OPTN

Committee Update

Continuous Distribution of Livers and Intestines Update, Summer 2024

OPTN Liver and Intestinal Organ Transplantation Committee

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Continuous Distribution of Livers and Intestines Update, Summer 2024

Sponsoring Committee: *Liver and Intestinal Organ Transplantation*
Public Comment Period: *July 31, 2024 – September 24, 2024*

Executive Summary

In December 2021, the OPTN Liver and Intestinal Organ Transplantation Committee (Committee) began working to convert the current classification-based allocation system for liver and intestines to a points-based framework, otherwise known as continuous distribution. Continuous distribution will replace the current classification-based approach, which draws hard boundaries between types of candidates (for example, blood type compatible vs. identical; inside vs. outside a circle), with a composite score that simultaneously takes into account donor and candidate attributes. This points-based allocation system will create a more equitable and efficient allocation system.

This concept paper is the fourth public comment document from the Committee that details the development of continuous distribution of livers and intestines.[1,2,3] The purpose of this concept paper is to continue to inform the community about the development of liver continuous distribution. Specific topics included in this update are related to the following attributes: *Body Surface Area (BSA), Medical Urgency Score, Utilization Efficiency, Hepatocellular Carcinoma (HCC) Stratification, Travel Efficiency*, and *Pediatric Priority*. Additionally, this document aims to detail the Committee's current project plan and the upcoming transition to begin using mathematical optimization to aid the Committee in their decisions. The Committee seeks community feedback on the work to date and welcomes input on additional topics that should be under Committee review within the scope of liver and intestine continuous distribution frameworks.

Considerations for the Community

- Please provide any feedback on the identified attributes as well as their drafted purposes and initial rating scales.
- Please provide any feedback on the Committee's decision to utilize MELD and PELD as the medical urgency score model within the first version of continuous distribution.
- Please provide any feedback specific to the pediatric population within liver continuous distribution.

[1] "Continuous Distribution of Livers and Intestines Concept Paper," OPTN, Concept Paper. Public Comment Period: August 3, 2022 – September 28, 2022. Available at https://optn.transplant.hrsa.gov/media/fzmjii35/continuous-distribution-of-livers-and-intestines-concept-paper_liver_pc-summer-2022.pdf.
[2] "Update on Continuous Distribution of Livers and Intestines," OPTN, Request for Feedback. Public Comment Period: January 19, 2023 – March 15, 2023. Available at https://optn.transplant.hrsa.gov/media/zc3lti1y/continuous-distribution-of-livers-and-intestines_liver_pc_winter-2023.pdf.
[3] "Update on Continuous Distribution of Livers and Intestines," OPTN, Committee Update. Public Comment Period: July 27, 2023 – September 19, 2023. Available at https://optn.transplant.hrsa.gov/media/enuh5gmk/liver_cd_update_incorporatehrsacomments_pcsummer2023.pdf.

- Please provide feedback on when your organization begins to fly rather than drive for organ procurement as well as any feedback on travel practices.
- Please provide feedback on the *BSA* attribute including the decision to use BSA, the options for rating scales, and donor modifiers.
- Please provide feedback on the *Utilization Efficiency* attribute including input on the options for how to award candidates points and the definition of a medically complex liver offer.
- Please provide feedback on how to incorporate exceptions into the continuous distribution framework, including HCC stratification, and whether any specific donor modifiers are necessary.
- Please provide feedback on other aspects of this project including any additional considerations that are not addressed in this paper which warrant Committee discussion.
- What areas can be improved to address the needs of patients including areas that need better communication and education?

Background

In 2018, the OPTN Board of Directors set the goal to replace the current classification-based allocation system with a points-based continuous distribution framework.[4] Continuous distribution aims to eliminate the hard boundaries between classifications that exist in the current liver and intestine allocation system, ultimately resulting in more equity for candidates on the waitlist for livers and intestines. In addition to the benefits of removing hard boundaries between classifications, continuous distribution also has more potential for flexibility, producing efficiencies not only in allocation but also in policy development and implementation. For more details on the background of continuous distribution, please refer to *Continuous Distribution of Livers and Intestines Concept Paper*.[5]

In December 2021, the Committee began developing a framework for the continuous distribution of livers and intestines. Also in December 2021, the OPTN Board of Directors approved a proposal to establish the continuous distribution of lungs, which was implemented on March 9, 2023.[6] In addition, the OPTN Kidney Transplantation Committee and OPTN Pancreas Transplantation Committee are collaborating on a project to convert the kidney and pancreas allocation systems to continuous distribution frameworks. The OPTN Heart Transplantation Committee is also in the process of developing their continuous distribution system. The goal is for all organs to eventually transition to a continuous distribution allocation system.

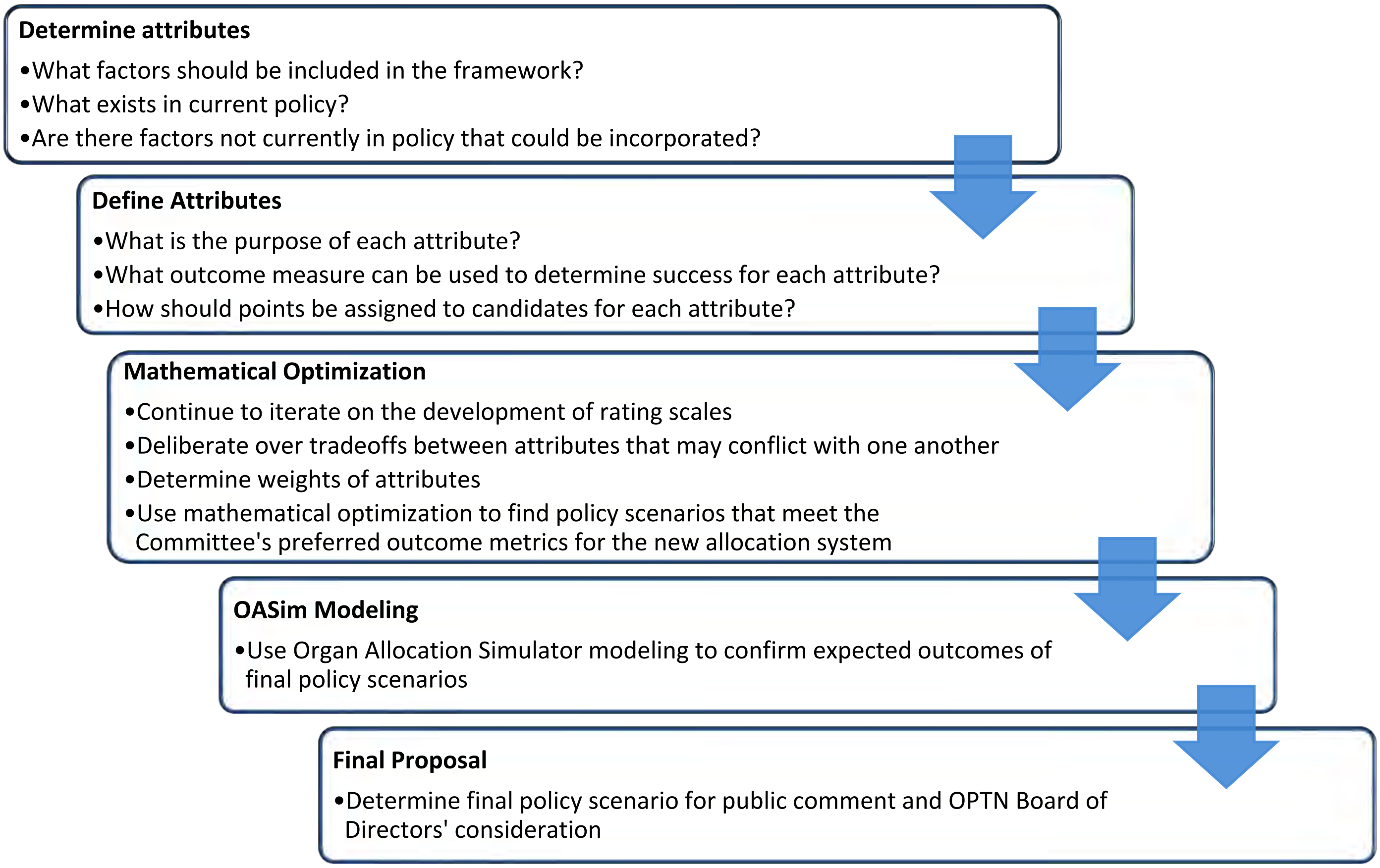
Project Plan

This is not a final policy proposal, and the Committee has not finalized any specific decision or recommendation. With such a significant change to the allocation system, community input is particularly important, and the Committee is eager for feedback from the transplant community.

The project plan for developing the continuous distribution of livers is depicted in **Figure 1** below. The project plan represents a novel approach to the OPTN policy development process, whereby the Committee will be able to iterate and understand the potential impact of many different policy scenarios before finalizing a proposal for public comment.

[4] OPTN Board of Directors. 2018, December 3-4. Executive Summary. Available at https://optn.transplant.hrsa.gov.
[5] "Continuous Distribution of Livers and Intestines Concept Paper," OPTN, Concept Paper. Public Comment Period: August 3, 2022 – September 28, 2022.
[6] "Establish Continuous Distribution of Lungs," OPTN, Briefing Paper. Board Approved: December 6, 2021. Available at https://optn.transplant.hrsa.gov/media/esjb4ztn/20211206-bp-lung-establish-cont-dist-lungs.pdf.

Figure 1: Overview of Project Plan



It is important to note that the project plan (**Figure 1**) is an iterative approach and any public comment feedback, directives, or additional information from simulation results could result in the Committee revisiting an earlier step in the project plan. At the moment, the Committee is currently finishing work on the *Define Attributes* phase and transitioning to the *Mathematical Optimization* stage (detailed more in a later section).

