OPTN

Briefing to the OPTN Board of Directors on

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

OPTN Liver and Intestinal Organ Transplantation Committee

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Improving Liver Allocation: MELD, PELD, Status 1A, 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 an important update to the liver allocation system to ensure that liver transplant candidates are appropriately ranked according to their medical urgency for transplant.

The current liver allocation system uses the MELD and PELD scores 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 underpredict 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.

The proposal also 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. Finally, the proposal includes minor changes to the policy for liver-intestine candidates and to pediatric National Liver Review Board (NLRB) guidance to align with the other proposed changes to policy.

[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 proposal 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 improvements 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 can inappropriately preclude candidates from accessing Status 1B priority. In addition, the most common reason candidates are listed as Status 1B by

[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.

exception is because they do not meet the MELD/PELD 25 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 and to remove the Glasgow Coma Score (GCS) criteria for both liver-alone and liver-intestine candidates, as it is not clinically relevant and rarely used as a means to be listed as Status 1B.[8,9] 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 utilizes 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 MELD score (for candidates age 12 and older) or the 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 incorporated 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.

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.

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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/.

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 original 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 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,

[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.
[28] Ibid.

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 underpredicts 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 allocation system 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] 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 can 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 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

[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.

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 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 outlined 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 some programs who are more willing to pursue a Status 1A/1B exception for a candidate than other programs. By updating the standard criteria for Status 1A and Status 1B, this proposal will increase equity and efficiency in the liver allocation system by reducing the need for the 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 receive zero points. Similarly, the candidate with the highest amount of waiting time at a particular 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]

This proposal expands upon this points-based system for sorting candidates to also include points based on diagnosis. The changes included in the proposal are specific to Status 1B and are intended to prioritize those candidates with higher risk of waitlist dropout due to death or too sick for transplant ahead of other less urgent Status 1B candidates.

[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/

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

Proposal for Board Consideration

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 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 necessary 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:[40]

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

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.[41]

Uni- and multivariable Cox models were used to predict survival up to 90 days after waitlist registration.[42] Model fit was tested using the concordance statistic (C-statistic) and reclassification.[43] 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.[44,45]

The authors considered age, sex, race, serum sodium, creatinine, INR, bilirubin, albumin, and height were all considered for inclusion in the model. They excluded more subjective variables, such as encephalopathy and ascites, 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

[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] A similar but slightly different calculation will be used for adolescent candidates (age 12 to 17). This calculation is described in more detail below.
[41] Ibid.
[42] Ibid.
[43] Ibid.
[44] Ibid.
[45] Liver Simulated Allocation Model MELD Analysis, Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021.

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.[46, 47] 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.[48] 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.[49]

Based on the splines and clinical input, the authors selected a creatinine level of 3.0 mg/dL as an inflection point, and set a cap 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.[50] 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.[51] 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.[52]

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

[46] 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.
[47] 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/.
[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] Ibid.
[51] 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.
[52] 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.

1.5g/dL and 3.5 g/dL, respectively, in MELD 3.0.[53] Similar to MELD Na, candidates who have received two or more dialysis treatments in the seven days prior to the serum creatinine test and candidates who received 24 hours of continuous veno-venous hemodialysis within the seven days prior to the serum creatinine test 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.[54]

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.[55]

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) when MELD Na was originally developed.[56]

Figure 1 below shows the net reclassification of candidates and deaths between MELD Na and MELD 3.0.[57] 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.[58] 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%.[59]

Figure 1: Reclassification of Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[60]

[53] Ibid.
[54] Ibid.
[55] OPTN Liver and Intestinal organ Transplantation Committee Meeting Summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/
[56] 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.
[57] Ibid.
[58] Ibid.
[59] Ibid.
[60] Ibid.

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.[61] 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.[62] In males, there was a net of 12 decedents (4.1%) appropriately reclassified.[63]

[61] Ibid.
[62] Ibid.
[63] Ibid.

Figure 2: Reclassification of Female Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[64]

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.

[64] Ibid.

Figure 3: Reclassification of Male Liver Transplant Candidates between MELD Na and MELD 3.0 in the Validation Set[65]

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 number of 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.[66] Therefore, it is important to highlight that MELD 3.0 does a better job discriminating risk of waitlist mortality for candidates with an ALD than MELD Na.[67]

MELD 3.0 includes 1.33 points for female candidates to adjust for underestimation of creatinine in the female population. Sex was demonstrated to be correlated with risk of waitlist mortality and the

[65] Ibid.
[66] 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.
[67] 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.

inclusion of a sex-based variable improves the predictive power of MELD 3.0 overall.[68] 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.[69,70] Additional details on the inclusion of albumin are included in subsequent sections.

In general, MELD 3.0 was supported throughout the public comment period. Some individual commenters had specific questions and concerns, which are addressed in the sections below. Overall, this aspect of the proposal was well supported throughout public comment and the community was supportive of the Committee's efforts to address a long-standing sex-based disparity through 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.[71]

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.[72] Results for the number of waitlist deaths from each of the ten simulations were averaged and compared to MELD Na.[73] 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.[74]

Table 1: *Gastroenterology* LSAM Modeling Results[75]

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 a cohort from July 1, 2015 to June 30, 2016.[76] The SRTR LSAM analysis provided results by sex, an important factor considering the inclusion of a sex-based variable in the

[68] Ibid.
[69] Ibid.
[70] See the OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[71] The SRTR provided the LSAM to the authors of the *Gastroenterology* paper. The LSAM is a discrete event simulator that uses historical data to model the US liver allocation system and predict the effects of changes to liver allocation policy on wait list outcome
[72] 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.
[73] Ibid.
[74] Ibid.
[75] 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.
[76] Liver Simulated Allocation Model MELD Analysis, prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021

