

Briefing Paper

Liver Review Board Guidance Documents

OPTN/UNOS Liver and Intestinal Organ Transplantation Committee

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Liver Review Board Guidance Documents

<i>Affected Policies:</i>	<i>None</i>
<i>Sponsoring Committee:</i>	<i>Liver and Intestinal Organ Transplantation</i>
<i>Public Comment Period:</i>	<i>January 24, 2016 – March 23, 2016</i>
<i>BOD Meeting Date:</i>	<i>June 5 - 6, 2017</i>

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.

Liver transplant programs may request exceptions for candidates with hepatocellular carcinoma (HCC), which is the most common diagnosis requiring a MELD or PELD score exception. 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 If a standardized exception is approved, the exception scores are determined by policy. Transplant programs are also permitted to request exceptions from the review board 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 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.

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.

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
10	363	68.0	121	22.7	50	9.3	534

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

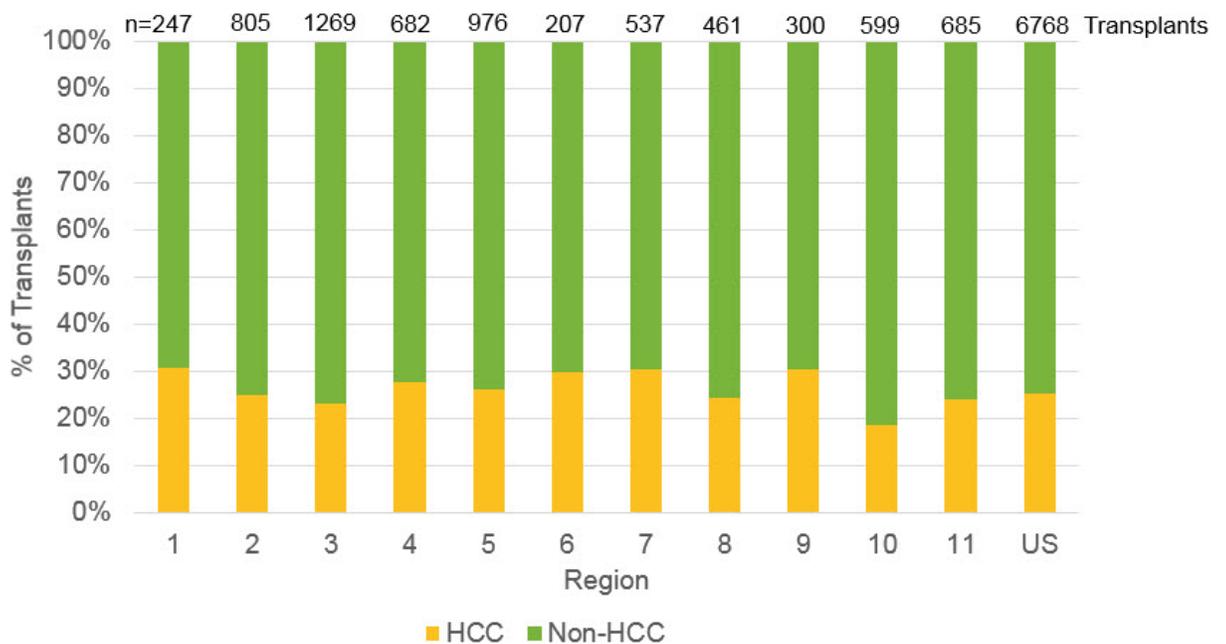
¹² Based on OPTN data as of July 8, 2016

Region	No Exception (N)	No Exception (%)	Standard Exception (N)	Standard Exception (%)	Non-Standard Exception (N)	Non-Standard Exception (%)	Total Transplants (N)
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.

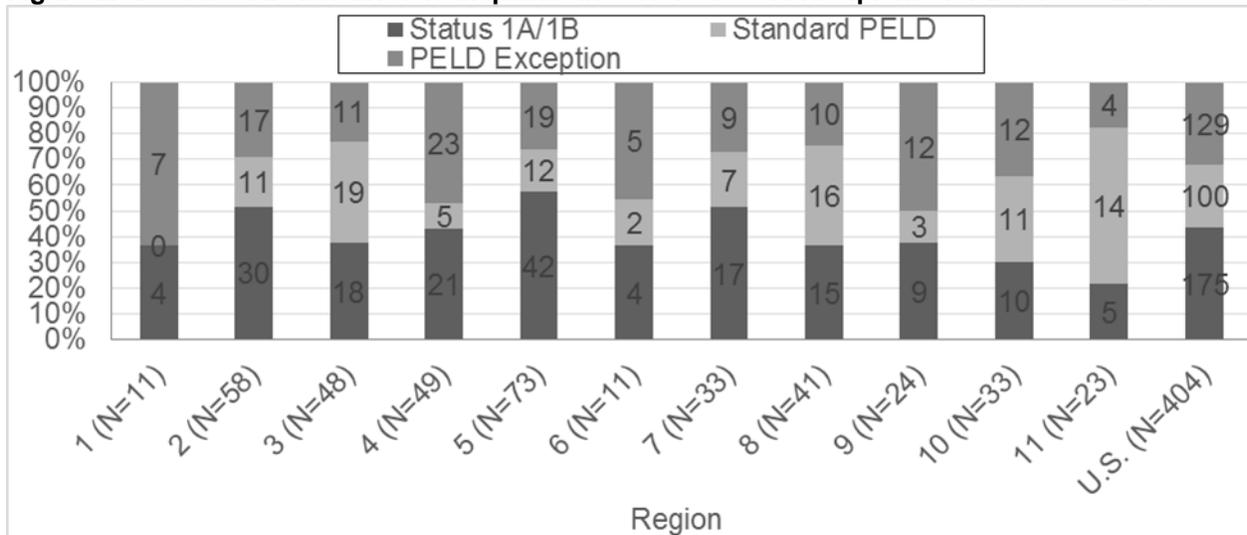
There is also evidence of regional variability in the award of HCC exception requests for candidates who not meet criteria for a standardized exception. In nearly all regions, review boards grant MELD exceptions to patients with lesions beyond T2 though the criteria are not consistently applied across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

