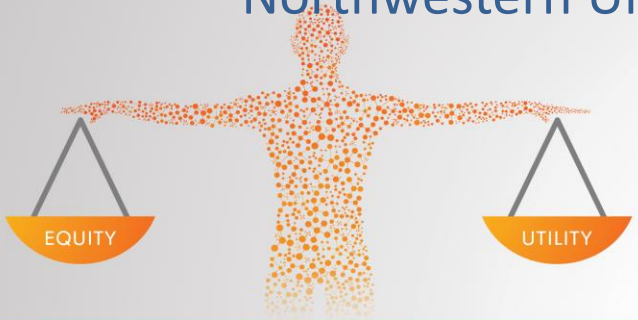
AST | AMERICAN SOCIETY OF TRANSPLANTATION

Standardizing Selection Criteria for Simultaneous Multi-Organ Transplantation

Josh Levitsky, MD, MS, FAST

Professor of Medicine, Surgery & Medical Education

Northwestern University Feinberg School of Medicine



CUTTING EDGE OF TRANSPLANTATION

TRANSPLANT SUMMIT 2020

BALANCING EQUITY AND UTILITY IN THE FACE OF AN ORGAN SHORTAGE

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

OPTN

Affected Policies:	*N/A*
Sponsoring Committee:	*Ethics Committee*
Public Comment Period:	*January 22, 2019 – March 22, 2019*
Board of Director's Date:	*June 10-11, 2019*