MELD 3.0 score.[77] Similar to the *Gastroenterology* analysis, the SRTR analysis compared MELD Na to MELD 3.0 with and without albumin.[78] In the LSAM analysis from the SRTR, pediatric candidates under the age of 12 utilized their current PELD score and adolescent candidates used their current MELD score, so it is difficult to draw any conclusions on the impact of MELD 3.0 on these populations using the LSAM results.[79,80]

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.[81]

Table 2: SRTR LSAM Overall Results[82]

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)

[77] Ibid.
[78] Ibid.
[79] Ibid.
[80] 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.
[81] 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.
[82] Liver Simulated Allocation Model MELD Analysis, Prepared for the OPTN Liver and Intestinal Organ Transplantation Committee, October 20, 2021

Table 3: SRTR LSAM Results by Sex[83]

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 of the project, 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.[84] During public comment, some commenters advocated for making larger chance to the liver allocation system as part of this proposal but the Committee did not make any updates to the proposal as a result of this feedback.

eGFR

When considering different MELD updates, the Committee discussed replacing creatinine with other measures of renal function, such as eGFR, but ultimately decided to rule out eGFR from the updated

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

MELD score.[85] Most commonly used eGFR calculations include a race variable and the OPTN Board of Directors is considering a proposal to only permit the use of race-neutral eGFR calculations.[86] 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.[87]

Throughout public comment, the Committee received a number of questions and comments suggesting they reconsider the use of creatinine and instead consider incorporating eGFR into the updated MELD score. The Committee discussed this feedback and continued to agree that the updated MELD score should maintain the use of creatinine as it remains the most objective measure of renal function.[88, 89]

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 closely correlated to low muscle mass than it is to a candidate's sex. Creatinine, which estimates GFR, is known to be lower in individuals with low muscle mass.[90] 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 account for the population of candidates whose renal function is overestimated by creatinine. 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, objective clinical measures. The Committee agreed that muscle mass is neither widely available nor is it an objective clinical value.[91] 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

[85] See Improving the MELD Calculation Work Group meeting summary, March 19, 2021. Available at https://optn.transplant.hrsa.gov
[86] 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/
[87] See Improving the MELD Calculation Work Group meeting summary, March 19, 2021. Available at https://optn.transplant.hrsa.gov/
[88] Ibid.
[89] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 4, 2022. Available at https://optn.transplant.hrsa.gov/
[90] 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.
[91] 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.

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.[92] The coefficients for the other 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.[93]

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 liver transplant and death 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. According to this analysis, 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[94]

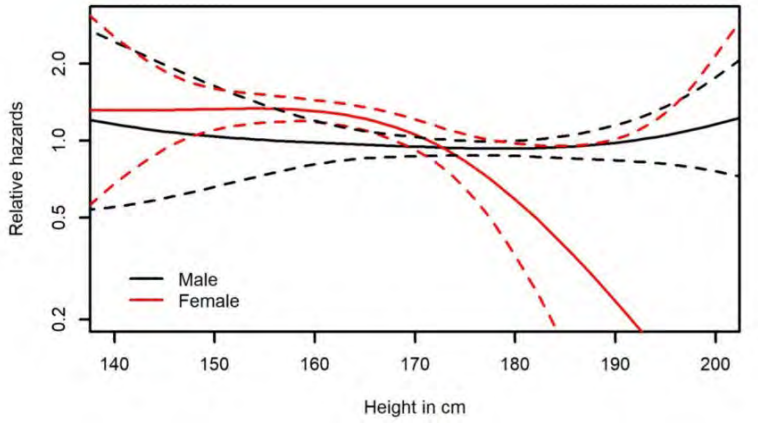
	Subdistribution Hazards					
	sHR (LT)			sHR (death)		
Description	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Short_Women vs Short_Men	1.074	0.956	1.207	**1.302**	**1.028**	**1.649**
Short_Women vs Tall_Men	**0.816**	**0.767**	**0.868**	**1.591**	**1.399**	**1.809**
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.[95] 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 of 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

[92] 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.
[93] Ibid.
[94] 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/
[95] 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.

suggests that sex, as opposed to height, is more correlated with risk of mortality for liver transplant candidates.

Figure 4: Relative Hazard of 90-day Mortality Based on Height, Stratified by Sex[96]



Taken together, the Committee interpreted these analyses to show that sex is more associated with risk of mortality, while height is more associated with access to transplant.[97] 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.[98]

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.[99]

During public comment, some commenters suggested the Committee reconsider the inclusion of a sex-based variable in MELD 3.0 and instead consider adding a factor for height, noting that MELD 3.0 may inadvertently provide additional points to high-muscle mass females, while not providing points to low-muscle mass males. The Committee discussed this and, based on the provided data, decided that no post-public comment changes are needed. [100]

SRTR-derived MELD Models vs. MELD 3.0

When the Committee started this project, the paper describing the MELD 3.0 model had been 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.[101] These MELD models were:

[96] Ibid.
[97] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/
[98] Ibid.
[99] Ibid.
[100] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 4, 2022. Available at https://optn.transplant.hrsa.gov/
[101] 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.