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



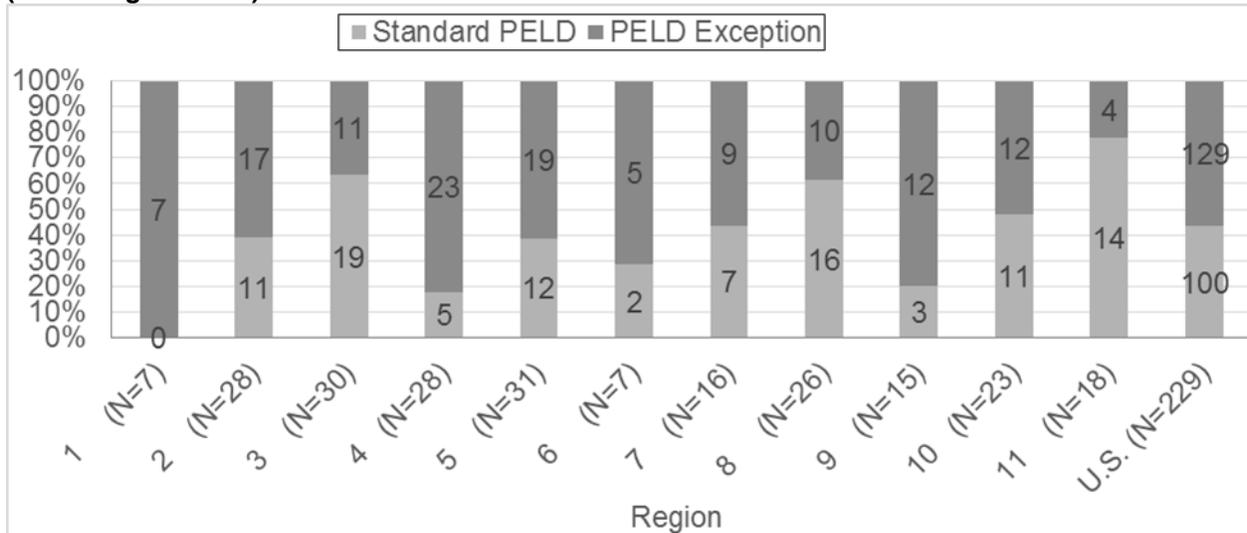
Regional variability exists among young pediatric liver transplant candidates as well. The percentage of pediatric candidates age 0 to 11 years old transplanted while listed with an exception varies widely across regions, from as low as 17% to as high as 64%.

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)



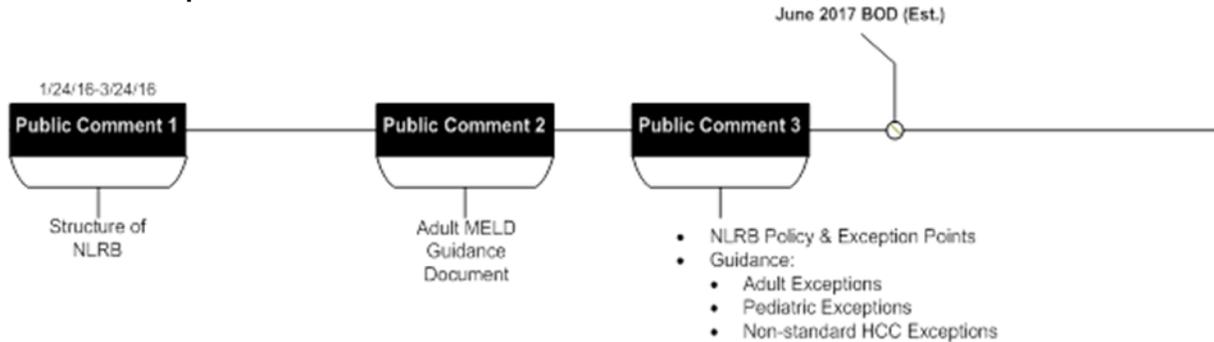
Why should you support this proposal?

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.

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

The updated proposal is also currently out for public comment during the January to March 2017 public comment cycle.

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 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 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-canenin 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 who 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

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

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.

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 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.

Was this proposal changed in response to public comment?

Yes, during the public comment period, the Committee made changes to the originally proposed guidance, and voted (14-Approve, 0-oppose, 0-abstentions) to send the modified proposal to the OPTN/UNOS Board of Directors for consideration during its June 2017 meeting.

Post-public Comment Changes

HCC Guidance Document

In the public comment proposal, the Committee included guidance regarding contraindications for Hepatocellular Carcinoma (HCC) exception requests. This included language stating that an exception may be appropriate for patients with macro-vascular invasion of branch portal vein, and ruptured HCC. Following public comment, the committee clarified this guidance by specifying *primary* portal vein branch invasion. The use of “primary” is more in line with appropriate clinical terminology. Within this section of guidance, the Committee also clarified that patients should remain stable for a prolonged (minimum of 12 months) interval after treatment.

Following a recommendation by the MELD Enhancements and Exceptions Subcommittee, the Committee has added additional guidance regarding the six month delay for HCC candidates that have recurrent tumor following resection. The Committee discussed this topic and ultimately feel that it is appropriate that candidates who presented with T2 HCC, who underwent complete resection and subsequently developed T1 (biopsy proven) tumor recurrence, should be considered for a MELD score exception without a six month delay period. The Committee concluded that candidates that pursue resection in contrast to transplant, and subsequently recur, should be considered for deviation from the normal 6 month delay.

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).

This guidance will serve as a resource for NLRB reviewers assigned to the HCC specialty board to use when reviewing cases that meet this clinical situation.

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.

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.

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.

