OPTN

Public Comment Proposal

Improving Liver Allocation: MELD, PELD, Status 1A and Status 1B

OPTN Liver and Intestinal Organ Transplantation Committee

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Improving Liver Allocation: MELD, PELD, Status 1A and Status 1B

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Affected Guidance:	*Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review*
Sponsoring Committee:	*Liver and Intestinal Organ Transplantation*
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Executive Summary

This proposal includes a number of changes intended to make the liver allocation system more equitable and efficient by improving the model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) scores, as well as updating current policies for pediatric Status 1A and 1B candidates. Together, these changes represent a broad update to the liver allocation system to ensure that liver transplant candidates are appropriately sorted and ranked according to their medical urgency for transplant.

In the current liver allocation system, the MELD and PELD scores are used to rank candidates based on their risk of 90 day waitlist mortality. The MELD score is used for adult and adolescent candidates and the PELD score is used for candidates under the age of 12. If candidates are particularly urgent, they can be listed at Status 1A or, if they are a pediatric candidate, they can also be listed as Status 1B.

This proposal updates the MELD score to address a sex-based disparity in liver allocation, while also improving the score's ability to predict overall risk of waitlist mortality. The updated MELD score, or MELD 3.0, includes the addition of two new variables (sex and albumin), updates the coefficients for existing variables (sodium, bilirubin, creatinine, and international normalized ratio (INR)), introduces interaction terms between bilirubin and sodium and between albumin and creatinine, and caps creatinine at 3.0 mg/dL.

The proposal also updates the PELD score, which has not been changed since it was implemented over 20 years ago and has been shown to under predict risk of mortality in the pediatric population by as

much as 17%.[1,2] The updated PELD score, or PELD Creatinine (Cr), includes the addition of a creatinine variable, makes age and growth failure continuous instead of categorical variables, updates the parameters for variables already included in the score (albumin, bilirubin, INR), and accounts for age-adjusted mortality for pediatric candidates.

Finally, the proposal includes a number of changes to the policy for pediatric Status 1A and 1B candidates. For Status 1A, it creates a more objective and clinically-relevant definition of hepatic encephalopathy. For Status 1B, the proposal updates the criteria for a pediatric candidate to qualify for Status 1B priority and better ranks candidates within Status 1B based on their diagnosis and risk of mortality.

The OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) is seeking public comment feedback on these proposed changes.

[1] Sue V. McDiarmid, Ravinder Anand, and Anne S. Lindblad, "Development of a Pediatric End-Stage Liver Disease Score to Predict Poor Outcome in Children Awaiting Liver transplantation1," *Transplantation* 74, no. 2 (2002): pp. 173-181, https://doi.org/10.1097/00007890-200207270-00006.

[2] Chung-Chou H. Chang et al., "Accuracy of the Pediatric End-Stage Liver Disease Score in Estimating Pretransplant Mortality among Pediatric Liver Transplant Candidates," *JAMA Pediatrics* 172, no. 11 (January 2018): p. 1070, https://doi.org/10.1001/jamapediatrics.2018.2541.

Purpose

The purpose of this project is to create a more equitable and efficient liver allocation system by updating the MELD and PELD scores and policy for Status 1A and 1B.

Summary of Proposed Changes

This proposal includes a multitude of changes to the liver allocation system and each of the proposed changes is described in extensive detail in the sections below. A summary of the proposed changes is provided here for reference.

MELD 3.0

This proposal improves the MELD score by incorporating additional variables (albumin and sex), updating coefficients for existing variables, introducing interaction terms, and lowering the maximum creatinine value from 4.0 to 3.0 mg/dL.[3] The proposed new MELD score, or MELD 3.0, will reduce the sex-based disparity for female candidates in the current liver allocation system and is better at predicting overall risk of mortality across the liver transplant candidate population.[4]

PELD Cr

The proposal improves the PELD score by incorporating a creatinine variable to capture renal function, updating parameters for existing coefficients, and converting age and growth failure from categorical to continuous variables. The updated PELD score, or PELD Cr, also includes a factor for age-adjusted mortality so the risk of waitlist mortality at a given PELD Cr scores aligns with the risk of waitlist mortality for an 18 year old candidate with an equivalent MELD score. The PELD Cr score better predicts risk of waitlist mortality for candidates under the age of 12 and will ensure that pediatric candidates are appropriately ranked relative to other pediatric candidates and adult candidates with a MELD score.

Status 1A

This proposal seeks to improve the Status 1A criteria for pediatric candidates with fulminant liver failure by updating the definition for hepatic encephalopathy so it aligns with the definition developed by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.[5]

Status 1B

The proposal includes a number of changes to Status 1B policy. First, the Committee is proposing to remove the MELD/PELD 25 threshold for liver-intestine and liver-alone candidates with chronic liver disease as the threshold is not clinically relevant and the most common reason candidates are listed as

[3] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[4] Ibid.
[5] James E. Squires et al., "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure," *Journal of Pediatric Gastroenterology & Nutrition* Publish Ahead of Print (March 2021), https://doi.org/10.1097/mpg.0000000000003268.

Status 1B by exception is because they do not meet the threshold.[6,7] The Committee is also proposing to change the gastro-intestinal (GI) bleeding threshold for liver-alone candidates to match the definition of persistent mild shock or moderate shock.[8] In addition, the Committee is proposing to remove the Glasgow Coma Score criteria for both liver-alone and liver-intestine candidates, as it not clinically relevant and rarely used as a means to be listed as Status 1B.[9] And finally, the Committee is proposing to better sort candidates within Status 1B by prioritizing candidates with chronic liver disease, who are at the highest risk of waitlist mortality.[10]

Background

The current liver allocation system is primarily based on the principle of medical urgency, wherein the liver candidates with the highest risk of waitlist mortality are prioritized for liver offers. Other factors, namely blood type compatibility, distance from donor hospital, and waiting time, also impact a candidate's place on a match run for a liver offer.[11] Medical urgency is quantified by the model for end-stage liver disease (MELD) score (for candidates age 12 and older) or the pediatric end-stage liver disease (PELD) score (for candidates age less than 12).

The MELD score, which was developed in 2001 and incorporated into OPTN policy in 2002, is calculated using objective laboratory values and is designed to predict the likelihood of 90 day mortality for candidates on the waitlist.[12] MELD was updated in 2016 to include serum sodium in the calculation.[13] Currently, the MELD score, typically called MELD Na, includes the following laboratory values: creatinine, bilirubin, INR, and sodium.[14] MELD scores range from six to 40, with higher scores indicating a higher risk of waitlist mortality and therefore increased urgency for transplant.

The PELD score was introduced into OPTN policy in 2002 and has not been updated since it was first developed in 2000.[15] Similar to MELD, it is calculated using objective lab values and is designed to predict the risk of 90 day waitlist mortality for pediatric candidates on the liver transplant waitlist. The PELD score is currently calculated using the following variables: age, albumin, bilirubin, INR, and growth failure.[16] PELD scores range from -99 to 99, although candidates generally have PELD scores between six and 40. Same as MELD, candidates with a higher PELD score are more at risk of waitlist mortality and are therefore ranked higher in liver allocation.

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[6] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/

[7] Descriptive Data Request: Status 1B Exceptions: A Data Overview, Prepared for the PELD/Status 1B Work Group, August 20, 2020

[8] Alyssa A. Riley et al., "Circulating Blood Volumes: A Review of Measurement Techniques and a Meta-Analysis in Children," *ASAIO Journal* 56, no. 3 (2010): pp. 260-264, https://doi.org/10.1097/mat.0b013e3181d0c28d.

[9] In the last three years, only 21 Status 1B forms were submitted with a GCS less than 10.

[10] Descriptive Data Request: Status 1B Waitlist Removals, Prepared for PELD/1B Work Group meeting on August 19, 2021

[11] MELD and PELD exception scores are assigned relative to median MELD at transplant (MMaT) and median PELD at transplant (MPaT), respectively. Currently, MMaT is calculated for each transplant program and is designed to assign exception scores that provide equitable access to transplant for MELD exception candidates. MPaT is calculated based on a national cohort. These scores balance the medical urgency of exception candidates with the scores needed to access transplant in the area where candidates are registered.

[12] Kamath PS, Wiesner RH, Malinchoc M, et al "A Model to Predict Survival in Patients with End-Stage Liver Disease," *Hepatology* 33, no. 2 (2001): pp. 464-470, https://doi.org/10.1053/jhep.2001.22172.

[13] See OPTN/UNOS Liver and Intestinal Organ Transplant Committee Report to the Board of Directors, June 2014

[14] See *OPTN Policy 9.1.D: MELD Score* for the full MELD calculation. Available at https://optn.transplant.hrsa.gov/

[15] Sue V. McDiarmid, Ravinder Anand, and Anne S. Lindblad, "Development of a Pediatric End-Stage Liver Disease Score to Predict Poor Outcome in Children Awaiting Liver transplantation1," *Transplantation* 74, no. 2 (2002): pp. 173-181, https://doi.org/10.1097/00007890-200207270-00006.

[16] See *OPTN Policy 9.1.E: PELD Score* for the full PELD calculation. Available at https://optn.transplant.hrsa.gov/

Importantly, both the MELD and PELD utilize widely-available, objective clinical values and their ability to predict risk of mortality using only a handful of objective variables has been a primary reason for their continued use in the liver allocation system.

In addition to the MELD and PELD scores, liver transplant candidates can be listed as Status 1A or 1B, if they are particularly urgent. These statuses are reserved for those candidates most in need of a liver transplant and candidates listed as Status 1A and 1B are provided priority in the allocation schema. Both pediatric and adult candidates can be listed as Status 1A, which is the most urgent status, while only pediatric candidates can be listed as Status 1B.

MELD

Even though MELD Na is still a useful predictor of waitlist mortality for liver transplant candidates, its ability to predict risk of waitlist mortality has decreased since the time it was developed.[17] A primary concern highlighted in recent literature is a disparity in access to transplant and waitlist outcomes for female candidates under the current MELD Na score. Specifically, since the implementation of the MELD score, female candidates have decreased odds of liver transplantation within three years of listing as compared to male candidates and are more likely than male candidates to die waiting for a transplant or be removed from the waitlist for being too sick for transplant.[18,19,20] There are a number of reasons why female candidates are disadvantaged in the liver allocation system including difficulty in accessing size appropriate donors, differences in hepatocellular carcinoma (HCC) prevalence between males and females, and creatinine overestimating kidney function in female candidates, and therefore underestimating their risk of waitlist mortality in the MELD score.[21,22] This proposal specifically seeks to address the issue with creatinine overestimating kidney function within the MELD score.

More specifically, research has shown that the use of creatinine in the MELD score disadvantages female candidates.[23, 24, 25] Female candidates tend to have lower muscle mass, and therefore lower creatinine compared to their actual renal function.[26] As a result, their true risk of waitlist mortality may not be appropriately captured by the current MELD Na calculation.[27] A recent publication showed that female

[17] Elizabeth L. Godfrey et al., "The Decreasing Predictive Power of MELD in an Era of Changing Etiology of Liver Disease," *American Journal of Transplantation* 19, no. 12 (April 2019): pp. 3299-3307, https://doi.org/10.1111/ajt.15559.
[18] Ibid.
[19] A. K. Mathur et al., "Sex-Based Disparities in Liver Transplant Rates in the United States," *American Journal of Transplantation* 11, no. 7 (June 30, 2011): 1435–43, https://doi.org/10.1111/j.1600-6143.2011.03498.x.
[20] J. C. Lai et al., "Height Contributes to the Gender Difference in Wait-List Mortality Under the MELD-Based Liver Allocation System," *American Journal of Transplantation* 10, no. 12 (November 18, 2010): 2658–64, https://doi.org/10.1111/j.1600-6143.2010.03326.x.
[21] Robert P. Myers et al., "Gender, Renal Function, and Outcomes on the Liver Transplant Waiting List: Assessment of Revised MELD Including Estimated Glomerular Filtration Rate," *Journal of Hepatology* 54, no. 3 (March 2011): 462–70, https://doi.org/10.1016/j.jhep.2010.07.015.
[22]Alina M. Allen et al., "Reduced Access to Liver Transplantation in Women," *Transplantation* 102, no. 10 (October 2018): 1710–16, https://doi.org/10.1097/tp.0000000000002196.
[23] E. Cholongitas et al., "Female Liver Transplant Recipients with the Same GFR as Male Recipients Have Lower MELD Scores: A Systematic Bias," *American Journal of Transplantation* 7, no. 3 (March 2007): 685–92, https://doi.org/10.1111/j.1600-6143.2007.01666.x.
[24] Samantha C. Huo et al., "Is the Corrected-Creatinine Model for End-Stage Liver Disease a Feasible Strategy to Adjust Gender Difference in Organ Allocation for Liver Transplantation?," *Transplantation* 84, no. 11 (December 2007): 1406–12, https://doi.org/10.1097/01.tp.0000282867.92367.d0.
[25] Ayse L. Mindikoglu et al., "Gender Disparity in Liver Transplant Waiting-List Mortality: The Importance of Kidney Function," *Liver Transplantation* 16, no. 10 (June 18, 2010): 1147–57, https://doi.org/10.1002/lt.22121.
[26] Alina M. Allen et al., "Reduced Access to Liver Transplantation in Women," *Transplantation* 102, no. 10 (October 2018): 1710–16, https://doi.org/10.1097/tp.0000000000002196.
[27] Ibid

candidates have 1 to 2.4 fewer MELD points as compared to male candidates with similar renal function and this disparity is likely larger with MELD Na.[28]

This proposal addresses the issue related to creatinine in the MELD score by incorporating additional variables (albumin and sex), updating coefficients for existing variables, introducing interaction terms, and lowering the maximum creatinine value from 4.0 to 3.0 mg/dL. The proposed new MELD score, or MELD 3.0, not only addresses this aspect of the sex-disparity in liver allocation, it also better predicts risk of 90 day waitlist mortality for all liver transplant candidates and represents an important step forward in the ongoing effort to improve the liver allocation system.

PELD

Recent research has shown that the current PELD score under-predicts the risk of pediatric waitlist mortality by as much as 17%, especially when compared to adult candidates with a MELD score.[29] Almost two-thirds of pediatric (age under 12) liver transplant candidates are listed with an exception score, which is provided when a candidate's calculated PELD score does not adequately capture their medical urgency for transplantation.[30] Clearly, when a majority of candidates need an exception score to appropriately capture their need for transplant, the underlying calculation can be improved.

The current PELD score provides additional PELD points to candidates with growth failure. However, growth failure is a categorical variable defined as being more than two standard deviations below the candidate's expected growth based on age and sex using Centers for Disease Control and Prevention's (CDC) growth charts. Research has shown that 17% of pediatric liver transplant candidates fall into the "growth failure gap," in which candidates have z-scores less than two but do not meet the current criteria in the PELD score and therefore inappropriately lose six to seven PELD points.[31] More significantly, candidates falling into the "growth failure gap" have an increased risk of waitlist mortality and post-transplant mortality.[32] And finally, growth failure has been identified as the most common reason for PELD exception requests.[33] This research suggests that growth failure should be converted to a continuous variable, as opposed to categorical, to address this situation.[34]

In addition, research has demonstrated that the PELD score could be improved by incorporating a measure of renal function, as renal dysfunction has been shown to independently predict risk of 90 day waitlist mortality.[35] The current PELD score does not include a measure of renal function.

The intent of this proposal is to improve the PELD score by incorporating a creatinine variable to capture renal function, updating parameters for existing coefficients based on an updated cohort, and

[28] Ibid.
[29] Chung-Chou H. Chang et al., "Accuracy of the Pediatric End-Stage Liver Disease Score in Estimating Pretransplant Mortality among Pediatric Liver Transplant Candidates," *JAMA Pediatrics* 172, no. 11 (January 2018): p. 1070, https://doi.org/10.1001/jamapediatrics.2018.2541.
[30] H. J. Braun et al., "Nonstandard Exception Requests Impact Outcomes for Pediatric Liver Transplant Candidates," *American Journal of Transplantation* 16, no. 11 (2016): pp. 3181-3191, https://doi.org/10.1111/ajt.13879.
[31] Sonja M. Swenson et al., "Impact of the Pediatric End-Stage Liver Disease (Peld) Growth Failure Thresholds on Mortality among Pediatric Liver Transplant Candidates," *American Journal of Transplantation* 19, no. 12 (March 2019): pp. 3308-3318, https://doi.org/10.1111/ajt.15552.
[32] Ibid.
[33] E. R. Perito et al., "Justifying Nonstandard Exception Requests for Pediatric Liver Transplant Candidates: An Analysis of Narratives Submitted to the United Network for Organ Sharing, 2009-2014," *American Journal of Transplantation* 17, no. 8 (2017): pp. 2144-2154, https://doi.org/10.1111/ajt.14216.
[34] Sonja M. Swenson et al., "Impact of the Pediatric End-Stage Liver Disease (Peld) Growth Failure Thresholds on Mortality among Pediatric Liver Transplant Candidates," *American Journal of Transplantation* 19, no. 12 (March 2019): pp. 3308-3318, https://doi.org/10.1111/ajt.15552.
[35] Leanne Thalji et al., "Renal Function Parameters and Serum Sodium Enhance Prediction of Wait-List Outcomes in Pediatric Liver Transplantation," *Hepatology* 73, no. 3 (2021): pp. 1117-1131, https://doi.org/10.1002/hep.31397.

converting age and growth failure from categorical to continuous variables. The updated PELD score, or PELD Cr, also includes an adjustment for age-adjusted mortality so the risk of waitlist mortality at a given PELD Cr scores aligns with the risk of waitlist mortality for an 18 year old candidate with an equivalent MELD score. The PELD Cr score better predicts risk of waitlist mortality and will ensure that pediatric candidates are appropriately ranked relative to other pediatric candidates and adult candidates with a MELD score.