Briefing Paper

Ethical Implications of Multi-Organ Transplants

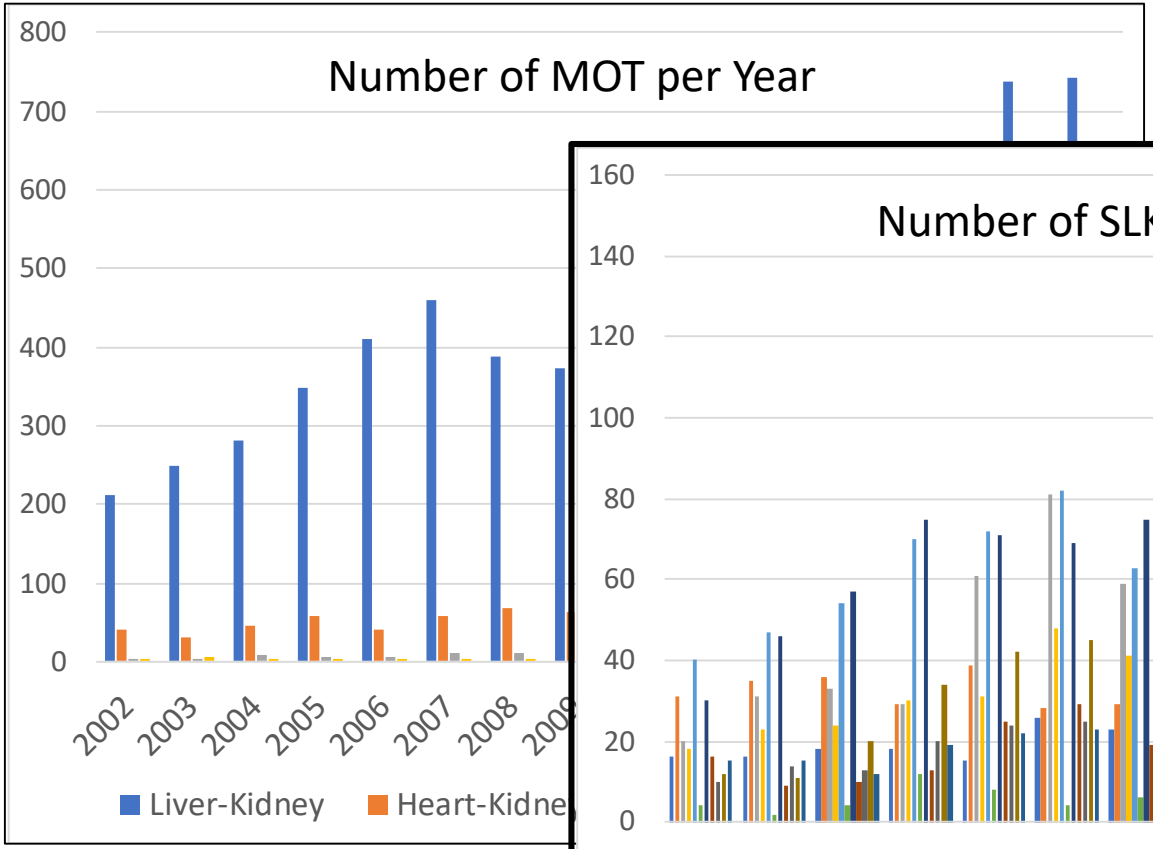
OPTN Ethics Committee

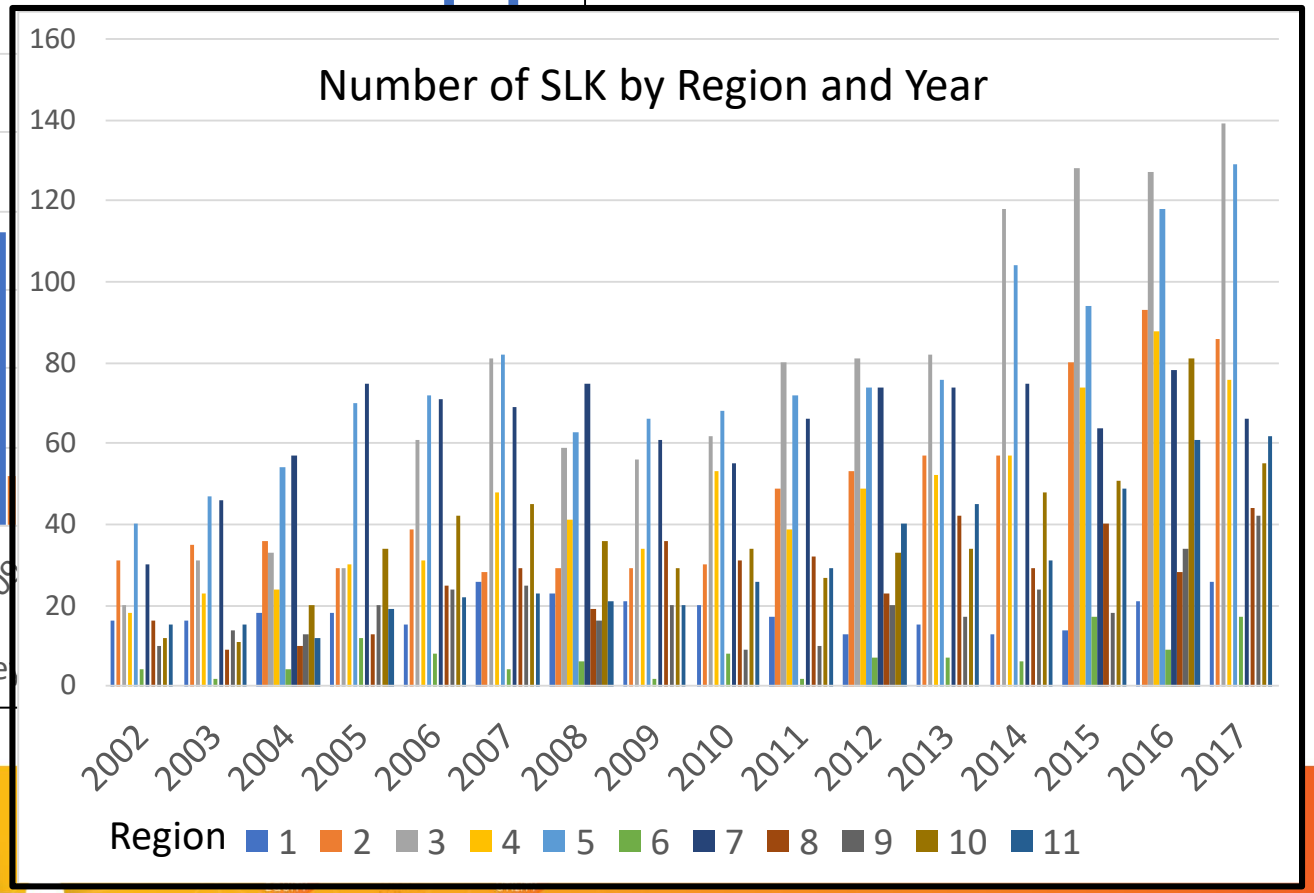
The 2018 OPTN Strategic Plan called for the OPTN to "measure equity in allocation, including geographic disparities and multi-organ disparities." This white paper lays the foundation for other committees to clarify or modify existing multi-organ allocation policy and to do so in a consistent, principled 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

