PELD exception request.
- 124 2) Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to
125 resection.
- 126 3) Tumors in the liver should meet the following radiographic characteristics on *either* CT or
127 MRI:
- 128 a. If CT Scan: Triple phase contrast
- 129 i. Lesions may be seen on only one of the three phases
- 130 ii. Arterial phase: may demonstrate a strong enhancement
- 131 iii. Large lesions can become necrotic/calcified
- 132 b. If MRI Appearance:
- 133 i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave
134 images
- 135 ii. Diffusion restriction
- 136 iii. Majority of lesions are hypervascular on arterial phase with wash –out
137 during portal venous phase

⁷⁶ Kachanov D, Teleshova M, Kim E, et al. Malignant rhabdoid tumor of the liver presented with initial tumor rupture. *Cancer Genet* 2014;207:412-4.

⁷⁷ Agarwala S. Primary malignant liver tumors in children. *Indian J Pediatr* 2012;79:793-800.

⁷⁸ Sugito K, Uekusa S, Kawashima H, et al. The clinical course in pediatric solid tumor patients with focal nodular hyperplasia of the liver. *Int J Clin Oncol* 2011;16:482-7.

⁷⁹ Marzano E, Lermite E, Nobili C, et al. Malignant rhabdoid tumour of the liver in the young adult: report of first two cases. *HPB Surg* 2009;2009:628206.

⁸⁰ Xue M, Masand P, Thompson P, Finegold M, Leung DH. Angiosarcoma successfully treated with liver transplantation and sirolimus. *Pediatr Transplant* 2014;18:E114-9.

⁸¹ Rodriguez, J.A., Becker, N.S., O'Mahony, C.A. et al. *J Gastrointest Surg* (2008) 12: 110. doi:10.1007/s11605-007-0247-3

⁸² V. Mazzaferro, C. Sposito, J. Coppa, et. al., The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors, *Am. J. Transplantation*, 16:(10), DOI 10.1111/ajt.13831

- 138 iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense
139 lesions are characteristics of NET
140 4) Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin
141 tumors with portal system drainage.
142
143 **Note: NET with the primary located in the lower rectum, esophagus, lung, adrenal**
144 **gland and thyroid are not candidates for automatic MELD exception.**
145
146 5) Lower - intermediate grade following the WHO classification. Only well differentiated
147 (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20
148 per 10 HPF with less than 20% ki 67 positive markers.
149 6) Tumor metastatic replacement should not exceed 50% of the total liver volume
150 7) Negative metastatic workup should include one of the following:
151 a. Positron emission tomography (PET scan)
152 b. Somatostatin receptor scintigraphy
153 c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-
154 tetraazacyclododecane-N, N', N'',N'''-tetraacetic acid (DOTA)-D-Phe1-Try3-
155 octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease,
156 especially bone metastasis.
157
158 **Note: Exploratory laparotomy and or laparoscopy is not required prior to MELD or**
159 **PELD exception request.**
160
161 8) No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup
162 at least 3 months prior to MELD or PELD exception request (submit date).
163 9) Recheck metastatic workup every 3 months for MELD or PELD exception increase
164 consideration by the Review Board. Occurrence of extra-hepatic progression – for
165 instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may
166 come back to the list if any extra-hepatic disease is zeroed and remained so for at least
167 6 months.
168 10) Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a
169 permanent exclusion criteria
170

171 **Hepatocellular Carcinoma (HCC)^{83,84,85,86}**

172 Status 1B exceptions may be considered for pediatric candidates with HCC in the presence of
173 metabolic liver disease (such as hereditary tyrosinemia).