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
 - i. Number of non-standardized exception requests
 - ii. Number of non-standardized exception requests approved
 - iii. Distribution of MELD/PELD scores among approved requests
 - iv. 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

1 RESOLVED, that the guidance documents entitled *Guidance to Liver Transplant Programs and the*
2 *National Liver Review Board for Adult MELD Exception Review, Guidance to Liver Transplant*
3 *Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review, and*
4 *Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD*
5 *Exceptions for Hepatocellular Carcinoma (HCC)*, as set forth below, are hereby approved, effective
6 pending implementation and notice to OPTN members.
7

8 Guidance to Liver Transplant Programs and the 9 National Liver Review Board for Adult MELD 10 Exception Review

11 Summary and Goals

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

- 22 • Ascites
- 23 • Budd Chiari
- 24 • GI Bleeding
- 25 • Hepatic Encephalopathy
- 26 • Hepatic Epithelioid Hemangioendothelioma
- 27 • Hepatic Hydrothorax
- 28 • Hereditary Hemorrhagic Telangiectasia
- 29 • Multiple Hepatic Adenomas
- 30 • Neuroendocrine Tumors (NET)
- 31 • Polycystic Liver Disease (PLD)
- 32 • Portopulmonary Hypertension
- 33 • Primary Sclerosing Cholangitis (PSC)
- 34 • Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection,
35 Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- 36 • Pruritus

37 These guidelines are intended to promote consistent review of these diagnoses and summarize

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

38 the Committee’s recommendations to the OPTN/UNOS Board of Directors.
39 This resource is not OPTN Policy, so it does not carry the monitoring or enforcement
40 implications of policy. It is not an official guideline for clinical practice, nor is it intended to be
41 clinically prescriptive or to define a standard of care. This resource is intended to provide
42 guidance to transplant programs and the Review Board.

43 **Guidance to Liver Transplant Programs and the** 44 **National Liver Review Board for Adult MELD** 45 **Exception Review**

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68

69

70 Background

71 A liver candidate receives a MELD² or, if less than 12 years old, a PELD³ score that is used for
 72 liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-
 73 month mortality without access to liver transplant. When the calculated score does not reflect
 74 the candidate's medical urgency, a liver transplant program may request an exception score. A
 75 candidate that meets the criteria for one of nine diagnoses in policy is approved for a
 76 standardized MELD exception.⁴ If the candidate does not meet criteria for standardized
 77 exception, the request is considered by the Review Board.

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

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

90 Recommendation

91 Ascites

92 **There is inadequate evidence to support granting a MELD exception for ascites in adult**
 93 **candidates with the typical clinical symptoms associated with this diagnosis.**

94 Ascites is a common clinical finding in liver transplant candidates. Refractory ascites, as defined
 95 by the International Ascites Club, occurs in 5-10% of patients with portal hypertension and has a
 96 1-year mortality rate of approximately 50%.^{5,6,7,8} Hyponatremia is common in patients with
 97 cirrhosis and refractory ascites from portal hypertension.^{9,10,11} In January 2016, the OPTN

²Model for End-Stage Liver Disease

³Pediatric End-Stage Liver Disease

⁴Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁵Moore, 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.

⁶Runyon, 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.

⁷Runyon, B.A., Committee APG. "Management of adult patients with ascites due to cirrhosis: an update." *Hepatology* 49 (2009): 2087-107.

⁸Gines P., A. Cardenas, V. Arroyo, et al. "Management of cirrhosis and ascites." *N Engl J Med* 350 (2004):1646-54.

⁹Biggins, S.W., W.R. Kim, N.A. Terrault, et al. "Evidence-based incorporation of serum sodium concentration into MELD." *Gastroenterology* 130 (2006):1652-60.

¹⁰Porcel, A., F. Diaz, P. Rendon, et al. "Dilutional hyponatremia in patients with cirrhosis and ascites." *Arch Intern Med* 162 (2002):323-8.

¹¹Gines, A., A. Escorsell, P. Gines, et al. "Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites." *Gastroenterology* 105 (1993):229-36.

98 implemented a modification to the MELD score to incorporate serum sodium for candidates with
 99 a calculated MELD greater than 11.¹² Much of the excess mortality risk related to ascites is
 100 similar to portal hypertension and hepatorenal syndrome and will be accurately reflected in the
 101 lab values used to calculate the MELD score, specifically the serum creatinine and serum
 102 sodium. Therefore, MELD exception for ascites is not recommended.

103 Budd Chiari

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

106 Budd Chiari syndrome is an uncommon manifestation of hepatic vein thrombosis and patients
 107 might present with evidence of decompensated portal hypertension (ascites and hepatic
 108 hydrothorax) among others.¹³ Medical management may include diuresis and anticoagulation;
 109 or more aggressive management with Transjugular Intrahepatic Portosystemic Shunt (TIPS),
 110 portosystemic shunting, or liver transplant.¹⁴ Anticoagulation and pharmacologic management is
 111 the cornerstone treatment.^{15,16} Patients with severe portal hypertension not controlled with the
 112 standard of care might have evidence of hyponatremia or renal impairment, but these will be
 113 accurately reflected by the calculated MELD score.

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

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

124

125 Gastrointestinal Bleeding

126 **There is inadequate evidence to support granting a specific MELD exception for**
 127 **gastrointestinal bleeding in adult candidates who experience acute or chronic blood loss**
 128 **independent of their calculated MELD.**

129 There is also inadequate evidence to support a MELD exception for transfusion dependence
 130 independent of MELD with one exception, spur cell hemolytic anemia (SCHA).¹⁷ However, due

¹²Biggins, 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.

¹³Janssen, H.L., J.C. Garcia-Pagan, E. Elias, et al. "Budd-Chiari syndrome: a review by an expert panel." *Hepatology* 38 (2003): 364-371.

¹⁴Seijo, 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.

¹⁵Plessier, A., A. Sibert, Y. Consigny, et al. "Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome." *Hepatology* 44 (2006):1308-16.

¹⁶DeLeve, L.D., D.C. Valla, G. Garcia-Tsao. "Vascular disorders of the liver AASLD practice guidelines." *Hepatology* 49 (2009): 1729-64.

¹⁷Alexopoulou, A., L. Vasileva, 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.

131 to the infrequent occurrence of SCHA in a transplant candidate, and its common association
 132 with recent alcohol use or active infection, MELD exception is not recommended. Similarly there
 133 is no evidence to support that candidates with transfusion dependence who develop antibodies
 134 while waiting warrant a MELD exception.^{18,19}

135 **Hepatic Encephalopathy**

136 Hepatic encephalopathy (HE) is a complication of chronic liver disease associated with
 137 significant morbidity. There is an absence of evidence of sufficient quality to support MELD
 138 exception for complications of HE.^{20,21,22,23}

139 **Hepatic Epithelioid Hemangioendothelioma**

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

142 Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma.
 143 HEHE is a rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity
 144 of the diagnosis, as well as the variability in presentation, the optimal treatment strategies are
 145 not fully established. However, for lesions which cannot be resected, liver transplant is
 146 associated with 1, 5, and 10-year patient survival rates of 97%, 83%, and 74%; with more
 147 favorable results occurring in patients without microvascular invasion. The presence of extra-
 148 hepatic disease has not been associated with decreased survival post liver transplant and
 149 therefore should not be an absolute contraindication. Controversy regarding the role of liver
 150 transplant in treating HEHE relates to the variable course of disease in the absence of liver
 151 transplant, with some patients demonstrating regression or stabilization of disease and
 152 prolonged survival.^{24,25}

153 **Hepatic Hydrothorax**

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

¹⁸Lyles, 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.

