The American Society of Transplantation (AST) responded to 11 items the OPTN released for public comment on January 23, 2024. The AST submitted the responses below through the OPTN website on March 15, 2024, after receiving input from the AST's communities of practice, OPTN Policy Committee, and Board of Directors.

1. Strategic Plan 2024-2027

The American Society of Transplantation (AST) supports the overarching concepts encompassed in the 2024-2027 OPTN strategic plan but is concerned that most of the key strategic goals of the 2021-2024 strategic plan transition into components of the OPTN Vision without making clear how achieving the Vision will be accomplished as a result of the proposed strategic plan goals. Without this clarity, the goals proposed in the 2024-2027 OPTN strategic plan can be perceived as priority policy actions rather than strategic goals.

In addition, the AST also believes there are multiple key priorities that should receive more focus in the 2024-2027 OPTN strategic plan, including:

- Maintaining a focus on increasing the number of organ donors in addition to increased utilization and efficiency
- Increasing equity in all domains
- The importance of living donation

Without greater, more explicit focus on the components of the Vision and the above considerations, the AST is concerned that efforts to improve on these matters will be under supported and deprioritized over time. Other key considerations as the OPTN implements the 2024-2047 strategic are:

- Ensuring that patient outcomes aren't negatively impacted
- Ensuring safety including reducing donor disease transmission
- Ensuring that any enacted policies take into consideration availability of transplant center resources and do not create the opportunity for new punitive measures

Further, the proposed strategic plan Goal 1 and Goal 2 appear to have the greatest potential impact on renal transplantation. The plan would benefit from additional clarity on how appropriate tactics will be developed to address these issues in non-renal transplantation. Moreover, making progress on these two goals will require a clearer, data driven understanding of the root causes of variability in offer acceptance and utilization as an initial step. This information would then be used to prioritize development of new policies and drive implementation of the broad set of tools and strategies currently being considered (i.e., patient and transplant center education, patient involvement in decision making, offer filters, and predictive analytics). Additional feedback on Goals 1-3 as included in the proposal is provided below.

- Goal 1: Enhance Organ Acceptance Rates
  - The goals are broad which allow specific objectives to be achieved while keeping in line with the strategic plan. This can also lead to uncertainty in creating granular plans with meaningful results. Increasing organ utilization without negatively impacting outcomes is a difficult objective to achieve and will require a more detailed review and evaluation than the metrics outlined. Organs at high risk of non-use such as those from donation after circulatory death (DCD) donors, high Kidney Donor Profile Index (KDPI) donors, and those with extended cold ischemic time need to be assessed carefully. It is not clear within the proposed strategic plan that the challenge of placing these organs will improve as many of the factors leading to

difficulty with organ placement are not clearly understood and therefore not addressed.
    - Addressing inefficiencies in organ acceptance begins with identification and articulation of the factors driving disparities between programs and regions. When looking at the reduction of organ non-use, the current allocation may represent a counter factor, with transportation of organs over further distances and costs associated with higher risk organs not accounted for. The development and deployment of incentive initiatives, creation of educational offerings to address gaps and standardize processes, and the collection of pre- and post-change metrics should all focus on the underlying factors.
    - The plan proposes increased educational support for transplant programs, with an emphasis on monitoring the uptake of these educational resources. This initiative by the OPTN is commendable, potentially alleviating the need for transplant programs to develop their own materials; however, the merit of tracking educational resource utilization is questionable. This may lead to superficial compliance rather than genuine improvement and could impose additional burdens on some transplant programs.