174 *Policy 9.3.F: Candidates with Hepatocellular Carcinoma (HCC) also permits the Review Board*

83 Jacfranz J. Guiteau, Ronald T. Cotton, Saul J. Karpen, Christine A. O'Mahony, John A. Goss, Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: The UNOS experience, *Pediatric Transplantation*, 2010, 14, 3, 326

84 Beaunoyer, Mona and Vanatta, Jason M. and Ogihara, Makoto and Strichartz, Debra and Dahl, Gary and Berquist, William E. and Castillo, Ricardo O. and Cox, Kenneth L. and Esquivel, Carlos O. Outcomes of transplantation in children with primary hepatic malignancy *Pediatric Transplantation* 11(6) url =<http://dx.doi.org/10.1111/j.1399-3046.2007.00751.x>, p655—660, 2007

85 Mazzaferro, V. and Sposito, C. and Coppa, J. and Miceli, R. and Bhoori, S. and Bongini, M. and Camerini, T. and Milione, M. and Regalia, E. and Spreafico, C. and Gangeri, L. and Buzzoni, R. and de Braud, F. G. and De Feo, T. and Mariani, L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors, *American Journal of Transplantation*, 16 (10) doi = (10.1111/ajt.13831), (2892--2902), 2016

86 Pham TA, Gallo AM, Concepcion W, Esquivel CO, Bonham CA. Effect of Liver Transplant on Long-Term Disease-Free Survival in Children with Hepatoblastoma and Hepatocellular Cancer. *JAMA Surg* 150(12): 1150-8, 2015)

175 to award exceptions for candidates with HCC in certain circumstances. In the absence of
176 metabolic disease, data from the Pediatric Liver Unresectable Tumor Observatory (PLUTO)
177 registry and other single center experience suggests criteria may be expanded beyond Milan
178 and University of California – San Francisco (UCSF) criteria. Extrahepatic metastasis should be
179 an absolute contraindication but exception points for unresectable HCC limited to liver may be
180 considered on a case by case basis in pediatric candidates.

- 181 • Children do not need to be within Milan criteria
- 182 • Documentation of metastatic work up (including cross-sectional imaging of the chest and
183 bone scan or PET) and no evidence of tumors outside the liver

184

185 **Hilar Cholangiocarcinoma**

186 Candidates with hilar cholangiocarcinoma may be considered for a MELD or PELD exception if
187 the candidate meets the requirements in *Policy 9.3.E: Candidates with Cholangiocarcinoma*.

188 [Chronic Liver Disease](#)^{87,88,89,90,91,92,93}

189 **Growth Failure or Nutritional Insufficiency**

190 There is insufficient evidence to support approval of exception points for pediatric candidates
191 with any broadly defined growth failure or nutritional insufficiency. However, exceptions should
192 be considered for candidates who meet any of the following criteria:

- 193 • Growth parameters⁹⁴
 - 194 ○ For candidates over 1 year of age, <5th percentile for: height, weight (may adjust
195 to estimated dry weight if ascites)^{95,96}
 - 196 ○ Z-score (Weight for height) less than 2 standard deviations
- 197 • Anthropometrics
 - 198 ○ Skin fold thickness < 5th percentile for age and gender for children > 1 year⁹⁷
- 199 • Failure of nasoenteric tube feedings as evidenced by failure to demonstrate
200 improvement in growth failure in the previous month based on either weight or
201 anthropometrics⁹⁸
- 202 • Requirement for TPN nutrition to allow for growth or to maintain euglycemia

203

204 **Infections**

⁸⁷ Tamir M et al pediatric liver Transplantation for Primary Sclerosing Cholangitis Liver Transplantation 17:925-933 2011

⁸⁸ Elgendy H et al The outcome of critically ill children after living donor liver transplant Exp Clin Transplant Suppl 1 : 100-7
2015

⁸⁹ Malatack et al Choosing a pediatric recipient for orthotopic liver transplantation J Pediatr 111: 479-489 1987

⁹⁰ Sarin SK et al Young adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival
Gut 29: 101-107 1988

⁹¹ Matloff RG The Kidney in Pediatric Liver Disease Curr Gastroenterol Rep 17: 36

⁹² Dara N et al Liver function, paraclinical tests, and mortality risk factors in pediatric liver transplant candidates Comparative
clinical Pathology 25 (1) : 189-195 2015

⁹³ Keating et al Clinical course of cirrhosis in young adults and therapeutic potential of liver transplantation Gut 26: 1359-
1363 1985

⁹⁴ Sokol RJ et al Anthropometric evaluation of children with chronic liver diseases Am J Nutrition 52:203-208 1980

⁹⁵ World Health Organization global Database on Child Growth and Malnutrition

⁹⁶ Yang et al Living donor liver transplantation with body weight more or less than 10 kilograms world J Gastroenterol 21 (23)
7248-53 2015

⁹⁷ UpToDate 2016. Table for skin fold thickness percentiles.