¹⁹Flores-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.

²⁰Cordoba 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.

²¹García-Martínez, R., M. Simón-Talero, J. Córdoba. "Prognostic assessment in patients with hepatic encephalopathy." *Dis Markers* 31 (2011): 171-9.

²²D'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.

²³Brandman, 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.

²⁴Lerut, 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.

²⁵Nudo, 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.

159 Hepatic hydrothorax is a relatively uncommon complication of endstage liver disease occurring
 160 in only 5-10% of patients with cirrhosis and portal hypertension.^{26,27,28} Hepatic hydrothorax can
 161 occur in either or both pleural spaces and can occur with or without portal hypertensive
 162 ascites.²⁹ By definition, hepatic hydrothorax is a transudative pleural effusion due to portal
 163 hypertension without a cardiopulmonary source. Infectious and malignant pleural effusions must
 164 be excluded. In this context, a serum pleural fluid albumin gradient (SPAG) of at least 1.1 g/dL
 165 may be more accurate in identifying hepatic hydrothorax than the more traditional Light's criteria
 166 for a transudative pleural effusion.^{22,30} The mostly like explanation for hepatic hydrothorax is
 167 passage of fluid from the peritoneal space to the pleural space through diaphragmatic defects
 168 which can be documented by intraperitoneal injection of 99mTc-tagged nanocolloids followed
 169 by scintigraphy.³¹ Unlike ascites, relatively small amounts of fluid in the pleural space (1 to 2 L)
 170 lead to severe symptoms such as shortness of breath and hypoxia. Initial management with
 171 dietary sodium restriction, diuretics, intravenous albumin, and therapeutic thoracentesis can be
 172 successful. Hepatic hydrothorax can be complicated by spontaneous bacterial empyema or
 173 iatrogenic complication of thoracentesis (infections, pneumothorax, or hemothorax). For chronic,
 174 recurrent, confirmed hepatic hydrothorax, transjugular intrahepatic portosystemic shunt,
 175 indwelling pleural catheter, and surgical repair of diaphragmatic defects can be effective in
 176 some patients yet risk additional complications. Like ascites, hepatic hydrothorax is similar to
 177 portal hypertension and hepatorenal syndrome and will be accurately reflected in the lab values
 178 used to calculate the MELD score, specifically the serum creatinine and serum sodium.
 179 Therefore, MELD exception for hepatic hydrothorax is not recommended in the majority of
 180 circumstances.

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

- 185 • At least 1 thoracentesis over 1 L weekly in last 4 weeks; report date and volume of each
- 186 thoracentesis
- 187 • Pleural fluid is transudative by pleural albumin-serum albumin gradient of at least 1.1
- 188 and by cell count
- 189 • No evidence of heart failure; provide objective evidence excluding heart failure
- 190 • Pleural fluid culture negative on 2 separate occasions
- 191 • Pleural fluid cytology is benign on 2 separate occasions
- 192 • There is contraindications to TIPS; specify specific contraindication
- 193 • Diuretic refractory
- 194

²⁶Norvell, J.P., J.R. Spivey. "Hepatic hydrothorax." *Clin Liver Dis* 18 (2014): 439-49.

²⁷Baikati, K., D.L. Le, I.I. Jabbour, et al. "Hepatic hydrothorax." *Am J Ther* 21 (2014): 43-51.

²⁸Cardenas, A., T. Kelleher, S. Chopra. "Review article: hepatic hydrothorax." *Aliment Pharmacol Ther* 20 (2004): 271-9.

²⁹Badillo, 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.

³⁰Porcel, J.M. "Identifying transudates misclassified by Light's criteria." *Current Opinion Pulmonary Medicine* 19 (2013): 362-7.

³¹Hewett, L.J., M.L. Bradshaw, L.L. Gordon, et al. "Diagnosis of isolated hepatic hydrothorax using peritoneal scintigraphy." *Hepatology* (2016).

195 **Hereditary Hemorrhagic Telangiectasia**

196 **Approval of MELD exception points for adult candidates with high output cardiac failure** 197 **due to multiple arteriovenous (AV) malformations may be appropriate in some instances.**

198 Hereditary hemorrhagic telangiectasia is an uncommon, autosomal dominant genetic disorder
199 characterized by mucocutaneous telangiectasias, as well as arteriovenous malformations in the
200 brain, spine, lungs, gastrointestinal tract, and liver. The AV malformations can progress to high
201 output cardiac failure, which eventually may be irreversible. In the future, there may be effective
202 non-transplant options, and if such agents become widely available, the recommendation to
203 offer MELD score exception will need to be revisited.^{32,33}

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

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

208 **Multiple Hepatic Adenomas**

209 Hepatic adenomas (HA) are rare benign nodules occurring principally in women taking oral
210 contraceptives, are solitary or multiple, and highly variable in size; there is no consensus for
211 their management except that once their size exceeds 5 cm nodules are resected to prevent 2
212 major complications: bleeding and malignant transformation. An exception to this is in men
213 where it is recommended to remove smaller nodules. The presence of HCC in HA is a well-
214 documented observation, the risk ranging from 5 to 9%; gene coding for β -catenin mutations
215 (15-18% of cases) are associated with a high risk of malignant transformation (together with
216 cytologic atypia). HA are a frequent mode of presentation in some genetic diseases, particularly
217 Glycogen Storage Disease (GSD) and congenital or acquired vascular anomalies.

³²Lee, 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.

³³Boillot, 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.

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

- 222 • Malignant transformation proven by biopsy
- 223 • Presence of glycogen storage disease which increases the risk for malignant
- 224 transformation

225

226 The identification of these criteria is mandatory to aid in the decision-making process.^{34,35,36,37}

227 **Neuroendocrine Tumors (NET)**

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

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

- 237 • Recipient age <60 years.
- 238 • Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at
- 239 least six months prior to MELD exception request.
- 240 • Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.