Progress to Date

The Committee has submitted prior updates to public comment for feedback.[7,8] The last update was provided during the summer 2023 public comment cycle and detailed the results from the values prioritization exercise (VPE), the purpose of the mathematical optimization analysis, and the recent deliberations on various attributes.[9] In the twelve months since the last update, the Committee has made progress by defining the purpose and metrics of success for all currently identified attributes as

[7] "Continuous Distribution of Livers and Intestines Concept Paper," OPTN, Concept Paper. Public Comment Period: August 3, 2022 – September 28, 2022.

[8] "Update on Continuous Distribution of Livers and Intestines," OPTN, Request for Feedback. Public Comment Period: January 19, 2023 – March 15, 2023.

[9] "Update on Continuous Distribution of Livers and Intestines," OPTN, Committee Update. Public Comment Period: July 27, 2023 – September 19, 2023.

well as developing initial rating scales for most identified attributes. Defining the purpose of each attribute helps guide subsequent decisions such as how to award points and measure whether the attribute is successful in achieving its defined purpose. The metrics of success are chosen to help analyze outcomes within the mathematical optimization which is detailed further in the next section. Metric of success will be used to quantify the impact of each attribute in the optimization tool while other standard outcome metrics will also be reviewed for potential impact. The currently identified attributes are found in **Figure 2** and the additional progress of developing each attribute is detailed in **Table 1**.

Figure 2: Attributes Identified for Liver Continuous Distribution

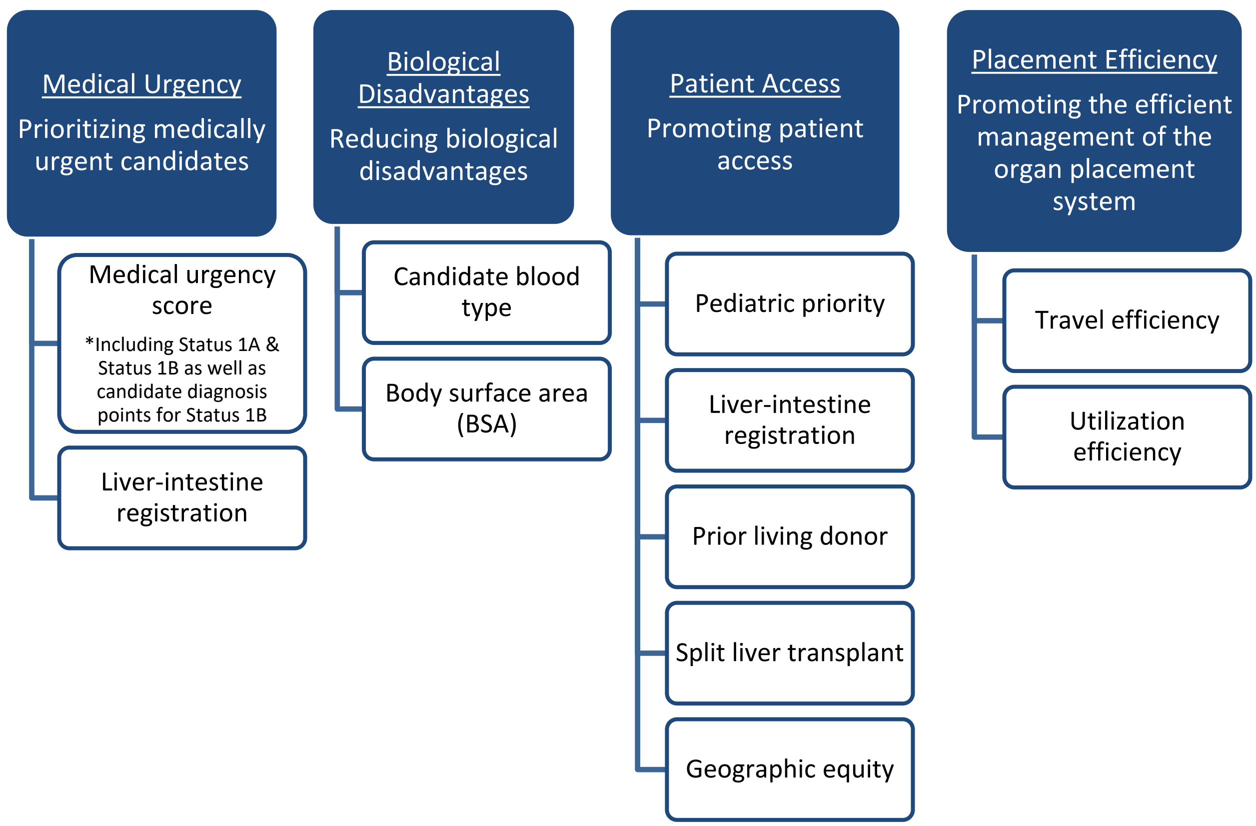


Table 1: Current Identified Attributes, Defined Purpose, Metrics of Success, & Initial Rating Scales

Attribute	Purpose	Metric of Success	Initial Rating Scale
Medical Urgency Score	• Prioritize candidates who are most likely to die/be removed from the waitlist without a transplant	• Count of waitlist deaths/removal for too sick for transplant	• Status 1A • Status 1B (including diagnosis points) • 90-day waitlist mortality (MELD/PELD)
Liver-Intestine Registration	• Provide increased access to appropriate donors for liver-intestine candidates • Prioritize liver-intestine candidates who are most likely to die/be removed from the waitlist without a transplant	• Sequence number: number of match runs for multivisceral donor with multivisceral candidates in top 10 divided by total active time on the waitlist • Count of waitlist deaths/removal for too sick for transplant for multivisceral candidates	• Binary (Y/N) • Donor modifiers: Liver-intestine candidates will receive additional points if the donor is not DCD, has a BMI less than or equal to 30, is age 40 or less, and has no history of diabetes
Blood Type	• Provide equal access to transplant for candidates regardless of their blood type	• Sequence number: number of match runs with candidate of each blood type in top 10 divided by total active time of the waitlist with MELD/PELD above 15	• Candidates who are compatible with fewer donors get more points, while candidates who are compatible with more donors get fewer points

Attribute	Purpose	Metric of Success	Initial Rating Scale
Body Surface Area (BSA)	• Provide equal access to transplant for candidates regardless of their stature	• Sequence number: number of match runs with candidate below certain BSA in top 10 divided by total active time on the waitlist with MELD/PELD above 15	• Binary (Y/N) • Option 1: Adult (age 18 years or older) candidates receive points if their BSA is in the bottom 15th percentile • Option 2: Same as above, plus adult candidates in the bottom 5th percentile receive additional points • Donor modifiers: If a donor is 18 years or older and if the donor is in the bottom 10th percentile of BSA
Pediatric Priority	• Eliminate the pediatric waitlist (reduce time on the waitlist for pediatric candidates)	• Count of pediatric transplants • Time to transplant (minimize active time on the waitlist)	• Binary (Y/N)
Prior Living Donor Priority	• Prioritize all living donors	• *Unable to model as not included in historic cohort*	• Binary (Y/N)
Split Liver	• Prioritize those candidates (e.g., pediatric candidates and small statured adults) willing and likely to initiate a split liver transplant for appropriate donors	• Numbers of match runs for splitable liver with pediatric or small stature candidates in top 10 divided by total active time on the waitlist with MELD/PELD above 15 • *Modeling constraints*	• Binary (Y/N) based on candidate's willingness to accept a split
Geographic Equity	• Provide equal access to transplant regardless of geographic location of transplant program	• Sequence number: number of match runs with candidates from each region in top 10 divided by total active time on the waitlist with MELD/PELD above 15	• Population density* **Pending review of data*

Attribute	Purpose	Metric of Success	Initial Rating Scale
Travel Efficiency	• Reduce distance between donor hospital and transplant program	• Median transport time • Median transport distance • Percentage of organs flown for transport	• Drive vs fly* **Seeking public input to develop further*
Utilization Efficiency	• Increase efficiency in organ placement system (make difficult to place grafts less difficult to place)	• Medically complex grafts accepted in top quartile of sequence number divided by total active time on the waitlist	• *Pending development* • Donor modifier: medically complex liver (DCD or age over 70)

As the Committee moves into the next phase of the project, it is important to describe the iterative process the Committee will take when utilizing the mathematical optimization dashboard, which is described in more detail below. Subsequent sections highlight various topics that have been under Committee consideration over the past year. The sections are intended to provide updates on high impact areas that are of interest to the community and are not an exhaustive summary of every topic and decision the Committee has made since the last update. The Committee is seeking public comment feedback on all information provided as well as any other continuous distribution related topics and offers specific questions for consideration by the community.

Mathematical Optimization Dashboard

The next major step in developing the continuous distribution of livers and intestines is mathematical optimization, which uses machine learning and artificial intelligence to augment Liver Simulated Allocation Modeling (LSAM) data to quickly and accurately predict outcomes from thousands of potential policy scenarios.[10] The use of mathematical optimization, machine learning, and artificial intelligence in the development of continuous distribution represents a significant improvement in how the OPTN develops organ allocation policy by allowing for a more iterative and flexible approach to policy development.

In the previous approach to modeling the potential impact of policy changes, OPTN committees would first develop a handful of policy scenarios to address specific problems and then work with the Scientific Registry of Transplant Recipients (SRTR) to model the potential impact of each policy scenario using LSAM, now known as the Organ Allocation Simulator (OASim). This process could take several months per round of modeling, may require multiple rounds of modeling, and would require OPTN Committees to develop potential policy solutions to their identified problem before knowing to what extent each potential solution would (or would not) solve the identified problem. OASim modeling would then quantify how the policy scenarios developed by the Committee may perform in accomplishing their stated goals.

However, with mathematical optimization, the Committee will be able to iterate through thousands of potential policy scenarios in near real-time, making the entire policy development process more flexible and responsive to the deliberations of the Committee. Rather than deciding on the policy scenarios they

[10] Theodore P Papalexopoulos et al., "Ethics-by-Design: Efficient, Fair and Inclusive Resource Allocation Using Machine Learning," Journal of Law and the Biosciences 9, no. 1 (2022), https://doi.org/10.1093/jlb/lsac012.

expect will achieve the desired outcomes first, and then seeing if those policy scenarios accomplish the intended outcomes, mathematical optimization reverses the order of this process by allowing the Committee first to determine the specific outcomes they intend to achieve and then find the policy scenario(s) that may achieve those outcomes.