- Goal 2: Optimize Organ Use
    - The AST supports the initiative to work collaboratively with stakeholders to identify barriers to organ utilization, acknowledging specific challenges and variability in acceptance patterns across centers. It's vital to continue assessing outcomes for higher-risk organs to determine their optimal use. The AST suggests that exclusion from outcome measures be considered as a component of quality improvement projects intended to increase utilization of organs "at high risk for nonacceptance." Additionally, ensuring transparency in the allocation process when organs are offered out of sequence is essential and the reason each potential transplant recipient on the match run before the recipient is bypassed should be clearly identified and reported.
    - The AST recommends that the OPTN work to develop a regulatory framework that establishes expectations that organ utilization will not be impacted by limits in access to operating rooms for transplantation, including dedicated operating rooms for transplant.
    - The AST supports utilization of turndown data to develop evidence-based predictors of organs that are at "high risk for nonacceptance."
    - While tracking access-to-transplant metrics is valuable, requiring transplant centers to report such metrics, which necessitate multiple data points, could be onerous. Alignment between HRSA, CMS, and transplant centers in data collection efforts is necessary to lessen this burden.

- Goal 3: Improve OPTN Efficiency
    - The OPTN policy making process should be timelier when possible; however, there are concerns about expediting the policy development process at the cost of stakeholder involvement and an increased possibility of significant, unintended consequences. While efficiency is important, it should be secondary to achieving the other goals and without compromising the important and valuable rigor that is fundamental to OPTN policy development.
    - The AST supports improving the time to implement policy as long as it is not achieved by systematically reducing the amount of time provided to transplant hospitals to prepare for implementation at their programs. It is very important that

transplant hospitals are given the tools that they need and a sufficient amount of time to implement all policy changes.
    - Stakeholder satisfaction is acceptable in principle, but more important is clinical outcomes. Also, the relevant stakeholders are not clearly identified.
    - Data optimization is perhaps the most ambitious aspect of this goal, but limited detail is provided. From a diagnostic perspective, it would be educational to know how the varying components of the pre-transplant workup (e.g., NAT infectious panel, procurement biopsy, crossmatch, etc.) that contribute to organ utilization/acceptance or to other outcomes measures such as cold ischemic time. These components can then be a focus for process improvement.

2. <u>Concepts for Modifying Multi-Organ Policies</u>

The American Society of Transplantation (AST) offers the following comments in response to the request for feedback, "Concepts for Modifying Multi-Organ Policies:"

- The AST supports the concept that policy should direct the order in which OPOs allocate organs. There should not be a geographic discrepancy arbitrarily introduced by OPOs for organ allocation, especially as broader sharing is implemented. OPOs will continue to struggle with simultaneous lists to guide allocation until all organs are allocated using continuous distribution systems and there are single, integrated match runs for each donor.
- To help address the waitlist mortality of multi-organ transplant (MOT) candidates, when two donor kidneys are available for transplant, the AST supports allocating one kidney to an MOT potential transplant recipient and the other kidney to a kidney transplant alone (KTA) or simultaneous pancreas kidney (SPK) potential transplant recipient. When only one donor kidney is available, the AST recommends prioritizing MOT candidates but consider establishing standard criteria for prioritization of certain KTA candidates before MOT candidates. Considerations for KTA prioritization should include pediatric patients, highly sensitized patients, medically urgent patients with exhausted access options, and previous living donors.
- The AST supports a policy that allocates at least one kidney from 0-34 KDPI donors to a pediatric recipient unless a competing adult MOT candidate meets predefined urgency criteria.
- The AST recommends more expansive safety net policies in future iterations in concert with development of other strategies to help with allocation of low-KDPI kidneys to KTA candidates. Data analysis of outcomes should drive further decisions on kidney allocation to MOT and KTA candidates.

3. <u>Modify Effect of Acceptance Policy</u>

The American Society of Transplantation (AST) generally supports the proposal, "Modify Effect of Acceptance Policy," and offers the following comments for consideration:

- The AST recognizes that including timeframes in the proposed policy language could create unnecessary confusion and inefficiencies for both OPOs and transplant hospitals; however, are there reasonable options that would circumvent these concerns and better address the allocation questions? The AST is interested in the OPTN Ad Hoc Multi-Organ Transplantation Committee's perspectives considering its ongoing analysis and discussions of these topics.

