Standardizing Selection Criteria for Simultaneous Multi-Organ Transplantation

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Disclosure

Advisory Board: Novartis, Mallinckrodt, Transplant Genomics Inc
Research Support: Novartis, Transplant Genomics Inc
Learning Objectives

- To understand the current trends in the use of MOT in the United States
- To understand the factors that must be considered in putting forward policies for candidate selection the MOT
- To understand the policy for simultaneous liver-kidney transplant that was developed and its impact
Standardizing Selection Criteria for Multi-Organ Transplant

Rational for use of MOT:
- Improved survival for individual patient
- Single surgery, single wait list period
- Possible immunologic benefit

Ethical Considerations:
- No selection criteria for most combinations
- Disadvantaging single organ transplant candidates
- Questionable overall utility on society level
The Organ Procurement and Transplantation Network (OPTN) Final Rule requires that the OPTN develop 12 allocation policies "specific for each organ type or combination of organ types to be transplanted into a transplant candidate."

The 2018 OPTN Strategic Plan called for the OPTN to "measure equity in allocation, including geographic disparities and multi-organ disparities." This white paper lays the foundation for other committees to clarify or modify existing multi-organ allocation policy and to do so in a consistent, principled manner, which aligns with the OPTN strategic goal to provide equity in access to transplant.
Multi-Organ Transplants Performed in the US from 2013-2017

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,459</td>
<td>1,508</td>
<td>1,625</td>
<td>1,801</td>
<td>1,853</td>
<td>8,246</td>
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<tr>
<td>Kidney-Pancreas</td>
<td>762</td>
<td>709</td>
<td>719</td>
<td>798</td>
<td>789</td>
<td>3,777</td>
</tr>
<tr>
<td>Liver-Kidney</td>
<td>494</td>
<td>558</td>
<td>627</td>
<td>730</td>
<td>739</td>
<td>3,148</td>
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<tr>
<td>Kidney-Heart</td>
<td>85</td>
<td>104</td>
<td>141</td>
<td>140</td>
<td>187</td>
<td>657</td>
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<tr>
<td>Liver-Intestines-Pancreas</td>
<td>50</td>
<td>69</td>
<td>67</td>
<td>58</td>
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<td>299</td>
</tr>
<tr>
<td>Liver-Heart</td>
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<td>18</td>
<td>28</td>
<td>18</td>
<td>29</td>
<td>109</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>23</td>
<td>24</td>
<td>15</td>
<td>18</td>
<td>29</td>
<td>109</td>
</tr>
<tr>
<td>Liver-Lung</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Intestines-Pancreas</td>
<td>5</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Kidney-Lung</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>24</td>
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<tr>
<td>Liver-Kidney-Intestines-Pancreas</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Kidney-Intestines</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Liver-Pancreas</td>
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<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Liver-Intestines</td>
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<td>0</td>
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<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Kidney-Heart-Lung</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Liver-Kidney-Heart</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Liver-Heart-Lung</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Liver-Kidney-Pancreas</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Liver-Pancreas-Lung</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- MOTs almost doubled in the last six years – from 625 in 2012 to 1,035 in 2017
- KP (~750 per year) and HL (~20 per year) have remained steady
MOT has become common, but with striking heterogeneity in patient selection across the US.
Allocation of MOTs

- The Organ Procurement and Transplantation Network (OPTN) Final Rule requires that the OPTN develop allocation policies “specific for each organ type or combination of organ types to be transplanted into a transplant candidate.”
- Different allocation strategies exist currently:
  - Allocated together (kidney-pancreas, heart-lung)
  - Allocated based upon immediately life-saving organ (liver or heart with kidney)
  - More than one immediately life-saving organ (heart-liver)
- There are many combinations that don’t have allocation policies
- Minimal listing criteria to guide and standardize recipient selection are generally lacking
Development and implementation of candidate selection criteria

SIMULTANEOUS LIVER-KIDNEY TRANSPLANT
Survival Advantage for SLK in Selected Recipients

OPTN SLK Allocation Briefing Paper
Additional Mean Survival Time Gained Based upon Mean 5-year Post-Transplant Survival (SLKT minus LTA): *not-on-dialysis*

![Graph showing additional survival gained by SLKT (4 months)](image)

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Mean</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLK</td>
<td>4.20 (out of 5) years</td>
<td>(4.04, 4.33)</td>
</tr>
<tr>
<td>LTA</td>
<td>3.86 (out of 5) years</td>
<td>(3.77, 3.96)</td>
</tr>
<tr>
<td>Difference (SLKT-LTA)</td>
<td>0.34 (out of 5) years</td>
<td>(0.15, 0.50)</td>
</tr>
</tbody>
</table>