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

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 C-statistics[102]

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.[103] It has a minimum MELD score of six and the mean and standard deviation are similar to MELD Na.[104] The SRTR-derived scores can have values less than six and initially had a lower mean and higher standard deviation than MELD Na.[105] Also, bilirubin and INR cannot be less than 1.0 in MELD 3.0, but they could be less than 1.0 in the SRTR models.[106, 107] The SRTR-derived MELD models have a slightly different structure than MELD Na, which the Committee noted could create confusion in the liver transplant community.[108]

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.[109]

[102] 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
[103] 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.
[104] Ibid.
[105] 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
[106] Ibid.
[107] 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.
[108] The SRTR-derived MELD formulas are included in the Appendix.
[109] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, August 27, 2021. Available at https://optn.transplant.hrsa.gov/

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 but hesitancy has remained in the transplant community due to the potential for a candidate's albumin concentration to be temporarily inflated due to external infusion of albumin, despite hypoalbuminemia being an indication of liver dysfunction.[110]

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.[111]

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.[112] The concordance values for each version of MELD 3.0 are compared to MELD Na in **Table 6** below. 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.[113]

Table 6: MELD 3.0 with and without Albumin[114]

MELD Score	Harrell et al.[114]	Uno et al.[115]
MELD 3.0 without albumin (includes sex)	.8665	.8342
MELD 3.0 with albumin (includes sex)	.8693	.8378
MELD Na	.8622	.8294

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.[117] 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.[118]

Table 7 below includes six different example candidates, highlighting the impact of albumin across different clinical situations. The first two candidates (Candidates 1 and 2) have high MELD scores and high levels of creatinine (Cr = 2.5 mg/dL). At this creatinine level, there are no points provided for albumin. The next two candidates (Candidates 3 and 4) have intermediate MELD scores and creatinine

[110] 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.
[111] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[112] 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.
[113] Ibid.
[114] Ibid.
[115] Hajime Uno et al., "Evaluating Prediction Rules for *t*-Year Survivors with Censored Regression Models," *Journal of the American Statistical Association* 102, no. 478 (2007): pp. 527-537, https://doi.org/10.1198/016214507000000149.
[116] Frank E. Harrell, "Evaluating the Yield of Medical Tests," *JAMA: The Journal of the American Medical Association* 247, no. 18 (1982): p. 2543, https://doi.org/10.1001/jama.1982.03320430047030.
[117] 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.
[118] Ibid.

levels set at 1.7 mg/dL. At this creatinine level, albumin contributes 1-2 points to the overall MELD 3.0 score. And finally, Candidates 5 and 6 have low MELD scores and normal creatinine values at 1.0 mg/dL. In these candidates, albumin can contribute up to 4 points to their final MELD 3.0 score. These example scenarios show how albumin is given less relative weight with increasing creatinine and how albumin has the largest impact in lower MELD scores.

Table 7: Impact of Albumin across MELD Scores and Creatinine Levels[119]

Candidate Number	Sex	Bilirubin	NA	INR	Cr	Albumin	MELD	MELD-NA	MELD 3.0
1	Male	8.0	135	2.0	2.5	3.5	31	32	33
2	Male	8.0	135	2.0	2.5	1.5	31	32	33
3	Male	4.0	135	2.0	1.7	3.5	25	26	26
4	Male	4.0	135	2.0	1.7	1.5	25	26	27
5	Female	2.0	135	1.5	1.0	3.5	14	16	15
6	Female	2.0	135	1.5	1.0	1.5	14	16	19

Throughout the public comment period, the inclusion of albumin garnered the most feedback and questions from the community. A number of commenters, including the American Society of Transplantation, expressed concern that physicians may withhold external administration of albumin when clinically indicated in order to maintain a higher MELD score for candidates. The Committee discussed these concerns both prior to public comment and in response to the feedback provided.

During their post-public comment discussions, the Committee reiterated the importance of the interaction between creatinine and albumin, as well as the fact that albumin plays only a small role in the overall MELD score, especially at higher scores. However, it is important to remember that the inclusion of albumin improves the overall predictive ability of MELD 3.0. In their discussion, the Committee also likened albumin to INR, which is already included in MELD Na. Both laboratory values can be influenced by clinicians but INR is still corrected when it's indicated, and similarly albumin would be given when needed.[120]

As such, the Committee elected not to make any post-public comment changes to this aspect of the proposal.[121]

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, the OPTN currently collects albumin but it is not a required field. Because it will be a variable in the updated MELD score, the OPTN will make albumin a required field and transplant programs will need to provide

[119] This table was created using the MELD 3.0 Calculator. Available at https://medcalculators.stanford.edu/meld.
[120] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 4, 2022. Available at https://optn.transplant.hrsa.gov/
[121] Ibid.

albumin values for their adult transplant candidates, similar to other laboratory values included in the MELD score.

In addition, new data collection is 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.[122] There is a separate, ongoing effort to change each of the "gender" fields to be "birth sex" across the OPTN. Regardless, as part of this proposal, there will be two new fields added to the candidate demographic form for liver candidates that will capture a candidate's current sex, which the OPTN will then use 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.[123]

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 the OPTN Waiting List. 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 a transplant program does not provide a response, 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 OPTN still plans to collect a candidate's birth sex, as it remains an important demographic variable.

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 a 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.[124]

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.

Throughout public comment, members of the transplant community asked about the proposed data collection, mainly to clarify how candidates will be categorized for the purposed of the MELD score. The

[122] 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

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

[124] Ibid.

