The American Society of Transplantation (AST) responded to eight items the OPTN released for public comment on July 31, 2024. The AST submitted the responses below through the OPTN website on September 12, 2024, after receiving input from the AST's communities of practice, OPTN Policy Committee, and Board of Directors.

1. Promote Efficiency of Lung Donor Testing

The American Society of Transplantation (AST) generally supports the proposal, "Promote Efficiency of Lung Donor Testing," and offers the following comments for consideration:

- The proposal strikes a reasonable balance between informational needs and feasibility but exemplifies the challenges with interventions to improve efficiency split between policy and guidance. The AST agrees that the outlined testing, timeline of testing, and proposed guidance would improve allocation efficiency and decrease the burden on transplant hospitals. Availability of the requested testing provided at the time of the initial lung offer would decrease the need for the transplant hospital to request additional and updated testing, allowing for a timely decision regarding organ acceptance. The policy has enough flexibility in the requirements, acknowledging varying available resources at donor hospitals, prioritizing transmission of vital information for transplant hospitals to decide on lung offer acceptance.

- The AST does not believe that any of the requirements listed in the policy should be moved to guidance. The proposed policy requirements are reasonable and necessary items for determination of lung suitability for transplant. The AST does recommend moving some considerations in the guidance to policy, specifically:
    - Information pertaining to bronchoscopy, imaging, echocardiogram, and right heart catheterization that is addressed in both guidance and policy. The AST suggests consolidating this information in OPTN policy to define clearly what is required.
    - For pediatric donors, lung measurements are helpful information that should be required by policy.

- The timely availability of the proposed data and images are essential for this proposal to achieve the aims of more efficient organ allocation. The AST recommends that the most recent chest x-ray image be available at the time of the initial lung offer, not just a report. Further, DICOM images are preferred and should be encouraged. Otherwise, the requested testing and timeline is reasonable for the majority of donor lung offers and should be feasible, understanding that there are some donor situations that are more challenging (e.g., DCD donors). The AST requests that the OPTN incorporate defined flexibility for those donor cases in which the donor hospital has limited resources to complete all requirements (documentation of these limitations should be required). Additionally, the AST suggests that the OPTN engage HRSA and CMS about increased scrutiny of existing hospital regulations requiring the available resources to accomplish these evaluation tasks in a timely manner. OPOs in some instances receive immense pushback from hospitals when asked to provide more in depth and more timely evaluations, especially regarding various imaging procedures.

- The AST believes guidance for fungal and bacterial cultures, chest CT scans, chest x-rays, and right heart catheterizations will be beneficial. The AST proposes "bacterial culture results" be changed to "bacterial lower respiratory tract cultures in process" and "fungal culture results" be changed to "fungal lower respiratory tract cultures in process"

to emphasize that these cultures may not be finalized and do not need to be finalized at the time of organ offer to avoid allocation delays. Additionally, the AST recommends the inclusion of donor antimicrobial treatment data in this guidance. The AST also suggests that the OPTN Lung Transplantation Committee collaborate with the ad hoc OPTN Disease Transmission Advisory Committee to assess the feasibility of screening for endemic infections in geographic areas of higher prevalence, e.g. coccidiomycosis.

- Defining donor ventilator settings using the evidence based National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network formula for Ideal Body Weight (IBW) definitions provide much needed guidance and standardization in donor ventilator management needed for donor optimization, ABG interpretation, and efficient allocation. Recognizing that the IBW formulas are validated for adults, how will this be calculated for pediatric donors?

2. <u>Require Reporting of HLA Critical Discrepancies and Crossmatching Events to the OPTN</u>

The American Society of Transplantation (AST) agrees that potentially clinically relevant HLA discrepancies should be reported and offers the following comments for consideration in response to the proposal, “Require Reporting of HLA Critical Discrepancies and Crossmatching Events to the OPTN:”

- The definition of what constitutes a critical HLA discrepancy requires further clarification. The proposal lists error categories for HLA-related events of "verification error, interpretation error, equipment malfunction, typing method error (assay failure), lab IT/ technical issue, etc.," but clear definitions of these categories of error would be beneficial. For example:
    - Some antigen splits and some eplet mismatches may have immunologic significance, such as (`A*02:01` vs `A*02:02`). The immunologic significance is dependent upon the recipient’s identified antibodies.
    - Reporting of HLA-DP typing is currently limited in the available options for reporting, which could lead to apparent discrepancies, as may be seen with DPB1. What if the true genotype wasn't explicitly enumerated in the attached PDF report, but the report simply states, "This genotype was chosen as the most likely; cannot exclude one or more rare genotypes?" When we transition to P-group level reporting in UNet, the proposal does not indicate if calling the wrong P-group within the same split antigen be considered a critical discrepancy.
    - For other HLA loci, there is a nonzero chance that an alternative genotype is the true genotype and some of the alternate genotypes are in a different split antigen category. If the alternative genotypes are listed in the attached PDF as not being ruled out by the assay, is that a critical discrepancy?
    - What if the true genotype has a broad antigen assignment of DQ1 and the true allele was in either DQ5 or 6?