Sharma P et al, Liver Transplant 2016
Historical heterogeneity in criteria has resulted in extreme variation in use of SLK across centers, DSAs and UNOS regions.
- Ranging from 2.2%-6.8% across regions
- Ranging from 5%-45% across centers

Reese P et al, AJT 2014; Nadim MK et al, AJT 2012
## Majority of KDPI<20% Kidneys are Used in MOT

Table 2. Disposition of Top 20 KDPI Organs Transplanted in Recipients With EPTS > 20%, by Region, January 1, 2015, to March 31, 2018.

<table>
<thead>
<tr>
<th>Region</th>
<th>KDPI ≤ 20% Kidneys Transplanted (n)</th>
<th>n (%) for Recipients With EPTS &gt; 20%</th>
<th>Among KDPI ≤ 20% Kidneys Transplanted in EPTS &gt; 20% Recipients</th>
<th>n (%) Used for cPRA &gt; 97%</th>
<th>n (%) Used for Multi-Organ Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117</td>
<td>54 (46%)</td>
<td>11 (20%)</td>
<td>28 (52%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>543</td>
<td>285 (52%)</td>
<td>68 (24%)</td>
<td>162 (57%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>766</td>
<td>399 (52%)</td>
<td>40 (10%)</td>
<td>282 (71%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>646</td>
<td>316 (49%)</td>
<td>46 (15%)</td>
<td>212 (67%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>772</td>
<td>387 (50%)</td>
<td>62 (16%)</td>
<td>263 (68%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>245</td>
<td>87 (36%)</td>
<td>5 (6%)</td>
<td>59 (68%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>387</td>
<td>204 (53%)</td>
<td>31 (15%)</td>
<td>147 (72%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>425</td>
<td>158 (37%)</td>
<td>19 (12%)</td>
<td>112 (71%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>215</td>
<td>98 (46%)</td>
<td>9 (9%)</td>
<td>55 (56%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>449</td>
<td>214 (48%)</td>
<td>23 (11%)</td>
<td>141 (66%)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>581</td>
<td>283 (49%)</td>
<td>53 (19%)</td>
<td>174 (61%)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5146</td>
<td>2485 (48%)</td>
<td>367 (15%)</td>
<td>1635 (66%)</td>
<td></td>
</tr>
</tbody>
</table>

^a P < .001

Husain A, et al, in press
Simultaneous Liver Kidney (SLK) Allocation

These recommendations are the result of two consensus conferences and three rounds of formal public comment. It incorporates feedback from the OPTN/UNOS Board of Directors, 11 OPTN/UNOS regions, several professional transplant societies, patient advocacy groups, and various OPTN/UNOS committees.
OPTN Briefing Paper

What problems will this solve?

1. **Final rule compliance**: Specifying that organ allocation policies must be based on sound medical judgment and standardized criteria

2. **Lack of Equity**: The lack of medical criteria results in allocation of high quality kidneys to liver candidates who may regain renal function after liver transplant and decreased access for kidney alone candidates

3. **Lack of clear liver-kidney allocation rules outside of DSA**
Candidates must meet at least one of the following conditions:

1) **CKD with GFR <60 mL/min for >90 days with:**
   - a) ESRD on chronic RRT, or
   - b) GFR <30 at time of listing for kidney

2) **Sustained AKI with:**
   - a) 6 consecutive weeks of RRT, or
   - b) GFR <25 mL/min for 6 consecutive weeks, or
   - c) Combination of 2a and 2b for 6 consecutive weeks

3) Metabolic disease (hyperoxaluria, aHUS, familial non-neuropathic systemic amyloidosis, or methylmalonic aciduria

**“Safety Net” Provision:**
Liver transplant recipients with continued dialysis dependency or GFR ≤ 20 ml/min in the period 2-12 months after liver transplant will receive priority for kidney allocation for kidneys with KDPI>20%
## Safety Net Allocation