A simple example of the benefits of mathematical optimization within the context of continuous distribution would be assigning relative weights to each attribute. Rather than assigning initial weights to each attribute and then seeing what outcomes those weights would achieve through OASim modeling, mathematical optimization starts with determining the outcomes the Committee wants to achieve and then finds the policy scenarios with the relative weights that will accomplish those desired outcomes.

In addition, mathematical optimization will allow the Committee to better quantify, understand, and deliberate over tradeoffs between attributes that may conflict with one another. As an example, if the Committee wants to focus on prioritizing the most medically urgent candidates with less regard for other attributes, that will likely cause an increase in the median distance between the donor hospital and transplant program, as the allocation system would be primarily focused on getting organ offers to the most medically urgent candidates, with less regard for distance. However, with mathematical optimization, the Committee can have a more nuanced discussion about the tradeoff between prioritizing the most medically urgent candidates and proximity. The mathematical optimization tool will be able to provide insight into how much an increase in priority for the most medically urgent candidates may influence median travel distance. For example, mathematical optimization may show that increasing the weight of the *Medical Urgency Score* attribute in the composite allocation score by 10% may decrease waitlist mortality/removal for too sick for transplant by 15%, but it would increase median travel distance by 25%. Alternatively, mathematical optimization could show that increasing the weight of the *Travel Efficiency* attribute by 10% will decrease median travel distance by 20% but may cause an increase in the waitlist mortality rate. With mathematical optimization, the Committee will be able to understand the tradeoffs between different attributes and make more informed decisions about the relative weights and rating scales for each attribute in the final policy proposal.

The Committee has almost completed the necessary work to build out the mathematical optimization dashboard. The Committee has determined specific outcome measures to quantify the impact of each attribute in the optimization tool. These outcome metrics, as well as other standard monitoring metrics, will be used to show if, and to what extent, any particular policy scenario accomplishes the stated purpose for the given attribute. Additionally, the Committee has decided on the majority of methods by which points will be assigned for each attribute (i.e., rating scales); this work can be referenced in **Table 1.** Importantly, with mathematical optimization, the Committee will have increased flexibility to include multiple rating scales for each attribute and iterate between different variations of these frameworks to compare the impact of each different policy scenario. The *Body Surface Area (BSA)* section elaborates on this further to provide an example of how the mathematical optimization tool can help the Committee compare the impact of different rating scales.

Once the Committee has used the mathematical optimization to identify a handful of specific policy scenarios that accomplish their desired outcomes, a modeling request will be submitted to the SRTR to simulate the policy scenarios using OASim, which will provide a more detailed and robust analysis of the potential impact of these policy scenarios before submitting a final proposal to public comment for community input and the OPTN Board of Directors for consideration.[11]

Medical Urgency Score

In prior updates, the Committee sought feedback on the potential to convert the medial urgency score from MELD and PELD to Optimized Prediction of Mortality (OPOM). The Committee had previously decided to use simulation modeling to help determine which medical urgency model to utilize. However, with the help of SRTR, it was pointed out that simulation analysis is a poor tool for comparing medical acuity measures and that utilizing empirical data is a preferred evaluation technique. This is because simulation inherently relies on statistical assumptions to generate data that does not exist. This approach can be helpful when attempting to answer research questions for which empirical data are not available (e.g., examining how a proposed allocation policy might impact access to transplant if it were to be implemented into the OPTN system). However, when empirical data are available for a particular research question, it is preferred to use such data, as these data do not rely on any statistical assumptions regarding how the data were generated. Empirical data is available for evaluating how well each of the medical acuity measures predicts transplant-censored death rates according to different medical acuity measures. For example, the outcomes observed among a historical cohort of waiting list candidates can be compared to the predicted outcomes obtained from applying the medical acuity measures to this same cohort of individuals to determine which medical urgency measure yields more accurate estimates of transplant-censored waiting list mortality. This empirical data evaluation should provide a fairer and more accurate comparison across acuity measures.

If the Committee found any medical urgency model to warrant incorporation into the first version of liver continuous distribution, SRTR indicated support in the evaluation of various models utilizing an empirical comparison across medical acuity measures. This spurred the Committee to revisit this discussion and spent the beginning of 2024 reviewing medical urgency models. In addition to MELD and OPOM, a new medical urgency model, Dynamic MELD for Equitable Prioritization (DynaMELD), was brought forward. The following paragraphs will provide an overview of each model and then the Committee's deliberations will be summarized. **Table 2** provides an overall summary of the three models. Each model was compared using the same consideration, as demonstrated in the left column. The Committee reviewed this information as well as more detailed information provided by the authors of each medical urgency model.

Table 2: Summary of Medical Urgency Score Model Comparisons

Consideration	MELD	DynaMELD	OPOM
Exceptions	• Does not incorporate	• Does not incorporate	• Two trees – one for candidates with an active HCC exception; one for candidates with no exception or a non-HCC exception

[11] Mathematical optimization will only provide analyses for liver allocation due to the tool using Liver Simulated Allocation Modeling (LSAM) data, which does not include information on intestine or liver-intestine allocation.

Consideration	MELD	DynaMELD	OPOM
Pediatric	• PELD	• Does not include pediatric candidates	• POPOM – current version incorporates age and time on the waiting list
Models	• Proportional hazards framework – established and vetted approach	• Proportional hazards framework incorporated with neural networks – new and less vetted approach	• Tree-based structure – new and less vetted approach
Variables	• Sex, serum sodium, creatinine, INR, bilirubin, albumin	• Sex, serum sodium, creatinine, INR, bilirubin, albumin • Whether primary diagnosis is PSC • Whether primary diagnosis is PBC • Additional rate of change variables: serum albumin, serum bilirubin, serum creatinine, serum sodium, INR	• Sex, serum sodium, creatinine, INR, bilirubin, albumin • Lab MELD 3.0 score, dialysis in prior week, time since listing • Additional HCC variables: number of tumors, sum of tumor sizes, AFP
Disparities	• Reduces disparities across key demographics	• Reduces disparities across key demographics	• Reduces disparities across key demographics • Performs better than current system for candidates with active HCC exception
Model Outcomes	• Time-to-event outcome of 90-day waiting list mortality • Included candidates who received a transplant within 90 days	• Time-to-event outcome of 90-day waiting list mortality • Included candidates who received a transplant within 90 days	1. Binary outcome of whether or not a candidate died within 90 days • Excluded candidates who received a transplant within 90 days
Results	• Harrell C= 0.8693 (0.8622, 0.8665) • Uno C = 0.8378 (0.8294, 0.8342)	• AUC for HCC candidates = 0.79 • AUC for non-HCC candidates= 0.85	• AUC = 0.852 (0.848, 0.857)

Consideration	MELD	DynaMELD	OPOM
Model Evaluation	• All models exhibited similar AUC/C-statistics, suggesting that each model has a similar ability to distinguish between candidates who will survive without a transplant versus those who will not, and correctly rank pairs of these candidates accordingly. However, because each study employed different study designs, data cohorts, and analytical methods, the AUC/C-statistics presented for each model are not directly comparable. Direct comparisons of model performance necessitate further information from the authors and validation by SRTR.		
Reproducibility	• Already validated and implemented in the system	• Resources needed to reproduce need to be provided to be validated and implemented	• Resources needed to reproduce need to be provided to be validated and implemented
Interpretability	• Utilizes a single equation • Does not capture non-linear relationships among variables • Score is continuous • Established clinical intuition	• Neural network • Captures non-linearities among variables • Covariates that are in both MELD and DynaMELD have similar directions of association, consistent with clinical intuition • Interpretation can be performed at both the population level and the individual level • SHAP values may make interpretation easier • More information is needed to determine whether results for rate-of-change variables align with clinical intuition	• Utilizes multiple branching pathways to produce probabilities of being in each bin • Captures non-linearities among variables • Bins are discrete, final score is discrete; “hard” splits might yield “vastly different scores for candidates with very similar characteristics” • Smoothing mitigates these concerns, but more information is needed to determine how to interpret the “smoothed” results • Clinical intuition would take time to develop

Consideration	MELD	DynaMELD	OPOM
Transparency	• Single equation illustrates impact of each variable on outcomes • Interpretation involves substituting patients' clinical values into this equation	• After application of SHAP values, each variable contributing to an individual's score can be interpreted as up- or down-adjusting the population expected average score	• Tree branches are defined by dichotomizing variables at different cut-points, with some variables appearing at multiple levels of the tree and others appearing at few levels • Interpretation involves tracing the specific path patients follow through the tree
Maintainability	• Adding or removing a variable does not alter the general structure of the model	• More information needed to answer this question	• Adding or removing a variable can yield an entirely different model structure
Transferability	• Single equation is shared among different stakeholders	• Neural network would need to be shared among different stakeholders	• Entire tree would need to be shared among different stakeholders

Optimizing Prediction of Mortality (OPOM)

OPOM was developed in 2019 and uses machine learning to rank adult liver transplant candidates based on their medical urgency for transplant.[12] The model has two classification trees, one for adult candidates with an active HCC exception and one for those with a non-HCC exception or no exception, to generate the prediction of an adult liver candidate's 3-month waitlist mortality or removal. The use of these two different trees allows OPOM to interdigitate HCC candidates among non-HCC candidates. It is important to distinguish that interdigitation involves comparing HCC candidates with similar mortality to candidates with non-HCC exceptions while stratification involves grouping HCC candidates within their own risk.