241

242 Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:

243

- 243 1. If CT Scan:
 - 244 a. Triple phase contrast Lesions may be seen on only one of the three phases
 - 245 b. Arterial phase: may demonstrate a strong enhancement
 - 246 c. Large lesions can become necrotic/calcified

246

247

- 247 2. If MRI Appearance:

³⁴Blanc, 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.

³⁵Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." *Liver Transplantation* 22 (2016): 516-526.

³⁶Alagusundaramoorthy, 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.

³⁷Dokmak, 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.

- 248 a. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
249 b. Diffusion restriction
250 c. Majority of lesions are hypervascular on arterial phase with wash –out during portal
251 venous phase
252 d. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are
253 characteristics of NET
254
255 1. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin
256 tumors with portal system drainage. Note: Neuroendocrine tumors with the primary
257 located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not
258 candidates for automatic MELD exception.
259 2. Lower - intermediate grade following the WHO classification. Only well differentiated
260 (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20
261 per 10 HPF with less than 20% ki 67 positive markers.
262 3. Tumor metastatic replacement should not exceed 50% of the total liver volume.
263 4. Negative metastatic workup should include one of the following:
264 a. Positron emission tomography (PET scan)
265 b. Somatostatin receptor scintigraphy
266 c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododecane-
267 N, N', N'',N'''-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other
268 scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

269
270 **Note:** *Exploratory laparotomy and or laparoscopy is not required prior to MELD*
271 *exception request.*
272

- 273 1. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup
274 at least 3 months prior to MELD exception request (submit date).
275 2. Recheck metastatic workup every 3 months for MELD exception increase consideration
276 by the Review Board. Occurrence of extra-hepatic progression – for instance lymph-
277 nodal Ga68 positive locations – should indicate de-listing. Patients may come back to
278 the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
279 3. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a
280 permanent exclusion criteria
281

282 Polycystic Liver Disease (PLD)

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

- 285 • Hepatic decompensation
 - 286 • Concurrent hemodialysis
 - 287 • GFR less than 20 ml/min
- 288

289 **Transplant programs should provide the following criteria when submitting**
290 **exceptions for PLD. The Review Board should consider the following criteria**
291 **when reviewing exception applications for candidates with PLD.**

- 292 1. Management of PLD

293

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

294

295

2. Surgical Management of PLD

296

- Indications:

297

- a. Types C* and D **and** at least 2 of the following:

298

- o Hepatic decompensation

299

- o Concurrent renal failure (dialysis)

300

- b. Compensated comorbidities

301

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

302

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

303

304

305

Portopulmonary Hypertension

306

Candidates meeting the criteria in *Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* are eligible for MELD or PELD score exceptions that do not require evaluation by the full Review Board. The transplant program must submit a request for a specific MELD or PELD score exception with a written narrative that supports the requested score. Templates were developed for these exceptions to aid the transplant programs in the process of submitting the required information to justify the exception.

312

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

313

314

315

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

316

317

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

318

319

320

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

321

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

327 **Primary Sclerosing Cholangitis**

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

331 **Transplant programs should provide the following criteria when submitting exceptions**
332 **for PSC. The Review Board should consider the following criteria when reviewing**
333 **exception applications for candidates with PSC.**

334 The candidate must meet both of the following two criteria:

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

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

- 339 • The candidate has biliary tract stricture which are not responsive to treatment by
340 interventional radiology (PTC) or therapeutic endoscopy (ERCP) or
- 341 • The candidate has been diagnosed with a highly-resistant infectious organism (e.g.
342 Vancomycin Resistant Enterococcus (VRE), Extended Spectrum Beta-Lactamase
343 (ESBL) producing gram negative organisms, Carbapenem-resistant Enterobacteriaceae
344 (CRE), and Multidrug-resistant Acinetobacter.)

346 **Post-Transplant Complications**

347 **Small for Size Syndrome**

348 Small for size syndrome refers to graft dysfunction of varying severity occurring in the early
349 post-operative period, less than 30 days, following transplantation of a size-reduced liver
350 allograft, with no other identified cause of graft dysfunction such as vascular thrombosis,
351 prolonged ischemia, or other etiology.³⁸ Typical findings include worsening cholestasis and
352 ascites. With optimal care, some patients may recover while others may require re-
353 transplantation.

354 **In many cases, the calculated MELD score will provide adequate priority. However,**
355 **mortality risk may not be adequately reflected by the calculated MELD score in cases of**
356 **severe dysfunction, and an exception may be appropriate.**

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

- 358 • Risk factor for small for size syndrome
- 359 • Interventions used to treat small for size syndrome

³⁸Jemura, 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.

- 360 • Clinical status of the patient (hospitalized, requiring ICU care, intubated)
361

362 Chronic Rejection

363 **There is inadequate evidence to support granting a MELD exception for chronic rejection**
364 **in adult candidates with the typical clinical symptoms associated with this diagnosis.**

365 In cases where re-transplantation is being considered, it is anticipated that progressive injury of
366 the allograft due to rejection will be reflected in the development of liver dysfunction, and
367 prioritization by MELD score may be appropriate. Cases with atypical clinical scenarios in which
368 the degree of liver dysfunction and risk of waitlist mortality are not reflected by the MELD score
369 may be considered on an individual basis.

370 Diffuse Ischemic Cholangiopathy

371 Diffuse ischemic cholangiopathy is a complication associated with donation after cardiac death
372 (DCD) donors. Analysis of waitlist outcomes for patients re-listed after undergoing liver
373 transplant from a DCD donor demonstrates that these patients have a similar or improved
374 waitlist survival compared to donation after brain death (DBD) candidates who are re-listed with
375 similar MELD scores.³⁹ However, patients with ischemic cholangiopathy may have significant
376 morbidity and require multiple repeat biliary interventions and repeat hospitalizations for
377 cholangitis. Despite similar waitlist outcomes as DBD donor liver recipients who are listed for
378 retransplant, the Committee supports increased priority for prior DCD donor liver recipients to
379 encourage use of DCD livers when appropriate.