Safety net: Match classification priority for liver recipients by KDPI sequence

<table>
<thead>
<tr>
<th>Sequence A</th>
<th>Sequence B</th>
<th>Sequence C</th>
<th>Sequence D</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDPI ≤ 20%</td>
<td>KDPI &gt;20% but &lt;35%</td>
<td>KDPI ≥35% but ≤85%</td>
<td>KDPI &gt;85%</td>
</tr>
<tr>
<td>Highly sensitized</td>
<td>Highly sensitized</td>
<td>Highly sensitized</td>
<td>Highly sensitized</td>
</tr>
<tr>
<td>0-ABDR mismatch</td>
<td>0-ABDR mismatch</td>
<td>0-ABDR mismatch</td>
<td>0-ABDR mismatch</td>
</tr>
<tr>
<td>Prior living donor</td>
<td>Prior living donor</td>
<td>Prior living donor</td>
<td>Local SLK safety net</td>
</tr>
<tr>
<td>Local pediatrics</td>
<td>Local pediatrics</td>
<td>Local SLK safety net</td>
<td>Local + regional</td>
</tr>
<tr>
<td>Local top 20% EPTS</td>
<td>Local SLK safety net</td>
<td>Local candidates</td>
<td>National candidates</td>
</tr>
<tr>
<td>0-ABDR mismatch (all)</td>
<td>Local adults</td>
<td>Regional candidates</td>
<td></td>
</tr>
<tr>
<td>Local (all)</td>
<td>Regional pediatrics</td>
<td>National candidates</td>
<td></td>
</tr>
<tr>
<td>Regional pediatrics</td>
<td>Regional adults</td>
<td>National pediatrics</td>
<td></td>
</tr>
<tr>
<td>Regional (top 20%)</td>
<td>National pediatrics</td>
<td>National adults</td>
<td></td>
</tr>
<tr>
<td>National pediatrics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National (top 20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National (all)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Estimated Number of Prior SLK Recipients (January 2005 – June 2015) that would have Met Medical Eligibility Criteria

<table>
<thead>
<tr>
<th>Would SLK Recipient Have Met Proposed SLK Eligibility Criteria?*</th>
<th>Detailed criteria</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>On Dialysis for ESRD at Time of Transplant</td>
<td>1,874</td>
<td>41.6</td>
</tr>
<tr>
<td></td>
<td>Not on Dialysis for ESRD, eGFR &lt;21</td>
<td>1,081</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>Not on Dialysis for ESRD, eGFR 21-25</td>
<td>328</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>Not on Dialysis for ESRD, eGFR 26-30</td>
<td>267</td>
<td>5.9</td>
</tr>
<tr>
<td>Sustained acute kidney injury</td>
<td>On dialysis for 6+ weeks before transplant #</td>
<td>101</td>
<td>2.2</td>
</tr>
<tr>
<td>Would not qualify for SLK</td>
<td>No Dialysis for ESRD or temporary dialysis for 6+ weeks, eGFR 31-35</td>
<td>213</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>No Dialysis for ESRD or temporary dialysis for 6+ weeks, eGFR &gt; 35</td>
<td>636</td>
<td>14.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4,500</td>
<td>100.0</td>
</tr>
</tbody>
</table>
SLKT and KALT (WL and transplants)

**SLKT**

- Year 2015: 1272 (WL), 627 (LT)
- Year 2016: 1274 (WL), 730 (LT)
- Year 2017: 1239 (WL), 740 (LT)
- Year 2018: 1161 (WL), 676 (LT)
- Year 2019: 1182 (WL), 723 (LT)

**KALT 1 year**

- Year 2015: 27 (WL), 6 (1y)
- Year 2016: 31 (WL), 9 (1y)
- Year 2017: 53 (WL), 16 (1y)
- Year 2018: 146 (WL), 51 (1y)
- Year 2019: 180 (WL), 54 (1y)

*New policy*
Better Biomarkers to Help Refine Allocation Criteria: SLK

- 7,000 annual liver transplants currently in the US
- 2,000 annual liver transplants with AKI

**Current clinical criteria for allocation**
- ~ 60-70% accuracy
  - 700 SLK allocation
  - 6,300 LT alone allocation

**Proposed allocation based on omics and biomarkers**
- ~ 85-90% accuracy
  - 200 SLK allocation
  - 6,800 LT alone allocation

Singal AK et al. Transpl Int 2019
Biomarkers Predictive of Renal Recovery After Liver Transplant

REVERSE Model: age, DM, OPN, TIMP-1 levels

Northwestern discovery

Baylor Cohort Validation

Levitsky, Baker et al. Hepatology 2014
Levitsky, Asrani et al. Hepatology 2019
Development and implementation of candidate selection criteria

HEART-KIDNEY TRANSPLANT
Adult Heart Transplants
Number and % of Multiorgan Transplants Reported by Year and Type of Transplant

JHLT. 2018 Oct; 37(10): 1155-1206
Renal Dysfunction in Heart Transplant

- Renal dysfunction is common in heart failure (HF) and is associated with higher all-cause mortality.
- Likelihood of worsening renal function is greater with higher baseline creatinine levels.
- Pre-transplant renal dysfunction predicts post-transplant outcomes.