- The AST agrees with requiring reporting through the Patient Safety Portal to standardize reporting and a timely review of this information.

3. Update Histocompatibility Bylaws

The American Society of Transplantation (AST) generally supports the proposal, "Update Histocompatibility Bylaws." Aligning OPTN Bylaws with Clinical Laboratory Improvements Act (CLIA) regulations – a well-established framework that sets high standards for laboratory operations – stands to simplify the regulatory landscape, reducing the burden on laboratories that must navigate multiple sets of rules.

Proposing a minimum number of cases a laboratory director must review per year and, separately, expanding the required General Supervisor qualifications could be a valuable addition. The AST recommends that the OPTN only pursue this if there are data that support the need for these additional qualifications and the specific proposed requirements, factoring the administrative burden that these additional requirements will create.

Finally, regarding the proposed removal of the requirement that written agreements between histocompatibility laboratories and transplant programs must include the duration for which specimens need to be stored for repeat or future testing. Has the Committee considered whether a requirement to store candidate or recipient specimens would be useful for root cause analysis of crossmatching events? For example, the wrong patient specimen was used, a physical crossmatch was negative, and the recipient experienced hyperacute rejection.

4. Revise Conditions for Access to the OPTN Computer System

The American Society of Transplantation (AST) generally supports the proposal, "Revise Conditions for Access to the OPTN Computer System and Reporting Privacy Incidents." While the proposal prohibits any organization accessing the OPTN Computer System for research purposes, the AST believes that refining the language with permissible reasons for accessing the OPTN Computer system is important. The AST recommends that the language proposed under 3.1: Access to OPTN Computer System explicitly require that, "facilitating organ transplantation, fulfilling OPTN obligations, and quality assurance and performance improvement (QAPI) in support of transplant programs or organ procurement organizations." Additionally, the Committee could consider defining different classes or tiers of external business partners and thus limit the scope of their access based on their support functions, which may provide assurance to current members and the Board of Directors. The AST requests that the OPTN explicitly clarify that the term "facilitating organ transplantation" includes post-transplant follow up of donor data, e.g., final donor culture results. The AST also suggests that the OPTN consider additional clarity to prevent access disruptions for third parties directly accessing the OPTN data systems to identify potential organs for research.

As noted in the proposal, the AST agrees that requiring removal of a user from the system within 12 hours of their last day of employment will pose a burden on OPTN members and may be unattainable in some instances. The AST recommends modifying the proposed policy to require that members make these updates as soon as possible, but no later than 24 hours after a user's last day of employment or a change in roles or responsibilities.

The AST has questions about who is responsible for the interconnection security agreement (ISA) when a member is using software licensed by another member that uses application programming interfaces (APIs) to access the OPTN computer system. For example, the Epic electronic health record has a transplant module; if it uses APIs, who is responsible for the ISA?

Finally, if the OPTN approves the proposed policy, it will be crucial to allow ample time for business members, transplant centers, OPOs, and HLA labs, to align their membership status and establish ISAs to prevent disruption to patient care. Likewise, simplicity in data use agreements must be encouraged to reduce administrative burdens. While security and data protection are top priorities, the overall administrative load on users should be minimized to maintain system efficiency.

5. <u>Continuous Distribution of Kidneys Update, Summer 2024</u>

The American Society of Transplantation (AST) is generally supportive of what is outlined in committee update, “Continuous Distribution of Kidneys Update, Summer 2024” and offers the following comments for consideration:

- The AST strongly opposes any policy changes that could disadvantage pediatric candidates. The AST supports stratification by distance, followed by a slight reduction in the weight of pediatric priority; however, there are concerns that offer filters and screening may impose significant burdens on kidney transplant programs, potentially disadvantaging patients at programs with less accessible airports. Regardless of adjustments made to the modeling, the AST advocates for a defined, early assessment period of six months to evaluate if pediatric weights are achieving their intended effect and evaluate for the existence of any unintended consequences such as delayed graft function, increased cold ischemia time, and transportation challenges. Additionally, the AST believes encouraging pediatric centers to use offer filters and candidate acceptance criteria to maximize efficiency in managing offers for each pediatric patient is reasonable.