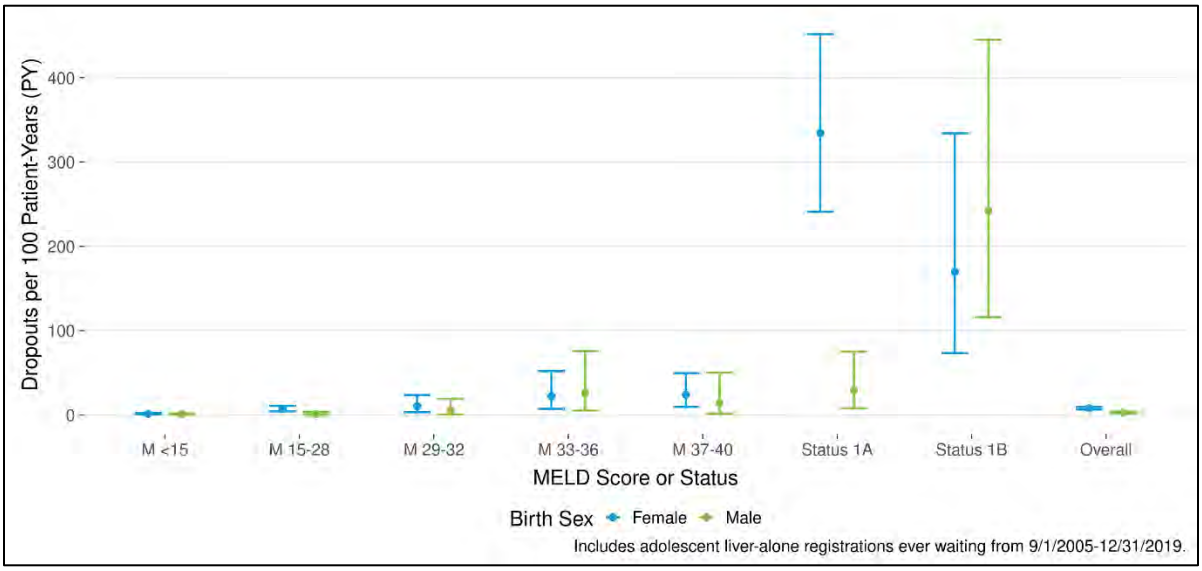
Committee reviewed this feedback and no post-public comment changes were made to this aspect of the proposal.[125]

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 major 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.

Figure 5: Adolescent (Age 12-17) Liver Waitlist Mortality Rates by Sex and MELD Score or Status[126]



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.[127] 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.[128] Under this proposed solution, any male liver transplant candidate who is registered before turning 18 and is older than 12 years old

[125] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 4, 2022. Available at https://optn.transplant.hrsa.gov/
[126] 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/.
[127] Ibid.
[128] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 16, 2021. Available at https://optn.transplant.hrsa.gov/

will receive the 1.33 MELD points. Male candidates registered after turning 18 will receive the standard MELD 3.0 score, which includes the 1.33 points only for female candidates.[129] The use of age at the time of 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.[130]

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

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 in conjunction with the SRTR using the article titled, "Improving the predictive ability of the pediatric end-stage liver disease score for young children awaiting liver transplant," as a starting point.[131]

The Committee is proposing the adoption of PELD Cr because it has an improved ability to discriminate 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] 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.
[130] See OTPN Ethical Principles of Pediatric Organ Allocation. Available at https://optn.transplant.hrsa.gov/
[131] 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 8: 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.[132] 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.[133] Candidates with cancer or a primary/secondary diagnosis that was not chronic liver disease were excluded.[134] 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 of transplant were also excluded from the cohort.[135]

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.[136] Similar to MELD, a major benefit of PELD is that it uses objective, widely available variables. The PELD/1B work group conducted

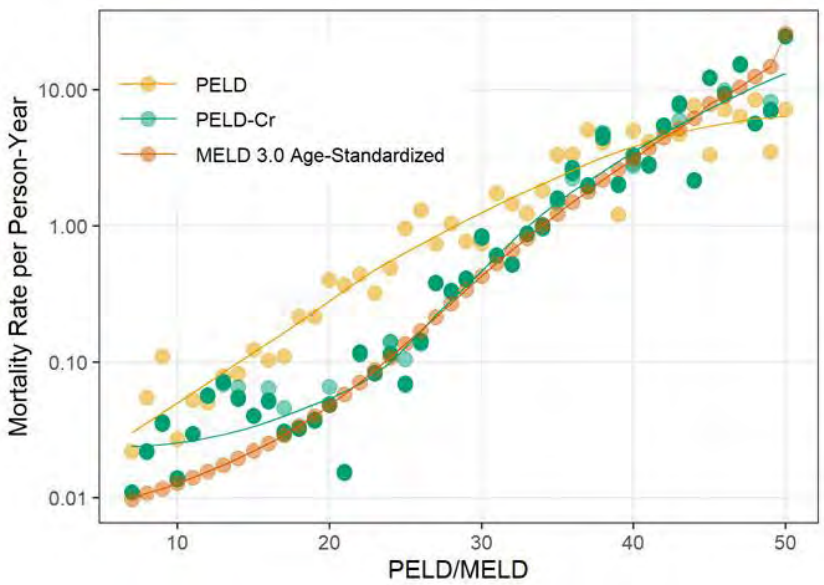
[132] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.
[133] Ibid.
[134] Ibid.
[135] Ibid.
[136] Ibid.

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 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. [137]

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.[138,139] 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.[140] 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 is adjusted so that the risk of mortality at a given score is the same.[141]

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

[137] Ibid.
[138] Ibid.
[139] 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.
[140] 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.
[141] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.

eGFR.[142] 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).[143] Given the modest improvement in discrimination and clinically contradictory results, the Committee did not further consider including a delta PELD or PELD trajectory variable.[144]

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).[145] In both updated PELD scores, age and growth failure were converted from categorical to continuous variables, representing a substantial upgrade over the current PELD score, where a candidate can have large changes in their score with only small changes in their age, height, or weight.[146]

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.[147] Given the issues with the use of creatinine as a measure of renal function in MELD, it is important to note that the same disparity does not exist for candidates under age 12.[148] As a result, the Committee is proposing the incorporation of PELD Cr into OPTN policy.

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.[149] PELD Cr, like the current version of PELD, will not be capped to allow particularly urgent pediatric candidates to access scores higher than the adult population and access transplant more quickly.[150,151]

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.