	2013	2014	2015	2016	2017	Total
Total	1,459	1,508	1,625	1,801	1,853	8,246
Kidney-Pancreas	762	709	719	798	789	3,777
Liver-Kidney	494	558	627	730	739	3,148
Kidney-Heart	85	104	141	140	187	657
Liver-Intestines-Pancreas	50	69	67	58	55	299
Liver-Heart	16	18	28	18	29	109
Heart-Lung	23	24	15	18	29	109
Liver-Lung	7	6	9	9	8	39
Intestines-Pancreas	5	8	9	8	3	33
Kidney-Lung	7	5	1	4	7	24
Liver-Kidney-Intestines-Pancreas	6	3	2	7	2	20
Kidney-Intestines	1	2	2	5	1	11
Liver-Pancreas	0	0	2	3	1	6
Liver-Intestines	2	0	2	2	0	6
Kidney-Heart-Lung	0	1	0	0	2	3
Liver-Kidney-Heart	1	0	0	1	0	2
Liver-Heart-Lung	0	0	0	0	1	1
Liver-Kidney-Pancreas	0	1	0	0	0	1
Liver-Pancreas-Lung	0	0	1	0	0	1

- 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





AST AMERICAN SOCIETY OF TRANSPLANTATION

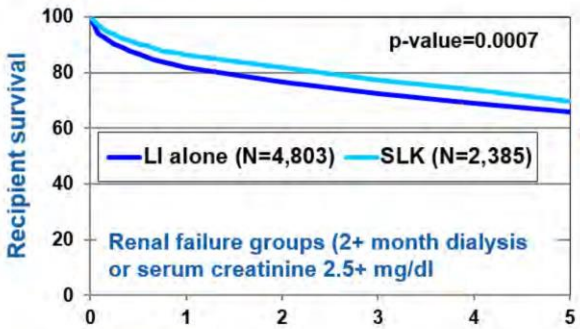
Allocation of MOTs

- 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 exit 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

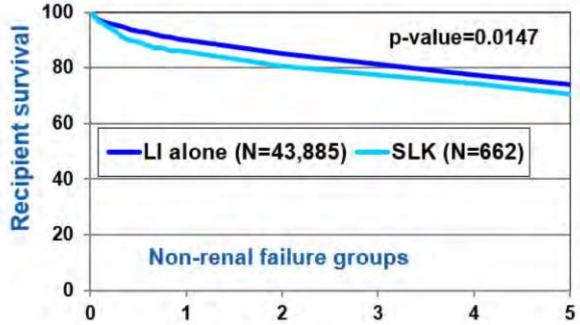
Development and implementation of candidate selection criteria