Status 1A and 1B

If a liver transplant candidate is particularly urgent, they can be listed as Status 1A or Status 1B. Both adults and pediatric candidates can be listed as Status 1A, while Status 1B is only for pediatric candidates. These priority statuses are reserved for those candidates at the highest risk of waitlist mortality and therefore most urgently in need of a liver transplant.

To be automatically listed as Status 1A, a candidate must meet specific, diagnosis-based criteria in OPTN policy. Candidates with acute liver failure, primary non-function of a transplanted liver, hepatic artery thrombosis, or acute decompensated Wilson's disease, who meet the discrete, clinical criteria listed in OPTN policy for the relevant diagnosis can be listed as Status 1A. Similarly, pediatric candidates with hepatoblastoma, metabolic disease (organic academia or urea cycle disorder), or chronic liver disease can qualify as Status 1B, as long as they meet the clinical criteria for their specific diagnosis.[36]

However, candidates can be listed as Status 1A or 1B by exception even if they do not meet the criteria listed in OPTN policy. These candidates are reviewed by the Committee to ensure their clinical situation necessitates the priority status.[37] Nonetheless, it is critical that the standard criteria in policy continue to match updated clinical practice and published research to ensure the appropriate candidates are able to access the priority statuses. While the exception review process is intended to provide a pathway for candidates not meeting standard criteria to be listed as Status 1A or 1B, there may be hesitancy from some transplant programs to request a Status 1A or 1B exception for a candidate not meeting standard criteria, which could impact a candidate's ability to access transplant. To that end, the proposal includes a number of changes to the standard criteria for Status 1A and Status 1B so that candidates needing a priority status are able to be automatically approved for Status 1A or 1B and are not subject to an exception review process.

In addition, within Status 1A and 1B, candidates are sorted on the match run based on blood type compatibility and waiting time points. Within a classification for a given status, candidates with the same blood type as the donor receive 10 points, candidates with a compatible blood type receive five points, and candidates with an incompatible blood type are provided zero points. Similarly, the candidate with the highest amount of waiting time at that status is provided 10 points and the remaining candidates each receive a fraction of 10 points relative to the waiting time for each candidate in that classification. Candidates are then sorted based on the number of points, from highest to lowest. If there is a tie, candidates are ranked based on their total waiting time at that status, also from highest to lowest.[38]

[36] See *OPTN Policies 9.1.A: Adult Status 1A Requirements, 9.1.B: Pediatric Status 1A Requirements,* and *9.1.C: Pediatric Status 1B Requirements* for relevant policy. Available at https://optn.transplant.hrsa.gov/
[37] See *OPTN Policy 9.3: Status Exceptions* for relevant policy. Available at https://optn.transplant.hrsa.gov/
[38] See *OPTN Policies 9.7: Liver Allocation Points* for relevant policy. Available at https://optn.transplant.hrsa.gov/

This proposal expands upon this points-based system for sorting candidates to also provide points based on diagnosis. The proposed changes included in the proposal are specific to Status 1B and are intended to prioritize those candidates with higher risk of waitlist dropout ahead of other, less urgent candidates at Status 1B.

Together, the changes to the MELD score, PELD score, Status 1A, and Status 1B represent a broad effort to update liver allocation in advance of future allocation changes.

Overview of Proposal

MELD 3.0

The Committee is proposing the incorporation of a new MELD score, or MELD 3.0, into OPTN policy for liver transplant candidates age 12 and over. MELD 3.0 was developed by Kim et. al. and is described in more detail in "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," which was published in the December 2021 issue of Gastroenterology.[39]

The Committee is recommending MELD 3.0 because it addresses the sex-based disparity in current liver allocation, better predicts risk of mortality for all candidates, incorporates two new objective variables (sex and albumin), updates coefficients for existing variables, adds important interaction terms, lowers the cap on creatinine, and maintains the existing MELD "intuition" that the liver transplant community has come to understand.

MELD 3.0 is calculated as follows:

$$\textit{MELD 3.0} = 1.33 \text{ (if female)} + [4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137 - \text{Sodium})] - [0.24 \times (137 - \text{Sodium}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_e(\text{creatinine})] + 6$$

MELD 3.0 was developed using data from adult candidates (age 18 or over) registered on the liver waitlist with end-stage liver disease from January 15, 2016 through December 31, 2018. Candidates registered for any multi-organ combination besides liver-kidney, candidates with a prior liver transplant, and candidates listed with an exception score were excluded from the cohort. These exclusion criteria are consistent with the development of prior MELD models.[40]

Uni- and multivariable Cox models were used to predict survival up to 90 days after waitlist registration.[41] Model fit was tested using the concordance statistic (C-statistic) and reclassification.[42] The impact of MELD 3.0 on waitlist outcomes was modelled separately by the authors of the Gastroenterology paper and the Scientific Registry of Transplant Recipients (SRTR) at the request of the Committee.[43,44]

[39] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[40] Ibid.
[41] Ibid.
[42] Ibid.
[43] Ibid.
[44] Liver Simulated Allocation Model MELD Analysis, Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021

Age, sex, race, serum sodium, creatinine, INR, bilirubin, albumin, and height were all considered for inclusion in the model. More subjective variables, such as encephalopathy and ascites, were excluded to ensure the MELD score continues to be calculated using objective variables. The authors considered including estimated glomerular filtration rate (eGFR) as a measure of renal function, instead of creatinine. However, the most common equations for measuring eGFR, Modification of Diet in Renal Disease-4 (MDRD-4) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), include race, creatinine, and sex. There is ongoing concern with the inclusion of race in eGFR, as the calculations have been shown to overestimate kidney function in Black patients and the OPTN is moving towards requiring race-neutral eGFR calculations.[45, 46] Cystatin C, which is race-neutral, was excluded because it is not widely available. The authors also performed an analysis comparing sex and height as predictors of waitlist mortality, probability of transplant, and as confounding variables. This analysis showed that sex and height were highly correlated and a model containing both variables would not perform as well as a model with either sex or height. The impact of sex was larger and more consistent than height and therefore sex, and not height, was included in the final model.[47] The Committee considered similar alternatives throughout the development of the project and agreed with the variables included in the MELD 3.0 analysis. More detail on the Committee's deliberations is provided below.

Based on the analyses performed, all variables included in MELD Na (MELD, sodium, creatinine, INR, and bilirubin), as well as MELD Na itself, sex=female, and albumin were found to be significantly associated with 90-day waitlist mortality. Smoothing splines were constructed for the five laboratory variables (sodium, albumin, creatinine, INR, bilirubin). Logarithmically transformed variables were a better fit for bilirubin, creatinine, and INR, while the natural scale worked best for sodium and albumin.[48]

Based on the splines and clinical input, a creatinine level of 3.0 mg/dL was selected as an inflection point, and a cap was set at 3.0 mg/dL for creatinine in MELD 3.0. This differs from MELD Na, whose creatinine cap is set at 4.0 mg/dL. Changing the maximum creatinine value from 4.0 to 3.0 mg/dL reduces the potential relative weight of creatinine on a candidate's MELD score. In MELD Na, the maximum number of points attributable to creatinine is 13, whereas it is 12 with MELD 3.0.[49] Lowering the cap on creatinine aligns with recent literature which has argued that the emphasis placed on creatinine in MELD Na has created an unfair advantage for candidates with higher levels of creatinine in accessing simultaneous liver-kidney transplant.[50] The reduced weight of creatinine in MELD 3.0 also accounts for the evolving indications for liver transplant, as the abnormal creatinine levels in candidates with nonalcoholic fatty liver disease with diabetic and/or hypertensive nephropathy are more likely a reflection of chronic kidney disease than acute kidney injury that is captured in the original MELD score.[51]

[45] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[46] Reassess Inclusion of Race in Estimated Glomerular Filtration Rate (eGFR) Equation, OPTN Minority Affairs and Kidney Transplantation Committees, August 2021, Available at https://optn.transplant.hrsa.gov/
[47] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[48] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[49] Ibid.
[50] Jonathan Merola, Richard N. Formica, and David C. Mulligan, "Changes in United Network for Organ Sharing Policy for Simultaneous Liver-Kidney Allocation," *Clinical Liver Disease* 9, no. 1 (2017): pp. 21-24, https://doi.org/10.1002/cld.609.
[51] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.

Same as MELD Na, values below 1.0 for bilirubin, creatinine, and INR were set to 1.0 in MELD 3.0. The lower and upper limits of sodium in MELD Na (125 mmol/L and 137 mmol/L, respectively) remained appropriate and are carried over into MELD 3.0. Finally, lower and upper limits for albumin were set at 1.5g/dL and 3.5 g/dL, respectively, in MELD 3.0.[52] Similar to MELD Na, candidates who have received two or more dialysis treatments in the last seven days and candidates who received 24 hours of continuous veno-venous hemodialysis within seven days are assigned the maximum allowable creatinine value, which is 3.0 g/dL in MELD 3.0.

With these parameters in place, the authors then conducted a multivariable Cox model predicting 90 day mortality that also considered possible interactions between variables. The final model includes female sex, bilirubin, INR, creatinine, sodium, and albumin. Significant interactions existed between bilirubin and sodium and between creatinine and albumin. The interaction term between creatinine and albumin is incorporated such that as creatinine increases, the relative weight of albumin decreases.[53]

The formula was then rescaled to maintain the current MELD "intuition," with a minimum score of 6 and the 80th percentile score set at 28. Importantly, the published MELD 3.0 does not include a cap at MELD 40. However, the Committee felt that it was necessary to have a maximum MELD of 40 to maintain consistency with the current allocation system.[54]

The C-statistic for MELD 3.0 was 0.869 compared to 0.862 for MELD Na. This difference is statistically significant ($P < .01$) and represents a similar improvement to the change in C-statistic between the original MELD and MELD Na (0.868 vs. 0.877).[55]

Figure 1 below shows the net reclassification of candidates and deaths between MELD Na and MELD 3.0.[56] This chart shows that more candidates moved to a higher MELD 3.0 score category (n=890; 10.1%) than moved to a lower MELD 3.0 score category (n=306; 3.5%) compared to MELD Na.[57] Out of 514 decedents, 435 (84.6%) remained in the score same category, while 62 (12.1%) moved to a higher MELD 3.0 score category and only 17 (3.3%) shifted to a lower MELD 3.0 score category, with a net improvement of 45 or 8.8%.[58]

[52] Ibid.
[53] Ibid.
[54] OPTN Liver and Intestinal organ Transplantation Committee Meeting Summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/
[55] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[56] Ibid.
[57] Ibid.
[58] Ibid.

Figure 1: Reclassification of Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[59]

Table 3. Reclassification of Liver Transplant Candidates Between MELDNa and MELD 3.0 in the Validation Set

		MELD 3.0				
Patients, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	1047	334	–	–	–
	10–19	66	3093	341	–	–
	20–29	–	150	2182	140	–
	30–39	–	–	64	1007	75
	40+	–	–	–	26	298

		MELD 3.0				
Deaths, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	6	4	–	–	–
	10–19	–	45	16	–	–
	20–29	–	6	166	23	–
	30–39	–	–	8	141	19
	40+	–	–	–	3	77

		MELD 3.0				
Deaths, %		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	0.6	1.2	–	–	–
	10–19	–	1.5	4.7	–	–
	20–29	–	4.0	7.6	16.4	–
	30–39	–	–	12.5	14.0	25.3
	40+	–	–	–	11.5	25.8

NOTE. The number of patients, number of deaths, and proportion of deaths (number of deaths divided by number of patients) are shown.

Figure 2 (female) and **Figure 3** (male) show the reclassification of candidates and decedents by sex.[60] There were more female candidates moving to a higher score category under MELD 3.0 (n=543; 16.7%) than moving to a lower score category under MELD 3.0 (n=23, 0.7%) and a net of 33 of the 221 female decedents (14.9%) were correctly reclassified, or moved to a higher score category under MELD 3.0.[61] In males, there was a net of 12 decedents (4.1%) appropriately reclassified.[62]

[59] Ibid.

[60] Ibid.
[61] Ibid.
[62] Ibid.

Figure 2: Reclassification of Female Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[63]

Supplementary Table 6. Reclassification of Female Liver Transplant Candidates Between MELD-Na and MELD 3.0 in the Validation Set

		MELD 3.0				
Patients, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	274	187	–	–	–
	10–19	–	1034	213	–	–
	20–29	–	11	838	98	–
	30–39	–	–	7	417	45
	40+	–	–	–	5	114

		MELD 3.0				
Deaths, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	–	1	–	–	–
	10–19	–	17	10	–	–
	20–29	–	1	71	19	–
	30–39	–	–	1	65	6
	40+	–	–	–	1	29

		MELD 3.0				
Deaths, %		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	–	0.5	–	–	–
	10–19	–	1.6	4.7	–	–
	20–29	–	9.1	8.5	19.4	–
	30–39	–	–	14.3	15.6	13.3
	40+	–	–	–	20.0	25.4

NOTE. The number of patients, number of deaths, and proportion of deaths (number of deaths divided by number of patients) are shown.

[63] Ibid.

Figure 3: Reclassification of Male Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[64]

Supplementary Table 7. Reclassification of Male Liver Transplant Candidates Between MELDNa and MELD 3.0 in the Validation Set

		MELD 3.0				
Patients, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	773	147	–	–	–
	10–19	66	2059	128	–	–
	20–29	–	139	1344	42	–
	30–39	–	–	57	590	30
	40+	–	–	–	21	184

		MELD 3.0				
Deaths, n		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	6	3	–	–	–
	10–19	–	28	6	–	–
	20–29	–	5	95	4	–
	30–39	–	–	7	76	13
	40+	–	–	–	2	48

		MELD 3.0				
Deaths, %		6–9	10–19	20–29	30–39	40+
MELDNa	6–9	0.8	2.0	–	–	–
	10–19	–	1.4	4.7	–	–
	20–29	–	3.6	7.1	9.5	–
	30–39	–	–	12.3	12.9	43.3
	40+	–	–	–	9.5	26.1

NOTE. The number of patients, number of deaths, and proportion of deaths (number of deaths divided by number of patients) are shown.

Over the past few years, there has been an evolution in the prevalence of diagnoses across the liver transplant candidate population. In 2016, alcohol-associated liver diseases (ALD) overtook chronic hepatitis C (HCV) as the leading indication for liver transplantation.[65] Therefore, it is important to highlight that MELD 3.0 does a better job of discriminating risk of waitlist mortality for candidates with an ALD than MELD Na.[66]

[64] Ibid.
[65] George Cholankeril and Aijaz Ahmed, "Alcoholic Liver Disease Replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States," Clinical Gastroenterology and Hepatology 16, no. 8 (2018): pp. 1356-1358, https://doi.org/10.1016/j.cgh.2017.11.045.
[66] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.

MELD 3.0 includes 1.33 points for female candidates to adjust for underestimation of creatinine in this population. Sex was demonstrated to be correlated with risk of waitlist mortality and the inclusion of a sex-based variable improves the predictive power of MELD 3.0 overall.[67] In the development of this proposal, the Committee considered multiple alternatives to the inclusion of a sex-based variable. These alternate solutions are described in more detail below.

In addition, the authors of the Gastroenterology paper developed an alternative MELD 3.0 model without albumin, due to ongoing concerns that albumin levels can be manipulated via external administration. The Committee is proposing that albumin be included in MELD 3.0 as it is an important predictor of waitlist mortality and improves the overall performance of the MELD score.[68,69] Additional details on the inclusion of albumin are included in subsequent sections.

In summary, the Committee is proposing the incorporation of MELD 3.0 into OPTN Policy because it reduces sex-based disparity in the current liver allocation system, improves overall performance in predicting risk of waitlist mortality for all liver transplant candidates and continues to use objective, widely-available clinical values. The Committee is seeking public comment feedback on MELD 3.0.

Liver Simulated Allocation Modelling (LSAM) Results:

The authors of the Gastroenterology paper, as well as the SRTR, modelled the impact of MELD 3.0 on waitlist outcomes using the LSAM.