Pre-HTx GFR of 30,090 patients who underwent HTx between 1988-2013

Adjusted mortality increases with lower eGFR (MDRD)

Habib PJ. J Heart Lung Transplant 2016;35:1471-1479
Survival Benefit of Heart-Kidney

Unmatched

Dialysis Dependent (Propensity Matched)

Non-Dialysis Dependent CKD (Propensity Matched)

Benefit of Heart-Kidney Transplant

Less ACR than OHT alone?

Less cardiac allograft vasculopathy than OHT alone?

% of Recipients Experiencing Treated Rejection within 1 Year

Multiorgan transplant (N=960)  Heart alone transplant (N=22,661)

JHLT. 2018 Oct; 37(10): 1155-1206

Sato T, Kobashigawa J. J Heart and Lung Transplant 2019;38(9):956–962
Consensus Conference on Combined Heart-Kidney Transplantation

A collaborative effort of the Thoracic and Critical Care Community of Practice and the Kidney Pancreas Community of Practice

Endorsed by the American Society of Transplantation

Chair: Jon Kobashigawa MD
Co-Chair: Darshana Dadhania MD

Saturday, June 1st, 2019
Boston, Massachusetts

CONFERENCE OBJECTIVES

• To develop needed guidelines for the interdisciplinary criteria for kidney transplantation in the combined heart/kidney transplant candidate.

• To evaluate the current allocation of kidneys to follow the heart for the heart/kidney transplant recipient.

• To develop standardized care recommendations for the collaborative management of heart/kidney transplant recipients, including immunosuppression, monitoring and treatment of post-transplant complications.

Information courtesy of Jon Kobashigawa
Consensus Conference on Combined Heart-Kidney Transplantation: Preliminary Conclusions

• The criteria for kidney alone include chronic kidney dialysis or eGFR ≤20ml/min

• From the available data and the discussions in the meeting eGFR >60ml/min is lower priority for a combined kidney transplant

• To determine when a kidney is needed also depends on the duration of impaired renal function in the setting of AKI and the negative renal effects from poor cardiac function (cardiorenal syndrome)

• Consideration of a “safety net” option similar to liver-kidney transplantation

Information courtesy of Jon Kobashigawa; manuscript in preparation
Development and implementation of candidate selection criteria

NON-KIDNEY MOT
Familial amyloid and heart failure with associated cirrhosis are the most common indications for Combined Heart-Liver Transplant.

Beal EW, et al. Transplantation 2016; Zhao K et al CLD 2019
Combined Heart-Liver Outcomes: Similar to Heart Alone

Zhao K et al CLD 2019
Indication for Liver Biopsy in Heart Transplant Candidates

Standard screening for all Tx candidates
- Albumin, AST/ALT
- Bilirubin
- Viral hepatitis panel
- Creatinine
- Calculation of MELD scores
- MELD-XI if on anticoagulation
- Abdominal sonogram

Specific concerns
- History of liver disease
- Past or present viral hepatitis
- Severe right heart failure
- Congenital heart disease
- Jaundice, recurrent ascites
- Encephalopathy, varices

Indications for liver biopsy
- Persistently impaired liver function after heart failure therapy optimization
- Sustained low albumin in the absence of other etiology
- Sustained elevation of total bilirubin/MELD scores
- Refractory/recurrent ascites
- Significant fibrosis or cirrhosis on imaging
- In consultation with a Hepatologist

Liver Disease Assessment in Heart Transplant Candidates

- Liver biopsy – with HVPG measurement to assess for portal hypertension
- MELD-XI (without INR) score
- Liver Risk Score = (Fibrosis stage + 1) x MELD-XI predictive of death among heart transplant recipients with liver dysfunction
- Noninvasive liver fibrosis assessment with elastography not accurate in the setting of hepatic congestion

Conclusions

• Specific minimal recipient selection criteria and allocation policies are needed for additional combinations of donor organs

• Policies must consider
  – Balancing substantial clinical advantages to individual recipients with potential decreased access to grafts for single organ candidates
  – Differences in allocation policies between organs: “sickest first” in liver/heart/lung vs. wait-time based in kidney

• Transparent reporting of center practices and standardized outcomes is essential

• “Safety nets” could be more broadly implemented to ensure more equitable allocation

• Better biomarkers of potential for kidney function recovery are needed