- The AST recommends making clearer that OPTN Policy 5.6.D (Effect of Acceptance) is referring to final organ acceptance and does not include “provisional yes.”

4. <u>National Liver Review Board (NLRB) Updates Related to Transplant Oncology</u>

The American Society of Transplantation (AST) generally supports the proposal, “National Liver Review Board (NLRB) Updates Related to Transplant Oncology,” and offers the following comments for consideration:

- The AST supports the reorganization of the NLRB with the creation of the Adult Transplant Oncology Review Board and the proposed guidance document changes to include non-standard MELD exception criteria for both colorectal liver metastases and small (≤3 cm) intrahepatic cholangiocarcinoma. These guidelines could serve to collect additional prospective data on the benefit of transplant in these populations as well as provide a basis for future expansion of indications. Specific comments on each section are provided below:
    - Colorectal Liver Metastases
        - The proposal recommends MMAT -20 with a MELD of at least 15 for all listed patients. It should be highlighted that candidates with colorectal liver metastases listed at aggressive centers in lower MELD regions may place these candidates in competition with other liver candidates listed for other indications. The AST recommends a minimum MELD of at least 18 to give these patients a reasonable opportunity to receive suitable offers.
        - The International Hepato-Pancreato Biliary Association (IHPBA) has documented international consensus for transplanting colorectal liver metastases based on data and expert opinion, some of which is not included in this proposal. For example, primary resection pathology of undifferentiated and signet cell carcinomas are ineligible for transplant and primary resection N2 status is a relative contraindication; the current proposal does not address these topics. The AST recommends including all the guidance from the IHPBA or explaining the rationale for excluding certain aspects.
    - Intrahepatic Cholangiocarcinoma
        - The proposal recommends MMAT-3 exception for unresectable, liver-limited tumors ≤3 cm in a background of cirrhosis that have demonstrated disease stability for >6 months on locoregional (LRT) or systemic therapy. The AST generally supports these proposed updates; however, there are a few concerns and questions:
            - The multicenter studies on which this recommendation was based were exclusively retrospective analyses of data derived from incidental or misdiagnosed intrahepatic cholangiocarcinoma (iCCA) or combined hepatocellular-cholangiocarcinoma (HCC/CCA).[1, 2] First, there was no requirement for 6 months of disease stability in these studies. This recommendation seems to have been extrapolated from the current HCC guidance literature and the prospective series on locally advanced iCCA which required disease stability on 6 months of prior chemotherapy.[3, 4] For small iCCA or HCC/CCA, there is no data to support 6 months of disease stability prior to exception. The AST does not oppose the initial inclusion of this criteria; however, it must be recognized that the recommendation is not supported by objective data. This also underscores that the OPTN must

carefully monitor the impact of these changes and make data-driven adjustments as needed.

- The retrospective multicenter studies serving as the basis for these recommendations[1, 2, 5] did not require any pretreatment with LRT, and patients who had received chemotherapy were excluded from analysis. Data for the use of pre-transplant chemotherapy is extrapolated from studies assessing liver transplant in patients with larger or multifocal tumors.[3, 4] In contrast, in the multicenter retrospective analysis comparing liver resection and liver transplant for patient with iCCA within Milan with considered tumors from 2-5 cm included 63 percent of patients with pre-transplant LRT. While LRT did not reach significance for tumor recurrence in all patients undergoing either resection or transplant in that study (HR for recurrence 0.41 [95% CI 0.16-1.05], p=0.06),[5] the AST believes the inclusion of pre-transplant therapy is reasonable. Again, this underscores the need to carefully monitor the impact of these changes to make data-driven adjustments as needed.
- The AST agrees with increasing the size threshold to at least 3 cm as <2 cm would be too restrictive. Even with inclusion of tumors up to 3 cm, the difficulty in diagnosing tumors of that size will significantly limit the patient population that may benefit from this exception.
- Given multicenter data suggesting that tumors with a cumulative diameter of up to 5 cm demonstrate a 5-year recurrence-free survival of 74%, the AST suggests that initial MELD exception consideration should be given to either (1) patients with a cumulative (additive) tumor diameter of up to 5 cm and disease stability for 6 months on chemotherapy or LRT or (2) patients with tumors >3 cm who are downstaged via LRT or chemotherapy to ≤3cm.