The authors of the Gastroenterology paper conducted ten simulations on the impact of MELD 3.0 (with and without albumin) and MELD Na on liver allocation using a cohort from July 1, 2013 to June 30, 2016.[70] Results for the number of waitlist deaths from each of the ten simulations were averaged and compared to MELD Na.[71] The results of this analysis are presented in **Table 1** below. Only MELD 3.0 with albumin produced a significant decrease in the predicted number of waitlist deaths when compared to MELD Na.[72]

Table 1: Gastroenterology LSAM Modeling Results[73]

MELD Model	Waitlist Deaths	Change in Waitlist Deaths	P-value
MELD Na	7,850	Not applicable	Not applicable
MELD 3.0 with albumin	7,788	-62	.02
MELD 3.0 without albumin	7,814	-36	.12

As part of the Committee's deliberations, the SRTR separately modeled the impact of MELD 3.0 using the LSAM. This analysis used the same cohort and timeframe as the Gastroenterology article.[74] The SRTR

[67] Ibid.
[68] Ibid.
[69] See the OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[70] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[71] Ibid.
[72] Ibid.
[73] This analysis was completed by the authors of "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," which appeared in the December 2021 edition of Gastroenterology.
[74] Liver Simulated Allocation Model MELD Analysis, Pan prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021

LSAM analysis provided results by sex, an important factor considering the inclusion of a sex-based variable in the MELD 3.0 score.[75] Similar to the Gastroenterology analysis, the SRTR analysis compared MELD Na to MELD 3.0 with and without albumin.[76] In the LSAM analysis from the SRTR, pediatric candidates under the age of 12 were assigned a current PELD score and adolescent candidates were assigned a current MELD score, so it is difficult to draw any conclusions on the impact of MELD 3.0 on these population using the LSAM results.[77,78]

Table 2 below provides an overview of the SRTR LSAM results. **Table 3** stratifies the results by sex. These results show that using MELD 3.0, either with or without albumin, may not change overall transplant rates, waitlist mortality or post-transplant mortality. However, both versions of MELD 3.0 are expected to equalize transplant rates between sexes, an important improvement over MELD Na. In addition, either version of MELD 3.0 is not expected to change overall median MELD at transplant.[79]

Table 2: SRTR LSAM Overall Results[80]

MELD Model	Transplant Rate	Transplant Count	Waitlist Mortality Rate	Waitlist Mortality Count	2 Year Post-Tx Mortality
MELD Na	41 (40.1,41.7)	5810 (5716,5902)	8.8 (8.5,9.1)	1254 (1207,1279)	16.4 (15.5,17.4)
MELD 3.0 with albumin	41 (40.1,41.6)	5805 (5737,5889)	8.9 (8.5,9.3)	1256 (1200,1320)	16.6 (15.9,17.3)
MELD 3.0 without albumin	40.9 (40.1,41.7)	5792 (5723,5894)	8.9 (8.5,9.2)	1262 (1219,1301)	16.5 (16.1,17)

[75] Ibid.
[76] Ibid.
[77] Ibid.
[78] The cohort used to model the impact of MELD 3.0 predates the implementation of the Acuity Circles allocation policy. However, the Acuity Circles allocation rules were incorporated into the analysis.
[79] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[80] Liver Simulated Allocation Model MELD Analysis, Pan prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021

Table 3: SRTR LSAM Results by Sex[81]

MELD Model	Transplant Rate	Transplant Count	Waitlist Mortality Rate	Waitlist Mortality Count	2 Year Post-Tx Mortality
MELD Na: Female	38.8 (38,40.2)	2059 (2021,2144)	8.8 (8.5,9.4)	468 (449,492)	17.2 (15.7,18.1)
MELD Na: Male	42.3 (41.2,44)	3751 (3687,3864)	8.9 (8.5,9.2)	787 (758,814)	15.9 (15.2,17.1)
MELD 3.0 with albumin: Female	41.2 (39.6,41.8)	2170 (2100,2216)	8.7 (8.1,9.2)	458 (426,481)	17.2 (15.3,18.5)
MELD 3.0 with albumin: Male	40.8 (40.3,41.6)	3635 (3596,3681)	9 (8.7,9.5)	798 (774,851)	16.2 (15.4,17)
MELD 3.0 without albumin: Female	41.3 (40.3,42.2)	2173 (2122,2227)	8.8 (8.4,9.2)	464 (442,483)	17 (15.7,18.3)
MELD 3.0 without albumin: Male	40.6 (39.8,41.6)	3620 (3565,3681)	9 (8.6,9.4)	799 (777,835)	16.1 (15.7,16.8)

Overall, both LSAM analyses show that MELD 3.0 is expected to have a positive impact on waitlist outcomes for liver transplant candidates.

Additional Considerations:

Before arriving at MELD 3.0, the Committee considered a number of alternative solutions for improving the MELD score. The sections below describe the relevant deliberations and decision points of the Committee during the development of this proposal.

MELD Models

Since the time MELD was implemented, there have been numerous publications highlighting potential ways to improve the MELD score. As such, the Committee reviewed the recent literature to identify any research that could inform their discussion on improving the MELD calculation. A list of all literature compiled and considered by the Committee is included in the Appendix.

At the outset, the Committee decided that the proposal should entail a modification to the current MELD score, but not the creation of a MELD alternative. With the general acceptance of MELD Na and potential for allocation changes on the horizon, the Committee felt it was most appropriate to work within the context of the current MELD calculation, rather than make a larger, more comprehensive change to the liver allocation system.[82]

eGFR

The Committee decided to rule out MELD options that replaced creatinine with eGFR for two reasons. First, the current eGFR calculations include a race variable and the OPTN is moving towards only

[81] Ibid.
[82] See Improving the MELD Calculation Work Group meeting summary, April 7, 2021. Available at https://optn.transplant.hrsa.gov/

permitting the use of race-neutral eGFR calculations.[83] Second, the Committee considered MELD options that replaced creatinine with newer, race-neutral eGFR models, like cystatin-C, but determined that these values are not widely-available for the liver transplant patient population and therefore should not be included in the updated MELD score.[84] Based on these factors, the Committee decided to instead focus on MELD options that maintained the use of creatinine, but included an adjustment for those candidates whose creatinine may be underestimated.[85]

The Committee is seeking public comment feedback on the use of creatinine rather than eGFR.

Sex vs. Height in the Context of Renal Function

MELD 3.0 includes an additional 1.33 points for liver transplant candidates whose current sex is female. Before agreeing upon the inclusion of a sex-based variable, the Committee had extensive discussions about the best way to capture the population whose renal function is overestimated in the MELD calculation.

Clinically, the underlying issue with the use of creatinine in the MELD score is more correlated to low muscle mass than it is tied to a candidate's sex. Creatinine, which estimates GFR, is known to be lower in individuals with low muscle mass.[86] In the context of the MELD score, it is liver transplant candidates with low muscle mass whose renal function can be overestimated by creatinine, thereby underestimating their risk of mortality in the MELD score.

As such, the question put before the Committee was how to best capture and account for the population of candidates whose creatinine is underestimated. The most direct way to capture this population would be to adjust the MELD score for those candidates with low muscle mass. However, as previously mentioned, a major benefit of the MELD score is that it is based on widely-available and object clinical measures. The Committee agreed that muscle mass is neither widely-available for the candidate population, nor is it an objective clinical value.[87] Therefore, the Committee did not further consider incorporating muscle mass as a factor in the MELD score.

Ultimately, the Committee focused on two more objective and readily-available variables that could appropriately capture the candidate population whose creatinine levels are underestimated in MELD Na – sex and height.

The Committee considered the exploratory analysis performed by the authors of the Gastroenterology article comparing sex and height as predictors of waitlist mortality, probability of transplant, and as confounding variables. This analysis showed that sex and height were collinear, meaning that they were highly correlated and a model containing both variables would not perform as well as a model with either sex or height. The authors also found that the impact of sex was larger and more consistent than height and therefore included sex, and not height in the final model.[88] The coefficients for the other

[83] Reassess Inclusion of Race in Estimated Glomerular Filtration Rate (eGFR) Equation, OPTN Minority Affairs and Kidney Transplantation Committees, August 2021, Available at https://optn.transplant.hrsa.gov/
[84] See Improving the MELD Calculation Work Group meeting summary, March 19, 2021. Available at https://optn.transplant.hrsa.gov/
[85] Ibid.
[86] Charat Thongprayoon, Wisit Cheungpasitporn, and Kianoush Kashani, "Serum Creatinine Level, a Surrogate of Muscle Mass, Predicts Mortality in Critically Ill Patients," *Journal of Thoracic Disease* 8, no. 5 (2016), https://doi.org/10.21037/jtd.2016.03.62.
[87] Fanny Buckinx et al., "Pitfalls in the Measurement of Muscle Mass: A Need for a Reference Standard," *Journal of Cachexia, Sarcopenia and Muscle* 9, no. 2 (2018): pp. 269-278, https://doi.org/10.1002/jcsm.12268.
[88] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021),

variables and their statistical significance remained similar with or without the inclusion of height, meaning that a height variable did not have a meaningful impact on MELD 3.0 in these analyses.[89]

The Committee also reviewed data comparing the effect of height and sex on risk of mortality and liver transplant. **Table 4** below includes hazard ratios comparing the risk of death and liver transplant between tall/short males and tall/short females. Point estimates higher than 1.0 indicate an increased risk for that event, while estimates below 1.0 indicate a reduced risk for that event. Estimates equal to 1.0 indicate no significant difference in risk.

This data shows that short females (< 167.6 cm) are at higher risk of mortality compared to short and tall males. Short females also had lower probability of transplant than tall males and tall females but not short males. And finally, the table shows that short males had lower probability of transplant compared to tall males and tall females but were not at increased risk of mortality. This data suggests that a candidate's sex is more correlated to risk of mortality, while height may have more impact on a candidate's ability to access transplant, a separate, albeit important, issue that is not addressed through the MELD score.

Table 4: Hazard Ratios for Death and Liver Transplant[90]

	Subdistribution Hazards					
	sHR (LT)			sHR (death)		
Description	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Short_Women vs Short_Men	1.074	0.956	1.207	1.302	1.028	1.649
Short_Women vs Tall_Men	0.816	0.767	0.868	1.591	1.399	1.809
Short_Women vs Tall_Women	0.908	0.824	1.000	1.430	1.159	1.763
Short_Men vs Tall_Men	0.760	0.681	0.848	1.221	0.968	1.541
Short_Men vs Tall_Women	0.845	0.740	0.966	1.098	0.825	1.461
Tall_Women vs Tall_Men	0.899	0.822	0.983	1.113	0.906	1.367

The Committee also reviewed **Figure 4** below, which was taken from the Gastroenterology paper.[91] This figure depicts the multivariable smoothing spline for the relative hazard of 90-day mortality based on height and stratified by sex. The figure shows that, overall, there is no impact of height on mortality in males (relative hazard spline is linear). However, there is an increased risk for mortality in female candidates with height < 175 centimeters (cm). Data are sparse for females taller than 175 cm, so the point estimate is unstable. Nonetheless, this data also suggests that sex, as opposed to height, is more correlated to risk of mortality for liver transplant candidates.

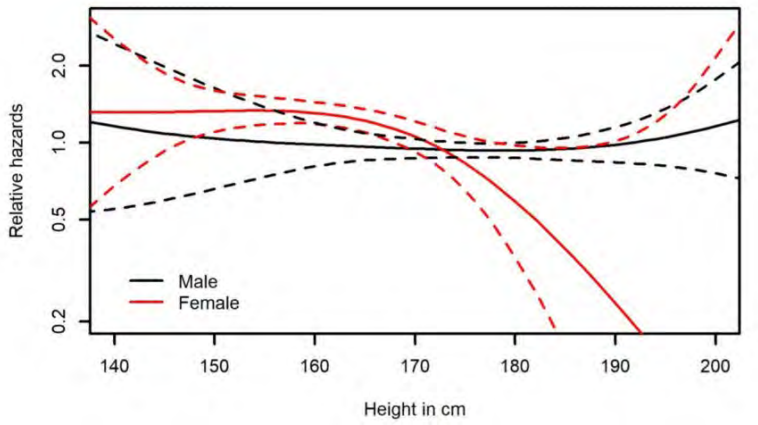
https://doi.org/10.1053/j.gastro.2021.08.050.

[89] Ibid.

[90] This table was created by the authors of "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," in response to reviewer comments. However, it was not included in the final paper. It was presented to the Committee during their meeting on August 27, 2021. See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/

[91] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.

Figure 4: Relative Hazard of 90-day Mortality Based on Height, Stratified by Sex



Taken together, the Committee interpreted this data to show that sex is more associated with risk of mortality, while height is more associated with access to transplant.[92] Because the MELD score is intended to predict risk of 90-day waitlist mortality, the Committee decided to move forward with a MELD model that includes a sex-based variable.[93]

Improving the liver allocation system to increase access to transplant for smaller-stature candidates would be a separate effort and the Committee intends to address better donor recipient size matching as part of future allocation changes.[94]

The Committee is seeking public comment feedback on the use of a sex-based variable in MELD 3.0.

SRTR-derived MELD Models vs. MELD 3.0

When this project was initiated, the paper describing the MELD 3.0 model had been developed and written but it had not yet been accepted for publication. Therefore, at least initially, the Committee agreed it was important to develop their own MELD models outside of MELD 3.0. As a result, the Committee worked with the SRTR to develop six independent MELD scores to compare to MELD Na, MELD 3.0 with albumin, and MELD 3.0 without albumin.[95] These MELD models were:

1. MELD Na (this model included the same variable as MELD Na but was refit using an updated cohort to align with other MELD models)
2. MELD Na + Sex
3. MELD Na + Height
4. MELD Na + Albumin
5. MELD Na + Albumin + Sex
6. MELD Na + Albumin + Height

[92] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/
[93] Ibid.
[94] Ibid.
[95] At this time in the project, the Committee had a draft manuscript of the MELD 3.0 paper but it was not yet published in Gastroenterology or publicly available.

After ruling out height as a potential variable in the updated MELD model, MELD Na + Height and MELD Na + Albumin + Height were no longer viable options. The Committee then focused on whether they should move forward with an SRTR-derived MELD score or MELD 3.0. The SRTR-derived MELD scores with a sex variable (with and without albumin) performed similarly to MELD 3.0 (with and without albumin). **Table 5** includes the 90-day C-statistics for each of the models across MELD score groupings.

Table 5: MELD 3.0 compared to SRTR-Derived MELD[96]

MELD Score	Overall	MELD ≤ 20	MELD 21-30	MELD 31+
MELD 3.0 without Albumin (includes sex)	82.7	65.0	70.6	67.8
MELD 3.0 with Albumin (includes sex)	83.1	66.5	71.1	68.1
SRTR MELD Na with Sex	83.0	65.4	71.6	69.7
SRTR MELD Na with Sex and Albumin	83.4	66.6	72.7	70.1

There was no significant difference in the performance of MELD 3.0 compared to SRTR-derived MELD options. However, there are a few important differences between the scores. First, MELD 3.0 was designed to maintain the same MELD "intuition" as MELD Na.[97] It has a minimum MELD score of six and the mean and standard deviation are similar to MELD Na.[98] The SRTR-derived scores can have values less than six and initially had a lower mean and higher standard deviation than MELD Na.[99] Also, bilirubin and INR cannot be less than 1.0 in MELD 3.0, but they can be less than 1.0 in the SRTR models.[100, 101] The SRTR-derived MELD models have a slightly different structure than MELD Na, which could create confusion in the liver transplant community.[102]

Ultimately, the Committee agreed that given the similarity in performance between the scores, MELD 3.0 was preferable because it maintains the current MELD "intuition" and would be easier for the liver transplant community to understand.[103]

The Committee is seeking public comment feedback on the use of MELD 3.0 rather than SRTR-derived MELD models.

Albumin vs. No Albumin

Another important decision point in the development of this proposal was the inclusion of albumin as a variable in the updated MELD score. Albumin has long been considered for inclusion in the MELD score

[96] Redeveloping MELD-NA: The effect of time-varying covariates and correcting for disparities across sex; Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, August 6, 2021
[97] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[98] Ibid.
[99] Redeveloping MELD-NA: The effect of time-varying covariates and correcting for disparities across sex; Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, August 6, 2021
[100] Ibid.
[101] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[102] The SRTR-derived MELD formulas are included in the Appendix.
[103] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/

but hesitancy has remained in the transplant community due to the potential for a candidate's albumin concentration to be temporarily inflated by administering albumin to the candidate, despite hypoalbuminemia being an indication of liver dysfunction.[104]

To that end, the Committee considered iterations of the MELD score both with and without albumin, but ultimately decided that the benefits of including albumin in the MELD score outweighed these potential concerns.[105]

In terms of discrimination, the concordance for MELD 3.0 with albumin was significantly higher than the concordance for MELD 3.0 without albumin, meaning the version with albumin does a better job of predicting risk of 90 day mortality and ranking candidates based on their urgency for transplant.[106] The concordance values for each version of MELD 3.0 are compared to MELD Na in **Table 6** below.

Table 6: MELD 3.0 with and without Albumin[107]

MELD Score	Harrell et al	Uno et al
MELD 3.0 without Albumin (includes sex)	.8665	.8342
MELD 3.0 with Albumin (includes sex)	.8693	.8378
MELD Na	.8622	.8294

Furthermore, in the LSAM analysis presented in the Gastroenterology article, only MELD 3.0 with albumin resulted in a statistically significant reduction in waitlist mortality compared to MELD Na.[108] In addition, it is important to note that the formula for MELD 3.0 with albumin is constructed such that as creatinine increases, albumin is given less relative weight.[109] This should allay concerns regarding the inclusion of albumin because in most circumstances where a candidate would benefit from external administration of albumin, the candidate is also likely to have elevated creatinine, which would reduce the impact of albumin on the candidate's MELD score.[110] Based on this information, the Committee decided to include albumin in the updated MELD 3.0 score.[111]

The Committee is seeking feedback on the inclusion of albumin in the proposed MELD 3.0 model.

Data Collection

As noted previously, a major benefit of the MELD score is that it is based on widely-available and objective clinical measures. With the addition of a sex variable and albumin in the updated MELD score, the OPTN will need to update data collection for adult liver transplant candidates. First, albumin is currently collected by the OPTN but it is not a required field. Because it will be a variable in the updated

[104] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[105] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[106] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.
[107] Ibid.
[108] Ibid.
[109] Ibid.
[110] Ibid.
[111] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/

MELD score, albumin will become a required field and transplant programs will be required to provide albumin values for their adult transplant candidates, similar to other laboratory values included in the MELD score.