- The AST supports the optimized CPRA rating scale to ensure access for the most highly sensitized candidates. The goal "equalize access across CPRA" does not seem to have been realized as there are still substantial differences in transplant rates across CPRA categories. The modeling data presented in the proposal in Figure 9 suggest that, overall, the four proposed policies do not significantly impact transplant rates across cPRA categories when compared to the current policy. If the goal is to increase transplant access for highly sensitized candidates, particularly those with a cPRA between 99.9% and 100%, no amount of points equivalent to waiting years will benefit these patients. These highly sensitized candidates are incompatible with almost all available donors and only HLA-identical donors will be compatible. Therefore, offering increased cPRA attributable weight for patients with a cPRA between 99.9% and 100% provides no significant benefit unless HLA-identical donors are prioritized for these patients.

- The AST generally supports a multi-faceted approach to defining hard-to-place kidneys and advocates for a comprehensive focus on data obtained after kidney recovery, such as vascular anatomy, anatomic abnormalities, biopsy results, pump metrics, and transportation challenges. The AST believes well defined definitions that recognize “hard-to-place” kidneys much earlier in the allocation process is critical to successful allocations and transplants. Additionally, standardized availability of digital pathology could positively impact acceptance of kidneys that may otherwise be declined when relying on the pathology report. The AST is less supportive of stratifying clinical criteria by KDPI, as the formula will soon be updated and currently does not capture many variables that may lead a transplant hospital to decline a kidney post-recovery.

- The AST favors using both allocation and cold ischemia time thresholds, as these are post-recovery data points, but recognize the need for ongoing evaluation of these parameters as they evolve.

- Standardized approaches to expedited placement with a focus on transparency are critical. The AST supports the proposed expedited placement research and the research already conducted. Specifically, the AST believes that the “time used” during kidney placement is poorly understood and that there are efficiency opportunities to accelerate the allocation process. Allocation efficiency would be improved with a better understanding of transplant center and OPO behavior and the use of mandatory and optional filters. Currently, the available data do not seem granular enough to make specific recommendations or changes in expedited placement.

6. <u>Continuous Distribution of Livers & Intestines Update, Summer 2024</u>

The American Society of Transplantation (AST) offers the following comments in response to the committee update, “Continuous Distribution of Livers & Intestines Update, Summer 2024:”

- The AST agrees with using Status 1A, Status 1B, and MELD/PELD as the medical urgency score model for the first version of liver continuous distribution. The Committee’s assessment not to implement a new medical urgency model simultaneously with implementation of the first iteration of liver continuous distribution is prudent, and the AST supports using MELD 3.0 for the medical urgency attribute in this first iteration. The AST remains enthusiastic about the Optimized Prediction of Mortality (OPOM) model’s potential and is in favor of its continued analysis and validation for possible incorporation in liver continuous distribution in the future to weigh other parameters affecting mortality in advanced liver diseases not considered in MELD 3.0.

- The AST suggests continuation of preferential allocation of pediatric grafts to pediatric recipients to improve waitlist mortality among pediatric recipients. The AST supports the Committee’s ongoing work to continue simulation exercises, including the incorporation of pediatric offer filters, for more accurate assessment of modeling results and the expected impact on pediatric liver recipients. The AST also recommends policy that would yield an increased volume of split liver transplants. Simplified allocation allowing pediatric and adult liver programs to collaborate more easily to allocate one segment of a split liver to an appropriate pediatric liver candidate and the remaining segment to an appropriate adult liver candidate would be beneficial.

- With regards to travel efficiency, the choice to fly or drive depends on center practices, population density/traffic patterns, weather, as well as distance. The AST cautions the incorporation of a specific “drive versus fly” metric, unless the intention is to award points based upon a candidate being within a set distance from a donor. Transportation choice hinges on specific practices of transplant centers which are likely diverse and geographically dependent. In general, auto transportation is used for many donors within a one-two hour distance from the transplant center. Current distribution prioritizes geographic distribution in terms of nautical miles from the transplant center, which accounts for this distance. Transplant hospitals in densely populated urban centers may use helicopters for transport even within close proximity, especially during heavy traffic times. The AST encourages the OPTN to consider whether local proximity should have

greater impact due to the high cost of transportation on the transplant process. Additional prioritization of livers to local centers, such as those with donor procurement at a recipient hospital, as well as those within the city limits of the transplant center should be explored. This may also improve utilization in instances where local backup could be provided.