▪ If systemic therapy is used, does a 6 month wait period start from the end of chemotherapy or start of chemotherapy to document the stability of the disease? This consideration would be worthwhile to clarify.

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5. Update on Continuous Distribution of Hearts

The American Society of Transplantation (AST) offers the following comments in response to the request for feedback, "Update on Continuous Distribution of Hearts:"

- The AST believes that attributes created (medical urgency, post-transplant survival, reducing biological disadvantages, patient access, and placement efficiency) are appropriate, albeit with anticipated challenges including the following:
  - Medical urgency – programs may ask for more exceptions as this is a major driver of where the patient ends up on the allocation list. As a result, exception requests may be used to increase priority of candidates with lower degree of medical urgency.[1] Furthermore with 95% approval rate of exception requests, without further monitoring and optimization of exception request process, the continuous distribution model may be further manipulated.[2] To incentivize durable LVADs, waitlist time with durable LVAD should be included in the composite allocation score as outlined in the concept paper. We would also emphasize that choosing variables that are truly reflective of medical urgency (Cr, disease entity, bilirubin, etc.) rather than just method of support will help further risk stratify and reduce gaming. This validated method is currently included in the new French allocation system.[3]
  - In addition to the status categories, the patient groups within the statuses should be further spread out in the risk stratification point assignment. For example, a status 2 for VT/VF has a much higher waitlist mortality than a patient on an IABP and thus should have more points.
  - Post-transplant survival – The AST believes that post-transplant survival is an appropriate attribute to consider; however, it should not be included in the first version of heart continuous distribution allocation policies. Post-transplant survival is variable based on patient co-morbidities, in hospital status 1-3, single vs multi-organ transplants, and the transplant program's level of expertise (e.g., certain centers may do more congenital cases than others or simply high-volume vs low volume transplant centers). As such, there should be a guidance document first advising which components would be included in the incorporation of a post-transplant survival score and then integrate the components in a follow up version. The new French allocation system accounts for donor and recipient variables, rendering a Transplant Risk Score (TRS) which factors into their allocation to assess for post-transplant survival (the score has been prospectively validated). The TRS includes seven recipient factors: age, indication for transplantation, previous cardiac surgery,

diabetes mellitus, mechanical ventilation, GFR, and total bilirubin level and two donor factors: age and gender.[3] Perhaps premature, but incorporation of more donor and recipient variables should be considered to help optimize patient outcomes.
    - Reducing biological disadvantages- The AST supports the inclusion of HLA sensitization. While there is a need to help those at a disadvantage, heart transplant centers vary on their definition of sensitization and may not use the same lab for cPRA calculation. Highly sensitized also varies in definition with cPRA anywhere between 20-80%, depending on the transplant hospital or study. To add this, the AST agrees the proposed method of listing unacceptable antigens to obtain points for desensitization is likely the best approach for this particular component.
    - Patient access – agree with this component
    - Placement efficiency – agree with this component
- The AST recommends the following to evaluate success toward the outcome of that specific attribute:
    - Medical Urgency: death on waitlist, increase in status requiring upgrades or additional tMCS or chemical support, removal of waitlist for further deterioration requiring durable MCS or palliation. Additionally, adverse events from tMCS such as limb ischemia, stroke, infection, and bleeding should be collected to assess rates of complication with success to transplant.
    - Post-transplant survival: not in this version until more data is available.
    - Reducing biological disadvantages: rate of highly sensitized patient time to transplant or time on waitlist, modification of listed unacceptable antigens based on waitlist time.
    - Placement Efficiency: Assess why hearts are turned down – if heart programs frequently turn down offers primarily due to distance and worry for post-transplant outcomes – is more research and technology optimization that allows broader sharing necessary? Are heart programs with access to NRP and advanced cooling mechanisms such as Sherpak, able to do more transplants with similar effects on post-transplant survival and outcomes?