During the Committee's recent discussions, the model was updated and presented as OPOM 2.0.[13] Updates to this model includes the addition of MELD 3.0 as a variable, the removal of age, and the use of soft trees which seeks to address the discontinuity inherent in "hard" splits that might result in vastly

[12] Dimitris Bertsimas et al., "Development and Validation of an Optimized Prediction of Mortality for Candidates Awaiting Liver Transplantation," American Journal of Transplantation 19, no. 4 (June 2018): pp. 1109-1118, https://doi.org/10.1111/ajt.15172.
[13] Bertsimas D, Everest L, Gu J, Peroni M, Stoumpou V. Deep trees for (un)structured data: Tractability, performance, and interpretability. Manuscript submitted for Publication, 2024.

different scores for candidates with very similar characteristics. For example, suppose that a particular node of the classification tree is defined based on whether a candidate's bilirubin is less than 2.1 mg/dL. In this example, under OPOM 1.0, a candidate with bilirubin equal to 2 mg/dL would follow a different path from an otherwise identical candidate with bilirubin equal to 2.2 mg/dL, because the two candidates fall on either side of the 2.1 mg/dL decision boundary. From a clinical perspective, however, the 0.2 mg/dL difference between these two candidates' bilirubin values might not be clinically meaningful. OPOM 2.0 attempts to mitigate this concern by essentially constructing a weighted average of the possible pathways that these two candidates can follow at this node based on the distance between the candidate's covariate value and the decision boundary (e.g., in the example above, both candidates would have a distance of 0.1 mg/dL). In other words, OPOM 2.0 smoothens out the probability at each node relative to OPOM resulting in a more robust output. At each node, OPOM 2.0 uses many variables whereas OPOM uses only one variable.

For adult candidates with active HCC exceptions, the performance of OPOM 2.0 was significantly stronger than MELD 3.0 (AUC = 0.79, 0.74).[14] For non-HCC exception adult candidates and adult candidates with no exceptions, the performance of OPOM 2.0 and MELD 3.0 were comparable (0.85, 0.84).[15] OPOM had previously developed a pediatric version, POPOM, which did not show significant improvement from the current system of PELD Cr.[16]

Dynamic MELD for Equitable Prioritization (DynaMELD)

DynaMELD is a medical urgency score model that aims to mitigate key sources of waitlist inequity by employing predictive models that can more accurately capture variation in risk among disadvantaged sub-populations, such as candidates with primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC).[17] DynaMELD utilizes a deep neural network within the proportional hazards framework underlying the MELD 3.0 to better account for candidate risk and individualize scores. To address disadvantaged sub-populations, DynaMELD incorporates sparse diagnosis indicator variables for PSC and PBC to mitigate these diagnosis-based inequities. Additionally, the model utilizes rates-of-change of time-varying biomarkers to adjust the score based on the observed trajectory of each candidate's disease.

For adult candidates, the performance of DynaMELD showed improvement to the 90-day concordance by 2.9% (0.818 vs 0.795).[18] Currently, DynaMELD was developed for adult candidates and does not incorporate the pediatric population.

Model for End-stage Liver Disease (MELD)

The current liver allocation utilizes MELD and Pediatric End-Stage Liver Disease (PELD) scores, which are calculations based on a number of clinical lab values that predict a candidate's likelihood of waitlist mortality within 90 days. MELD scores are calculated for individuals over the age of 18 (adult candidates) while PELD scores are calculated for individuals under the age of 12 (pediatric candidates).

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[14] Bertsimas D, Everest L, Gu J, Peroni M, Stoumpou V. Deep trees for (un)structured data: Tractability, performance, and interpretability. Manuscript submitted for Publication, 2024.
[15] Ibid.
[16] OPTN Liver and Intestinal Organ Transplantation Committee, Meeting Summary, April 3, 2023. Available at https://optn.transplant.hrsa.gov/about/committees/liver-intestinal-organ-transplantation-committee/.
[17] Cooper MJ, Khoroshchuk D, Krishnan RG, Bhat M. DynaMELD: A Dynamic Model of End-Stage Liver Disease for Equitable Prioritization. Manuscript Submitted for Publication, 2024.
[18] Ibid.

While liver allocation has utilized MELD and PELD scores for over 20 years, the calculation has been reviewed and subsequently modified. It is not the same calculation now as it was when it was first integrated into allocation.

The MELD score was created using the multivariable Cox regression methods to identify predictors of survival up to 90 days. MELD is a measure of physiological abnormalities associated with end-stage liver disease and is not currently designed to address other conditions for which liver transplantation is performed (i.e., exception cases).[19] MELD has been shown to improve equity in transplant allocation, first in racial disparity and then most recently in sex disparities.[20]

Recent updates, MELD 3.0 and PELD Cr, were implemented in July 2023.[21] Improvements to MELD 3.0 were incorporated to better predict the risk of waitlist mortality for all candidates and provide priority to female candidates to address a long-standing sex disparity on the waitlist. PELD Cr improved the PELD score by better predicting mortality for pediatric candidates and addressing the "growth failure gap." Results from the three-month monitoring[22] of the changes show that the transplant rate for females significantly increased pre- to post-policy implementation, whereas the transplant rate for males remained roughly the same pre- to post-policy. Under PELD-Cr, there were no significant changes in transplant rates or waiting list removal rates for death or too sick, but the median and degree of skewness of PELD scores at transplant decreased pre- to post-policy.

Committee Discussions on Medical Urgency Models

The Committee received presentations from developers of each of the three models and spent subsequent meetings discussing whether either of the alternative models, as they currently stand, warrant incorporation into the first version of liver continuous distribution.

Regarding OPOM, the Committee was most interested in the model's ability to interdigitate adult candidates with active HCC exceptions among adult candidates with active non-HCC exceptions and those with no exceptions.[23] While the area under the curve (AUC) was more significant for candidates with standard HCC exceptions, the AUC was relatively similar for candidates without active standard HCC exceptions. Further, the Committee noted there may be a benefit in having an independent model to address standard HCC exceptions. An independent model could stratify HCC candidates among other liver candidates on the waitlist without having it incorporated into a medical urgency score model. This means that any updates needed to address the HCC candidate population may be easier to address without having to modify an entire medical urgency scoring model.[24] Since the impact seen with OPOM is most relative to the HCC candidate population, the Committee reasoned that stratification of HCC candidates could be achieved through the framework of continuous distribution. As such, the Committee concluded that it may not be beneficial to change the medical urgency score at the same

[19] 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.
[20] Ibid.
[21] "Improving Liver Allocation: MELD, PELD, Status 1A, Status 1B," OPTN, Policy Notice. Board Approved: June 27, 2022. Available at https://optn.transplant.hrsa.gov/media/3idbp5vq/policy-guid-change_impr-liv-alloc-meld-peld-sta-1a-sta-1b_liv.pdf
[22] MELD 3.0 and PELD-CR Three Month Monitoring Report. Available at https://optn.transplant.hrsa.gov/media/ipxa02eb/monitoringreport_liver_20240221_rptn.pdf.
[23] OPTN Liver and Intestinal Organ Transplantation Committee, April 19, 2024, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.
[24] OPTN Liver and Intestinal Organ Transplantation Committee, April 15, 2024, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.

time as changing to a continuous distribution system.[25] The Committee recognized that OPOM has the opportunity to address other exceptions in addition to HCC, as the framework for interdigitating HCC could also be applied to other standard exceptions related to medical urgency. [26]

With DynaMELD, the Committee was interested in the use of a neural network to develop a medical urgency score.[27] The Committee particularly liked that DynaMELD incorporated priority for the cholestatic population as that is a current deficiency of the MELD model.[28] However, the Committee remained concerned that the change variables in the model may have unintended consequences for candidates who become rapidly sick.[29] Additionally, since the Committee saw potential benefits in a neural network-based system, they requested more information on the impact of DynaMELD if other sub-populations were addressed in the model such as adult candidates with active exceptions.

The Committee sought the patient perspective on their feedback regarding the transparency and explainability of both OPOM and DynaMELD to patients. Some benefits were noted in that both OPOM and DynaMELD models allow for honest conversations with candidates when it comes to expectations for health status and potential outcomes following transplantation. Other feedback remained concerned that switching the medical urgency score at the same time as implementing a new liver allocation framework would be too complex. Ultimately, the patient representatives on the Committee emphasized that the most important aspect of a medical urgency score is that it allows for the appropriate ranking of candidates, noting that patients will understand that the sickest candidates receive the highest priority therefore making any complexity of a model less burdensome. Another key factor from a patient perspective when considering medical urgency scores is that it should be able to provide specific parameters that candidates can track to know how their scores, timing of potential transplant, and stability for transplant will all be impacted. These tangible factors may reduce some frustration or anxiety that individuals experience.

MELD as the Input for the Medical Urgency Score Attribute

It was determined that if OPOM or DynaMELD warranted possible incorporation, then the SRTR was available to help the Committee in further analysis, evaluation, and comparison. Due to each model using different methodologies as well as different cohorts of data, further information and evaluation is necessary to provide more direct comparisons and prove robustness. However, the Committee decided to continue the use of MELD and PELD in the first version of liver continuous distribution unless further evidence modifies the Committee's assessment of the alternative models.[30] The Committee emphasizes the strength of the MELD model and is encouraged by the recent results of the MELD 3.0 implementation. Additionally, the Committee notes that switching to a new medical urgency score at the same time as modifying the entire liver allocation may be high risk and has the potential to result in unintended consequences that are not understood.

With the current strength of the MELD system and familiarity among providers and patients, the Committee feels comfortable continuing its use in the first version of liver continuous distribution. Implementing a new medical urgency score at the same time as implementing a new liver allocation

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[25] OPTN Liver and Intestinal Organ Transplantation Committee, May 3, 2024, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.
[26] OPTN Liver and Intestinal Organ Transplantation Committee, May 3, 2024, Meeting Summary.
[27] OPTN Liver and Intestinal Organ Transplantation Committee, April 19, 2024, Meeting Summary.
[28] Ibid.
[29] Ibid.
[30] OPTN Liver and Intestinal Organ Transplantation Committee, May 3, 2024, Meeting Summary.

system would result in difficulty when assessing the effects of the changes. For example, if a monitoring report showed that there was an increase in waiting list mortality, it would be difficult to conclude whether that outcome was affected by the change in medical urgency score or a different part of the new allocation system. With continuous distribution being such a substantial change to the system, it may be beneficial to transition as much status quo as possible to effectively monitor the impact of the new system. The Committee acknowledges the current gap MELD and PELD have when addressing exceptions and seeks to further analyze how a continuous distribution system may help address these gaps.