SIMULTANEOUS LIVER-KIDNEY TRANSPLANT

Survival Advantage for SLK in Selected Recipients



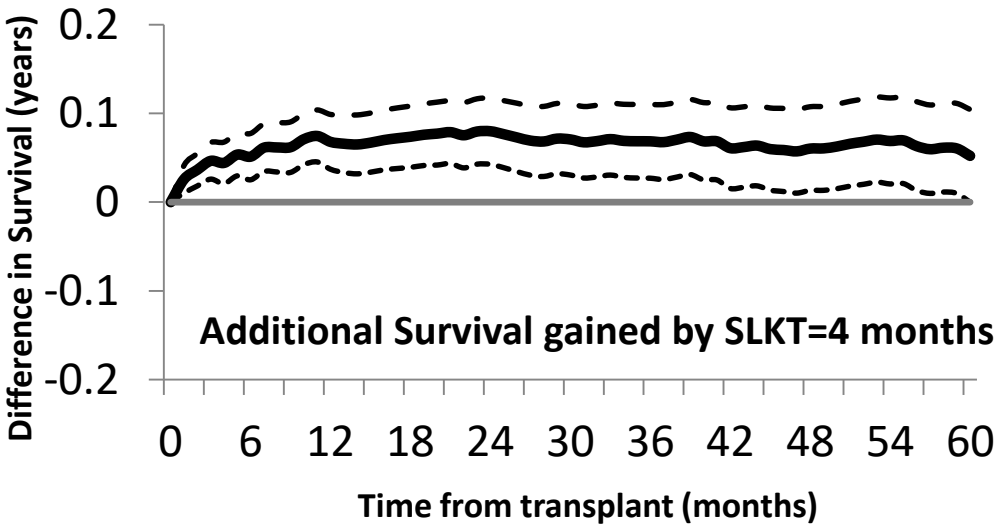
	LI Alone	SLK
White	70%	62%
Diabetes	27%	41%
MELD*	36	27
KDPI%	46	35
Age*	55	56
LI CIT*	6.9	6.4



	LI Alone	SLK
White	73%	65%
Diabetes	23%	38%
MELD*	17	28
KDPI%	52	37
Age*	55	57
LI CIT*	6.7	6.5

OPTN SLK Allocation Briefing Paper

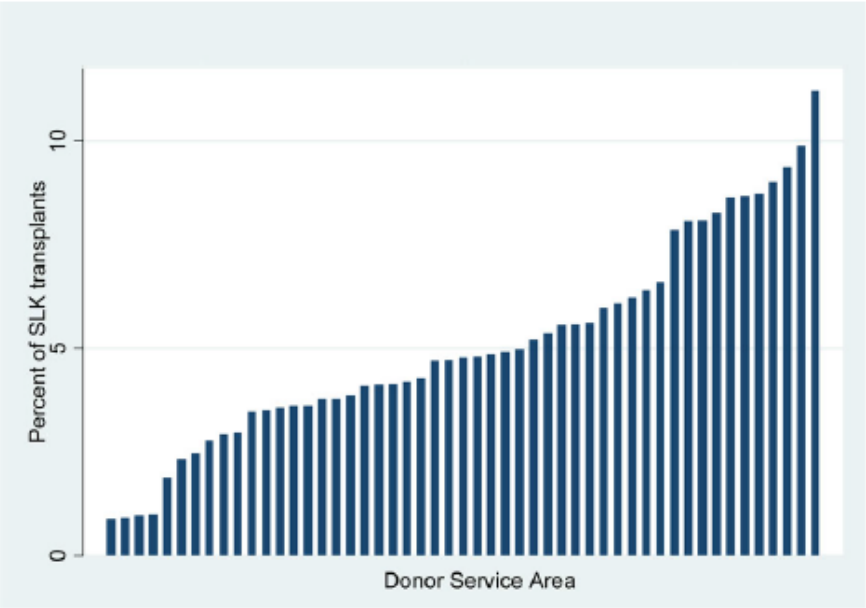
Additional Mean Survival Time Gained Based upon Mean 5-year Post-Transplant Survival (SLKT minus LTA): *not-on-dialysis*



Type of Transplant	Mean	(95% CI)
SLK	**4.20** (out of 5) years	(4.04, 4.33)
LTA	**3.86** (out of 5) years	(3.77, 3.96)
Difference (SLKT-LTA)	**0.34** (out of 5) years	(0.15, 0.50)

Sharma P et al, Liver Transplant 2016

Highly Variable use of SLK by DSA



- 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.