⁹⁸ Chin SE the nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation Am J Clin
Nutr 56:164-168 1992

205 Approval of MELD or PELD exception points for pediatric candidates with recurrent cholangitis
206 or other life-threatening infection may be appropriate in some instances. Documentation
207 submitted for case review should indicate one of the following:

- 208 • Two or more episodes of spontaneous bacterial peritonitis (SBP)⁹⁹ (specify date of each
209 episode)
- 210 • At least one episode of other life-threatening infection with sepsis requiring ICU stay
- 211 • Two or more episodes of cholangitis within 6 months requiring IV antibiotics requiring
212 placement of a PICC or central line for > 2 continuous weeks for ongoing administration
213 of antibiotics (specify date of each episode)

214

215 **Complications of portal hypertension, including ascites**

216 Approval of MELD or PELD exception points for hospitalized pediatric candidates with
217 complications of portal hypertension may be appropriate in some instances. Documentation
218 submitted for case review should indicate:

- 219 • Gastrointestinal bleeding with on-going transfusion requirement¹⁰⁰
- 220 • Transjugular intrahepatic portosystemic shunt (TIPS) placement as a bridge to
221 transplant. Indicate if TIPS is not an option or variceal bleeding unresponsive to ablative
222 therapy
- 223 • Ongoing octreotide administration

224

225 There is insufficient evidence to support approval of exception points in the presence of
226 splenomegaly or varices without bleeding. There is also insufficient evidence to support
227 approval of exception points for pediatric candidates with ascites controlled by diuretics in the
228 outpatient setting. Exception points may be considered for candidates with severe or
229 complicated ascites in at least one of the following clinical scenarios:

- 230 • Serum sodium less than 130, two times greater than 2 weeks apart¹⁰¹
- 231 • Multiple therapeutic paracenteses (at least 2 in the previous 30 days, not including
232 diagnostic paracentesis)
- 233 • Hydrothorax requiring chest tube or therapeutic thoracentesis

234

235 **Encephalopathy**

236 Approval of MELD or PELD exception points for hospitalized pediatric candidates with
237 symptomatic encephalopathy may be appropriate in any of the following instances:

- 238 • Clinically refractory to medical management with lactulose or rifaximin
- 239 • Infant Glasgow coma score less than 12

240

241 **Hepatopulmonary Syndrome**

⁹⁹ Larcher VF Spontaneous bacterial peritonitis in children with chronic liver disease, clinical features *jpediatr* 106: 907-912 1985

¹⁰⁰ Iwatsuki S et al: Liver transplantation in the treatment of bleeding esophageal varices *Surgery* 104 (4) : 697-705 1988

¹⁰¹ Pugliese R et al Ascites and serum sodium are markers o increased waiting list mortality in children with chronic liver failure *Hepatology* 59: 1964-7 2014

242 Approval of additional MELD or PELD exception points for pediatric candidates who meet the
243 standardized criteria for hepatopulmonary syndrome according to *Policy 9.3.C: Specific*
244 *MELD/PELD Exceptions* may be appropriate in some instances, such as if the candidate is
245 hospitalized, or if the candidate is debilitated or exhibits progressive decompensation.

246 **Developmental Delay**

247 There is insufficient evidence to support approval of exception points for pediatric candidates
248 with developmental delay.

249 **Pruritus**

250 Approval of MELD or PELD exception points for pediatric candidates with pruritus may be
251 appropriate in some instances. Documentation submitted for case review should indicate that
252 the candidate has evidence of cutaneous mutilation with bleeding and scratching nonresponsive
253 to medications such as rifampin, ursodiol and naltrexone.

254 Candidates should not be awarded additional MELD or PELD exceptions points on the basis of
255 xanthomas or an indwelling biliary catheter.

256 **Metabolic Bone Disease**

257 Approval of MELD or PELD exception points for pediatric candidates with metabolic bone
258 disease may be appropriate in some instances. Documentation submitted for case review
259 should indicate:

- 260 • Documented pathologic fractures or bone deformity
- 261 • Patient is unresponsive to vitamin D, mineral supplementation

262

263 **Congenital Portosystemic Shunts**

264 Pediatric patients with congenital portosystemic shunts as Abernathy syndrome may be
265 evaluated on the basis of their complications (hyperammonemia and encephalopathy or
266 hepatopulmonary syndrome) rather than as a unique disease category.