In addition, new data collection will be required to account for the inclusion of a sex-based variable in MELD 3.0. Currently, there is a field on the candidate demographic form labeled "gender," with a data definition that more closely describes birth sex.[112] There is a separate, ongoing effort to change each of the "gender" fields to be labeled "birth sex" across the OPTN. Regardless, as part of this proposal, there will be two new fields added to the candidate demographic form that are intended to capture a candidate's current sex, which will be used for the purposes of the updated MELD score.

For most liver transplant candidates, their current sex, or sex at the time of liver waitlist registration, will be the same as their sex at the time of birth. However, there will be instances where a candidate's current sex is not the same as their sex at the time of birth. These could be candidates with gender dysphoria who have undergone sex reassignment surgery or prolonged hormonal manipulation, candidates with testicular feminization, or any other number of similar situations causing current sex to differ than sex at the time of birth.[113]

To account for these situations, the Committee is proposing the addition of two new fields immediately following the "birth sex" (currently "gender") field on the candidate demographic form in Waitlist[SM]. After asking for a candidate's birth sex, the first new field will ask if the candidate's current sex is the same as his or her birth sex. For the majority of candidates, the answer to this question will be yes and the OPTN will use birth sex for the purposes of the MELD score. This first field will be optional and if no response is provided, the candidate's birth sex will be used for the MELD score. However, if the response is no, there will be a subsequent field asking the transplant program to provide the candidate's current sex. This field will be required (provided the response to the prior question is no) and will ensure that those candidates whose current sex differs from birth sex are appropriately categorized for the purposes of the MELD score.

The Committee consulted with subject matter experts in the field of transgender medicine to develop this data collection solution. The Committee discussed if it would be feasible to create an objective definition for current sex based on testosterone levels or time on hormonal therapy, but the subject matter experts advised that no such universal definition exists. As such, the submission of this data will be left to the clinical judgement of the transplant program in consultation with the candidate and their clinical team.[114]

This data solution was reviewed by the OPTN Data Advisory Committee (DAC), who endorsed the new data collection. The new fields were evaluated using the 2019 Data Element Standard of Review Checklist and the OPTN Data Collection Principles. The intent of the new data collection is to develop transplant, donation, and allocation policies.

The Committee is seeking public comment feedback on the proposed data collection changes.

[112] The current data definition for the "gender" field is: Indicate if the patient is Male or Female. Report patient sex (male or female), based on biologic and physiologic traits at birth. This is a required field

[113] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/

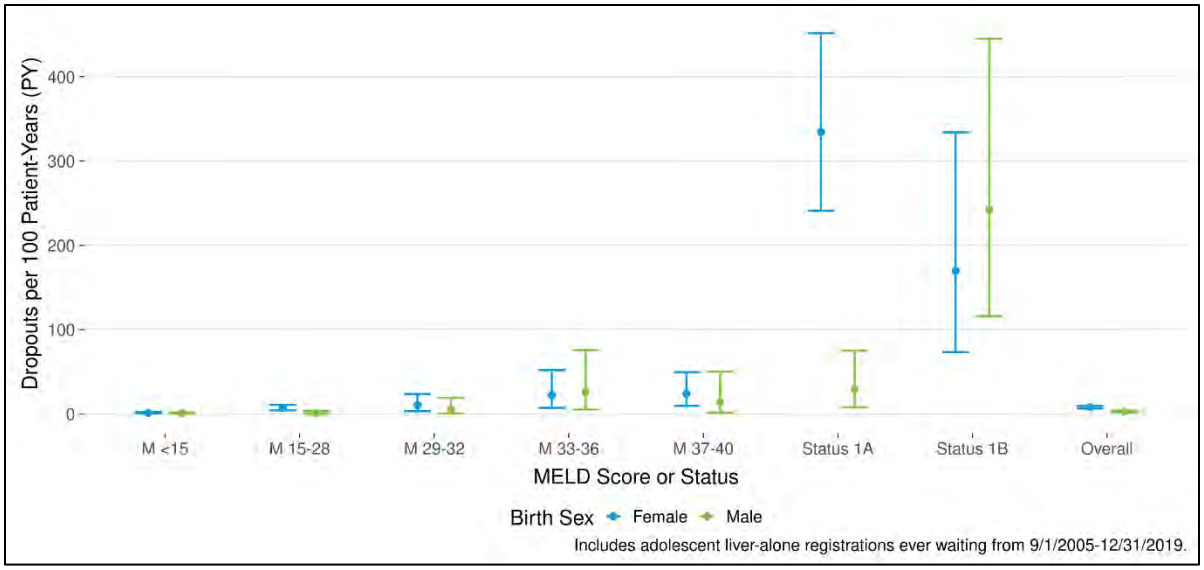
[114] Ibid.

Adolescent Candidates

In the current liver allocation system, adolescent candidates (age at least 12 and less than 18) are assigned a MELD score. In this proposal, adolescent candidates will continue to utilize MELD 3.0 but both male and female adolescent candidates will get the 1.33 points that are otherwise reserved for female adult candidates.

As noted above, one benefit of MELD 3.0 is that it addresses the sex-based disparity in liver allocation by providing 1.33 points to candidates who are female. However, there is no evidence to suggest the same disparity exists between male and female adolescent candidates. **Figure 5** shows waitlist mortality rates for adolescent liver candidates. This data does not show a difference in waitlist mortality between male and female candidates with MELD scores.[115]

Figure 5: Adolescent Liver Waitlist Mortality Rates by Sex and MELD Score or Status



In addition, the Committee reviewed anthropometric data comparing the distribution of height, weight, body mass index (BMI), and body surface area (BSA) between male and female adolescent candidates, which showed no significant differences between adolescent males and females. This further suggests that there is no disparity related to creatinine for the adolescent population.[116] Given this information, the Committee agreed that both adolescent male and female candidates should be provided the 1.33 points so all adolescent candidates are treated in the same manner.[117] Under this proposed solution, any male liver transplant candidate registered before turning 18 and older than 12 years old will receive the 1.33 MELD points. Male candidates registered after turning 18 will receive the standard MELD 3.0 score, which provides the 1.33 points only to female candidates.[118] The use of age at the time of

[115] This data was prepared for the OPTN Liver and Intestinal Organ Transplantation Committee meeting on November 16, 2021. A meeting summary is available at https://optn.transplant.hrsa.gov/.
[116] Ibid.
[117] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 16, 2021. Available at https://optn.transplant.hrsa.gov/
[118] Transplant programs have the ability to submit a waiting time modification request as outlined in *OPTN Policy 3.7: Waiting Time Modifications*. If a waiting time modification request is approved resulting in a male candidate being registered prior to turning 18, the candidate will receive the 1.33 points.

registration matches how pediatric priority is defined elsewhere in liver allocation. This prioritization of pediatric candidates aligns with the Ethical Principles of Pediatric Organ Allocation.[119]

The Committee considered switching adolescent candidates from MELD to PELD Cr and the PELD/1B Work Group recommended that adolescent candidates move from MELD to PELD Cr as part of this proposal.[120] The members of the PELD/1B Work Group recommended this approach so that all pediatric candidates would be treated the same (all would have PELD Cr) which would help with waitlist management for transplant programs. In addition, PELD Cr is uncapped so adolescent candidates would be able to access scores higher than 40, giving them access to donors before adult candidates with MELD scores 40 and below.[121]

However, after the implementation of the Acuity Circles policy in February 2020, the adolescent candidate population has generally seen positive outcomes, with liver alone transplants increasing by 62 (96 pre-policy vs. 158 post-policy) and registrations removed due to death or too sick for transplant decreasing by 12 (15 pre-policy vs. 3 post-policy) in the 18 months following implementation.[122] The Committee felt that adolescent candidates are faring well under the current allocation system and keeping the system consistent for them was appropriate.[123]

In addition, switching adolescent candidates from MELD to PELD would create additional complexities that could have deleterious effects on other aspects of the liver allocation system. If adolescent candidates were switched to PELD Cr, they would need to be included in the median PELD at transplant (MPaT) calculation, which is used to assign exception scores for candidates with a PELD score. The Committee discussed including adolescent candidates in the MPaT but noted that including adolescent transplants could deflate the score, which could reduce access to transplant for other PELD exception candidates.[124] In addition, the Committee discussed transitioning adolescent exception candidates from an exception score based on median MELD at transplant (MMaT) to an exception score based on MPaT by assigning the candidates a score with the same relative adjustment to MPaT as they had relative to MMaT (i.e. if candidate has an exception for MMaT-3, they would get MPaT-3).[125] Finally, the Committee discussed switching policy-assigned exception scores for adolescent candidates to be the same as the policy-assigned scores for all PELD candidates.[126]

Ultimately, the Committee decided that adolescent candidates have fared well with a MELD score and switching them to PELD Cr would create additional complexity and had the potential for negative unintended consequences.[127] Therefore, the Committee is recommending that adolescent candidates stick with MELD 3.0 but both male and female adolescent candidates be assigned the 1.33 female points.[128]

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[119] See OTPN Ethical Principles of Pediatric Organ Allocation. Available at https://optn.transplant.hrsa.gov/
[120] The PELD/1B Work Group is an OPTN Work Group consisting of subject matter experts in pediatric liver transplantation. This group developed most of the proposed changes related to pediatric candidates outlined in this proposal.
[121] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 5, 2021. Available at https://optn.transplant.hrsa.gov/
[122] OPTN Descriptive Data Request. "18 Month Monitoring Report of Liver and Intestine Acuity Circle Allocation Removal of DSA and Region as Units of Allocation" Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, December 3, 2021
[123] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 5, 2021. Available at https://optn.transplant.hrsa.gov/
[124] Ibid.
[125] Ibid.
[126] Ibid.
[127] Ibid.
[128] Ibid.

The Committee is seeking public comment feedback on which score should be used for adolescent candidates.

PELD Creatinine (PELD Cr)

The Committee is proposing the incorporation of a new PELD score, or PELD Cr, into OPTN policy for liver transplant candidates under the age of 12. PELD Cr was developed by the SRTR using the article by Hsu et. al. titled, "Improving the predictive ability of the pediatric end-stage liver disease score for young children awaiting liver transplant," as a starting point.[129]

The Committee is proposing the adoption of PELD Cr because it has an improved ability to discriminate on risk of waitlist mortality and therefore rank pediatric candidates on the waitlist, it adds a creatinine variable as a measure of renal function, it includes continuous variables for age and growth failure instead of categorical variables, and it incorporates an age-adjusted mortality factor to align with risk of mortality in the adult population.

PELD Cr is calculated as follows:

[129] Evelyn Hsu et al., "Improving the Predictive Ability of the Pediatric End-Stage Liver Disease Score for Young Children Awaiting Liver Transplant," *American Journal of Transplantation* 21, no. 1 (2020): pp. 222-228, https://doi.org/10.1111/ajt.15925.

Table 7: PELD Cr Calculation

	If the value is:	Then the value's contribution to PELD is:
Candidate Age (fractional calendar year)	< 1	-0.1967 * 1
	1 to 5.5	-0.1967 * age at the time of most recent lab reported for use in the PELD score (fractional calendar year)
	> 5.5 and < 12	-0.1967 * 5.5
Albumin (g/dL)	1 to 1.9	-1.842 * ln(albumin)
	> 1.9	-1.842 * ln(1.9)
Total bilirubin (mg/dL)	1 to 4	0.7854 * ln(bilirubin) + 0.3434 * ln(4)
	> 4 to 40	0.7854 * ln(4) + 0.3434 * ln(bilirubin)
	> 40	0.7854 * ln(4) + 0.3434 * ln(40)
INR	1 to 2	1.981 * ln(INR) + 0.7298 * ln(2)
	> 2 to 10	1.981 * ln(2) + 0.7298 * ln(INR)
	> 10	1.981 * ln(2) + 0.7298 * ln(10)
Minimum of CDC height or weight Z-score	< -5.0	-0.1807 * (-5)
	-5.0 to -2.1	-0.1807 * (minimum z-score)
	> -2.1	-0.1807 * (-2.1)
Creatinine (mg/dL)	< 0.2	1.453 * ln(0.2)
	0.2 to 1.3	1.453 * ln(creatinine)
	> 1.3	1.453 * ln(1.3)

PELD Cr = (sum of all terms as outlined in **Table 7: PELD Score Calculation** + 1.5287) x 10 + 2.82

PELD Cr was developed using a cohort that included all pediatric candidates younger than age 12 with chronic liver disease listed for liver transplant between September 1, 2005 (after start of Status 1A/1B) through December 31, 2019.[130] Candidates who were re-listed were included and for candidates who were multi-listed (listed at multiple centers at the same time), the earliest listing was used.[131] Candidates with cancer or a primary/secondary diagnosis that was not chronic liver disease were excluded.[132] Candidates whose first active status was Status 1A due to primary non-function and/or hepatic artery thrombosis of a transplanted liver within seven days if transplant were also excluded from the cohort.[133]

The SRTR considered the following variables in the analysis: age, albumin, total bilirubin, INR, sodium, minimum of height or weight Z-score based on Centers for Disease Control and Prevention (CDC) growth charts from 2000, eGFR (modified Schwartz equation), and creatinine.[134] Similar to MELD, a major

[130] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.
[131] Ibid.
[132] Ibid.
[133] Ibid.
[134] Ibid.

benefit of PELD is that it uses objective, widely available variables. The PELD/1B work group conducted an extensive review of the literature to create a list of variables for consideration. More detail is provided in the subsequent section on how this list was developed.

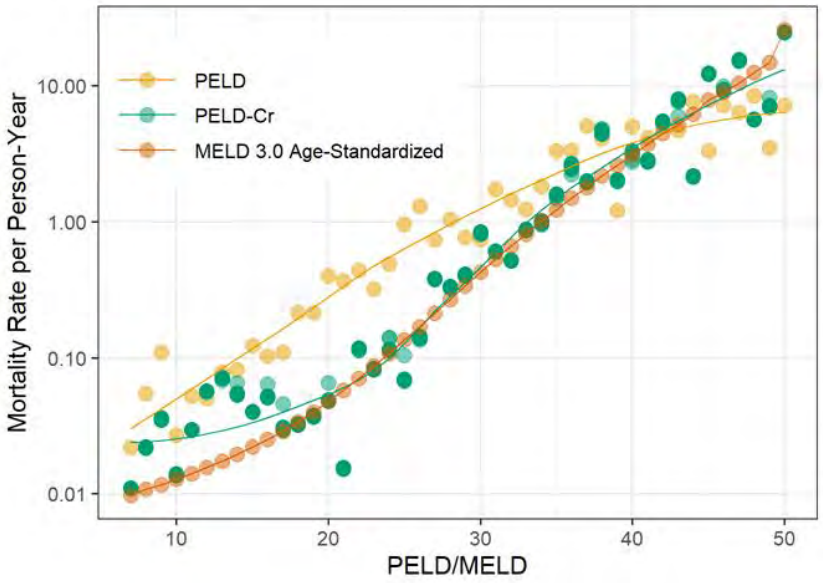
The SRTR used Cox proportional hazards models with time-varying covariates, with values changing at each status update.[135] The outcome of interest was time to waitlist mortality (n=442).[136] Variables were set at each active status and treated as time-varying.[137] All variables except age and z-score were log-transformed to reduce skewness.[138] If a candidate was on dialysis, creatinine was set to 4 and eGFR was set to 0.[139] Splines were developed for each variable of interest and knots for splines were visually selected from inflection points in penalized splines.[140] Backward model selection with linear splines with a p-value of .05 was used to determine final model variables.[141]

The SRTR developed two PELD options for the Committee to consider: PELD Cr and PELD eGFR, the main difference being, as the names imply, the former model incorporates creatinine, while the latter model incorporates eGFR, as measures of renal function. After deriving the updated models, the SRTR then scaled the new PELDs to have the same mean and standard deviation as the current PELD. Similar to MELD 3.0 above, this scaling allowed the new PELD models to maintain the same PELD "intuition" that exists within the transplant community. [142]

The SRTR then calibrated the new PELD scores so that pediatric mortality risk was the same as the age standardized mortality risk for 18 year old adults with a MELD score.[143,144] This age-adjusted mortality factor ensures that candidates at a given MELD or PELD score have the same risk of mortality. This is not the case in the current system where candidates with a PELD score have higher mortality rates than adults at a given MELD score.[145] For PELD Cr, the age-adjusted mortality factor adds 2.82 points to each candidate's PELD score. **Figure 6** compares mortality risk at a given score between PELD, PELD Cr, and MELD 3.0. As the figure shows, at PELD scores below 40, a candidate at a given PELD score has a higher risk of mortality than an 18 year old candidate at that same MELD score. However, PELD Cr has been adjusted so that the risk of mortality at a given score is the same.[146]

[135] Ibid.
[136] Ibid.
[137] Ibid.
[138] Ibid.
[139] Ibid.
[140] Ibid.
[141] Ibid.
[142] Ibid.
[143] Ibid.
[144] The age-adjusted mortality factor in PELD Cr was developed in reference to MELD Na. The SRTR compared the waitlist mortality curves of MELD Na and MELD 3.0 and there was no meaningful difference, and as such no changes were made to PELD Cr.
[145] Chung-Chou H. Chang et al., "Accuracy of the Pediatric End-Stage Liver Disease Score in Estimating Pretransplant Mortality among Pediatric Liver Transplant Candidates," *JAMA Pediatrics* 172, no. 11 (January 2018): p. 1070, https://doi.org/10.1001/jamapediatrics.2018.2541.
[146] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.