References:

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6. Promote Efficiency of Lung Allocation

The American Society of Transplantation (AST) generally supports the proposal, “Promote Efficiency of Lung Allocation,” and offers the following comments for consideration:

- The AST supports providing additional tools to transplant programs to make efficient and customized decisions. We recommend continuing to collect data to determine the holistic impact and to further optimize these systems.
- The AST supports the proposed new data fields that will provide a greater opportunity to increase allocation efficiency and minimize lung offers that a program would only accept

in very specific circumstances. Lung programs have seen an exponential increase in offers since the OPTN implemented continuous distribution for lung allocation. This has decreased efficiency in allocation as well as inundated centers with an increased number of offers they would not accept based on donor characteristics.

- Most of the proposed filter data is currently collected by OPOs which should help minimize any data collection burden upon implementation. As for additional possible fields that could be helpful:
  - Predicted total lung capacity (pTLC): Programs often screen donors based on pTLC, but manual calculations are error-prone and may impact acceptance or organ placement. The AST suggests that pTLC be pre-calculated in UNet using information already available for both donors and candidates, including age, height, and gender. This will increase efficiency and allow transplant programs to apply pTLC screening criteria at the time of candidate registration.
  - CMV serology and EBV serology: the addition for CMV and EBV serologies results (+/-) to enhance patient safety at time of organ offer and to minimize the need for manual screening.
  - Additional donor information and other filter adjustments will likely be needed as filters are introduced and the community becomes familiar with their usage.
- The addition of a button to bypass candidates who would not accept an offer if only a single lung is available is appropriate. The AST also supports a system enhancement that would require transplant programs to opt in for offers from geographically isolated areas. This would create an increased layer of efficiency for those programs that have no intention of accepting organs from Alaska, Hawaii, or Puerto Rico due to their relative geographic separation.

7. <u>Update Post-Transplant Histocompatibility Data Collection</u>

The American Society of Transplantation (AST) generally supports the proposal, "Update Post-Transplant Histocompatibility Data Collection," and offers the following comments for consideration:

- The 'cytotoxicity method' is no longer used to identify HLA antibodies and the AST agrees with its removal from donor recipient histocompatibility forms. However, there are different methods for solid phase antibody testing that should be included. The primary techniques currently used are flow cytometry, Luminex technology, and ELISA. The AST recommends capturing which technique is used to understand any differences that may be attributed to the specific technique used.
- The AST agrees with the decision to separate the virtual crossmatch and physical crossmatch sections and removing the response options "Cytotoxicity no AHG" and "Cytotoxicity AHG" on the donor and recipient histocompatibility forms. The AST strongly recommends that "cytotoxicity crossmatch" remain a response option as both T and B cell cytotoxicity assays have not been abandoned by all programs.
- The AST suggests that the OPTN consider a stated definition in OPTN policy for prospective virtual crossmatch, including upper limits for serum age. The immunological risk in a candidate who, for example, had a one-time historical DSA six months prior to transplant followed by repeated negative testing is different than a patient with positive DSA prior to transplant.
- The AST suggests that another field be added to collect pre-transplant CPRA. In most cases, the most recent CPRA in Waitlist is not the same as the CPRA at time of

transplant. The AST suggests adding this field to capture the CPRA value closest to the time of transplant.

- The AST would agree that the proposed data elements, including those recommended in this response, are predominantly collected in discreet fields within a laboratory information system.
- The AST suggests collecting the date of the HLA antibody screen used for virtual crossmatching to inform future optimization of virtual crossmatch strategies.
- The AST suggests collecting the threshold used to designate an antibody (corresponding antigen) an avoid for the calculation of the CPRA.