While the Committee recognizes that the innovative technology of OPOM and DynaMELD are impressive, and likely where the community is headed in the future, they did not find a significant amount of benefit to move to a new medical urgency model at the same time as the implementation of the first version of liver continuous distribution.[31] Additionally, the Committee began to consider how policy could be maintained, evolved, and updated and acknowledged the additional complexities of incorporating a new technology.

The Committee remains interested in understanding the feasibility of collecting prospective data to analyze and compare medical urgency models among each other in the continuous distribution framework. The Committee has offered to continue relationships with each of the medical urgency model teams to remain up to date on any possible updates to the models. The Committee emphasizes the importance of incorporating standard exceptions related to medical urgency into each medical urgency model. However, MELD 3.0 and PELD Cr offer a consistent and robust medical urgency model for the first iteration of continuous distribution. And continuous distribution offers a new opportunity to address both standard and non-standard exceptions.

Exceptions

Transplant programs can submit exception requests when they believe a liver candidate's MELD or PELD score does not accurately reflect their need for transplant. Liver allocation incorporates standard exceptions and non-standard exceptions. The following sections will detail recent discussions regarding standard exceptions, particularly standard HCC exceptions, as well as future discussions the Committee will have when addressing the non-standard exceptions that are reviewed by the National Liver Review Board (NLRB).

The continuous distribution framework allows for a new solution for how to incorporate standard exceptions in liver allocation. Current allocation ties all the standard exceptions to medical urgency (i.e., MELD or PELD) while the continuous distribution system can account for the true purpose of any standard exception. That means, for example, that developing a stratification system for HCC candidates does not need to be tied to MELD or PELD scores – HCC candidates meeting standard criteria could be given more points within a composite allocation score through other mechanisms such as accounting for their access to transplant. Other exceptions, such as hepatic artery thrombosis (HAT), may have a simpler solution as the purpose of that attribute is medical urgency and could continue to be addressed through increases in MELD or PELD scores.

[31] OPTN Liver and Intestinal Organ Transplantation Committee, May 3, 2024, Meeting Summary.

Also, it is important to clarify that the current way exceptions are considered is a misnomer. There are nine diagnoses in OPTN policy with specific criteria, and if a candidate meets the criteria for one of these diagnoses, they are automatically approved for an "exception." These situations are "standard exceptions". However, if an exception is something that does not follow a rule, then these "standard exceptions" are not exceptions in the true sense of the word. If the criteria in policy are the rules, then candidates meeting those rules are provided additional MELD or PELD points. This situation is not an exception to the rule; it follows a rule. That may seem like a trivial distinction, but it highlights how such "exceptions" could be handled under continuous distribution. When constructing the comprehensive framework, the Committee could consider incorporating these "standard exceptions" directly into the composite allocation score. The Committee is considering alternate terminology for the current terminology of "standard exceptions"; possible ideas include "clinical condition points", "condition-associated priority points", or "diagnosis priority points", as they feel this implies current candidate status and diagnosis.[32]

HCC Stratification Attribute

As a brief background, HCC candidates meeting specific criteria in Policy 9.5.I: *Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exception* are provided a MELD or PELD exception score.[33] After a six-month delay, adult HCC candidates are assigned an exception score equal to the median MELD at transplant (MMaT) minus three. Pediatric and adolescent HCC candidates are assigned a score equal to MELD or PELD 40. However, the same scores are assigned regardless of the differing tumor burden between candidates. This presents an opportunity for improvement because current literature indicates that this population has a variable risk of waitlist dropout and overall transplant benefit.[34] Therefore, the Committee has been interested in exploring the feasibility of incorporating an attribute that would further stratify HCC candidates based on additional clinical factors such as tumor size and alpha-fetoprotein (AFP).

The Committee had previously tabled discussions regarding an *HCC Stratification* attribute because of the possibility of utilizing OPOM, which interdigitates adult HCC candidates, as the medical urgency score. However, with the decision to utilize MELD and PELD as the medical urgency score within the first version of continuous distribution, the Committee is revisiting the potential to incorporate an *HCC Stratification* attribute. The Committee notes that the purpose of an *HCC Stratification* attribute is to address both medical urgency and patient access and as such intends to produce outcomes related to both goals. However, to utilize the goals of continuous distribution as a foundation to develop how points will be awarded, the Committee determined that the *HCC stratification* attribute aligns more closely with the goal of patient access.[35]

The Committee determined that patient access was the overall goal of HCC exceptions because it is important to ensure that candidates with HCC receive access to a transplant before their cancer progresses.[36] It was reasoned that waitlist drop out does not drive the need for transplant for candidates

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[32] OPTN Liver and Intestinal Organ Transplantation Committee, May 3, 2024, Meeting Summary.

[33] Policy 9.5.I: *Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exception,* as of July 2024. Available at https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.

[34] Mehta N, Dodge JL, Hirose R, Roberts JP, Yao FY. Predictors of low risk for dropout from the liver transplant waiting list for hepatocellular carcinoma in long wait time regions: Implications for organ allocation. Am J Transplant. 2019 Aug;19(8):2210-2218. doi: 10.1111/ajt.15353. Epub 2019 Apr 5. PMID: 30861298; PMCID: PMC7072024.

[35] OPTN Liver and Intestinal Organ Transplantation Committee, June 21, 2024, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.

[36] Ibid.

with HCC exceptions; the need for transplant is one of ensuring access while the candidate remains within the required criteria.

Regarding the goal of medical urgency, the Committee concluded that there is an urgency for transplant based on the progression of the cancer.[37] As the HCC progresses, candidates may fall outside of the criteria in Policy 9.5.I and drop off the wait list which means there is an urgency for transplant for those candidates. Additionally, the Committee noted that the need to stratify HCC candidates implies that there are differences in medical urgency due to differences in tumor biology resulting in the need for some candidates to receive more points.[38]

The Committee also acknowledged the role of post-transplant survival within HCC exceptions and emphasized that the current criteria in Policy 9.5.I, will continue forward into a continuous distribution system.[39] So, while candidates with an HCC exception may not receive extra points within the goal of post-transplant survival, Policy 9.5.I will provide guardrails to help ensure that post-transplant survival is accounted for.

As the Committee continues to refine the *HCC Stratification* attribute, they will review available models[40,41,42,43,44] and determine which variables they want to incorporate.

Other Standard Exceptions

Including HCC, there are currently nine standard exceptions in Policy 9.5: *Specific Standardized MELD or PELD Score Exceptions.*[45] **Figure 3** provides a high-level, hypothetical example of how points could be awarded to exception candidates within a continuous distribution system. In the example, Candidate A does not have an exception while Candidate B, C, and D all have what is now considered a "standard exception". For each of these "standard exceptions", the candidates are assigned a certain number of points either in the medical urgency sub-score or the patient access sub-score. For instance, Candidate B has a hilar cholangiocarcinoma diagnosis and provided additional medical urgency points because they meet the criteria for a hilar cholangiocarcinoma "standard exception" per Policy 9.5.A: *Requirements for Cholangiocarcinoma MELD or PELD Score Exceptions.* Similarly, Candidate C is provided additional patient access points because they have an HCC "standard exception", and Candidate D is assigned more medical urgency points because they have a hepatic artery thrombosis (HAT) "standard exception". A continuous distribution allocation system will continue to recognize that the medical urgency score may

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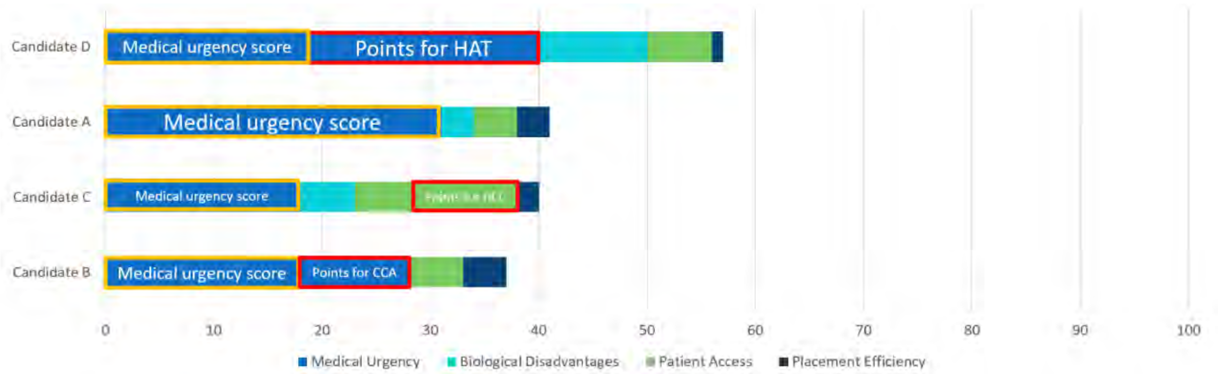
[37] OPTN Liver and Intestinal Organ Transplantation Committee, June 7, 2024, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.
[38] OPTN Liver and Intestinal Organ Transplantation Committee, June 7, 2024, Meeting Summary.
[39] Ibid.
[40] Mehta N, Dodge JL, Roberts JP, Yao FY. A novel waitlist dropout score for hepatocellular carcinoma - identifying a threshold that predicts worse post-transplant survival. J Hepatol. 2021;74(4):829-837. doi:10.1016/j.jhep.2020.10.033
[41] Toso C, Dupuis-Lozeron E, Majno P, et al. A model for dropout assessment of candidates with or without hepatocellular carcinoma on a common liver transplant waiting list. Hepatology. 2012;56(1):149-156. doi:10.1002/hep.25603
[42] Vitale A, Volk ML, De Feo TM, et al. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list. Journal of Hepatology. 2014;60(2):290-297. doi:10.1016/j.jhep.2013.10.010
[43] Bertsimas D, Kung J, Trichakis N, Wang Y, Hirose R, Vagefi PA. Development and validation of an optimized prediction of mortality for candidates awaiting liver transplantation. Am J Transplant. 2019;19(4):1109-1118. doi:10.1111/ajt.15172
[44] Marvin MR, Ferguson N, Cannon RM, Jones CM, Brock GN. MELD EQ : An alternative Model for End-Stage Liver Disease score for patients with hepatocellular carcinoma: HCC-MELD-AFP Interaction. Liver Transpl. 2015;21(5):612-622. doi:10.1002/lt.24098
[45] Policy 9.5: *Specific Standardized MELD or PELD Score Exceptions,* as of July 2024.

underestimate certain candidates' mortality risk who meet specific criteria and include additional points for these candidate populations within a composite allocation score.