PELD Cr was supported throughout public comment and the Committee is not recommending any major post-public comment changes to this aspect of the proposal. However, there is one substantive update to the policy language for how growth failure is calculated within the PELD Cr score. The version of policy that the Committee put out for public comment stated that growth failure would be calculated using a candidate's birth sex, height, weight, and age in months at the time of the most recent *submission* of height or weight values. However, because of OPTN lab submission policies, the use of age

[142] Ibid.
[143] Ibid.
[144] See PELD/Status 1B Work Group meeting summary, February 18, 2021. Available at https://optn.transplant.hrsa.gov/
[145] See *Analysis Report: Data Request from the PELD/Status 1B Criteria Work Group of the OPTN Liver Committee*, March 19, 2021.
[146] Ibid.
[147] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, April 14, 2021. Available at https://optn.transplant.hrsa.gov/
[148] 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.

[149] At the time of implementation, all candidates with a PELD Cr score less than 6 will have their scores set at 6.
[150] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, November 5, 2021. Available at https://optn.transplant.hrsa.gov/
[151] See OTPN Ethical Principles of Pediatric Organ Allocation. Available at https://optn.transplant.hrsa.gov/

at the time the height/weight values are submitted could create a situation where the variables in the growth failure calculation are not aligned. In some instances, the OPTN allows the submission of laboratory values that were measured up to 30 days in the past. For the growth failure calculation, this would mean that a transplant program could measure a candidate's height/weight and then would not be required to submit those values for another 30 days. In the previous PELD Cr policy, growth failure would then be calculated using the candidate's age at the time the values were submitted, even though the lab values were measured up to 30 days in the past. To address this situation, the updated policy uses a candidate's age in months at the time the height and weight values used in the PELD calculation were *measured*, not submitted.

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 existed to show that the characteristics were associated with risk of mortality. They also determined if the characteristics were 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 9** below lists the 21 characteristics considered.

Table 9: Potential PELD Variables

Characteristic	Outcome
Included in PELD Cr	
Age	Included in PELD Cr
Age-adjusted mortality	Included in PELD Cr
Bilirubin	Included in PELD Cr
Renal function (eGFR/creatinine)	Included in PELD Cr
Albumin	Included in PELD Cr
INR	Included in PELD Cr
Growth Failure	Included in PELD Cr
Not included in PELD Cr	
Sodium	Included in PELD derivation request but not associated with mortality
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-scores; 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

Additional PELD Points

The Committee considered including additional points for each candidate with a PELD score. 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.[152]

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. Adding points would improve pediatric access to transplant, but is unrelated to waitlist mortality. The

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

Committee agreed that further prioritization of pediatric candidates in liver allocation could be considered as a part of future allocation changes.[153]

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.[154] However, encephalopathy is difficult to diagnose in young children and such diagnoses can be unreliable.[155]

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.[156] 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 10** outlines the proposed changes.

Table 10: 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

This aspect of the proposal was supported throughout public comment and no post-public comment changes were made.

Status 1B

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

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
4. Sorting of candidates within Status 1B classifications

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

[154] 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.

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

[156] 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.

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

Table 11: 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 veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD) • Has a Glasgow come score (GCS) less than 10 within 48 hours before the status 1B assignment or extension	Chronic liver disease with an adjusted MELD/PELD score greater than 25 and has at least one of the following: • Is on a mechanical ventilator • Has GI 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

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 meet the standard criteria for 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*.[157] 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.[158]

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, these candidates will almost always meet the threshold set at MELD/PELD 25 and the Committee is proposing the threshold be removed for liver-intestine candidates.[159]

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

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

greater than 25. **Table 12** includes the specific reasons Status 1B exception requests did not meet the standard 1B criteria.[160] 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.[161]

Table 12: Criteria Not Met for Status 1B Cases

Criteria Not Met for Status 1B Requests that Do Not Meet Standard Critera	Case Outcome	
	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%)

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.[162] In addition, Committee reviewed data during the development of the proposal, which showed that, 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.[163]

[160] Descriptive Data Request: Status 1B Exceptions: A Data Overview, Prepared for the PELD/Status 1B Work Group, August 20, 2020
[161] Ibid.
[162] The Committee is proposing the removal of the criterion for Glasgow Coma Score as part of this proposal.
[163] Descriptive Data Request: Status 1B Waitlist Removals, Prepared for PELD/1B Work Group meeting on August 19, 2021

Instead of removing the threshold, the Committee considered lowering the threshold to 15.[164] 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.[165]

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

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.[166] 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.[167] The Committee is not proposing a change to the GI bleeding threshold for liver-intestine candidates as this criterion remains clinically appropriate.[168]

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.[169]

This proposed change received positive feedback throughout public comment and no post-public comment changes were made.

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.[170] 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.[171]

This aspect of the proposal did not receive significant public comment feedback and the Committee did not make any post-public comment changes.

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[164] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, October 20, 2021. Available at https://optn.transplant.hrsa.gov/
[165] Ibid.
[166] See *OPTN Policy 9.1.C: Pediatric Status 1B Requirements*. Available at https://optn.transplant.hrsa.gov/
[167] 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.
[168] 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/
[169] See PELD/Status 1B Work Group meeting summary, October 25, 2021. Available at https://optn.transplant.hrsa.gov/
[170] See *OPTN Policy 9.1.C: Pediatric Status 1B Requirements*. Available at https://optn.transplant.hrsa.gov/
[171] In the last three years, only 21 Status 1B forms were submitted with a GCS less than 10.