Region	KDPI ≤ 20% Kidneys Transplanted (n)	n (%) for Recipients With EPTS > 20%[a]	Among KDPI ≤ 20% Kidneys Transplanted in EPTS > 20% Recipients	
			n (%) Used for cPRA > 97%[a]	n (%) Used for Multi-Organ Transplants[b]
1	117	54 (46%)	11 (20%)	28 (52%)
2	543	285 (52%)	68 (24%)	162 (57%)
3	766	399 (52%)	40 (10%)	282 (71%)
4	646	316 (49%)	46 (15%)	212 (67%)
5	772	387 (50%)	62 (16%)	263 (68%)
6	245	87 (36%)	5 (6%)	59 (68%)
7	387	204 (53%)	31 (15%)	147 (72%)
8	425	158 (37%)	19 (12%)	112 (71%)
9	215	98 (46%)	9 (9%)	55 (56%)
10	449	214 (48%)	23 (11%)	141 (66%)
11	581	283 (49%)	53 (19%)	174 (61%)
Overall	5146	2485 (48%)	367 (15%)	1635 (66%)
		$P < .001$	$P < .001$	$P < .001$

Husain A, et al, in press

OPTN | UNOS Briefing Paper

OPTN/UNOS Kidney Transplantation Committee

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**

OPTN/UNOS criteria for eligibility for SLK- implemented in Aug 2017

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

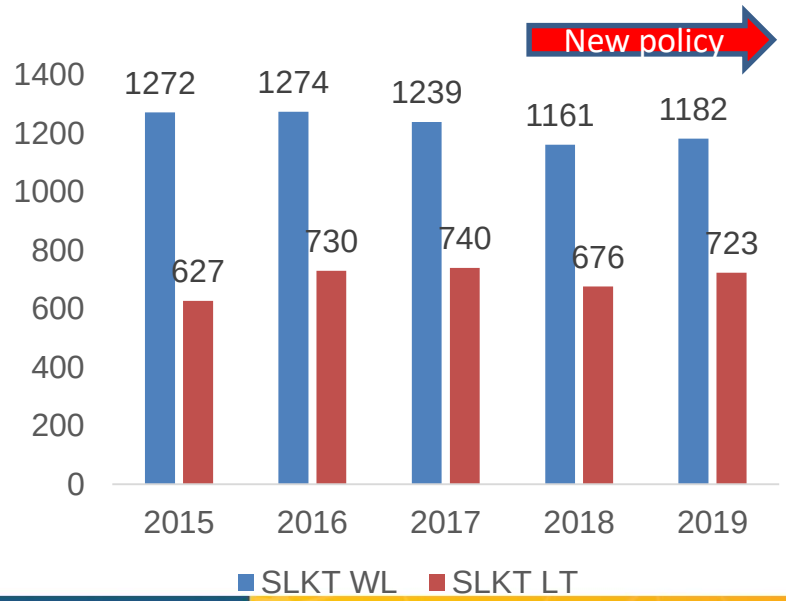
Sequence A **KDPI ≤ 20%**	**Sequence B** **KDPI >20% but <35%**	**Sequence C** **KDPI ≥35% but ≤85%**	**Sequence D** **KDPI >85%**
Highly sensitized	Highly sensitized	Highly sensitized	Highly sensitized
0-ABDR mismatch	0-ABDR mismatch	0-ABDR mismatch	0-ABDR mismatch
Prior living donor	Prior living donor	Prior living donor	Local SLK safety net
Local pediatrics	Local pediatrics	Local SLK safety net	Local + regional
Local top 20% EPTS	Local SLK safety net	Local candidates	National candidates
0-ABDR mismatch (all)	Local adults	Regional candidates	
Local (all)	Regional pediatrics	National candidates	
Regional pediatrics	Regional adults		
Regional (top 20%)	National pediatrics		
Regional (all)	National adults		
National pediatrics			
National (top 20%)			
National (all)			