Figure 3: Example of Incorporating Standard Exceptions into a Composite Allocation Score



- **Candidate A**: Medical urgency sub-score is driven by medical urgency score(i.e. calculated MELD)
- **Candidate B:** Calculated MELD is low, but receives more medical urgency points for CCA
- **Candidate C:** HCC candidate, is not medically urgent but receives more points in the patient access sub-score
- **Candidate D:** Calculated MELD is low, but the candidate receives more medical urgency points for HAT

The standard exceptions could be conceptualized to be categorized into "condition-associated priority points" (or another name as previously suggested) and if a candidate meets the criteria for any of the nine diagnoses, as currently required by Policy 9.5, then the candidate would receive condition-associated priority points. The Committee acknowledges that the purpose of the majority of the standard exceptions have dual functions and will eventually determine the overarching goal alignment of each standard exception.[46] Regardless of the main purpose, or goal, of the standard exception multiple outcome metrics will be analyzed to ensure that standard exceptions continue to maintain the status quo within a continuous distribution system. [47]

Table 3 shows the areas of outcomes that the Committee determined to be important when analyzing the impact of each standard exception. For patient access, the Committee seeks to ensure that transplant rates remain the same or improve within the continuous distribution system, while medical urgency monitors that waitlist dropout or death rates remain the same or do not increase. The Committee will also look at additional outcome metrics.

As seen in **Table 3,** the Committee reasoned that the majority of the standard exceptions address both patient access and medical urgency, with the exception of HAT, which solely intends to address medical urgency. During these discussions, the Committee interpreted patient access to apply to standard exceptions when the treatment of the underlying condition is limited by the severity of liver disease, thus requiring increased access to transplant. For example, the severity of liver disease impairs the treatment ability for HCC, so the risk of death is above what is accounted for in the medical urgency score (i.e., MELD or PELD) requiring an additional increase in access to transplant.

[46] OPTN Liver and Intestinal Organ Transplantation Committee, June 21, 2024, Meeting Summary.
[47] OPTN Liver and Intestinal Organ Transplantation Committee, June 21, 2024, Meeting Summary.

As noted, the purpose for the standard exception for HAT is solely addressed through medical urgency. At minimum, the Committee seeks to maintain the status quo for candidates with HAT exceptions. However, additional considerations could be made to ensure proper priority for candidates with HAT exceptions such as creating a Status 1B for adults.

It is important to note that the Committee does not intend to change the current criteria for any standard exception in policy unless deemed necessary. Therefore, in a continuous distribution system, a candidate will continue to have to meet the criteria set in policy to receive the standard exception; the way candidates receive points for these exceptions will be different. These discussions are preliminary and subject to change based on community input, review of data, or analysis within the mathematical optimization dashboard. Please provide feedback for any or all standard exceptions.

Table 3: Metrics of Success for Standard Exceptions Found in Policy 9.5: Specific Standardized MELD or PELD Score Exceptions

Standard Exception	Metrics of Success
Hepatic Artery Thrombosis	• Medical Urgency
Hilar Cholangiocarcinoma	• Patient Access • Medical Urgency
Cystic Fibrosis	• Patient Access • Medical Urgency
Familial Amyloid Polyneuropathy	• Patient Access • Medical Urgency
Hepatopulmonary Syndrome	• Patient Access • Medical Urgency
Metabolic Disease	• Patient Access • Medical Urgency
Portopulmonary Hypertension	• Patient Access • Medical Urgency
Primary Hyperoxaluria	• Patient Access • Medical Urgency
Hepatocellular Carcinoma	• Patient Access • Medical Urgency

The Committee will continue to refine the purposes of each standard exception and will utilize mathematical optimization tools to review impacts on various outcomes and determine potential weights.

Non-Standard Exceptions & the National Liver Review Board (NLRB)

In addition to standard exceptions, liver allocation also incorporates non-standard exceptions. Non-standard exceptions are those that do not meet the criteria in OPTN policy and as such necessitate review by the NLRB. The review board framework – or chiefly the ability of transplant programs to request changes to their candidates' prioritization and for that request to be evaluated by a group of peers – is an important part of current liver allocation. As the OPTN transitions to points-based scores for all organs, this component will be a necessary and consistent part of continuous distribution for all organs.

The Committee expects to continue to utilize some form of review board to evaluate instances where a candidate's clinical situation is not appropriately represented by their composite allocation score. Likely, what constitutes a MELD or PELD exception and the process through which exceptions are considered will need to change within the context of continuous distribution. While the Committee has not yet discussed how to handle exceptions in-depth, the structure of the review boards within lung allocation may offer insight into how these reviews could occur with consideration to a composite allocation score.

With the implementation of lung continuous distribution, the Lung Review Board was updated to review exception requests for candidates whose composite allocation score may not appropriately prioritize them for transplant. Exceptions may be requested for any components of the score that can be determined before the match run: waiting list survival, posttransplant outcomes, candidate biology, and patient access. Exceptions are not available for placement efficiency, since points for placement efficiency are calculated at the time the match run is executed, based on the location of the donor.

Exceptions are reviewed prospectively by the Lung Review Board, and exceptions do not expire. Transplant programs request a percentage of the maximum points allowed for a goal when requesting an exception. For example, a lung transplant program could request 6.35% of the possible 25 waitlist survival points, which equates to 1.5875 points. Based on data as of January 2023, this would place a candidate around the 90th percentile for the waitlist survival score. Transplant programs utilize the national percentile data as a guide to help determine what percentage of points to request when submitting an exception to the Lung Review Board.

The NLRB will have to adapt to reviewing exception requests based on the different components of a composite allocation score and not solely those tied to medical urgency (i.e., MELD or PELD scores). This will require the Committee to consider the purpose of each non-standard exception that is detailed in NLRB guidance as well as create guidance for transplant programs to determine how to submit non-standard exceptions that are not currently addressed in guidance.

Body Surface Area (BSA)

The Committee identified the need to incorporate an attribute to address short-statured liver candidates' access to transplantation, as they typically have lower transplant rates, longer wait times, and higher mortality on the waitlist.[48] There is a tendency to use smaller deceased donor livers for larger candidates, making small, deceased donor livers less accessible for small candidates. This disproportionately affects female, Hispanic, and Asian candidates.[49,50,51] This has been noted as a problem of access to appropriate-sized grafts, which can have detrimental effects on outcomes. If two

[48] Ge J, Lai JC. Identifying a clinically relevant cutoff for height that is associated with a higher risk of waitlist mortality in liver transplant candidates. Am J Transplant. 2020 Mar;20(3):852-854. doi: 10.1111/ajt.15644. Epub 2019 Nov 4. PMID: 31597006; PMCID: PMC7042034.

[49] Ge J, Lai JC. Identifying a clinically relevant cutoff for height that is associated with a higher risk of waitlist mortality in liver transplant candidates. Am J Transplant. 2020 Mar;20(3):852-854. doi: 10.1111/ajt.15644. Epub 2019 Nov 4. PMID: 31597006; PMCID: PMC7042034.

[50] Bernards S, Lee E, Leung N, Akan M, Gan K, Zhao H, Sarkar M, Tayur S, Mehta N. Awarding additional MELD points to the shortest waitlist candidates improves sex disparity in access to liver transplant in the United States. Am J Transplant. 2022 Dec;22(12):2912-2920. doi: 10.1111/ajt.17159. Epub 2022 Aug 3. PMID: 35871752.

[51] Kling CE, Biggins SW, Bambha KM, et al. Association of Body Surface Area With Access to Deceased Donor Liver Transplant and Novel Allocation Policies. *JAMA Surg.* 2023;158(6):610–616. doi:10.1001/jamasurg.2023.0191

recipients have the same MELD score, the smaller candidate would have a more difficult time finding a liver.

Currently, size is not addressed in liver allocation policy, but the Committee seeks to incorporate an attribute to address this inequity. The purpose of this attribute in continuous distribution is to provide equal access to transplant for candidates regardless of their stature. During the Committee's initial discussions regarding the identification of attributes to include in liver continuous distribution, donor-recipient size matching was determined to be a necessary attribute. The attribute evolved to be referred to as the *Height/Body Surface Area (BSA)* attribute and now is referred to as the *BSA* attribute since the Committee has determined to utilize BSA as the input for the rating scale.

The Committee reviewed height, BSA, and anteroposterior (AP) diameter as potential inputs for a size-based rating scale for this attribute. Since height is a two-dimensional measurement and the liver is a three-dimensional organ, the Committee sought a more appropriate input for the rating scale related to size. While AP diameter may be a "gold standard" measurement, the Committee noted it would be difficult to incorporate into OPTN policy because additional metrics would need to be captured to calculate it. [52] Therefore, they reviewed literature that observed that BSA measurements have a better correlation to AP diameter than height and as such determined to utilize BSA measurements as the input to a size-based attribute and rating scale.