Sorting within Status 1B

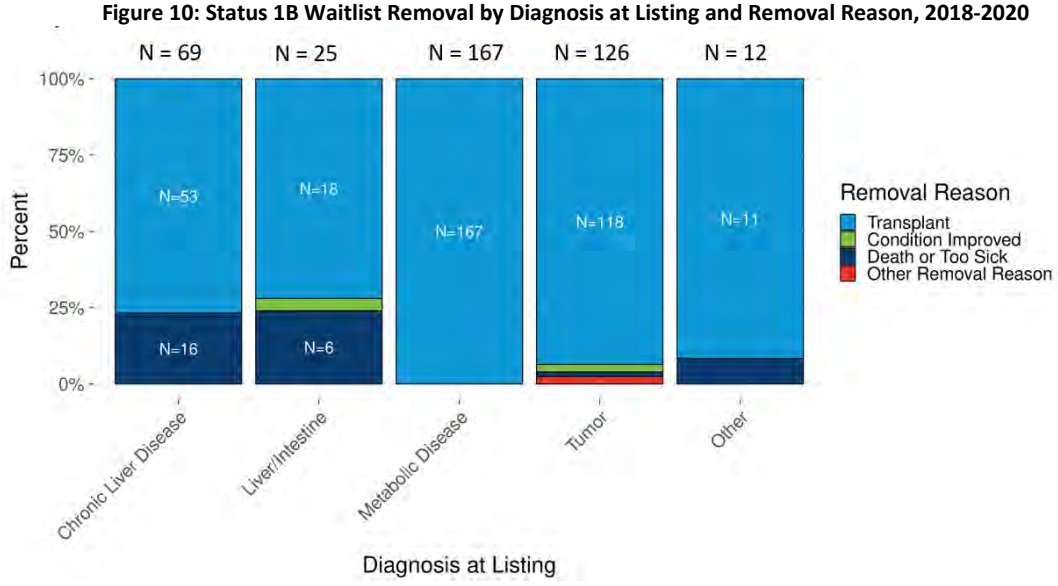
Within a given classification for Status 1B, candidates are sorted based on their waiting time at Status 1B and blood type compatibility using a points-based system.[172] Waiting time points are assigned at the time of the match run such that the candidate with the most waiting time at Status 1B is assigned 10 points.[173] 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.[174]

For blood type, candidates with the same blood type as the donor receive 10 points, candidates that have a compatible blood type as the donor receive five points, and candidates with an incompatible blood type receive zero points.[175] 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.[176] Candidates are then ranked within the classification based on the total number of points from highest to lowest.[177]

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 found in candidates with chronic liver disease.[178] 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



[172] See *OPTN Policy 9.7: Liver Allocation Points*. Available at https://optn.transplant.hrsa.gov/
[173] See *OPTN Policy 9.7.A: Points for Waiting Time*. Available at https://optn.transplant.hrsa.gov/
[174] Ibid.
[175] See *OPTN Policy 9.7.B: Points Assigned by Blood Type*. Available at https://optn.transplant.hrsa.gov/
[176] Ibid.
[177] See *OPTN Policy 9.8.D: Sorting within each Classification*. Available at https://optn.transplant.hrsa.gov/
[178] 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.[179] 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.[180] The Committee agreed that candidates with a tumor diagnosis have increased mortality risk and therefore the updated policy language assigns five points for hepatoblastoma.[181] The data suggest that candidates with metabolic disease are at lower risk of waitlist mortality and therefore are not provided any diagnosis points.[182]

Finally, **Table 13** shows a snapshot of the Status 1B population at different points in time.[183] 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 significantly decrease access to transplant for other Status 1B candidates.

Table 123: 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%)

Throughout public comment, this aspect of the proposal was generally supported. Some commenters suggested that candidates with metabolic disease should not get Status 1B priority at all. This proposed change was outside the scope of the current project and the Committee opted to move forward without any post-public comment changes.[184]

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.[185] Liver-intestine candidates who are age 18 or older

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

receive an additional increase in their MELD or PELD score equivalent to a 10 percentage point increase in risk of 3-month mortality.[186] 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 candidate is provided pediatric priority as long as he or she is registered before turning 18.[187] 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.[188,189]

This aspect of the proposal was supported throughout public comment and no post-public comment were made.

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.[190] 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.

[186] Ibid.
[187] See *OPTN Policy 9.1: Status and Score Assignments*. Available at https://optn.transplant.hrsa.gov/
[188] See OPTN Liver and Intestinal Organ Transplantation Committee meeting summary, December 3, 2021. Available at https://optn.transplant.hrsa.gov/
[189] 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.
[190] 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 recommending a minor post-public comment change to this aspect of the proposal that switches the term “gender” to “sex,” which is the biologically-appropriate term, and switches “transplant center” to “transplant program”.