380 In addition, analyses has shown that patients with a prior DCD transplant and an approved
381 MELD score exception had an improved survival compared to those who never had an
382 exception approved.⁴⁰ Patients with biliary injuries and need for biliary interventions also have
383 been demonstrated to have an increased risk of graft loss and death.⁴¹ **Therefore, patients**
384 **with a prior DCD transplant that demonstrated two or more of the following criteria within**
385 **12 months of transplant should be considered for MELD exception:**

- 386 • Persistent cholestasis as defined by abnormal bilirubin (greater than 2 mg/dl)
387 • Two or more episodes of cholangitis with an associated bacteremia requiring hospital
388 admission
389 • Evidence of non-anastomotic biliary strictures not responsive to further treatment

390 Late Vascular Complications

391 Patients with hepatic artery thrombosis occurring within 7 days of transplant with associated
392 severe graft dysfunction may be eligible for Status 1A, or occurring within 14 days of
393 transplantation without severe graft dysfunction may be eligible for a standard exception of
394 40.^{42,43} Cases of late hepatic artery thrombosis which do not meet these criteria are not eligible

³⁹Allen, 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.

⁴⁰Makuda, R.C., P.L. Abt, D.S. Goldberg. "Use of Model for End-Stage Liver Disease exceptions for donation after cardiac death graft recipients relisted for liver transplantation." *Liver Transpl* 21 (2015):554-60.

⁴¹Axelrod, 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.

⁴²Policy 9.1.A: Adult Status 1A Requirements, Organ Procurement and Transplantation Network Policies.

⁴³Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

395 for standard MELD exception. **Due to the highly variable outcomes associated with late**
396 **hepatic artery thrombosis, there is inadequate evidence to support granting a MELD**
397 **exception in adult candidates with the typical clinical symptoms, including hepatic**
398 **abscess and intrahepatic biliary strictures that may be associated with late HAT.**
399 **However, patients with atypical severe complications may be considered for MELD**
400 **exception on an individual basis.** Complications that warrant consideration of MELD
401 exception are similar to those criteria noted for DCD cholangiopathy (with 2 or more episodes of
402 cholangitis requiring hospital admission over a 3 months period plus biliary strictures not
403 responsive to further treatment or bacteremia with highly resistant organisms). Patients with
404 early HAT just beyond 7 or 14 day cut off with evidence of severe graft dysfunction may be
405 considered for MELD exception, depending on the clinical scenario.

406 Pruritus

407 **There is inadequate evidence to support granting a MELD exception for pruritus in adult**
408 **candidates with the typical clinical symptoms associated with this diagnosis.** Pruritus is a
409 manifestation of predominantly cholestatic liver diseases. It had been reported that chronic
410 pruritus may lead to a decreased quality of life, prolonged wound healing, skin infections, and
411 sleep disturbance.⁴⁴ The frequency ranges from 80-100% for patients suffering from Primary
412 Biliary Cirrhosis; 20-40% for patients with primary Sclerosing Cholangitis and Chronic Viral
413 Hepatitis among other diseases.⁴⁵ The pruritus increases as the disease is progresses. So far
414 data have failed to support an endpoint related to quantity but rather of quality of life and were
415 considered inappropriate for additional MELD points.⁴⁶ Due to inadequate evidence of increased
416 risk of pre-transplant mortality, or a widely-accepted threshold for access to liver transplant,
417 MELD score exception for isolated clinical finding of pruritus is not recommended.

418 Conclusion

419 Review Board members should consult this resource when assessing adult MELD exception
420 requests. Liver programs should also consider this guidance when submitting exception
421 requests for adult candidates with these diagnoses. However, these guidelines are not
422 prescriptive of clinical practice.

⁴⁴Pruritus in chronic cholestatic liver disease. Bunchorntavakul C, Reddy KR Clin Liver Dis. 2012 May;16(2):331-46.

⁴⁵Elman, 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

⁴⁶Martin, 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.

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 MELD¹ or PELD² 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.³ 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
 - Complications of portal hypertension, including ascites

¹ Model for End-Stage Liver Disease

² Pediatric End-Stage Liver Disease

³ Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

- 38 ○ Encephalopathy
- 39 ○ Hepatopulmonary syndrome
- 40 ○ Developmental delay
- 41 ○ Pruritus
- 42 ○ Metabolic bone disease
- 43 ● Congenital Portosystemic Shunts
- 44 ● Post-transplant complications
 - 45 ○ Chronic Rejection
 - 46 ○ Cholangiopathy
 - 47 ○ Vascular Complications

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

55 56 **Background**

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

63 The MELD and PELD scores are intended to reflect the candidate’s disease severity, based on
64 the risk of 3-month mortality without access to liver transplant. When the calculated score does
65 not reflect the candidate’s medical urgency, a liver transplant program may request an
66 exception for a higher score. A candidate that meets the criteria for one of the diagnoses in
67 policy is approved for a standardized MELD or PELD exception.⁴ If the candidate does not meet
68 criteria for standardized exception, the Review Board considers the request. Pediatric
69 candidates with approved exceptions who turn 18 while still waiting with an approved exception
70 continue to be eligible to receive pediatric exceptions unless or until the candidate is removed
71 from the waiting list.⁵

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

76 This guidance replaces any independent criteria that OPTN regions use to request and approve
77 exceptions, commonly referred to as “regional agreements.” Review Board members, transplant

⁴ Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.

⁵ Policy 9.1: Status and Score Exceptions, Organ Procurement and Transplantation Network Policies.

78 centers, and the Committee should consult this resource when considering status or
79 MELD/PELD exception requests for pediatric candidates less than 18 years old. Any guidance
80 contained within this document that differs from the guidance offered for adult MELD exceptions
81 is intentional, and is based on peer-review literature and/or clinical practice.

82 Recommendation

83 Status 1B

84 Status 1B - Chronic liver disease

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

92 Status 1B – Neoplasm

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

- 96 • Candidates less than 8 years old with hepatoblastoma⁶ but not biopsied with
97 radiographic criteria consistent with unresectable hepatoblastoma, and all of the
98 following:
 - 99 ○ No evidence of metastasis at time of listing
 - 100 ○ AFP greater than 100
- 101 • Candidates with a biopsy-confirmed embryonal sarcoma that has not
102 metastasized^{7,8,9}
- 103 • Candidates with vascular malformation (congenital, infantile, or other) and
104 hospitalized with presence of Kasabach-Merritt syndrome or presence of high output
105 cardiac failure requiring pressor or ventilatory support

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

⁶ Meyers et al, in press, Lancet Oncology, 2016

⁷ 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.