Figure 6: Age-adjusted Mortality Rate per Person-Year



While sodium was included in the initial list of variables to consider for inclusion in the updated PELD score, it was not associated with risk of waitlist mortality and was not included in either PELD Cr or PELD eGFR.[147] In addition, the SRTR explored the incorporation of a delta PELD or PELD trajectory variable, but found that both a sudden increase and a sudden decrease in PELD were associated with mortality and the improvement in the c-statistic was modest (.003 improvement).[148] Given the modest improvement in discrimination and clinically contradictory results, the Committee did not further consider including a delta PELD or PELD trajectory variable.[149]

After deriving the final PELD models, the SRTR computed C-statistics for each version to evaluate model fit. Both PELD Cr (c-statistic = .909) and PELD eGFR (c-statistic = .908) represented significant improvements over the current PELD (c-statistic = .842).[150] In addition, in both updated PELD scores, age and growth failure were converted from categorical to continuous variables, representing a significant upgrade over the current PELD score, where a candidate can have large changes in their score with only small changes in either age, height, or weight.[151]

The Committee is proposing that the new PELD score have a minimum value of 6. The current PELD score can range from -99 to 99, but few candidates have score below 6, which is the minimum MELD score, and those candidates that do have a PELD below 6 are not typically being transplanted. Therefore, to align with MELD, the Committee is proposing that PELD Cr have a minimum value of 6.[152] PELD Cr, like the current version of PELD, will not be capped at 40 to allow particularly urgent pediatric candidates to access scores higher than the adult population and access transplant more quickly.[153,154]

[147] Ibid.
[148] Ibid.
[149] See PELD/Status 1B Work Group meeting summary, February 18, 2021. Available at https://optn.transplant.hrsa.gov/
[150] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.
[151] Ibid.
[152] At the time of implementation, all candidates with a PELD Cr score less than 6 will have their scores set at 6.
[153] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 5, 2021. Available at https://optn.transplant.hrsa.gov/
[154] See OTPN Ethical Principles of Pediatric Organ Allocation. Available at https://optn.transplant.hrsa.gov/

Both PELD Cr and PELD eGFR represent important improvements over the current PELD score as they have a better ability to discriminate on risk of mortality, incorporate new variables, reparametrize existing variables, convert categorical variable to continuous variables, and account for age-adjusted mortality.

Ultimately, the Committee is recommending PELD Cr because it is simpler and avoids the use of eGFR, as eGFR already includes age and height, which are also included in the PELD model.[155] Given the issues with the use of creatinine as a measure of renal function in MELD, it is necessary to note that the same disparity does not exist for candidates under age 12.[156] As a result, the Committee is proposing the incorporation of PELD Cr into OPTN policy.

Currently, creatinine is a required field for candidates over the age of 10. With the incorporation of creatinine in the updated PELD score, transplant programs will be required to provide creatinine lab values for all PELD candidates.

The Committee is seeking public comment feedback on PELD Cr.

Review of Characteristics

To start the effort to update the PELD score, the PELD/1B work group first created a list of 21 clinical variables that could be associated with pediatric waitlist mortality. They then reviewed the available literature to determine if evidence exists showing that the characteristics are associated with risk of mortality. They also determined if the characteristics are objective, widely-available, or already collected by the OPTN. If a characteristic was either not associated with risk of mortality or not objective, widely-available, or currently collected by the OPTN, it was not considered for inclusion in the PELD score. **Table 8** below lists the 21 characteristics considered.

[155] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 14, 2021. Available at https://optn.transplant.hrsa.gov/

[156] Osamu Uemura et al., "Age, Gender, and Body Length Effects on Reference Serum Creatinine Levels Determined by an Enzymatic Method in Japanese Children: A Multicenter Study," *Clinical and Experimental Nephrology* 15, no. 5 (2011): pp. 694-699, https://doi.org/10.1007/s10157-011-0452-y.

Table 8: Potential PELD Variables

Characteristic	Outcome
Age	Included in updated PELD
Age-adjusted mortality	Included in updated PELD
Bilirubin	Included in updated PELD
Sodium	Included in PELD derivation request but not associated with mortality
Renal function (eGFR/creatinine)	Included in updated PELD
Albumin	Included in updated PELD
INR	Included in updated PELD
Decompensated chronic liver disease	Difficult to define, similar to delta PELD
Infections	Difficult to define and can be subjective, goal is to transplant candidates before infection
Portal Hypertensive Bleeding	Included in Status 1B policy but more research needed for inclusion in PELD
Parenteral Nutrition	Concern that programs could initiate parenteral nutrition to gain additional points
Plasmapheresis/dialysis	Renal function is captured by eGFR/creatinine
Rapid downward trajectory of illness (Delta PELD)	Include in PELD derivation request but did not significantly improve model accuracy
Ascites	Difficult to quantify, more research needed
Cirrhotic Cardiomyopathy	Not collected by OPTN
Encephalopathy	Difficult to objectively define, especially in pediatric candidates
Micro-nutrient deficiencies	More likely associated with morbidity and quality of life issues
Sarcopenia	Would need age/sex specific percentiles; not clear if it is any better than height/weight z-score; some measurement methods require repeated radiation exposure
Frailty	Functional test not applicable across all ages/developmental abilities; time-intensive/novel test
Pruritus	Difficult to objectively quantify, not collected by OPTN
Growth Failure	Included in updated PELD

Additional PELD Points

The Committee considered including additional points for each candidate with a PELD score. For example, the Committee reviewed options where every candidate with a PELD Cr score would be provided an additional 3, 5, 7, 10, 20, or 30 points on top of their PELD Cr score. The purpose of these additional points was to further prioritize pediatric candidates in the liver allocation system.[157]

However, the Committee agreed that including additional points was outside the scope of the current project. The purpose of the PELD Cr score is to rank candidates based on their risk of waitlist mortality.

[157] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/

Adding points would improve pediatric access to transplant, but is unrelated to waitlist mortality. The Committee agreed that further prioritization of pediatric candidates in liver allocation could be considered as part future allocation changes.[158]

The Committee is seeking public comment feedback on the inclusion of additional PELD points.

Status 1A

In current OPTN policy, a pediatric candidate can qualify for Status 1A with fulminant liver failure, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease, if the candidate has an INR greater than 2.0.[159] However, encephalopathy is difficult to diagnose in young children and such diagnoses can be unreliable.[160]

As a result, the Committee is proposing to change the criteria for a pediatric candidate with fulminant liver failure to qualify for Status 1A priority. The updated criteria matches the definition for hepatic encephalopathy as outlined by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.[161] The proposed policy would allow a pediatric candidate with fulminant liver failure to be listed as Status 1A if the candidate has an INR greater than or equal to 1.5 and less than 2.0 with a diagnosis of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. A pediatric candidate can also be listed as Status 1A with fulminant liver failure if the candidate has an INR greater than or equal to 2.0, with or without encephalopathy. **Table 8** outlines the proposed changes.

Table 9: Proposed Changes to Pediatric Status 1A Criteria

Current Policy	Proposed Policy
Fulminant liver failure, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease AND has an INR greater than 2.0	Fulminant liver failure AND candidate either has: • INR greater than or equal to 1.5 and less than 2.0 and a diagnosis of hepatic encephalopathy within 56 days of the first signs for symptoms of liver disease • INR greater than or equal to 2.0

The Committee is seeking public comment feedback on this proposed changed to Status 1A policy for pediatric candidates.

Status 1B

The Committee is proposing a number of changes to the policy for Status 1B candidates including:

1. MELD/PELD threshold for candidates with chronic liver disease
2. Gastro-intestinal (GI) bleeding threshold for candidates with chronic liver disease
3. Glasgow Coma Score criteria for candidates with chronic liver disease

[158] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 5, 2021. Available at https://optn.transplant.hrsa.gov/

[159] A candidate can qualify for Status 1A with fulminant liver failure by meeting other criteria as outlined in OPTN Policy 9.1.B. These criteria are not changing as part of this proposal.

[160] See PELD/Status 1B Work Group meeting summary, October 25, 2021. Available at https://optn.transplant.hrsa.gov/

[161] James E. Squires et al., "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure," *Journal of Pediatric Gastroenterology & Nutrition* Publish Ahead of Print (March 2021), https://doi.org/10.1097/mpg.0000000000003268.

4. Sorting of candidates within Status 1B classifications

The first three changes are all related to the standard Status 1B criteria for liver-alone and liver-intestine candidates with chronic liver disease and will ensure that the appropriate candidates are able to efficiently access Status 1B priority without the need for an exception. The fourth update will more accurately rank Status 1B candidates based their urgency for transplant.

Changes to Status 1B Criteria for Liver-Alone and Liver-Intestine Candidates

Table 10 summarizes the current criteria a pediatric liver-alone or liver-intestine candidate must meet in order to be listed as Status 1B.

Table 10: Status 1B Criteria for Liver-Alone and Liver-Intestine Candidates with Chronic Liver Disease

Liver-Alone	Liver-Intestine
Chronic liver disease with a calculated MELD/PELD greater than 25 and has at least one of the following: • Is on a mechanical ventilator • Has GI bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous 24 hours • Has renal failure or renal insufficiency requiring dialysis, continuous venovenous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD) • Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.	Chronic liver disease with and adjusted MELD/PELD score greater than 25 and has at least one of the following: • Is on a mechanical ventilator • Has gastrointestinal bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours • Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD) • Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension

The Committee is proposing to change the MELD/PELD 25 threshold for liver-alone and liver-intestine candidates, the GI bleeding threshold for liver-alone candidates, and the GCS criteria for liver-alone and liver-intestine candidates.

MELD/PELD Threshold

OPTN Policy 9.1.C: Pediatric Status 1B Requirements requires pediatric liver-alone and liver-intestine candidates with chronic liver disease to have a MELD or PELD score greater than 25 in order to be automatically listed as Status 1B. Liver-alone candidates must have a *calculated* MELD or PELD score greater than 25 and liver-intestine candidates must have an *adjusted* MELD or PELD score greater than 25, which includes the addition of liver-intestine points as outlined in *OPTN Policy 9.1.F: Liver-Intestine Candidates*.[162] The Committee is proposing that these MELD/PELD score thresholds be removed as there is no clinical significance to MELD/PELD 25 and the threshold may inappropriately prohibit some candidates from accessing Status 1B priority.[163]

[162] See *OPTN Policy 9.1.F: Liver-Intestine Candidates*. Available at https://optn.transplant.hrsa.gov/
[163] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/

Candidates under the age of 18 who are registered for both a liver and intestine receive 23 points added to their MELD or PELD score. By adding 23 points to their MELD or PELD scores, candidates will almost always meet the threshold set at MELD/PELD 25. Therefore, the Committee is proposing the threshold be removed for liver-intestine candidates.[164]

The Committee is also proposing the threshold be removed for liver-alone candidates as the primary reason candidates are listed as Status 1B by exception is due to not having a calculated MELD or PELD greater than 25. **Table 11** includes the specific reasons Status 1B exception requests did not meet the standard 1B criteria.[165] This data shows that of all Status 1B exception requests, 48% (29 of 61) were because the candidate did not have a calculated MELD/PELD greater than 25. Of these 29 cases, 72% (21 of 29) were ultimately approved by the Committee, meaning the candidate needed to be listed as Status 1B despite not meeting the threshold. And finally, the 21 approved exception requests for not meeting the MELD/PELD 25 threshold represented nearly half (49%) of all approved Status 1B exception requests.[166]

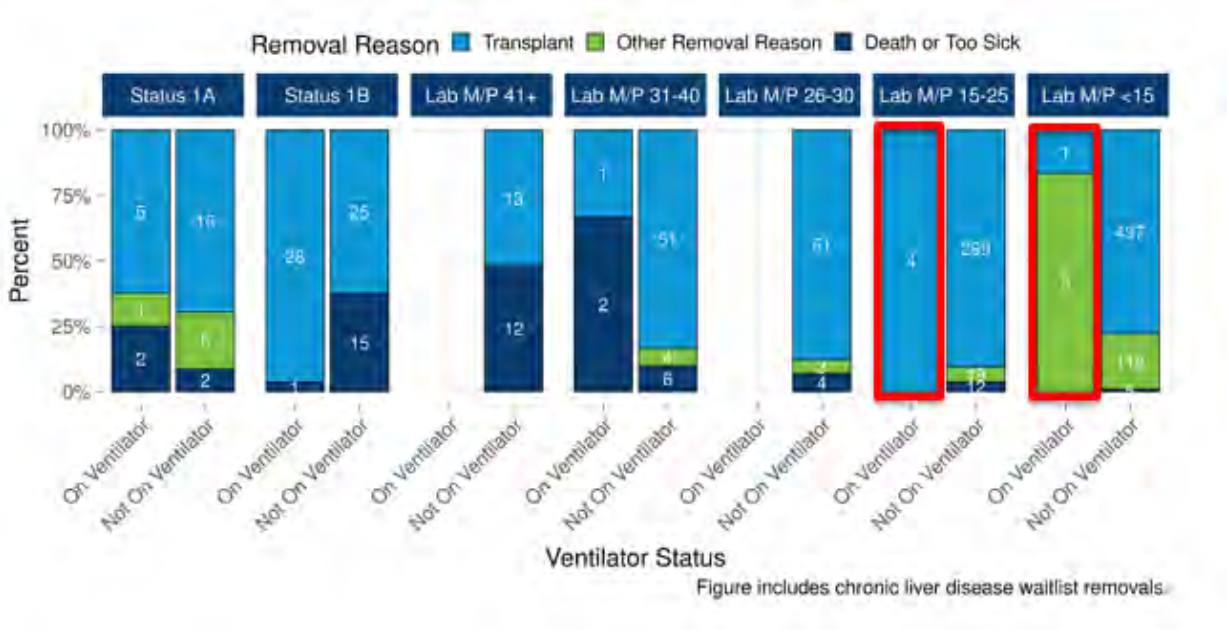
Table 11: Criteria Not Met for Status 1B Cases

	Case Outcome	
Criteria Not Met for Status 1B Requests that Do Not Meet Standard Critera	Approved	Denied
Candidate does not have chronic liver disease, non-metastatic hepatoblastoma, or metabolic disease	5 (11.63%)	4 (22.22%)
Chronic liver disease BUT calculated MELD/PELD score is less than or equal to 25	21 (48.84%)	8 (44.44%)
Chronic Liver Disease with MELD/PELD > 25 BUT Candidate is not on dialysis, CVVH, or CVVD does not have a GI Bleed requiring at least 30 cc/kg(for Liver Only candidate) of red blood cell replacement or 10 cc/kg(for combined liver and intestine candidate) of red blood cell replacement, and does not have a Glasgow coma score <=10	3 (6.98%)	2 (11.11%)
Chronic liver disease with MELD/PELD greater than 25 and GI bleeding requiring blood cell replacement BUT blood cell replacement date NOT within past 24 hours	0 (0.00%)	1 (5.56%)
Chronic liver disease with MELD/PELD greater than 25 and GI bleeding requiring red blood cell replacement BUT amount indicated is less than 33 cc/kg for initial forms or less than 1 cc/kg for extensions (for Liver Only candidate)	1 (2.33%)	1 (5.56%)
Metabolic disease BUT candidate does not have a MELD/PELD Exception for Metabolic Disease for a MELD/PELD score of at least 30 points	1 (2.33%)	0 (0.00%)
Metabolic disease BUT candidate does not have an approved MELD/PELD Exception meeting standard criteria for metabolic disease for at least 30 days	2 (4.65%)	0 (0.00%)
Metabolic disease BUT candidate does not have urea cycle defects or organic acidemias	4 (9.30%)	2 (11.11%)
Metabolic disease BUT MELD/PELD Exception for Metabolic Disease is not at least 30 days old for MELD/PELD greater than or equal to 30 points	3 (6.98%)	0 (0.00%)
Non-metastatic Hepatoblastoma BUT no biopsy	3 (6.98%)	0 (0.00%)
Total	43 (100.00%)	18 (100.00%)

[164] Ibid.
[165] Descriptive Data Request: Status 1B Exceptions: A Data Overview, Prepared for the PELD/Status 1B Work Group, August 20, 2020
[166] Ibid.

Some Committee members and members of the PELD/Status 1B work group were concerned that removing the threshold for liver-alone candidates would cause Status 1B to be inundated with candidates. However, pediatric candidates must still have chronic liver disease and either be on a ventilator, have GI bleeding, or be on dialysis in order to automatically qualify for Status 1B.[167] In addition, **Figures 7, 8, and 9** show that, based on historical data, if the MELD/PELD threshold were removed, there would still only be a small number of candidates meeting the criteria for Status 1B with chronic liver disease.[168] The red boxes highlight candidates with MELD/PELD scores 25 or below with chronic liver disease meeting one of the other criteria included in the current policy for Status 1B.