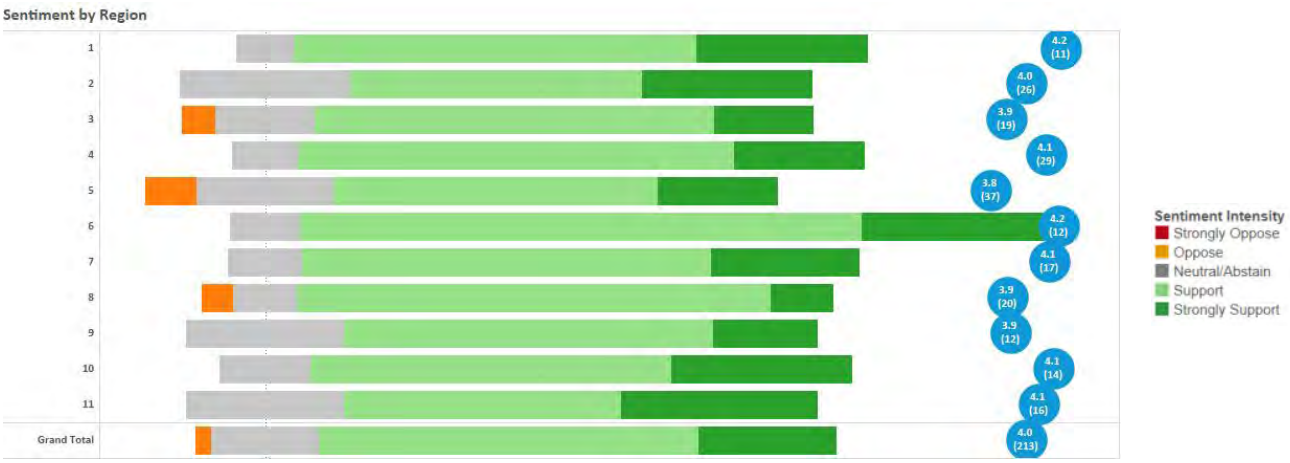
Overall Sentiment from Public Comment

The proposal was out for public comment from January 27, 2022 to March 23, 2022. The proposal was presented at 11 regional meetings and received additional feedback on the OPTN website. The proposal was presented to the OPTN Pediatric Transplantation Committee, the OPTN Transplant Administrators Committee, and the OPTN Minority Affairs Committee.

A number of stakeholder organizations provided feedback on the proposal throughout public comment, including the American Society of Transplantation (AST), the American Society of Transplant Surgeons (ASTS), and the Society for Pediatric Liver Transplantation (SPLIT).

The proposal was supported at all regional meetings. Public comment sentiment from each of the 11 OPTN regions is shown in **Figure 11.**[191]

Figure 11: Sentiment at OPTN Regional Meetings

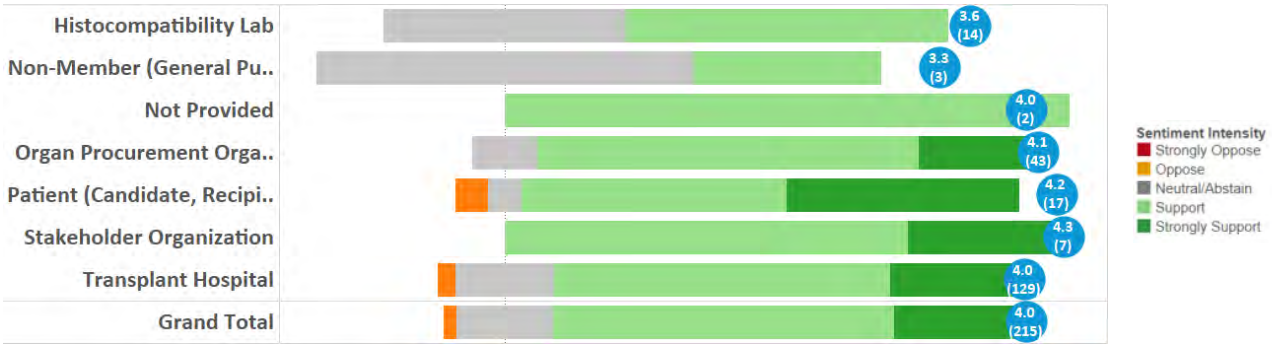


Public comment sentiment by member type is below in **Figure 12.**[192]

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

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

Figure 12: Sentiment by Member Type



Despite being widely supported, a few themes emerged throughout public comment. Primarily, commenters were concerned with the inclusion of albumin and the potential for physicians to withhold external administration of albumin when clinically indicated in order to obtain a higher MELD score for their candidates. The AST was particularly concerned with the inclusion of albumin due to variability in albumin levels that result from candidates receiving IV albumin and the potential for physicians to hesitate to infuse IV albumin when clinically indicated due to a potential reduction in the candidate's MELD score. The Committee reviewed and discussed these concerns, but ultimately agreed that albumin remains an important predictor of waitlist mortality and recommend keeping albumin in the updated MELD model.[193] The Committee noted the way in which albumin is incorporated into MELD 3.0 and the interaction term with creatinine limits the imapct of albumin in high MELD candidates, who are more likely to need an albumin infusion.[194] The Committee also drew a parallel between albumin and INR, which can also be influenced by clinical practice but is still corrected when indicated.[195]

In addition, some commenters, including the AST and ASTS, advocated for adding eGFR into MELD 3.0 instead of creatinine. However, the Committee previously ruled out eGFR as a potential variable in the MELD score due to concerns with race-based eGFR calculations. Race-neutral eGFR calculations are not widely available for the liver transplant commuinty and therefore could not be incorporated into the MELD score at this time.

Other commenters suggested including a height variable instead of sex to capture those candidates with low muscle mass. As described previously, the Committee considered MELD models with a height variable when developing the proposal and are recommending MELD 3.0 because sex is more correlated with waitlist mortality, while data suggested height is more correlated with access to transplant.

SPLIT strongly supported the proposal and highlighted the need to comprehemsive post-implementation monitoring.

The OPTN Pediatric Transplantation Committee, the OPTN Transplant Administrators Committee, and the OPTN Minority Affairs Committee all supported the proposal.

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

Compliance Analysis

NOTA and OPTN Final Rule

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…"[196], 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."[197] 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."[198] This proposal:

- **Is based on sound medical judgment**[199] because it is an evidenced-based change relying on the following evidence:
    - OPTN data, SRTR analyses and peer-reviewed 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 and definition of hepatic encephalopathy should be updated to align with clinically-accepted definitions
- **Seeks to achieve the best use of donated organs**[200] 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.
- **Is designed to…promote patient access to transplantation**[201] 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

[196] 42 USC §274(b)(2)(B).
[197] 42 C.F.R. §121.4(a)(1)
[198] 42 CFR §121.8(a).
[199] 42 CFR §121.8(a)(1).
[200] 42 CFR §121.8(a)(2).
[201] Ibid.