Estimated Number of Prior SLK Recipients (January 2005 – June 2015) that would have Met Medical Eligibility Criteria

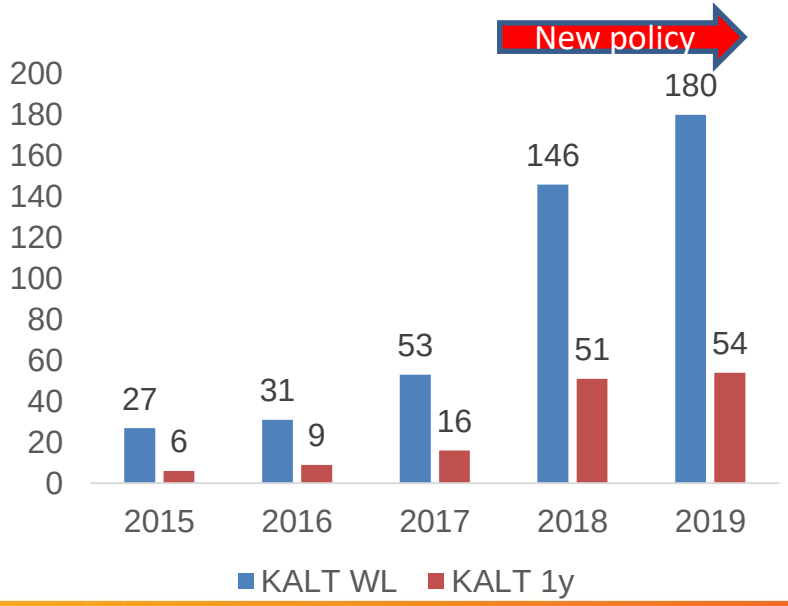
Would SLK Recipient Have Met Proposed SLK Eligibility Criteria?*	Detailed criteria	N	%
Chronic kidney disease	On Dialysis for ESRD at Time of Transplant	1,874	41.6
	Not on Dialysis for ESRD, eGFR <21	1,081	24.0
	Not on Dialysis for ESRD, eGFR 21-25	328	7.3
	Not on Dialysis for ESRD, eGFR 26-30	267	5.9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

SLKT and KALT (WL and transplants)