With the Committee determining to utilize BSA and the input for the rating scale, the next step they took was to develop the rating scale and determine necessary donor modifiers.[53] The initial options the Committee considered are based as binary rating scales. This means that a candidate below a set BSA threshold would receive all the points available in the rating scale and those above the threshold would receive no points. The threshold is based on Kling et al. 2023 and was validated in OPTN data.[54] However, the Committee noted that solely awarding points to small-statured candidates does not completely address the issue because the small-statured candidate needs access to an appropriately sized liver. This is where a donor modifier will help. Incorporating a donor modifier for the size-based rating scale will identify the livers that may be more appropriately sized for small-statured candidates and give those candidates additional points when these livers become available. The Committee supports incorporating a donor modifier for this attribute because there is clinical justification since small-statured candidates are more likely to experience waitlist mortality and there are benefits from an efficiency standpoint.

[52] OPTN Liver and Intestinal Organ Transplantation Committee, August 18, 2023, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.

[53] Donor modifiers are a function within continuous distribution that modify the order of the match run based upon donor characteristics. It either emphasizes or deemphasizes an attribute dependent upon donor characteristics. Information must be known at the time of the match run to be incorporated as a donor modifier.

[54] Kling CE, Biggins SW, Bambha KM, et al. Association of Body Surface Area With Access to Deceased Donor Liver Transplant and Novel Allocation Policies. *JAMA Surg.* 2023;158(6):610–616. doi:10.1001/jamasurg.2023.0191

The current two initial rating scales are summarized in **Figure 4**. Each option incorporates a donor modifier which intends to target appropriately sized livers to small-statured candidates.

Figure 4: Rating Scale and Donor Modifier Options for *BSA* Attribute

Option 1: Adult candidates (at least 18 years old) receive points within their score if their BSA is in the bottom 15th percentile.

Option 2: Adult candidates (at least 18 years old) receive points within their score if their BSA is in the bottom 15th percentile and for those in the bottom 5th percentile of BSA additional points are awarded.

Donor Modifier: Both options incorporate a donor modifier of awarding these *BSA* attribute based points in situations where the deceased donor is at least 18 years old and is in the bottom 10th percentile of donor BSA.

The next steps include utilizing mathematical optimization to review the potential impacts each rating scale may have on outcomes and choose the most appropriate. The *BSA* attribute provides a helpful example of how the mathematical optimization dashboard will aid the Committee in refining the project in terms of deciding which rating scales to optimize. The mathematical optimization system preloads the simulation results of over ten-thousand possible allocation policies. The mathematical optimization dashboard has both rating scale options available in the system and users can develop potential policy scenarios by switching out the rating scale. Then the dashboard will produce analyses of the impact of each potential policy scenario, as seen in **Figure 5**, and the user will be able to compare the impacts of the different rating scales.

Figure 5: Example Comparison of the Impacts of Rating Scales

The Committee remains interested in exploring more continuous rating scales and donor modifiers and reviewing more complex options that could incorporate size-matching. However, the Committee acknowledges the impact of incorporating any points based on size as a beneficial solution and will further refine as deemed necessary.

Utilization Efficiency

During initial discussions, the Committee referred to this attribute as the *Proximity Efficiency* attribute. This is aligned with how lung and kidney approached the attributes under the goal of Placement Efficiency. However, as the Committee began more detailed discussions, they determined that this attribute's purpose in the context of liver continuous distribution was related to increasing efficiency and renamed it to Utilization Efficiency attribute.

Specifically, the Committee concluded that the Utilization Efficiency attribute's purpose is to increase efficiency in the organ placement system by making difficult-to-place grafts less difficult to place. Since medically complex livers are grafts that are more difficult to place, the Committee sought to define a medically complex liver and determined that the criteria should appropriate the current system which is DCD or age over 70. The Committee recognizes that the definition of a medically complex liver may evolve in the future given the advancement of the machine perfusion field. The Committee was also interested in including fat content for the criteria for medically complex liver grafts but acknowledged that to award points in an allocation system, the information must be known at the time of the match run, and fat content is not always known.

Upcoming Committee discussions will be determining how to award points to candidates within a composite allocation score to increase efficiency in placing medically complex livers. One option could be to award points to candidates willing to accept a medically complex liver offer. This means that when a liver that is DCD or age over 70 is offered, any candidate who indicated willingness to accept such an offer will receive additional points within their composite allocation score. An additional option could be to determine the clinical characteristics of a candidate who would be more likely to accept a medically complex liver offer. This removes the opt-in basis for awarding points and would award points to candidates who meet specific clinical criteria for a DCD or age over 70 liver offer. However, the Committee notes that just because a candidate indicates a willingness to accept a medically complex liver or has the identified clinical criteria, they may be at a transplant program that does not accept offers for medically complex livers.

Therefore, another option is to award points to candidates who are listed at transplant programs that have historically accepted medically complex liver offers. This could be based on a transplant program's offer acceptance ratio. This means that if a transplant program's offer acceptance ratio is high for medically complex livers, then the transplant program would receive a higher number of points in this rating scale, and thus receive more offers. By the virtue of receiving more offers, it will increase the number of offers that a transplant program is expected to accept and therefore create negative pressure on the offer acceptance ratio. However, the opposite can also occur, where a transplant program has a lower offer acceptance ratio, so they receive fewer points within a utilization efficiency rating scale, thus receiving fewer offers. However, by receiving fewer offers, the expected offer acceptance will be lower, which may increase the offer acceptance ratio through positive pressure. The weight of the *Utilization Efficiency* attribute can remain low to mitigate some of the concerns about a feedback loop which was noted by the Committee.[55] This solution addresses the issue of having candidates appear higher on match runs where the transplant program they are listed at may not perform transplants with medically complex livers, thereby not increasing efficiency. However, it would award points based on transplant programs rather than candidate characteristics.

There may be an opportunity to combine some of these options. While some of these concepts may seem new, they can be equated to allocation solutions related to split livers. A candidate may be willing to accept a split liver segment but would need to be located at a transplant program that has the expertise to perform these types of transplants. Therefore, transplant programs that perform split liver transplants may indicate specific candidates at their program are willing to accept a split liver segment in order to increase their access to transplant as well as efficiency of receiving acceptable split liver offers. The Committee plans to have more detailed discussions about split liver allocation in the context of continuous distribution, but this example offers a comparison to a familiar concept.

Pediatric Attribute

There are several instances where the current liver allocation system addresses the needs of the pediatric population. The Committee has determined that it is vital to continue to include similar, if not additional, forms of pediatric priority in the points-based framework. The Committee seeks to collaborate with pediatric stakeholders throughout the development of continuous distribution to ensure pediatric candidates are appropriately considered and provided sufficient access and priority to liver transplant.

The Committee continues to develop the continuous distribution framework to have multiple considerations toward pediatric priority within allocation. Importantly, there is a *Pediatric Priority* attribute within continuous distribution that intends to eliminate the pediatric waitlist, measured by reducing time on the waitlist for pediatric candidates. The Committee agreed that the *Pediatric Priority* attribute should be based on a binary rating scale, meaning that if a candidate is registered before turning 18, they receive points for pediatric priority, and if a candidate is registered after turning 18, they receive no points for pediatric priority.

Additionally, the Committee has begun to determine how to incorporate Status 1B priority into the new points-based system. Status 1B is notable because the status itself already incorporates a points-based ranking based on diagnosis, as seen in **Table 4**. These points prioritize pediatric candidates with chronic liver disease, who are at the highest risk of mortality, ahead of other Status 1B candidates. Candidates with hepatoblastoma also received additional points. The Committee intends to keep this level of priority within Status 1B for pediatric candidates with chronic liver disease in the continuous distribution system.

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

Table 4: OPTN Policy 9.7.C: *Points Assigned by Diagnosis*

Diagnosis	Status 1B Points
Chronic Liver Disease	15
Hepatoblastoma	5
Metabolic Disease (Such as Organic Acidemia or Urea Cycle Defect)	0
Any other diagnosis	0

Feedback from the OPTN Pediatric Transplantation Committee has provided the Committee with further direction, recommending that Status 1B candidates should receive more points than any MELD or PELD candidate, but fewer points than Status 1A candidates.[56] In rare instances, the OPTN Pediatric Transplantation Committee felt it may be acceptable to review modeling analyses for situations where a highly urgent MELD or PELD candidate to be ranked higher than a Status 1B candidate on a match run.[57]

Current allocation policy typically results in pediatric candidates accepting pediatric donors. With the increased priority expected to be provided to pediatric candidates in continuous distribution, the Committee recognizes that pediatric candidates may now see more adult donor organ offers than they have historically. Since statistical modeling relies on historical data, this expected increase in adult offer volume for pediatric candidates may yield overly optimistic transplant rates in simulation results. The Committee is aware of this limitation and will work closely with the simulation scientists to ensure that modeling results are as accurate as possible. Initial thoughts are to incorporate pediatric offer filters into the simulation.

Additional pediatric considerations are warranted and hope to be addressed in the *BSA* attribute, which is detailed in the *Body Surface Area (BSA)* section above. The Committee encourages feedback on these topics as well as any others to ensure that the needs of the pediatric liver candidate population are being addressed.

Travel Efficiency

The Committee has continued to discuss the *Travel Efficiency* attribute and would like community input to further build out a rating scale. The Committee seeks to develop a rating scale that considers the distance between donor hospitals and transplant programs in maximizing the efficiency of allocation processes. Furthermore, the Committee determined that the *Travel Efficiency* attribute should be based on the differences in flying versus driving, and not incorporate cost-related considerations. In concept, this means that a potential rating scale would award points to candidates who are closer to the donor hospital from which the deceased donor liver is offered because the organ could be transported via cars, and fewer points to candidates farther away because a flight would be required. However, the Committee recognizes there are variations in travel practices around the nation and seeks to develop a more nuanced rating scale.