267 **Post-Transplant Complications**

268 **Chronic rejection**

269 Chronic rejection (CR) may cause long-term graft dysfunction and fibrosis. The Banff group
270 defined the minimal histological features of CR as biliary epithelial changes affecting a majority
271 of bile ducts with or without duct loss, foam cell obliterative arteriopathy, or bile duct loss
272 affecting greater than 50% of portal tracts.^{102,103}

273 In the Studies of Pediatric Liver Transplantation (SPLIT) database, CR remains at a less than
274 5% incidence; however 38% of reported patients proceeded to retransplantation.¹⁰⁴ When

¹⁰² Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. *Pediatrics*2008;122:e1128-e1135.

¹⁰³ Wallot MA, Mathot M, Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience. *Liver Transpl* 2002;8:615-622.

¹⁰⁴ Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. *Pediatrics*2008;122:e1128-e1135.

275 evaluating late graft loss (more than one year after transplant), 37% of all lost grafts in SPLIT
276 were due to CR. Retransplantation is indicated for those patients who do not respond to
277 treatment of rejection.

278 Chronic rejection alone is not sufficient for an exception. Exceptions for clinical complications or
279 manifestations of chronic rejection may be appropriate if the transplant program submits
280 evidence of a comorbid condition from the Chronic Liver Disease section above, as well as
281 other evidence including:

- 282 • Evidence of chronic rejection on liver biopsy
- 283 • Recurrent infections – cholangitis, spontaneous bacterial peritonitis (SBP) (similar
284 criteria regarding quantification and severity of infections to cholestatic patients)
- 285 • Growth failure/nutritional insufficiency, complication of portal hypertension, hyponatremia
286 – sodium less than 130, intractable ascites, intractable pruritis

287

288 **Cholangiopathy**

289 The rates for biliary strictures range from 5% to 25% in pediatric liver graft recipients (Duffy,
290 Tanaka).^{105,106} The main cause of late biliary strictures is graft ischemia; ischemic biliary
291 strictures are frequently multiple and affect all aspects of the biliary tree. In contrast, solitary
292 anastomotic strictures are usually short and may respond to percutaneous or endoscopic
293 dilatation. Non-anastomotic strictures are harder to manage, and often result from Hepatic
294 Artery Thrombosis (HAT) or ischemia-reperfusion injury. Some can also be due to primary
295 immune injury. Cholangitis remains the most common manifestation along with progressive
296 fibrosis. Retransplantation may be required for diffuse and multiple biliary strictures and
297 particularly for those associated with late HAT; retransplantation should be considered in
298 patients with diffuse cholangiopathy.¹⁰⁷

299 Exceptions for clinical complications or manifestations of chronic graft dysfunction due to biliary
300 cause may be appropriate if the transplant program submits evidence of a comorbid condition
301 from the Chronic Liver Disease section above, as well as other evidence including:

- 302 • Radiological evidence (imaging study such as MR; percutaneous or endoscopic findings
303 of cholangiopathy) of cholangiopathy is required specify:
- 304 • Recurrent infections/cholangitis, including:
 - 305 ○ development or evolution of bacterial resistance
 - 306 ○ SBP (similar criteria regarding quantification and severity of infections to
307 cholestatic patients)
 - 308 ○ Growth failure/nutritional insufficiency
 - 309 ○ Complication of portal hypertension
 - 310 ○ Hyponatremia – sodium less than 130

¹⁰⁵ Duffy JP, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg* 2010;252:652-661.

¹⁰⁶ Tanaka H, Fukuda A, Shigeta T, Kuroda T, Kimura T, Sakamoto S, Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. *J Pediatr Surg* 2010;45:1668-1675.

¹⁰⁷ Sunku B, Salvalaggio PR, Donaldson JS, Rigsby CK, Neighbors K, Superina RA, Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. *Liver Transpl* 2006;12:821-826.