⁸ 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.

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

108 with rhabdoid tumors.^{10,11,12,13} There is also inadequate evidence to support approving Status
109 1B exception for pediatric candidates with angiosarcoma.¹⁴

110 Neoplasms

111 Hepatoblastoma

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

114 Epithelioid Hemangioendothelioma (HEHE)

115 Candidates with (HEHE) with unresectable lesions unresponsive to therapy may be considered
116 for exceptions.¹⁵

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.¹⁶

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
 - 138 iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense
139 lesions are characteristics of NET

¹⁰ 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.

¹¹ Agarwala S. Primary malignant liver tumors in children. *Indian J Pediatr* 2012;79:793-800.

¹² 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.

¹³ 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.

¹⁴ Xue M, Masand P, Thompson P, Finegold M, Leung DH. Angiosarcoma successfully treated with liver transplantation and sirolimus. *Pediatr Transplant* 2014;18:E114-9.

¹⁵ 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

¹⁶ 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

- 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)**^{17,18,19,20}

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

175 *Exceptions* also permits the Review Board to award exceptions for candidates with HCC in

17 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

18 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

19 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

20 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)

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

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

185

186 **Hilar Cholangiocarcinoma**

187 Candidates with hilar cholangiocarcinoma may be considered for a MELD or PELD exception if
 188 the candidate meets the requirements in *Policy 9.5.A: Requirements for Cholangiocarcinoma*
 189 *(CCA) MELD or PELD Score Exceptions.*

190 **Chronic Liver Disease^{21,22,23,24,25,26,27}**

191 **Growth Failure or Nutritional Insufficiency**

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

- 195 • Growth parameters²⁸
 - 196 ○ For candidates over 1 year of age, <5th percentile for: height, weight (may adjust
 197 to estimated dry weight if ascites)^{29,30}
 - 198 ○ Z-score (Weight for height) less than 2 standard deviations
- 199 • Anthropometrics
 - 200 ○ Skin fold thickness < 5th percentile for age and gender for children > 1 year³¹
- 201 • Failure of nasoenteric tube feedings as evidenced by failure to demonstrate
 202 improvement in growth failure in the previous month based on either weight or
 203 anthropometrics³²
- 204 • Requirement for TPN nutrition to allow for growth or to maintain euglycemia

²¹ Tamir M et al pediatric liver Transplantation for Primary Sclerosing Cholangitis Liver Transplantation 17:925-933 2011

²² Elgendy H et al The outcome of critically ill children after living donor liver transplant Exp Clin Transplant Suppl 1 : 100-7 2015

²³ Malatack et al Choosing a pediatric recipient for orthotopic liver transplantation J Pediatr 111: 479-489 1987

²⁴ Sarin SK et al Young adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival Gut 29: 101-107 1988

²⁵ Matloff RG The Kidney in Pediatric Liver Disease Curr Gastroenterol Rep 17: 36

²⁶ 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

²⁷ Keating et al Clinical course of cirrhosis in young adults and therapeutic potential of liver transplantation Gut 26: 1359-1363 1985

²⁸ Sokol RJ et al Anthropometric evaluation of children with chronic liver diseases Am J Nutrition 52:203-208 1980

²⁹ World Health Organization global Database on Child Growth and Malnutrition

³⁰ Yang et al Living donor liver transplantation with body weight more or less than 10 kilograms world J Gastroenterol 21 (23) 7248-53 2015

³¹ UpToDate 2016. Table for skin fold thickness percentiles.

³² 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 **Infections**

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

- 209 • Two or more episodes of spontaneous bacterial peritonitis (SBP)³³ (specify date of each
210 episode)
- 211 • At least one episode of other life-threatening infection with sepsis requiring ICU stay
- 212 • Two or more episodes of cholangitis within 6 months requiring IV antibiotics requiring
213 placement of a PICC or central line for > 2 continuous weeks for ongoing administration
214 of antibiotics (specify date of each episode)

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

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

- 220 • Gastrointestinal bleeding with on-going transfusion requirement³⁴
- 221 • Transjugular intrahepatic portosystemic shunt (TIPS) placement as a bridge to
222 transplant. Indicate if TIPS is not an option or variceal bleeding unresponsive to ablative
223 therapy
- 224 • Ongoing octreotide administration

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

- 231 • Serum sodium less than 130, two times greater than 2 weeks apart³⁵
- 232 • Multiple therapeutic paracenteses (at least 2 in the previous 30 days, not including
233 diagnostic paracentesis)
- 234 • Hydrothorax requiring chest tube or therapeutic thoracentesis

235
236 **Encephalopathy**

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

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

241

³³Larcher VF Spontaneous bacterial peritonitis in children with chronic liver disease, clinical features *Jpediatr* 106: 907-912 1985

³⁴Iwatsuki S et al: Liver transplantation in the treatment of bleeding esophageal varices *Surgery* 104 (4) : 697-705 1988

³⁵Pugliese R et al Ascites and serum sodium are markers of increased waiting list mortality in children with chronic liver failure *Hepatology* 59: 1964-7 2014

242 **Hepatopulmonary Syndrome**

243 Approval of additional MELD or PELD exception points for pediatric candidates who meet the
244 standardized criteria for hepatopulmonary syndrome according to *Policy 9.5: Specific*
245 *Standardized MELD or PELD Score Exceptions* may be appropriate in some instances, such as
246 if the candidate is hospitalized, or if the candidate is debilitated or exhibits progressive
247 decompensation.

248 **Developmental Delay**

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

251 **Pruritus**

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

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

258 **Metabolic Bone Disease**

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

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

264

265 **Congenital Portosystemic Shunts**

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

269 **Post-Transplant Complications**

270 **Chronic rejection**

271 Chronic rejection (CR) may cause long-term graft dysfunction and fibrosis. The Banff group
272 defined the minimal histological features of CR as biliary epithelial changes affecting a majority
273 of bile ducts with or without duct loss, foam cell obliterative arteriopathy, or bile duct loss
274 affecting greater than 50% of portal tracts.^{36,37}

³⁶ 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.

³⁷ 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.