To provide an initial framework, the Committee reviewed the lung and kidney *Travel Efficiency* attribute rating scales and aligned more closely with the lung rating scale, however noting a few caveats. Livers

[56] OPTN Pediatric Transplantation Committee, August 18, 2023, Meeting Summary. Available at https://optn.transplant.hrsa.gov/.
[57] OPTN Pediatric Transplantation Committee, August 18, 2023, Meeting Summary.

are more similar to lungs in terms of cold ischemic times than kidneys, and livers and lungs have more biological necessity than kidneys in terms of cold ischemic time. The Committee seeks to refine this rating scale to have it account for the specific nuances of liver allocation and incorporate a wider array of experience. The Committee seeks to understand travel practices across the nation for both transplant programs and organ procurement organizations. Please leave feedback regarding at what point the preference for travel switches from driving to flying or any other travel-related practices.

NOTA and Final Rule Analysis

The Committees submit this concept paper 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."[58] 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."[59] While this paper does not propose policy changes at this time, the concepts presented in this paper:

Are based on sound medical judgment:[60] The construction of the individual ratings scales and weights will be based on objective data, including simulation modeling, published research, and mathematical optimization. The Committee will rely upon peer-reviewed literature and data analyses as well as their own clinical experience and judgment in making determinations regarding assigning weights and ratings to each attribute.

Seek to achieve the best use of donated organs:[61] The Committee will need to balance how to prioritize the most medically urgent candidates against the need to optimize post-transplant outcomes, ultimately resulting in the best use of donated organs. Before the policy proposal is released for public comment, it will be modeled by the SRTR to assess its impact on waitlist mortality and post-transplant outcomes. If necessary, the Committee will adjust the rating scales or weights of the attributes to balance these outcomes.

Are specific for each organ:[62] In this case, the allocation systems will be tailored to livers and intestines.

Are designed to avoid wasting organs:[63] The Committee identified multiple attributes specifically designed to avoid wasting organs: utilization efficiency, body surface area, medical urgency, and

[58] 42 CFR §121.4(a).
[59] 42 C.F.R. §121.8(a).
[60] 42 CFR §121.8(a)(1).
[61] 42 CFR §121.8(a)(2)
[62] 42 CFR §121.8(a)(4)
[63] 42 CFR §121.8(a)(5).

travel efficiency. If necessary, the Committee will be able to adjust the weighting of the attributes to balance the number of transplants against other attributes.

Are designed to…promote patient access to transplantation:[64] The Committee identified several attributes that specifically ensure similarly situated candidates have equitable opportunities to receive an organ offer: medical urgency and HCC stratification. The inclusion of these attributes is likely to increase access to transplantation for these candidates.

Are designed to…promote the efficient management of organ placement:[65] The Committee will consider indicators of efficiency associated with procuring and transplanting livers and intestines, including travel costs and the proximity between the donor and transplant hospitals.

Not be based on the candidate's place of residence or place of listing, except to the extent required [by the aforementioned criteria]:[66] The Committee is considering the candidate's place of listing to the extent that is required for the purpose of achieving efficient placement of the organs, specifically for travel efficiency, placement efficiency, and supply/demand.

Consider whether to adopt transition procedures:[67] A points-based framework will facilitate the use of transition procedures for existing candidates. For example, the OPTN may be able to compare the policy proposal with the results of a revealed preference analysis and modeling to determine who is impacted and if there is a need for transition procedures. This would allow members and patients time to prepare for these changes.

Conclusion

Continuous distribution utilizes a points-based system for organ allocation and will be more equitable and flexible than the current allocation system. By separating the specific attributes and developing attribute-specific rating scales and weights, there will be more nuanced solutions for how certain candidate populations are prioritized, thereby improving equity in access to organ transplantation. This project serves as an opportunity to rethink how the OPTN and the transplant community develop organ allocation policies.

This update paper explains the work the Committee has completed to date and seeks community feedback on the project thus far. The Committee is interested in the community's input on the overall project plan and any other aspects of the allocation system that are relevant to continuous distribution.

This is one step in a multi-phase project to convert the current classification-based allocation system to a continuous distribution framework. The Committee will continue to engage the community throughout the project's development and appreciates broad input to inform a robust allocation proposal.

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[64] 42 CFR §121.8(a)(2).
[65] 42 CFR §121.8(a)(5).
[66] 42 CFR §121.8(a)(8).
[67] 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.

Considerations for the Community

- Please provide any feedback on the identified attributes as well as their drafted purposes and initial rating scales.
- Please provide any feedback on the Committee's decision to utilize MELD and PELD as the medical urgency score model within the first version of continuous distribution.
- Please provide any feedback specific to the pediatric population within liver continuous distribution.
- Please provide feedback on when your organization begins to fly rather than drive for organ procurement as well as any feedback on travel practices.
- Please provide feedback on the *BSA* attribute including the decision to use BSA, the options for rating scales, and donor modifiers.
- Please provide feedback on the *Utilization Efficiency* attribute including input on the options for how to award candidates points and the definition of a medically complex liver offer.
- Please provide feedback on how to incorporate exceptions into the continuous distribution framework, including HCC stratification, and whether any specific donor modifiers are necessary.
- Please provide feedback on other aspects of this project including any additional considerations that are not addressed in this paper which warrant Committee discussion.
- What areas can be improved to address the needs of patients including areas that need better communication and education?

Appendix A: Glossary of Terms

The following terms are used throughout the concept paper.

Acuity Circles (AC): The current liver allocation policy that utilizes a series of concentric circles and MELD/PELD groupings to rank liver and liver-intestine candidates on the match run.

Analytical Hierarchy Process (AHP): An AHP is an example of a stated preference analysis. This analysis asks participants to state their preferences in a pairwise comparison.

Attribute: Criteria used to classify, sort, and prioritize candidates.

Classification-based framework: Groups similar candidates into classifications or groupings. The candidates are then sorted within those classifications. This is the framework currently used to allocate organs.

Composite Allocation Score: Combines points from multiple attributes together. This concept paper proposes the use of composite allocation scores in a points-based framework.

Concentric Circles: This distribution framework utilizes the distance between the donor hospital and the candidate's transplant hospital to prioritize organ offers to candidates. These distances are grouped into zones at specific nautical mile distances.

Calculated Panel Reactive Antibody (CPRA): The percentage of deceased donors expected to have one or more of the unacceptable antigens indicated on the waiting list for the candidate. The CPRA is derived from HLA antigen/allele group and haplotype frequencies for the different ethnic groups in proportion to their representation in the national deceased donor population.

Exception (standardized): When the calculated MELD or PELD score does not reflect the candidate's medical urgency, a liver transplant program may request an exception score. A candidate that meets the criteria for one of nine diagnoses in OPTN policy is approved for a standardized exception.

Exception (non-standard): When the calculated MELD or PELD score does not reflect the candidate's medical urgency, a liver transplant may request an exception score. If the candidate does not meet the criteria for a standardized exception as outlined in OPTN policy, the request is considered by the National Liver Review Board (NLRB).

Framework: A collection of policies and procedures used to distribute organs. Examples include concentric circles and continuous distribution.

Goals: Five goals constitute the overall composite allocation score. These goals align with the requirements in the NOTA and the OPTN Final Rule: Medical urgency, post-transplant survival, candidate biology, patient access, and placement efficiency.

Human Leukocyte Antigen (HLA): A type of molecule found on the surface of most cells in the body. Human leukocyte antigens play an important part in the body's immune response to foreign substances.

Ischemic Time: Ischemic time is broken into three subparts: procurement, transit, and transplant time. Procurement time begins at cross-clamp and ends at transit departure time. OPO and procurement practices, among other things, influence procurement-related ischemic time. Transit time is the time between departure from the procurement location and delivery at the transplant hospital. Transplant time is then the time between delivery at the transplant hospital and the start of anastomosis.

MELD: Model for End-Stage Liver Disease; the scoring system used to measure illness severity in the allocation of livers to adults and adolescents.

MMaT: Median MELD at Transplant; The MMaT is calculated by using the median of the MELD scores for transplants performed within 150 nautical miles (NM) of each donor hospital. Exception candidates on a match run are assigned an exception score relative to the MMaT for the donor hospital where the match is run and ranked against each other based on time since submission of the earliest approved exception.

NLRB: National Liver Review Board; A review board of members drawn from a nationwide pool of liver transplant physicians and surgeons, who review non-standard exception requests from transplant programs for candidates whose calculated MELD score or PELD score does not accurately reflect the candidate's medical urgency for transplant.

PELD: Pediatric End-Stage Liver Disease model; The scoring system used to measure illness severity in the allocation of livers to candidates under the age of 12.

Points-based framework: A points-based framework gives each candidate a score or points. Organs are then offered in descending order based on the candidate's score. This concept paper proposes a points-based framework for organ allocation.

Rating Scale: Describes how much preference is provided to candidates within each attribute. Applying the rating scale to each candidate's information and combining it with the weight of the attribute results in an overall composite score for prioritizing candidates.

Revealed Preference: A revealed preference analysis looks at actual decisions to determine the implicit preferences of the decision maker. This is compared with a stated preference analysis (for example, AHP) that asks the decision maker to state their preferences in an experiment.

Weight: Weights are the relative importance or priority of each attribute toward our overall goal of organ allocation. Combined with the rating scale and each candidate's information, this results in an overall composite score for prioritizing candidates.

Appendix B: Continuous Distribution Resources

For additional information on the continuous distribution framework and the work of the OPTN, visit: https://optn.transplant.hrsa.gov/policies-bylaws/a-closer-look/continuous-distribution/

The OPTN Liver and Intestinal Organ Transplantation Committee previously released a previous concept papers and committee updates on the continuous distribution of livers and intestines.

- https://optn.transplant.hrsa.gov/media/enuh5qmk/liver_cd_update_incorporatehrsacomments_pcsummer2023.pdf
- https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/update-on-continuous-distribution-of-livers-and-intestines/
- https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/continuous-distribution-of-livers-and-intestines-concept-paper/

Other continuous distribution resources:

- Continuous Distribution of Livers and Intestines
- Continuous Distribution of Lungs
- Continuous Distribution of Kidneys and Pancreata
- Continuous Distribution of Hearts

Ethical Considerations of Continuous Distribution in Organ Allocation White Paper