8. Refit Kidney Donor Profile Index without Race and Hepatitis C Virus

The American Society of Transplantation (AST) generally supports the proposal, "Refit Kidney Donor Profile Index without Race and Hepatitis C Virus," and offers the following comments for consideration:

- The AST strongly supports removing race as a variable in calculating the Kidney Donor Profile Index (KDPI), as inclusion of the Black race as a coefficient inaccurately scores the quality and predicted function of a kidney from a deceased organ donor to be worse than that of a non-Black organ donor. The AST also supports removing hepatitis C virus from the KDPI calculations. The removal of these variables supports an evidence-based and more equitable donation and allocation process.
- Evidence provided by the SRTR modeling offers adequate rationale for this approach. Whether these changes will impact acceptance behavior is unclear; refitting the KDPI alone is not expected to cause a significant decline in organ non-use.
- With these changes, the AST also recommends additional study to explore whether these changes impact the predictive power of KDPI. It has been a decade since the implementation of KDPI, and it may be beneficial to rederive the multivariate hazards as described in Rao et al to determine the continued relevance of donor race and other factors on graft outcome using contemporary donor populations.
- The AST appreciates the question of whether the inclusion of APOL1 genes as a potential variable of the Kidney Donor Risk Index (KDRI) should be revisited after data from the APOLLO study become available and the efficacy of APOL1 gene testing is more clearly understood.

9. Standardize Six-Minute Walk for Lung Allocation

The American Society of Transplantation (AST) generally supports the proposal, "Standardize Six-Minute Walk for Lung Allocation," and offers the following comments for consideration:

- A timeframe within which the oxygen titration test must be completed ahead of the six-minute walk test may be difficult due to logistical issues and individual patient status. Although a specific interval may not be feasible, consider adding to the guidance language that lung programs should allow adequate time for the patient to fully recover between oxygen titration and the six-minute walk test and when possible, these tests should be done on separate days.
- The guidance language should more clearly emphasize that the resting oxygen determination and titration should be reported and performed using continuous flow oxygen (as opposed to pulse delivery systems).

- Candidates who live at a significantly different altitude compared to the transplant hospital where they are listed requires additional, careful consideration. The AST recommends that the OPTN Lung Transplantation Committee assess additional altitude considerations separately to assure equity for all patients.
- Finally, while this document addresses standardization and the AST supports this approach, it should be noted that the six-minute walk test is an imperfect biomarker due to its inherent variability. As a parameter intended to reflect both severity of lung disease and extrapulmonary conditioning and as a component of both waitlist survival and post-transplant survival in the lung composite allocation score (CAS), it's value as a biomarker for the CAS should be reexamined. Some of the risk elements reflected in the six-minute walk test and CAS components interact with one another, including variables such as functional class and resting oxygen needs. Because of this interaction, it is unclear how well the six-minute walk test further stratifies patients with reference to waitlist survival and post-transplant survival. For future consideration, the AST recommends that the OPTN Lung Transplantation Committee review this impact by evaluating potential changes that might result from removing the six-minute walk test from pre- and post-transplant survival components. Alternative variables that may more accurately and specifically address physical performance status independent of severity of lung disease should be considered in the future.

10. Clarify Requirements for Pronouncement of Death

The American Society of Transplantation (AST) supports the proposal, "Clarify Requirements for Pronouncement of Death." This is a helpful clarification to ensure OPTN policy is consistent with current terminology and practices while maintaining the clear separation between the healthcare provider who declares a donor's death and the subsequent recovery and transplant of that donor's organs. The two sections in the policy (2.14.A and 2.15.G) are now duplicative and could be combined into one.

11. Standardize the Patient Safety Contact and Reduce Duplicate Reporting

The American Society of Transplantation (AST) strongly supports the proposal, "Standardize the Patient Safety Contact and Reduce Duplicate Reporting."