Figure 7: Pediatric Chronic Liver Disease Removals by Ventilator Status, Lab MELD/PELD, and Removal Reason, 2018-2020



[167] The Committee is proposing the removal of the criterion for Glasgow Coma Score as part of this proposal.
[168] Descriptive Data Request: Status 1B Waitlist Removals, Prepared for PELD/1B Work Group meeting on August 19, 2021

Figure 8: Pediatric Chronic Liver Disease Removals by Dialysis, Lab MELD/PELD, and Removal Reason, 2018-2020

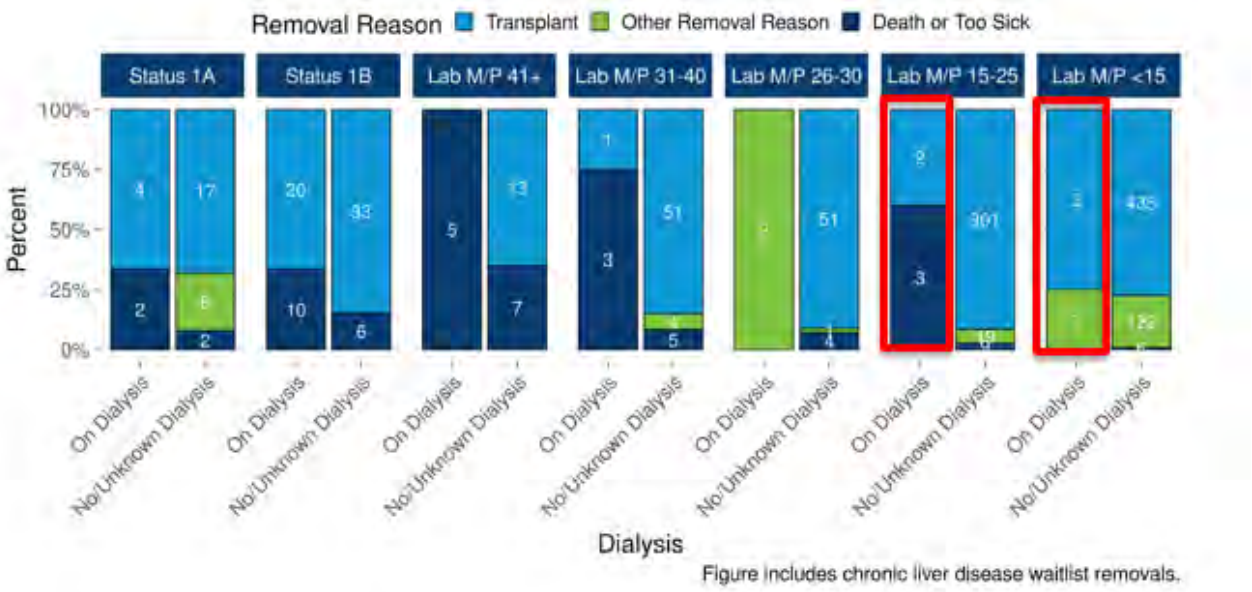
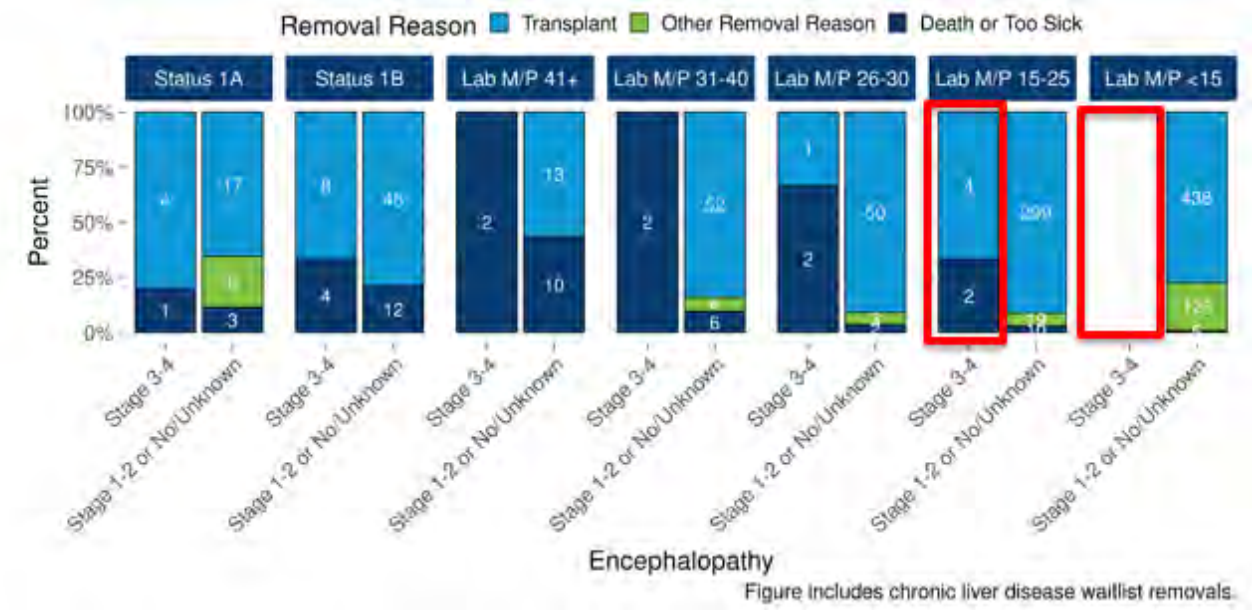


Figure 9: Pediatric Chronic Liver Disease Removals by Encephalopathy, Lab MELD/PELD, and Removal Reason, 2018-2020



Instead of removing the threshold, the Committee considered lowering the threshold to 15.[169] However, there is no clinical significance to setting the threshold at 15 and the Committee felt that candidates with chronic liver disease who are either intubated, have GI bleeding, or are on dialysis are at a high-risk of waitlist mortality regardless of their calculated MELD or PELD score.[170]

[169] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[170] Ibid.

The Committee is seeking public comment feedback on the removal of the MELD/PELD threshold for candidates with chronic liver disease.

GI Bleeding Threshold

Pediatric liver-alone candidates with chronic liver disease can automatically qualify for Status 1B if they have GI bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous 24 hours.[171] The Committee is proposing to change the GI bleeding requirement for liver-alone candidates to match an updated definition of persistent mild shock or moderate shock.

The proposed policy would change the GI bleeding threshold for liver-alone candidates to be 30 mL/kg in the previous 96 hours or 20 mL/kg in the previous 24 hours. This updated threshold matches the definition of persistent mild shock or moderate shock and will ensure that the appropriate candidates are able to access Status 1B priority.[172] The Committee is not proposing a change to the GI bleeding threshold for liver-intestine candidates.[173]
In addition, candidates with a GI bleed as the reason for their initial Status 1B upgrade must have had another bleed of at least 1 mL/kg in the past 7 days to continue to meet the extension criteria for Status 1B. The PELD/1B work group reviewed this policy and determined that no changes are needed.[174]

The Committee is seeking public comment feedback on the updated GI bleeding threshold and the GI bleeding extension criterion.

Glasgow Coma Score Criteria

Similar to the GI bleeding threshold, pediatric candidates with chronic liver disease can be listed as Status 1B if they have a Glasgow Coma Score (GCS) less than 10 within 48 hours before Status 1B assignment or extension.[175] This criterion applies to both liver-alone and liver-intestine candidates. The Committee is proposing to remove this criterion from the list of qualifying criteria for both liver-alone and liver intestine candidates as it not clinically relevant and rarely used as a means to be listed as Status 1B.[176]

The Committee is seeking public comment feedback on the removal of these criteria from Status 1B policy.

Sorting within Status 1B

Within a given classification for Status 1B, candidates are sorted based on their waiting time at Status 1B and blood type compatibility using a points-based system.[177] Waiting time points are assigned at the

[171] See *OPTN Policy 9.1.C: Pediatric Status 1B Requirements*. Available at https://optn.transplant.hrsa.gov/
[172] Alyssa A. Riley et al., "Circulating Blood Volumes: A Review of Measurement Techniques and a Meta-Analysis in Children," *ASAIO Journal* 56, no. 3 (2010): pp. 260-264, https://doi.org/10.1097/mat.0b013e3181d0c28d.
[173] Liver-intestine candidates with chronic liver disease can automatically qualify for Status 1B if they have GI bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours, as outlined in *OPTN Policy 9.1.C: Pediatric Status 1B Requirements*. Available at https://optn.transplant.hrsa.gov/
[174] See PELD/Status 1B Work Group meeting summary, October 25, 2021. Available at https://optn.transplant.hrsa.gov/
[175] See *OPTN Policy 9.1.C: Pediatric Status 1B Requirements*. Available at https://optn.transplant.hrsa.gov/
[176] In the last three years, only 21 Status 1B forms were submitted with a GCS less than 10.
[177] See *OPTN Policy 9.7: Liver Allocation Points*. Available at https://optn.transplant.hrsa.gov/

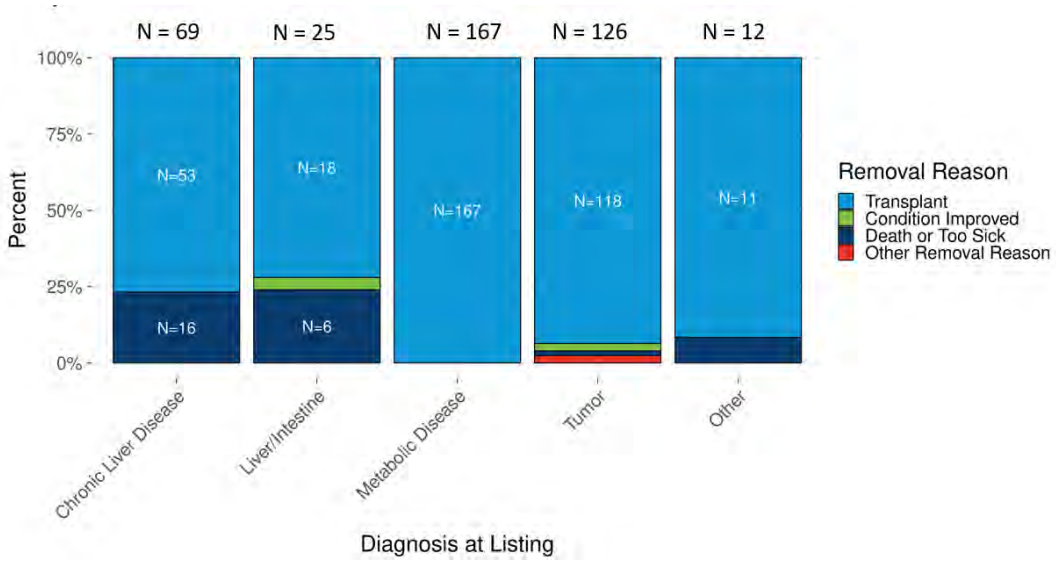
time of the match run such that the candidate with the most waiting time at Status 1B is assigned 10 points.[178] The remaining candidates are then assigned a fraction of 10 points that is proportional to the candidate's waiting time compared to other candidates in that classification.[179]

For blood type, candidates with the same blood type as the donor receive ten points, candidates that have a compatible blood type as the donor receive five points, and candidates with an incompatible blood type receive zero points.[180] Blood type O candidates who will accept a liver from a blood type A, non-A1 blood type donor will receive five points for blood type incompatible matching.[181] Candidates are then ranked within the classification based on the total number of points from highest to lowest.[182]

In addition to sorting Status 1B candidates based on waiting time and blood type, the Committee is proposing that Status 1B candidates also be sorted based on their diagnosis. The proposed policy will provide 15 points to candidates with chronic liver disease (liver-alone and liver-intestine), five points for candidates with hepatoblastoma, zero points for candidates with metabolic disease, and zero points for candidates listed as Status 1B with any other diagnosis.

Figure 10 shows Status 1B waitlist removals by diagnosis at listing and removal reason from 2018-2020. In this time period, almost all of the waitlist mortality for this population is candidates with chronic liver disease.[183] As such, the proposed diagnosis points will prioritize candidates with chronic liver disease ahead of candidates with other diagnoses.

Figure 10: Status 1B Waitlist Removal by Diagnosis at Listing and Removal Reason, 2018-2020



[178] See *OPTN Policy 9.7.A: Points for Waiting Time*. Available at https://optn.transplant.hrsa.gov/
[179] Ibid.
[180] See *OPTN Policy 9.7.B: Points Assigned by Blood Type*. Available at https://optn.transplant.hrsa.gov/
[181] Ibid.
[182] See *OPTN Policy 9.8.D: Sorting within each Classification*. Available at https://optn.transplant.hrsa.gov/

[183] Descriptive Data Request: Status 1B Waitlist Removals, Prepared for PELD/1B Work Group meeting on August 19, 2021

The Committee is proposing that candidates with chronic liver disease receive 15 points because the increased risk of waitlist mortality that exists for candidates with this diagnosis supersedes having the most waiting time or being blood type identical to the donor.[184] In addition, the points-based sorting system will still allow candidates with other diagnoses to be listed higher on a particular match run based on waiting time or blood type.[185] The Committee also agreed that candidates with tumor have increased mortality risk and therefore the updated policy language assigns five points for hepatoblastoma.[186] The data suggest that candidates with metabolic disease are at lower risk of waitlist mortality and therefore are not provided any diagnosis points.[187]

Finally, **Table 11** shows a snapshot of the Status 1B population at different points in time.[188] This table shows that there are typically few candidates with chronic liver disease compared to other diagnoses so prioritizing candidates with chronic liver disease will not create an undue burden on other Status 1B candidates.

Table 11: Snapshot of Status 1B Registrations at Various Points in Time by Diagnosis at Listing, 2018-2020

	Snapshot Date		
Diagnosis at Listing	June 30, 2018	March 31, 2019	December 31, 2020
Chronic Liver Disease	1 (3.57%)	1 (3.45%)	0 (0.00%)
Liver/Intestine	5 (17.86%)	2 (6.90%)	0 (0.00%)
Metabolic Disease	19 (67.86%)	22 (75.86%)	14 (93.33%)
Tumor	3 (10.71%)	4 (13.79%)	1 (6.67%)
Total	28 (100.00%)	29 (100.00%)	15 (100.00%)

The Committee is seeking public comment feedback on the proposed policy for sorting Status 1B candidates.

Other Considerations

In addition to the more significant changes described in the preceding sections, there are a handful of additional updates included in this proposal.

Liver-Intestine Points

Currently, candidates registered for both a liver and intestine who are under the age of 18 are provided 23 points in addition to their MELD or PELD score.[189] Liver-intestine candidates who are age 18 or older receive an additional increase in their MELD or PELD score equivalent to a 10 percentage point increase

[184] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[185] Ibid.
[186] Ibid.
[187] Descriptive Data Request: Status 1B Waitlist Removals, Prepared for PELD/1B Work Group meeting on August 19, 2021
[188] Ibid.
[189] See *OPTN Policy 9.1.F: Liver-Intestine Candidates*. Available at https://optn.transplant.hrsa.gov/

in risk of 3-month mortality.[190] These liver-intestine points are assigned based on a candidate's current age, meaning that on the day a candidate turns 18, he or she will switch from the 23 additional points to the 10% increase in mortality risk.

The use of a candidate's current age is different than how age is used elsewhere in liver allocation. For the purposes of liver and liver-intestine allocation, a candidates is provided pediatric priority as long as he or she is registered before turning 18.[191] Similarly, adolescent male candidates will receive the 1.33 female points in MELD 3.0 as long as they are registered before turning 18.

To create consistency across the liver allocation system, the Committee is proposing that liver-intestine points be based on a candidate's age at the time of liver registration, instead of current age. This means that any candidate listed for a liver and intestine who was registered for a liver before turning 18 will receive the 23 additional points and keep those points even after turning 18 for as long as they remain registered on the liver waitlist.[192,193]

The Committee is seeking public comment feedback on this proposed change to liver-intestine points.

Pediatric National Liver Review Board (NLRB) Guidance

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

Under the NLRB, candidates who meet the criteria outlined in OPTN policy for one of the nine standardized diagnoses are eligible to have their exception automatically approved. In addition, each of the three specialty review boards (Pediatric, Adult - Hepatocellular Carcinoma (HCC), and Adult - Other Diagnosis) has an associated guidance document.[194] The guidance documents contain information for review board members and transplant programs on diagnoses and clinical situations not included as one of the standardized diagnoses in policy. They provide recommendations on which candidates should be considered for a MELD or PELD exception and are based on published research, clinical guidelines, medical experience, and data. The documents are intended to help ensure consistent and equitable review of exception cases and are not OPTN policy.

The Committee is recommending two changes to the guidance document for the pediatric NLRB to align with changes included in this proposal.

First, the current guidance recommends that candidates be considered for a Status 1B exception if they have chronic liver disease and do not have a MELD or PELD score greater than 25. With the removal of the MELD or PELD 25 threshold, this guidance is no longer necessary and should be removed.

[190] Ibid.
[191] See *OPTN Policy 9.1: Status and Score Assignments*. Available at https://optn.transplant.hrsa.gov/
[192] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, December 3, 2021. Available at https://optn.transplant.hrsa.gov/
[193] Liver-intestine candidates registered before turning 18 who are older than 18 at the time of implementation will be provided the 23 liver-intestine points instead of the 10% mortality increase at the time of implementation.

[194] All NLRB guidance documents are available at https://optn.transplant.hrsa.gov/.

Similarly, there is guidance that notes the current PELD score does not adequately capture all candidates with growth failure using height and weight z-scores. The proposed guidance reflects the fact that PELD Cr does a better job incorporating growth failure via height and weight z-scores.

The Committee is seeking public comment feedback on the proposed changed to pediatric NLRB guidance.