Newer technologies (e.g., normothermic regional perfusion, hypothermic machine perfusion) are likely to greatly impact the ability to transport livers over large distances with minimal impact on graft function, even with longer cold ischemic time. Availability of machine perfusion may need to be factored to allow for broader distribution of such organs; however, there are concerns regarding the broad availability and liver program experience with such technologies, which may exacerbate disparities.

- The efforts to increase access to appropriate-sized grafts is appreciated- this is an important consideration to avoid unintended consequences resulting in liver candidates with small body habitus being underserved by the new liver continuous distribution allocation algorithm. The AST has concerns that the body surface area (BSA) alone as an attribute may vary greatly in patients with increased total water volume due to fluid shifts and ascites, resulting in a falsely elevated BSA for candidates with greater ascites. Similarly, obese patients with short stature may have small abdominal domain, but these patients will continue to be underserved due to elevation of their BSA resulting from increased adipose tissue. Further, size matching for a specific donor liver to a recipient involves more than BSA and includes assessing the size of the donor liver, abdominal domain and size of recipient, presence of ascites, primary vs. secondary liver transplant, where does the recipient carries their weight, etc. Additional information detailing the BSA attribute's impact on waiting list mortality and how the size-based rating scale donor modifier will impact matching pairs of high/low BSA is needed.

- Medically complex donors are currently defined as DCD or age greater than 70. Additional donor factors that could be considered include high BMI, donor instability (e.g., high pressor requirements), prolonged donor hospitalization, significantly elevated donor liver enzymes, intraoperative reallocations, and decreasing the donor age limit to 65 years. All such factors impact the likelihood of organ acceptance and may impact ultimate donor allograft function. Additionally, perhaps a metric such as the Discard Risk Index (DSRI) could be considered and modeled.[1]

  Availability of hypothermic machine perfusion and normothermic regional perfusion may increase the usability of DCD grafts and broaden the recipient population to which these grafts are targeted. As experience increases, use of normothermic regional perfusion for a DCD donor may need to be factored into the utilization efficiency attribute.

- HCC and other oncologic indications for transplant have been recently deprioritized to decrease waitlist mortality among patients with highest biologic MELD. The risk of progression on the waitlist needs to be carefully balanced with prioritization based on medical urgency to optimize organ resource utilization. Given that cancer recipients may often be more appropriate for medically complex donors, increased weight donors, DCD or other extended-criteria donors, may be considered for HCC patients. Additionally, the

[1] Rana A, Sigireddi RR, Halazun KJ, et al. Predicting Liver Allograft Discard: The Discard Risk Index. *Transplantation*. 2018;102(9):1520-1529. doi:10.1097/TP.0000000000002151

incorporation of “exception” points into the composite allocation score (versus MELD) as “diagnosis priority points” alleviates the misnomer and associated confusion with exception points given that they indeed follow allocation rules.

HCC stratification has the potential to address the urgency within different tiers of HCC progression, such that a patient is less likely to progress to the point of being disqualified for transplantation. In the current system, waiting time for HCC candidates may still experience significant geographic variability, and some candidates may experience prolonged wait times greater than one year. While the six-month rule generally allows a period of observation to prevent transplanting patients with highly aggressive tumors, prolonged wait-time — particularly beyond 6 months — increases risk for recurrent or de novo disease. The AST suggests the OPTN consider stratification based on tumor size and increased prioritization of HCC patients with prolonged waiting times (e.g., greater than one year) to help prevent non-transplant removals from the waiting list in high waiting time regions.

- The AST believes the following additional considerations warrant Committee discussion:
  - The AST agrees with awarding additional points for liver-intestinal candidates within ideal candidate criteria. Due to limited access for intestinal transplant candidates, increased waiting time should be considered due to increased risk for patient mortality.
  - Clarification is necessary regarding additional prioritization that will be awarded to the other nine current standard exception categories, and to the non-standard exceptions granted by the National Liver Review Board, meant to equalize mortality risk in at-risk populations.
  - In consideration of a population density metric, this could de-prioritize patients listed within a less population dense region, thus inducing geographic disparities. It is unclear how this would contribute to increased access.
  - The omission of post-transplant survival metrics in the current model is questionable given the lifesaving nature of liver transplantation and the need to appropriately support ethical principles of allocation. Acknowledging there are currently no reliable patient-level survival estimates, SRTR data could inform the creation of such a metric. If such a model was available, its inclusion would be consistent with allocation principles and the weights in other organ continuous distribution models. The AST recommends taking an approach similar to that employed by the OPTN Heart Transplantation Committee with the continuous distribution of hearts, in which post-transplant survival is maintained as a component of the continuous distribution model for future elaboration.