275 In the Studies of Pediatric Liver Transplantation (SPLIT) database, CR remains at a less than
276 5% incidence; however 38% of reported patients proceeded to retransplantation.³⁸ When
277 evaluating late graft loss (more than one year after transplant), 37% of all lost grafts in SPLIT
278 were due to CR. Retransplantation is indicated for those patients who do not respond to
279 treatment of rejection.

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

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

289

290 **Cholangiopathy**

291 The rates for biliary strictures range from 5% to 25% in pediatric liver graft recipients (Duffy,
292 Tanaka).^{39,40} The main cause of late biliary strictures is graft ischemia; ischemic biliary strictures
293 are frequently multiple and affect all aspects of the biliary tree. In contrast, solitary anastomotic
294 strictures are usually short and may respond to percutaneous or endoscopic dilatation. Non-
295 anastomotic strictures are harder to manage, and often result from Hepatic Artery Thrombosis
296 (HAT) or ischemia-reperfusion injury. Some can also be due to primary immune injury.
297 Cholangitis remains the most common manifestation along with progressive fibrosis.
298 Retransplantation may be required for diffuse and multiple biliary strictures and particularly for
299 those associated with late HAT; retransplantation should be considered in patients with diffuse
300 cholangiopathy.⁴¹

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

- 304 • Radiological evidence (imaging study such as MR; percutaneous or endoscopic findings
305 of cholangiopathy) of cholangiopathy is required specify:
- 306 • Recurrent infections/cholangitis, including:
 - 307 ○ development or evolution of bacterial resistance
 - 308 ○ SBP (similar criteria regarding quantification and severity of infections to

³⁸ 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.

³⁹ 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.

⁴⁰ 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.

⁴¹ 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.

- 309 cholestatic patients)
- 310 ○ Growth failure/nutritional insufficiency
- 311 ○ Complication of portal hypertension
- 312 ○ Hyponatremia – sodium less than 130
- 313 ○ Intractable ascites
- 314 ○ Intractable pruritis

315

316 **Vascular complications**^{42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58}

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

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

⁴² 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.

⁴³ Wallot MA, Mathot M, Janssen M, Höltter 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.

⁴⁴ 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.

⁴⁵ 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.

⁴⁶ 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.

⁴⁷ Yazigi NA. Long term outcomes after pediatric liver transplantation. *Pediatr Gastroenterol Hepatol Nutr*. 2013 Dec;16(4):207-18

⁴⁸ Marshalleck F. Pediatric arterial interventions. *Tech Vasc Interv Radiol*2010;13:238-243

⁴⁹ 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.

⁵⁰ 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.

⁵¹ iraglia 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.

⁵² 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.

⁵³ 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.

⁵⁴ 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.

⁵⁵ 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.

⁵⁶ Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. *Surgery*. 2011;150(4):692-702.

⁵⁷ 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

⁵⁸ 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.

- 327 ○ Intractable ascites
- 328 ○ Intractable pruritis

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

332 **Late HAT**

333 Late HAT (greater than 30 days post-transplant) are underrecognized and are usually
334 due to ischemic or immunologic injuries.⁵⁹ The liver function is usually fairly preserved
335 due to the presence of extensive collateralization, and bile ducts complications are the
336 defining morbidities. Because the blood supply to transplanted bile ducts is derived
337 solely from the hepatic artery, HAT is frequently associated with biliary pathology –
338 typically non-anastomotic strictures, often in the hilum and complex in nature. Bilomas
339 and biliary sepsis are common.

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

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

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

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

356 **Portal Vein Thrombosis (PVT)^{60,61}**

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

⁵⁹ Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. Liver Transpl 2009; 15(Suppl 2): S12–S18

⁶⁰ 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

⁶¹ 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. Transplantation1996;62:71-75.

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

363 Data requested to substantiate exception requests include:

- 364 • evidence of PVT on imaging study or angiography required with complication
365 requiring retransplantation (i.e. refractory complications of portal hypertension,
366 hepatopulmonary syndrome)
- 367 • Contraindication to surgical shunt: specify
- 368 • Failure of surgical shunt: specify

369

370 Conclusion

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

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 MELD¹ or, if less than 12 years old, a PELD² 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.³ 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

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

2. 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

¹Model for End-Stage Liver Disease

²Pediatric End-Stage Liver Disease

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

- 37 determine the current stage suitability for MELD exception, and MELD exception score
 38 assignment.
- 39 3. Patients beyond standard criteria who have continued progression while waiting despite
 40 LRT are generally not acceptable candidates for HCC MELD exception.
- 41 4. Patients with AFP>1000 who do not respond to treatment to achieve an AFP below 500
 42 are not eligible for standard MELD exception, and must be reviewed by the HCC review
 43 board to be considered. In general, these patients are not suitable for HCC MELD
 44 exception but may be appropriate in some cases.
- 45 5. Patients with HCC beyond standard down-staging criteria who are able to be
 46 successfully downstaged to T2 may be appropriate for MELD exception, as long as there
 47 is no evidence of metastasis outside the liver, or macrovascular invasion, or AFP
 48 >1,000. Imaging should be performed at least 4 weeks after last down-staging
 49 treatment. Patients must still wait for 6 months from the time of the first request to be
 50 eligible for an HCC exception score.
- 51 6. Patients with cirrhosis who presented with stage T2 resectable HCC (one lesion >2 cm
 52 and <5 cm in size, or two or three lesions >1 cm and <3 cm in size, based on resection
 53 specimen pathology) who underwent complete resection but developed T1 (biopsy
 54 proven), or T2 HCC (LI-RADS 5) following complete resection should be considered for
 55 MELD score exception, without a six month delay period.

56
 57 Patients with cirrhosis and HCC beyond T2 but within generally accepted criteria for
 58 down-staging (such as up to 5 lesions, total tumor volume <8 cm based on resection
 59 pathology) who underwent complete resection with negative margins and developed T1
 60 (biopsy proven) or T2 recurrence (LI-RADS 5) may also be considered for MELD score
 61 exception for HCC. Because the larger tumor size, the 6 month delay is appropriate to
 62 ensure favorable tumor biology.

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

65 **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

Feature:	CT scans should meet the below specifications:
Dynamic phases (Timing)	Use the bolus tracking or timing bolus

67
68**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.
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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