  - Adjust 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**[202]

This proposal also preserves the ability of a transplant program to decline an offer or not use the organ for a potential recipient,[203] and it is specific to an organ type, in this case livers and intestines.[204]

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[205]
- Is designed to avoid futile transplants[206]
- Promotes the efficient management of organ placement[207]

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.[208] 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.[209] 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."[210] 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,"[211] 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 such records and information electronically…"[212] This proposal collects additional data on transplant candidates in order to appropriately prioritize them.

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[202] 42 CFR §121.8(a)(8).
[203] 42 CFR §121.8(a)(3).
[204] 42 CFR §121.8(a)(4).
[205] 42 CFR §121.8(a)(5).
[206] Ibid.
[207] Ibid.
[208] 2019 OPTN Contract Task 3.2.4: Development, revision, maintenance, of OPTN Bylaws, policies, standards and guidelines for the operation of the OPTN.
[209] 42 C.F.R. §121.8(b)(4)
[210] 42 U.S.C. §274(b)(2)(M)
[211] 42 U.S.C. §274(b)(2)(I)
[212] 42 C.F.R. §121.11(a)(1)(i)-(iii)

OPTN Strategic Plan

Improve equity in access to transplants: This proposal seeks to address a long-standing sex-based disparity in liver allocation by updating the MELD score with additional variable. The proposal also improves the ability of the MELD and PELD scores to predict waitlist mortality and updates Status 1A and Status 1B policy, ensuring the sickest candidates are appropriately prioritized for transplant.

Implementation Considerations

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.[213]

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 on a match run. 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.

[213] 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.

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 implementation 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 programs 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 the OPTN Computer System. 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.

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. 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.

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 OPTN Contractor estimates 5,660 hours for implementation. Implementation will involve changes in the OPTN Computer System, distribution of education and communication materials about the changes, and updates to site survey documents. The OPTN Contractor estimates 600 hours for ongoing support. Ongoing support will involve answering member questions and monitoring at three months, six months, one year and two years post-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."[214]

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

[214] 42 CFR §121.8(a)(7).

Site surveyors will also continue to verify that lab results reported in the OPTN Computer System 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."[215]

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
- The above metrics will be stratified by height, 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

[215] 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 pediatric Status 1A and Status 1B candidates. 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.

Policy and Guidance Language

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

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~~ transplant candidates at least 12 years old.

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

b. 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.

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

d. 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 red blood cell replacement of at least 30 mL/kg ~~of red blood cell replacement~~ within the previous ~~24~~ 96 hours or 20 mL/kg 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.~~

   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:

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

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:

$MELD = [4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137-\text{sodium})] – [0.24 \times (137-\text{sodium}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine})] + [1.85 \times (3.5-\text{albumin})] – [1.83 \times (3.5 – \text{albumin}) \times \log_e(\text{creatinine})] + 7.33$

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 when calculating a candidate's MELD score:

- 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 under the age of 12 ~~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) 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 Center for Disease Control and Prevention's (CDC) height or weight Z-score uses the lambda-mu-alpha (LMS) method 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 the height and weight values used in the PELD calculation were measured.

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 when calculating a candidate's PELD score:

- 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~~2*.

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~~2: 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~~2*, 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 acidemia 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 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.[216] 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.[217]

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~~ programs, 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 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

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

support device (such as Molecular Adsorbent Recirculating System (MARS), albumin dialysis, plasmapheresis).

Chronic Liver Disease[218,219,220,221,222,223,224]

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 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[225]
  - <5th percentile for: height, weight (may adjust to estimated dry weight if ascites)[226,227]
  - Z-score (~~weight, height, or~~ BMI/weight-for-length) less than 2 standard deviations below the mean for age and ~~gender~~ sex
- Anthropometrics
  - Triceps skin fold thickness or mid-arm muscle circumference < 5th percentile for age and ~~gender~~ sex [228]
- 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[229]
- Requirement for TPN nutrition to allow for growth or to maintain euglycemia

#

[218] Tamir M et al pediatric liver Transplantation for Primary Sclerosing Cholangitis Liver Transplantation 17:925-933 2011
[219] Elgendy H et al The outcome of critically ill children afterliving donor liver transplant Exp Clin Transplant Suppl 1 : 100-7 2015
[220] Malatack etal Choosing a pediatric recipient for orthotopic liver transplantation J Pediatr 111: 479-489 1987
[221] Sarin SK etal Young adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival Gut 29: 101-107 1988
[222] Matloff RG The Kidney in Pediatric Liver Disease Curr Gastroenterol Rep 17: 36
[223] Dara N et al Liver function, paraclinical tests, and mortality risk factors in pediatric liver transplant candidates Comparative clinical Pathology 25 (1) : 189-195 2015
[224] Keating et al Clinical course of cirrhosis in young adults and therapeutic potential of liver transplantation Gut 26: 1359-1363 1985
[225] Sokol RJ etal Anthropometric evaluation of children with chronic liver diseases Am J Nutrition 52:203-208 1980
[226] World Health Organization global Database on Child Growth and Malnutrition
[227] Yang etal Living donor liver transplantation with body weight more or less than 10 kilograms world J Gastroenterol 21 (23) 7248-53 2015
[228] UptoDate 2016. Table for skin fold thickness percentiles.
[229] Chin SE the nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation Am J Clin Nutr 56:164-168 1992

Appendix

Literature Reviewed by the Committee in Developing the New MELD Calculation

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SRTR-Derived MELD Scores[230]

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	-

[230] 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[231]

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

[231] 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.