- 311 ○ Intractable ascites
- 312 ○ Intractable pruritis
- 313

314 **Vascular complications**^{108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124}

315 Exceptions for clinical complications/manifestations of late vascular complications may be
316 appropriate if the transplant program submits evidence of a comorbid condition from the
317 Chronic Liver Disease section above, as well as other evidence including:

- 318 ● Recurrent infections, including:
 - 319 ○ cholangitis
 - 320 ○ SBP (similar criteria regarding quantification and severity of infections to
 - 321 cholestatic patients)
 - 322 ○ Growth failure/nutritional insufficiency
 - 323 ○ Complication of portal hypertension
 - 324 ○ Hyponatremia – Sodium less than 130
 - 325 ○ Intractable ascites
 - 326 ○ Intractable pruritis

327
328 Specific criteria for arterial, or vascular cause of graft dysfunction requiring transplantation are
329 listed below.

¹⁰⁸ Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. *Pediatrics* 2008;122:e1128-e1135.

¹⁰⁹ Wallot MA, Mathot M, Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience. *Liver Transpl* 2002;8:615-622.

¹¹⁰ Duffy JP, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg* 2010;252:652-661.

¹¹¹ Tanaka H, Fukuda A, Shigeta T, Kuroda T, Kimura T, Sakamoto S, Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. *J Pediatr Surg* 2010;45:1668-1675.

¹¹² Sunku B, Salvalaggio PR, Donaldson JS, Rigsby CK, Neighbors K, Superina RA, Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. *Liver Transpl* 2006;12:821-826.

¹¹³ Yazigi NA. Long term outcomes after pediatric liver transplantation. *Pediatr Gastroenterol Hepatol Nutr*. 2013 Dec;16(4):207-18

¹¹⁴ Marshalleck F. Pediatric arterial interventions. *Tech Vasc Interv Radiol* 2010;13:238-243

¹¹⁵ Kelly DA, Bucuvalas JC, Alonso EM, et al Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013 Aug;19(8):798-825.

¹¹⁶ Buell JF, Funaki B, Cronin DC, Yoshida A, Perlman MK, Lorenz J, et al. Long-term venous complications after full-size and segmental pediatric liver transplantation. *Ann Surg* 2002;236:658-666.

¹¹⁷ Miraglia R, Maruzzelli L, Caruso S, Marrone G, Carollo V, Spada M, et al. Interventional radiology procedures in pediatric patients with complications after liver transplantation. *Radiographics* 2009;29:567-584.

¹¹⁸ Cheng YF, Chen CL, Huang TL, Chen TY, Chen YS, Wang CC, et al. Angioplasty treatment of hepatic vein stenosis in pediatric liver transplants: long-term results. *Transpl Int* 2005;18:556-561.

¹¹⁹ Skaro AI, Jay CL, Baker TB, et al. The impact of ischemic cholangiopathy in liver transplantation using donors after cardiac death: the untold story. *Surgery*. 2009;146(4):543-553.

¹²⁰ Berrocal T, Parrón M, Alvarez-Luque A, Prieto C, Santamaría ML. Pediatric liver transplantation: a pictorial essay of early and late complications. *Radiographics* 2006;26:1187-1209.

¹²¹ Maheshwari A, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. *Liver Transpl*. 2007;13(12):1645-1653.

¹²² Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. *Surgery*. 2011;150(4):692-702.

¹²³ Hong JC, Venick R, Yersiz H, et al. Liver transplantation in children using organ donation after circulatory death: a case-control outcomes analysis of a 20-year experience in a single center. *JAMA Surg*. 2014 Jan;149(1):77-82

¹²⁴ Bartlett A, Vara R, Muiesan P, et al. A single center experience of donation after cardiac death liver transplantation in pediatric recipients. *Pediatr Transplant*. 2010;14(3):388-392.

330 **Late HAT**

331 Late HAT (greater than 30 days post-transplant) are underrecognized and are usually
332 due to ischemic or immunologic injuries.¹²⁵ The liver function is usually fairly preserved
333 due to the presence of extensive collateralization, and bile ducts complications are the
334 defining morbidities. Because the blood supply to transplanted bile ducts is derived
335 solely from the hepatic artery, HAT is frequently associated with biliary pathology –
336 typically non-anastomotic strictures, often in the hilum and complex in nature. Bilomas
337 and biliary sepsis are common.