NOTA and Final Rule Analysis

The Committee submits the following proposal for the Board consideration under the authority of the National Organ Transplantation Act, which states, "The Organ Procurement and Transplantation Network shall…establish…medical criteria for allocating organs and provide to members of the public an opportunity to comment with respect to such criteria…"[195], and under the authority of the OPTN Final Rule, which states "The OPTN Board of Directors shall be responsible for developing…policies for the equitable allocation for cadaveric organs."[196] The Final Rule requires that when developing policies for the equitable allocation of cadaveric organs, such policies must be developed "in accordance with §121.8," which requires that allocation policies "(1) Shall be based on sound medical judgment; (2) Shall seek to achieve the best use of donated organs; (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(d) and (e); (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate; (5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;…(8) Shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section."[197] This proposal:

- **Is based on sound medical judgment[198]** because it is an evidenced-based change relying on the following evidence:
    - OPTN Data, SRTR analyses and peer-review literature showing that MELD 3.0 and PELD Cr better predict risk of waitlist mortality and rank liver transplant candidates based on medical urgency for transplant
    - OPTN data and medical judgment that Status 1B candidates with chronic liver disease are at higher risk of mortality, and that the MELD/PELD 25 threshold for Status 1B candidates is not clinically relevant.
    - Literature showing the GI bleeding threshold should be updated to align with clinically-accepted definitions
- **Seeks to achieve the best use of donated organs[199] by** ensuring organs are allocated and transplanted according to medical urgency. This proposal will:
    - Reduce waitlist mortality as shown by MELD 3.0 LSAM modeling, which indicates the most medically urgent patients will be transplanted and less likely to die while waiting for a transplant
    - Ensure that the most urgent candidates are prioritized by updating Status 1A/1B policy and improving ability of MELD and PELD to predict risk of mortality.

[195] 42 USC §274(b)(2)(B).
[196] 42 C.F.R. §121.4(a)(1)
[197] 42 CFR §121.8(a).
[198] 42 CFR §121.8(a)(1).
[199] 42 CFR §121.8(a)(2).

- **Is designed to…promote patient access to transplantation[200] by** giving similarly situated candidates equitable opportunities to receive an organ offer.
    - Reduce disparity in liver allocation between male and female candidates by equalizing transplant rates between male and female candidates as shown by MELD 3.0 LSAM modelling
    - Adjusts the PELD score to align risk of mortality with adults at a given MELD score
    - Prioritize Status 1B candidates at highest risk of mortality
    - Ensure appropriate candidates are able to access Status 1A and Status 1B priority
- **Is not based on the candidate's place of residence or place of listing**

This proposal also preserves the ability of a transplant program to decline an offer or not use the organ for a potential recipient,[201] and it is specific to an organ type, in this case livers and intestines.[202]

Although the proposal outlined in this briefing paper addresses certain aspects of the Final Rule listed above, the Committee does not expect impacts on the following aspects of the Final Rule:

- Is designed to avoid wasting organs
- Is designed to avoid futile transplants
- Promotes the efficient management of organ placement

The OPTN issues the *Guidance to Liver Transplant Programs and the National Liver Review Board for Pediatric MELD/PELD Exception Review* for the operation of the OPTN.[203] This guidance will support the operation of the NLRB by assisting the reviewers with evaluating exception requests. The OPTN Final Rule requires the Board to establish performance goals for allocation policies, including "reducing inter-transplant program variance" in performance indicators.[204] The changes to these guidance documents will assist in reducing inter-transplant program variance in the types of cases reviewed and approved by the NLRB by facilitating more consistent review of exception cases.

The Committee also submits this proposal under the authority of NOTA, which requires the OPTN to, "recognize the differences in health and in organ transplantation issues between children and adults throughout the system and adopt criteria, polices, and procedures that address the unique health care needs of children."[205] This proposal was developed to account for the unique needs of pediatric candidates by providing them distinct, evidence-based waitlist mortality scores, priority statuses, and NLRB guidance.

In addition, the Committee submits this proposal under the authority of NOTA, which requires the OPTN to "collect, analyze, and publish data concerning organ donation and transplants,"[206] and the OPTN Final Rule, which requires the OPTN to "(i) Maintain and operate an automated system for managing information about transplant candidates, transplant recipients, and organ donors, including a computerized list of individuals waiting for transplants; (ii) Maintain records of all transplant candidates, all organ donors and all transplant recipients; [and] (iii) Operate, maintain, receive, publish, and transmit

[200] Id.
[201] 42 CFR §121.8(a)(3).
[202] 42 CFR §121.8(a)(4).
[203] 2019 OPTN Contract Task 3.2.4: Development, revision, maintenance, of OPTN Bylaws, policies, standards and guidelines for the operation of the OPTN.
[204] 42 C.F.R. §121.8(b)(4)
[205] 42 U.S.C. §274(b)(2)(M)
[206] 42 U.S.C. §274(b)(2)(I)

such records and information electronically…" This proposal collects additional data on transplant candidates in order to appropriately prioritize them.

Implementation Considerations

Member and OPTN Operations

Operations affecting Histocompatibility Laboratories

This proposal will have no operational impact on histocompatibility laboratories

Operations affecting Organ Procurement Organizations

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

Operations affecting Transplant Hospitals

Transplant hospitals will need to educate staff and candidates about the changes to the MELD and PELD scores and Status 1A and 1B policy. MELD and PELD scores for candidates will change at the time of implementation. Transplant programs will need to inform their candidates of any potential changes in their MELD or PELD score as a result of the new policy, especially if a candidate's new score will be lower. Similarly, the laboratory update schedule could change based on their new MELD or PELD score at the time of implementation. The OPTN will consider transition procedures to ensure transplant programs have sufficient time to update any required lab values, but transplant programs will need to be proactive in submitting the required laboratory values.

Transplant programs will need to submit albumin values for all adult MELD candidates prior to implementation. They will also have the opportunity to provide a candidate's current sex if it does not match the candidate's birth sex.

In addition, transplant programs are not currently required to submit creatinine values for candidates age 10 and under. With the incorporation of creatinine in PELD Cr, transplant candidates will need to submit creatinine values for all PELD candidates.

At the time of implementation, no Status 1A or Status 1B candidates will lose their priority status. However, these candidates will need to meet the updated requirements in policy to continue at the respective status.

Operations affecting the OPTN

The OPTN will implement the proposed changes to policy in UNet^{SM}. There will be limited changes to data collection related to albumin, creatinine, and current sex. The OPTN plans to distribute education materials and communications related to the changes in advance of implementation. The OPTN will update the MELD and PELD calculators on the OPTN website.

The OPTN will consider ways to ensure a smooth transition prior to implementation of the new MELD and PELD scores, such as providing transplant programs with tools to understand how specific candidate scores may change at the time of implementation.

Potential Impact on Select Patient Populations

This proposal has the potential to impact select patient populations. First, an intended impact of the proposed changes to the MELD score is to reduce the sex-based disparity in the current allocation system. As the LSAM modelling showed, this could entail not only an increase in the transplant rate for female candidates but also a reduction in transplant rates for male candidates. This is an intended impact of this proposal, and despite the potential negative impact on male candidates, the Committee does not recommend any specific transition procedures as it does not recommend perpetuating the existing relative advantage such candidates have otherwise experienced.[207]

In addition, some candidates will have lower MELD or PELD scores under the new calculations. The new scores are more accurate in predicting risk of mortality, and as such, any decrease in a candidate's MELD or PELD score is likely a more accurate representation of their urgency for transplant. The Committee therefore does not recommend any specific transition procedures for this population.

Candidates with an exception score may also be impacted upon implementation of the new MELD and PELD scores. MMaT and MPaT are calculated using a historic cohort, and as such, it will take time for MMaT and MPaT to calibrate to MELD 3.0 and PELD Cr. In the meantime, candidates with an exception score may see slightly reduced access to transplant, although this impact remains hypothetical. The Committee does not recommend any transition procedures for this population as the Committee does not anticipate large changes in MMaT or MPaT that would drastically and immediately impact exception candidates' access to transplant.

Due to the prioritization of Status 1B candidates with chronic liver disease, Status 1B candidates with other diagnoses may see slightly reduced access to transplant, although they will still have Status 1B priority and be listed ahead of MELD and PELD candidates. This is an intended impact of the proposal to more appropriately stratify such candidates by medical urgency, and the Committee therefore does not recommend any transition procedures for this population. In addition, the proposed changes to the MELD/PELD threshold and GI bleeding threshold in Status 1B policy should increase the number of candidates meeting Status 1B criteria. Candidates who are listed as Status 1B with chronic liver disease with a GCS score less than 10 will not lose their Status 1B priority upon implementation but will need to meet the updated criteria upon their first extension after implementation.

Projected Fiscal Impact

This proposal is projected to have a fiscal impact on the OPTN and minimal fiscal impact on organ procurement organizations, transplant hospitals, and histocompatibility laboratories. This proposal does not significantly alter data collection and does not require new tests or requirements. Members will need to be aware of the new MELD and PELD score calculations and how the new scores will affect their candidates. There could be a long-term cost savings if this updated scores lead to better outcomes. Long-term, this proposal could also increase volume, which would have a positive fiscal impact.

[207] 42 C.F.R. § 121.8(d). The Final Rule requires the OPTN to "consider whether to adopt transition procedures that would treat people on the waiting list and awaiting transplantation prior to the adoption or effective date of the revised policies no less favorably than they would have been treated under the previous policies" whenever organ allocation policies are revised.

Projected Impact on Histocompatibility Laboratories

No impact.

Projected Impact on Organ Procurement Organizations

Minimal impact.

Projected Impact on Transplant Hospitals

Minimal impact.

Projected Impact on the OPTN

The proposed changes will need to be implemented in UNet[SM]. Implementation of the proposed policy will require detailed member communication and education to instruct transplant programs about the nature of the changes. A thorough patient education plan will also be needed to ensure that transplant candidates and their caregivers understand the rationale for the changes and the specific aspects of the new policy as it affects their prioritization. Tactics include creation and ongoing maintenance of a resource toolkit for members, as well as appropriate revisions of general patient education materials and development of other patient resources. Site survey documentation and site survey practices will need to be updated. The proposal will be continuously monitored after implementation.

Post-implementation Monitoring

Member Compliance

The Final Rule requires that allocation policies "include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program."[208]

At transplant hospitals, site surveyors will continue to review a sample of medical records, and any material incorporated into the medical record by reference, to verify that data reported in UNet℠ are consistent with source documentation, including:

- Qualifying criteria reported on the pediatric status 1A and 1B justification forms
- Data that affects a candidate's MELD score, including new variables:
    - Albumin
    - Birth sex (or current sex, if applicable)
- Data that affects a candidate's PELD score, including new variables:
    - Creatinine
    - Two or more dialysis treatments within the 7 days before the creatinine test, if applicable

[208] 42 CFR §121.8(a)(7).

- 24 hours of continuous veno-venous hemodialysis (CVVHD) within the 7 days before the creatinine test, if applicable

Site surveyors will also continue to verify that lab results reported in UNet to update a candidate's MELD or PELD score were the most recent results available at the time of entry.

Policy Evaluation

The Final Rule requires that allocation policies "be reviewed periodically and revised as appropriate."[209]

The following policy changes will be monitored at 3 months, 6 months, 12 months, 18 months, and 2 years post-implementation, as requested by the Committee.

To monitor if MELD 3.0 reduced the disparity in waitlist removal rates for death or too sick to transplant and liver transplant rates between males and females, a pre- and post-policy implementation analysis of liver candidates and transplant recipients (age 12 years and older) will include:

- Changes in the number and percent of liver transplants, overall and by recipient sex
- Changes in the median allocation Model for End-Stage Liver Disease (MELD) score at transplant, overall and by recipient sex
- Changes in the number of liver candidates removed from the waitlist by reported removal reason, overall and by candidate sex
- Changes in waitlist removal rates for death or too sick to transplant, overall and by recipient sex (as sample size allows)
- Changes in transplant rates, overall and by recipient sex (as sample size allows)
- The above metrics will be stratified by age group (12-17 years vs. 18+ years), as appropriate

To monitor if PELD Cr reduced pediatric waitlist mortality, a pre- and post-policy implementation analysis of liver candidates and transplant recipients (age 0-11 years) will include:

- Changes in the number and percent of liver transplants, overall and by age group
- Changes in the median allocation Pediatric End-Stage Liver Disease (PELD) score at transplant, overall and by age group
- Changes in the number of liver candidates removed from the waitlist by reported removal reason, overall and by candidate age group
- Changes in waitlist removal rates for death or too sick to transplant, overall and by age group (as sample size allows)
- Changes in transplant rates, overall and by age group (as sample size allows)

To monitor if the Status 1A and 1B policy changes reduced pediatric waitlist mortality, a pre- and post-policy implementation analysis will include:

- Changes in the number of pediatric Status 1A and 1B transplants, overall and by diagnosis
- Changes in the number of pediatric liver candidates with Status 1A and 1B removed from the waitlist by reported removal reason, overall and by diagnosis
- Changes in the number of pediatric Status 1B cases that did not meet standard criteria by case outcome and turndown reason

[209] 42 CFR §121.8(a)(6).

Conclusion

This proposal includes a number of important changes to the liver allocation system including: improving the MELD and PELD score and updating policy for Status 1A and Status 1B. The new MELD score, or MELD 3.0, includes the addition of two new variables (sex and albumin), updates the coefficients for existing variables (sodium, bilirubin, creatinine, and international normalized ratio (INR)), introduces interaction terms between bilirubin and sodium and between albumin and creatinine, and caps creatinine at 3.0 mg/dL. The updated PELD score, or PELD Creatinine (Cr), includes the addition of a creatinine variable, makes age and growth failure continuous instead of categorical variables, updates the parameters for variables already included in the score (albumin, bilirubin, INR), and accounts for age-adjusted mortality for pediatric candidates.

Finally, the proposal includes a number of changes to the policy for pediatric Status 1A and 1B candidates. For Status 1A, it creates a more objective and clinically-relevant definition of hepatic encephalopathy. For Status 1B, the proposal seeks to update the criteria for a pediatric candidate to qualify for Status 1B priority and better sort candidates within Status 1B based on their diagnosis and risk of mortality.

Together, these changes will make the liver allocation system more equitable and efficient.

Policy Language

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

1.2 Definitions

The definitions that follow are used to define terms specific to the OPTN Policies.

M

Model for End Stage Liver Disease (MELD)
The scoring system used to measure illness severity in the allocation of livers to adults and adolescents.

P

Pediatric End Stage Liver Disease (PELD)
The scoring system used to measure illness severity in the allocation of livers to pediatric candidates under the age of 12.

9.1.B Pediatric Status 1A Requirements

To assign a candidate pediatric status 1A, the candidate's transplant hospital must submit a *Liver Status 1A Justification Form* to the OPTN. A candidate is not assigned pediatric status 1A until this form is submitted.

The candidate's transplant program may assign the candidate pediatric status 1A if *all* the following conditions are met:

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.
2. The candidate has at least *one* of the following conditions:

    a. Fulminant liver failure~~, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. In addition~~ and the candidate:

i. Must not have a pre-existing diagnosis of liver disease. For purposes of this section, any diagnoses of liver disease that occurred prior to a subsequent liver transplant do not constitute pre-existing liver disease.

ii. Must meet at least *one* of the following conditions:

1. Is ventilator dependent
2. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
3. Has an international normalized ratio (INR) greater than or equal to 1.5 and less than 2.0 and a diagnosis of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease
4. Has an ~~international normalized ratio (~~INR~~)~~ greater than or equal to 2.0

a. Diagnosis of primary non-function of a transplanted liver within 7 days of transplant, evidenced by at least *two* of the following:

i. Alanine aminotransferase (ALT) greater than or equal to 2,000 U/L
ii. INR greater than or equal to 2.5
iii. Total bilirubin greater than or equal to 10 mg/dL
iv. Acidosis, defined as *one* of the following:

- Arterial pH less than or equal to 7.30
- Venous pH less than or equal to 7.25
- Lactate greater than or equal to 4 mmol/L

All laboratory results reported for any tests required for the primary non-function of a transplanted liver diagnosis above must be from the same blood draw taken between 24 hours and 7 days after the transplant.

b. Diagnosis of hepatic artery thrombosis (HAT) in a transplanted liver within 14 days of transplant

c. Acute decompensated Wilson's disease

9.1.C Pediatric Status 1B Requirements

To assign a candidate pediatric status 1B, the candidate's transplant hospital must submit a *Liver Status 1B Justification Form* to the OPTN. A candidate is not registered as status 1B until this form is submitted.

The candidate's transplant program may assign the candidate pediatric status 1B if *all* the following conditions are met:

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.

2. The candidate has *one* of the following conditions:

   a. The candidate has a biopsy-proven hepatoblastoma without evidence of metastatic disease.

   b. The candidate has an organic acidemia or urea cycle defect and an approved MELD or PELD exception meeting standard criteria for metabolic disease for at least 30 days.

   c. Chronic liver disease ~~with a calculated MELD or PELD greater than 25~~ and ~~has~~ meets at least *one* of the following criteria due to complications of chronic liver disease:
      i. Is on a mechanical ventilator
      ii. Has gastrointestinal bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous ~~24~~ 96 hours or 20 ml/kg in the previous 24 hours
      iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
      ~~iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.~~

   d. Chronic liver disease and is a combined liver-intestine candidate ~~with an adjusted MELD or PELD score greater than 25 according to *Policy 9.1.F: Liver-Intestine Candidates*~~ and ~~has~~ meets at least *one* of the following criteria due to complications of chronic liver disease:
      i. Is on a mechanical ventilator
      ii. Has gastrointestinal bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours
      iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
      ~~iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.~~

9.1.D MELD Score

~~Candidates who are at least 12 years old receive an initial $MELD_{(i)}$ score equal to: *0.957 x Loge(creatinine mg/dL) + 0. 378 x Log_e(bilirubin mg/dL) + 1.120 x Loge (INR) + 0.643*~~

~~Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score.~~

~~The following candidates will receive a creatinine value of 4.0 mg/dL:~~

- ~~Candidates with a creatinine value greater than 4.0 mg/dL~~
- ~~Candidates who received two or more dialysis treatments within the prior 7 days~~
- ~~Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days~~

~~The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.~~

~~For candidates with an initial MELD score greater than 11, the MELD score is then re-calculated as follows:~~

~~MELD = $MELD_{(i)}$ + 1.32*(137-Na) – [0.033*$MELD_{(i)}$*(137-Na)]~~

~~Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.~~

Candidates who are at least 18 years old at the time of registration receive a MELD score equal to:

MELD = 1.33 (if female) + [4.56 x $\log_e$(bilirubin)] + [0.82 x (137-Sodium)] – [0.24 x (137-Sodium) x $\log_e$(bilirubin)] + [9.09 x $\log_e$(INR)] + [11.14 x $\log_e$(creatinine)] + [1.85 x (3.5-albumin)] – [1.83 x (3.5 – albumin) x $\log_e$(creatinine)] + 6

Candidates who are currently at least 12 years old and were less than 18 years old at the time of registration receive a MELD score equal to:

MELD = [4.56 x $\log_e$(bilirubin)] + [0.82 x (137-Sodium)] – [0.24 x (137-Sodium) x $\log_e$(bilirubin)] + [9.09 x $\log_e$(INR)] + [11.14 x $\log_e$(creatinine)] + [1.85 x (3.5-albumin)] – [1.83 x (3.5 – albumin) x $\log_e$(creatinine)] + 7.33

Bilirubin, INR, and creatinine values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score.