- Continuous distribution may be a difficult concept for transplant candidates to understand. Development of education documents for liver transplant candidates may improve candidate understanding of the allocation system and their waitlist priority.

7. Continuous Distribution of Hearts Update, Summer 2024

The American Society of Transplantation (AST) offers the following comments in response to the committee update, “Continuous Distribution of Hearts Update, Summer 2024:”

- The AST remains in support of
  - all sub-categories of priority except for post-transplant survival, with the proviso that a second iteration of this policy incorporates post-transplant survival into

prioritization. A suggestion for eventually incorporating post-transplant survival is to include this attribute for weighting but assigning all candidates the same score until an accurate predictive model is developed.
    - standardized allocation points for highly sensitized candidates, if unacceptable antigens are recorded in Donornet.
    - continued pediatric priority, including continuous monitoring pre- and post-implementation to ensure vulnerable populations such as pediatric recipients are not impacted by unintended consequences not evident in the ongoing analyses to develop a heart continuous distribution allocation algorithm. The current proposal removes the additional priority that children receive in existing policy for pediatric donors. The AST recommends that the Committee consider modeling the addition of points for pediatric candidates when the donor is pediatric (or to add points for donor/recipient pairs that fall within the age brackets mentioned in the comment below).

- The AST's overarching concern is how the new policy will manage medical urgency. Medical urgency continues to be prioritized in every iteration of heart allocation, without specific regard for age or co-morbidities – attributes which drive post-transplant survival. There is a broad range of risks within each status and thus all the patients within a status should not receive the same points or weight. Data should drive this separation of risk because post-transplant survival remains somewhat problematic, given associations with center expertise (access) and socioeconomic circumstances (insurance coverage of important therapies). One way to incorporate age and co-morbidities into pre-transplant priority is to give points for an age differential less than or equal to 15 years between the candidate and donor. If a candidate is 70 years old, they are prioritized to receive donor offers between 55-70. If a candidate is 25 years old, they are prioritized to receive donor offers between 25-40. This age bracketing component is part of the French Allocation System. All candidates are open to all age donors but gain priority points for age bracketed donor pools.

- The heart allocation system implemented by the OPTN in 2018 included more than 40 mandatory variables collected to move to a cardiac allocation score (CAS). How will these data be used in the development of the heart continuous distribution system? While the hope and goal of continuous distribution is that the different components of the CAS can be changed more expediently without requiring a total policy overhaul, and there are new components that are of great interest to the transplant community (biologic disadvantage), medical urgency of both adult and pediatric heart candidates remain at the forefront of concerns in the heart transplant community.

- The AST believes that patients in need of re-transplantation for severe cardiac allograft vasculopathy including restrictive cardiac physiology (as defined using the International Society for Heart and Lung Transplantation standardized nomenclature for CAV3), should have a higher status than current policy provides due to their high mortality risk.

- The AST agrees with and would like to reiterate prior public comments that prior durable left ventricular assist devices (LVAD) should provide priority status similar to having been a prior organ donor. Every patient who accepts an LVAD instead of a heart transplant allows for a heart that can be transplanted in another patient who anatomically cannot accept LVAD therapy. Given that some patients on LVAD do recover heart

function enough to be weaned off, this further increases the donor pool for patients who do not recover.

8. Continuous Distribution of Pancreata Update, Summer 2024

The American Society of Transplantation (AST) is generally supportive of what is outlined in committee update, “Continuous Distribution of Pancreata Update, Summer 2024.”

The AST supports the medical urgency criteria for pancreas candidates as outlined in the paper. The AST is also entirely supportive of enhancing equity, transparency, and more data analysis to evaluate the feasibility of including utilization and non-use models in pancreas allocation, as reviewed in this update. The AST believes it would be beneficial to focus on those topics highlighted for possible inclusion in a future guidance document on pancreas procurement and utilization. Instead of possible punitive measures for programs with high non-utilization rates, the current focus should be to reduce the numerous barriers that drive pancreata non-utilization. Having expertly trained personnel available within organ procurement organization procurement teams would be a step towards addressing current barriers to successful pancreas procurement. Additionally, encouraging separate pancreas and kidney transplant program directors could positively impact pancreata utilization and outcomes; however, the OPTN should not require this separation to avoid unduly burdening small and medium sized programs that could lead to the closure of some pancreas programs.

The AST also supports increased collaboration with those interested in transplantation at the American Diabetes Association (ADA). As part of this collaboration and acknowledging the significant advancements in medical management of diabetes, the AST suggests developing education about adequate management of diabetes to be provided in parallel with information about pancreas transplant.