338 A definitive diagnosis of late HAT requires more advanced imaging (e.g. CT, MR, or
339 standard angiographies). If treatment is required, thrombolysis and anticoagulation are
340 rarely effective, and surgical reconstruction is contraindicated. Radiological treatment of
341 biliary strictures is indicated if necessary, and drainage of intrahepatic
342 abscesses/bilomas is required. For symptomatic late HAT with cholangitis, hepatic
343 abscesses, or diffuse biliary stricturing, retransplantation is frequently necessary.

344 Specific information regarding the following is helpful to substantiate the request:

- 345 • Radiological or angiographic evidence of HAT complicated by both of the
346 following:
- 347 ○ Recurrent infections – cholangitis, sepsis
 - 348 ○ Failure or inapplicability of percutaneous or endoscopic biliary
349 interventions: specify
- 350

351 Patients with early HAT just beyond the 7 day status 1A cut off or the 14 day standard
352 exception cut off with evidence of severe graft dysfunction may be considered for MELD
353 exception, depending on the clinical scenario.

354 **Portal Vein Thrombosis (PVT)^{126,127}**

355 PVT is estimated at 2-10% in all pediatric recipients. Portal hypertensive complications
356 manifest mostly as hypersplenism and gastrointestinal (GI) bleeding. Currently scarce
357 systematic data is available on those patients' outcomes. Surgical shunts (selective
358 distal splenorenal, systemic mesocaval, and meso-Rex) are useful, but retransplantation
359 may be indicated. A REX shunt (meso-rax bypass) is favored when technically feasible.

360 Endovascular interventions should be attempted in patients with portal vein stenosis.

361 Data requested to substantiate exception requests include:

- 362 • evidence of PVT on imaging study or angiography required with complication
363 requiring retransplantation (i.e. refractory complications of portal hypertension,

¹²⁵ Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. Liver Transpl 2009; 15(Suppl 2): S12–S18

¹²⁶ Jensen MK, Campbell KM, Alonso MH, Nathan JD, Ryckman FC, Tiao GM. Management and long-term consequences of portal vein thrombosis after liver transplantation in children. Liver Transpl. 2013;19:315–321

¹²⁷ de Ville de Goyet J, Gibbs P, Clapuyt P, Reding R, Sokal EM, Otte JB. Original extrahilar approach for hepatic portal revascularization and relief of extrahepatic portal hypertension related to later portal vein thrombosis after pediatric liver transplantation. Long term results. Transplantation 1996;62:71-75.

- 364 hepatopulmonary syndrome)
- 365 • Contraindication to surgical shunt: specify
- 366 • Failure of surgical shunt: specify

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368 Conclusion

369 Liver transplant programs, Review Board members and the Committee should consult this
370 resource when assessing pediatric MELD, PELD and status exception requests. Liver programs
371 should also consider this guidance when submitting exception requests for pediatric candidates
372 with these diagnoses. However, these guidelines are not prescriptive of clinical practice.

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

Background

A liver candidate receives a MELD¹²⁸ or, if less than 12 years old, a PELD¹²⁹ 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.¹³⁰ If the candidate does not meet criteria for standardized exception, the request is considered by the Review Board.

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

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

Recommendation

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

HCC MELD exception may be appropriate for patients with macro-vascular invasion of branch portal vein and ruptured HCC.

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

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

¹²⁸Model for End-Stage Liver Disease

¹²⁹Pediatric End-Stage Liver Disease

¹³⁰Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

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

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

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

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

Feature:	CT scans should meet the below specifications:
Scanner type	Multidetector row scanner
Detector type	Minimum of 8 detector rows and must be able to image the entire liver during brief late arterial phase time window
Slice thickness	Minimum of 5 mm reconstructed slice thickness; thinner slices are preferable especially if multiplanar reconstructions are performed
Injector	Power injector, preferably dual chamber injector with saline flush and bolus tracking recommended
Contrast injection rate	3 mL/sec minimum, better 4-6 mL/sec with minimum of 300 mg I/mL or higher, for dose of 1.5 mL/kg body weight
Mandatory dynamic phases on contrast-enhanced MDCT	<ol style="list-style-type: none"> 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

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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	<ol style="list-style-type: none"> 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 breathholding before and during scan.

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