The following candidates will receive a creatinine value of 3.0 mg/dL:

- Candidates with a creatinine value greater than 3.0 mg/dL
- Candidates who received two or more dialysis treatments within the 7 days prior to the serum creatinine test
- Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the 7 days prior to the serum creatinine test

Sodium values less than 125 mmol/L will be set to 125 mmol/L, and values greater than 137 mmol/L will be set to 137 mmol/L.

Albumin values less than 1.5 g/dL will be set to 1.5 g/dL, and values greater than 3.5 g/dL will be set to 3.5 g/dL.

The minimum MELD score is 6. The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the nearest whole number.

9.1.E PELD Score

Candidates who are less than 12 years old receive a PELD score equal to:

~~*0.436 (Age (<1 YR.)) – 0.687 x Log$_e$ (albumin g/dL) + 0.480 x Log$_e$ (total bilirubin mg/dL) + 1.857 x Log$_e$ (INR) +0.667 (Growth failure (<- 2 Std. Deviations present))*~~

~~The PELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.~~

~~Scores for candidates registered for liver transplantation before the candidate's first birthday continue to include the value of 0.436 until the candidate is 24 months old.~~

~~Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's PELD score.~~

~~A candidate has growth failure if the candidate is more than two standard deviations below the candidate's expected growth based on age and gender using the most recent Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics pediatric clinical growth chart.~~

Table 9-1: PELD Score Calculation

	If the value is:	Then the value's contribution to PELD is:
Candidate Age (fractional calendar year)	< 1	-0.1967 * 1
	1 to 5.5	-0.1967 * age at the time of most recent lab reported for use in the PELD score (fractional calendar year)
	> 5.5 and < 12	-0.1967 * 5.5
Albumin (g/dL)	1 to 1.9	-1.842 * ln(albumin)
	> 1.9	-1.842 * ln(1.9)
Total bilirubin (mg/dL)	1 to 4	0.7854 * ln(bilirubin) + 0.3434 * ln(4)
	> 4 to 40	0.7854 * ln(4) + 0.3434 * ln(bilirubin)
	> 40	0.7854 * ln(4) + 0.3434 * ln(40)
INR	1 to 2	1.981 * ln(INR) + 0.7298 * ln(2)
	> 2 to 10	1.981 * ln(2) + 0.7298 * ln(INR)
	> 10	1.981 * ln(2) + 0.7298 * ln(10)
Minimum of CDC height or weight Z-score	< -5.0	-0.1807 * (-5)
	-5.0 to -2.1	-0.1807 * (minimum z-score)
	> -2.1	-0.1807 * (-2.1)
Creatinine (mg/dL)	< 0.2	1.453 * ln(0.2)
	0.2 to 1.3	1.453 * ln(creatinine)
	> 1.3	1.453 * ln(1.3)

A candidate's PELD score will then be calculated as follows:

PELD = (sum of all terms as outlined in **Table 9-1: PELD Score Calculation** + 1.5287) x 10 + 2.82

The minimum of CDC height or weight Z-score utilizes the LMS method as used by the CDC and is based on the 2000 CDC Growth Charts for the United States. The calculation uses the candidate's birth sex, most recent values submitted for height and weight, and the candidate's age in months at the time of the most recent submission of height or weight values.

Albumin, Bilirubin, and INR values less than 1.0 will be set to 1.0 when calculating a candidate's PELD score

The following candidates will receive a creatinine value of 1.3 mg/dL:

- Candidates with a creatinine value greater than 1.3 mg/dL
- Candidates who received two or more dialysis treatments within the 7 days prior to the serum creatinine test
- Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the 7 days prior to the serum creatinine test

The minimum PELD score is 6. The PELD score derived from this calculation will be rounded to the nearest whole number.

9.1.F Liver-Intestine Candidates

~~Adult liver candidates who are also registered and active on the waiting list for an intestine transplant at that transplant hospital~~ Liver candidates who are registered on the waiting list after turning 18 years old and are also registered and active on the waiting list for an intestine transplant at that transplant hospital will automatically receive an additional increase in their MELD or PELD score equivalent to a 10 percentage point increase in risk of 3-month mortality. Liver candidates who are registered on the waiting list before turning 18 years old and are also registered and active on the waiting list for an intestine transplant at that transplant hospital ~~Candidates less than 18 years old~~ will receive 23 additional points to their calculated MELD or PELD score ~~instead of the 10 percentage point increase~~. The transplant hospital must document in the candidate's medical record the medical justification for the combined liver-intestine transplant and that the transplant was completed.

9.2 Status and Laboratory Values Update Schedule

The OPTN will notify the transplant hospital within 2 days of the deadline for recertification when a candidate's laboratory values need to be updated. Transplant hospitals must recertify a candidate's values according to *Table 9-1*.

When reporting laboratory values to the OPTN, transplant hospitals must submit the most recent results including the dates of the laboratory tests. In order to change a MELD or PELD score voluntarily, all laboratory values must be obtained within the same 2 day period.

Table 9-1: Liver Status Update Schedule

If the candidate is:	The new laboratory values must be reported every:	And when reported, the new laboratory values must be no older than :
Status 1A or 1B	7 days	2 days
MELD 25 or greater (ages 18 or older)	7 days	2 days
MELD/PELD 25 or greater (less than 18 years old)	14 days	3 days
MELD/PELD 19 to 24	30 days	7 days
MELD/PELD 11 to 18	90 days	14 days
MELD/PELD 10 or less	365 days	30 days

Status 1B candidates have these further requirements for certification:

- Candidates with a gastrointestinal bleed as the reason for the initial status 1B upgrade criteria must have had another bleed in the past 7 days immediately before the upgrade in order to recertify as status 1B.
- Candidates indicating a metabolic disease or a hepatoblastoma require recertification every 90 days with lab values no older than 14 days.

If a candidate is not recertified by the deadline according to *Table 9-1*, the candidate will be re-assigned to their previous lower MELD or PELD score. The candidate may remain at that previous lower score for the period allowed based on the recertification schedule for the previous lower score, minus the time spent in the uncertified score.

If the candidate remains uncertified past the recertification due date for the previous lower score, the candidate will be assigned a MELD or PELD score of 6. If a candidate has no previous lower MELD or PELD score, and is not recertified according to the schedule, the candidate will be reassigned to a MELD or PELD score of 6~~, or will remain at the uncertified PELD score if it is less than 6~~.

9.7 Liver Allocation Points

Points are used for sorting liver candidates according to *Policy 9.8.D: Sorting Within Each Classification*.

9.7.A Points for Waiting Time

Points are assigned so that the status 1A or 1B candidate with the longest waiting time receives the most points as follows:

- 10 points for the candidate with the greatest total status 1A or status 1B waiting time within each classification
- A fraction of 10 points divided up among the remaining status 1A or status 1B candidates within each classification, based on the potential recipient's total waiting time

9.7.B Points Assigned by Blood Type

For status 1A and 1B transplant candidates, those with the same blood type as the deceased liver donor will receive 10 points. Candidates with compatible but not identical blood types will receive 5 points, and candidates with incompatible types will receive 0 points. Blood type O candidates who will accept a liver from a blood type A, non-A1 blood type donor will receive 5 points for blood type incompatible matching.

9.7.C Points Assigned by Diagnosis

Status 1B candidates will be assigned points based on diagnosis as follows:

- If the candidate's diagnosis is chronic liver disease, the candidate will receive 15 points. If the candidate's diagnosis is hepatoblastoma, the candidate will receive 5 points.
- If the candidate's diagnosis is an organic academia or urea cycle defect, the candidate will receive 0 points.
- If the candidate has any other diagnosis, the candidate will receive 0 points.

9.8.D Sorting Within Each Classification

Within each status 1A allocation classification, candidates are sorted in the following order:

1. ~~Total~~ The sum of waiting time and blood type compatibility points ~~(highest to lowest)~~, according to *Policy 9.7: Liver Allocation Points* (highest to lowest)
2. Total waiting time at status 1A (highest to lowest)

Within each status 1B allocation classification, candidates are sorted in the following order:

1. ~~Total~~ The sum of waiting time, ~~and~~ blood type compatibility ~~points~~, and diagnosis points ~~(highest to lowest),~~ according to *Policy 9.7: Liver Allocation Points* (highest to lowest)
2. Total waiting time at status 1B (highest to lowest)

Within each MELD or PELD score allocation classification, all candidates are sorted in the following order:

1. Allocation MELD or PELD score (highest to lowest)

2. Blood type compatibility (identical, compatible, then incompatible)
3. Age at time of registration on the liver waitlist (less than 18 years old followed by 18 years or older)
4. Allocation MELD or PELD score type (calculated, including liver-intestine points, then exception)
5. Allocation MELD or PELD score waiting time (highest to lowest)
6. Total waiting time (highest to lowest)

Guidance

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

Background

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

The MELD and PELD scores are intended to reflect the candidate's disease severity, based on 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 for a higher score. A candidate that meets the criteria for one of the diagnoses in policy is approved for a standardized MELD or PELD exception.[210] If the candidate does not meet criteria for standardized exception, the Review Board considers the request. Pediatric candidates with approved exceptions who turn 18 while still waiting with an approved exception continue to be eligible to receive pediatric exceptions unless or until the candidate is removed from the waiting list.[211]

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

This guidance replaces any independent criteria that OPTN regions use to request and approve exceptions, commonly referred to as "regional agreements." Review Board members, transplant centers, and the Committee should consult this resource when considering status or MELD/PELD exception requests for pediatric candidates registered before turning 18 years old ~~less than 18 years old~~. Any guidance contained within this document that differs from the guidance offered for adult MELD exceptions is intentional, and is based on peer-review literature and/or clinical practice.

Status 1B

Status 1B - Chronic liver disease

Generally candidates that do not meet criteria in *Policy 9.1.C: Pediatric Status 1B Requirements* should not receive a status 1B exception~~. Candidates that meet criteria in *Policy 9.1.C.2.c* or *9.1.C.2.d* but~~

[210] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[211] Policy 9.1: Status and Score Exceptions, Organ Procurement and Transplantation Network Policies.

~~without a PELD score of at least 25 may be considered for status 1B exception if the candidate is critically ill and admitted in the Intensive Care Unit (ICU).~~ Candidates without renal replacement therapy may be considered for a status 1B exception if they meet all other criteria in policy and require a liver support device (such as Molecular Adsorbent Recirculating System (MARS), albumin dialysis, plasmapheresis).

Chronic Liver Disease[212,213,214,215,216,217,218]

Growth Failure or Nutritional Insufficiency

~~It is now known that the PELD score, as currently calculated, does not accurately capture growth failure for all children.~~ The PELD-Cr score improves accuracy of capturing growth failure, but still may not entirely capture growth failure as it is accounts only for height and weight-z-scores, and does not correct the weight for ascites or organomegaly. Exceptions should be considered for candidates who meet any of the following criteria:

- Growth parameters[219]
  - <5th percentile for: height, weight (may adjust to estimated dry weight if ascites)[220,221]
  - Z-score (~~weight, height, or~~ BMI/weight-for-length) less than 2 standard deviations below the mean for age and gender
- Anthropometrics
  - Triceps skin fold thickness or mid-arm muscle circumference < 5th percentile for age and gender [222]
- Failure of nasoenteric tube feedings as evidenced by failure to demonstrate improvement in growth failure in the previous month based on either weight or anthropometrics[223]
- Requirement for TPN nutrition to allow for growth or to maintain euglycemia

#

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Appendix

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SRTR-Derived MELD Scores[224]

MELD Na

Variable	Interval	Beta	Constant
log(Bilirubin)	All values	0.451	0.000
log(INR)	All values	2.559	0.000
log(Creatinine)	Less than 1	1.814	0.000
log(Creatinine)	Greater than 1	0.524	1.814
Sodium - 137	Less than -5	-0.168	0.000
Sodium - 137	Greater than -5	-0.143	0.842
Sodium - 137 x log(Bilirubin)	Less than -5	-0.001	0.000
Sodium - 137 x log(Bilirubin)	Greater than -5	0.070	0.007
Sodium - 137 x log(INR)	Less than -5	0.120	0.000
Sodium - 137 x log(INR)	Greater than -5	-0.030	-0.601
Normalizing shift	-	-10.000	-

MELD Na + Sex

Variable	Interval	Beta	Constant
Sex	F	0.241	0.000
log(Bilirubin)	All values	0.441	0.000
log(INR)	All values	2.584	0.000
log(Creatinine)	Less than 1	1.826	0.000
log(Creatinine)	Greater than 1	0.478	1.826
Sodium - 137	Less than -5	-0.169	0.000
Sodium - 137	Greater than -5	-0.143	0.844
Sodium - 137 x log(Bilirubin)	Less than -5	-0.002	0.000
Sodium - 137 x log(Bilirubin)	Greater than -5	0.071	0.011
Sodium - 137 x log(INR)	Less than -5	0.123	0.000
Sodium - 137 x log(INR)	Greater than -5	-0.034	-0.613
Normalizing shift	-	-11.000	-

[224] Redeveloping MELD-NA: The effect of time-varying covariates and correcting for disparities across sex; Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, August 6, 2021

MELD Na + Height

Variable	Interval	Beta	Constant
Height	Less than 160	-0.011	0.000
Height	Between 160 and 172	-0.026	-1.808
Height	Greater than 172	-0.002	-2.124
log(Bilirubin)	All values	0.668	0.000
log(INR)	All values	1.699	0.000
log(Creatinine)	Less than 1	1.849	0.000
log(Creatinine)	Greater than 1	0.472	1.849
Sodium - 137	Less than -5	-0.069	0.000
Sodium - 137	Greater than -5	-0.037	0.347
Normalizing shift	-	13.000	-

MELD Na + Albumin

Variable	Interval	Beta	Constant
Albumin - 3.5	All values	-0.335	0.000
Albumin - 3.5 x log(Creatinine)	All values	0.223	0.000
log(Bilirubin)	All values	0.667	0.000
log(INR)	All values	1.692	0.000
log(Creatinine)	Less than 1	2.041	0.000
log(Creatinine)	Greater than 1	0.566	2.041
Sodium - 137	Less than -5	-0.070	0.000
Sodium - 137	Greater than -5	-0.026	0.352
Normalizing shift	-	-10.000	-

MELD Na + Albumin + Sex

Variable	Interval	Beta	Constant
Albumin - 3.5	Less than -1	-0.746	0.000
Albumin - 3.5	Greater than -1	-0.126	0.746
Albumin - 3.5 x log(Creatinine)	Less than -1	0.430	0.000
Albumin - 3.5 x log(Creatinine)	Greater than -1	0.068	-0.430
Sex	F	0.244	0.000
log(Bilirubin)	All values	0.619	0.000
log(INR)	All values	1.717	0.000
log(Creatinine)	Less than 1	2.318	0.000
log(Creatinine)	Greater than 1	0.822	2.318
Sodium - 137	Less than -5	-0.132	0.000
Sodium - 137	Greater than -5	-0.147	0.662
Sodium - 137 x log(Bilirubin)	Less than -5	0.026	0.000
Sodium - 137 x log(Bilirubin)	Greater than -5	0.064	-0.128
Normalizing shift	-	-16.000	-

MELD Na + Albumin + Height

Variable	Interval	Beta	Constant
Albumin - 3.5	Less than -1	-0.500	0.000
Albumin - 3.5	Greater than -1	-0.095	0.500
Height	Less than 160	-0.011	0.000
Height	Between 160 and 172	-0.027	-1.730
Height	Greater than 172	-0.001	-2.054
log(Bilirubin)	All values	0.666	0.000
log(INR)	All values	1.685	0.000
log(Creatinine)	Less than 1	1.902	0.000
log(Creatinine)	Greater than 1	0.438	1.902
Sodium - 137	Less than -5	-0.071	0.000
Sodium - 137	Greater than -5	-0.027	0.356
Normalizing shift	-	7.000	-

MELD 3.0 without Albumin[225]

MELD 3.0 without albumin is calculated as follows:

MELD 3.0 = 1.40 (if female) + [4.85 x $\log_e$(bilirubin)] + [0.88 x (137-Sodium)] – [0.25 x (137-Sodium) x $\log_e$(bilirubin)] + [9.66 x $\log_e$(INR)] + [10.47 x $\log_e$(creatinine)] + 6

[225] W. Ray Kim et al., "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era," *Gastroenterology* 161, no. 6 (2021), https://doi.org/10.1053/j.gastro.2021.08.050.