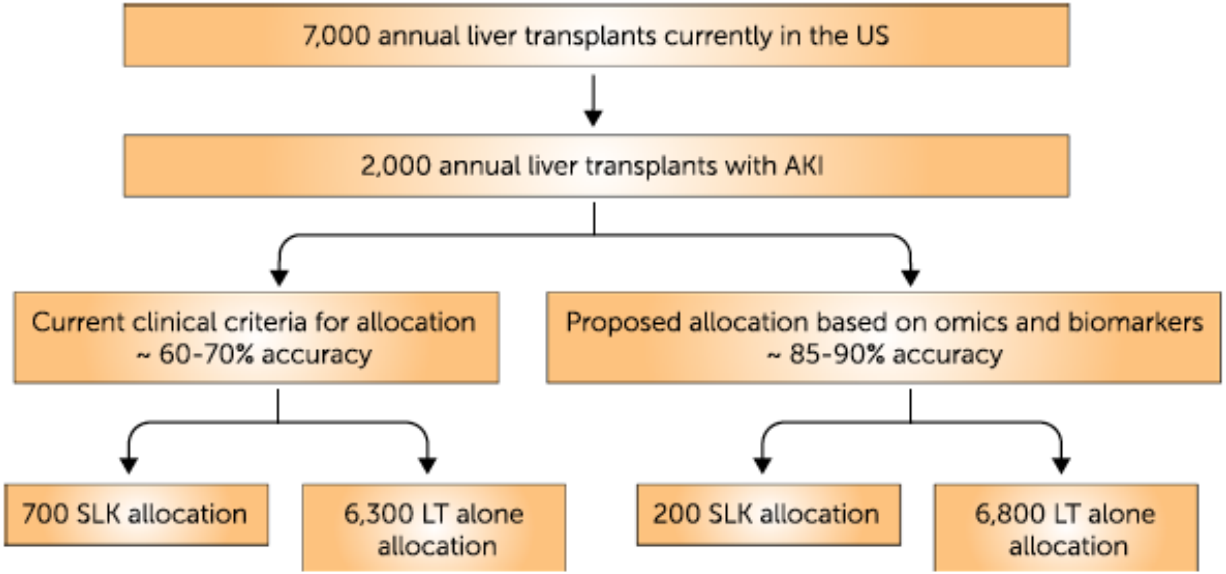
SLKT



KALT 1 year



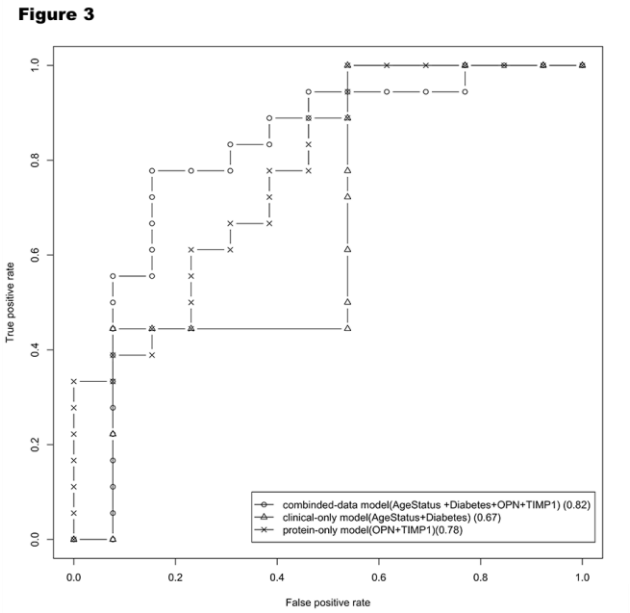
Better Biomarkers to Help Refine Allocation Criteria: SLK



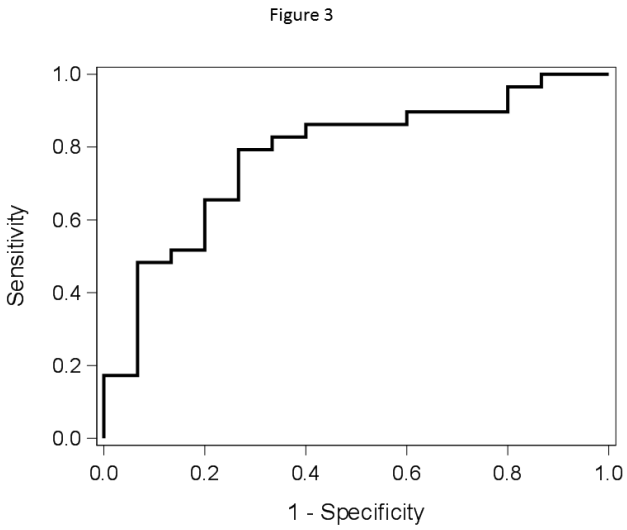
Singal AK et al. Transpl Int 2019

Biomarkers Predictive of Renal Recovery After Liver Transplant

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



Northwestern discovery



Baylor Cohort Validation

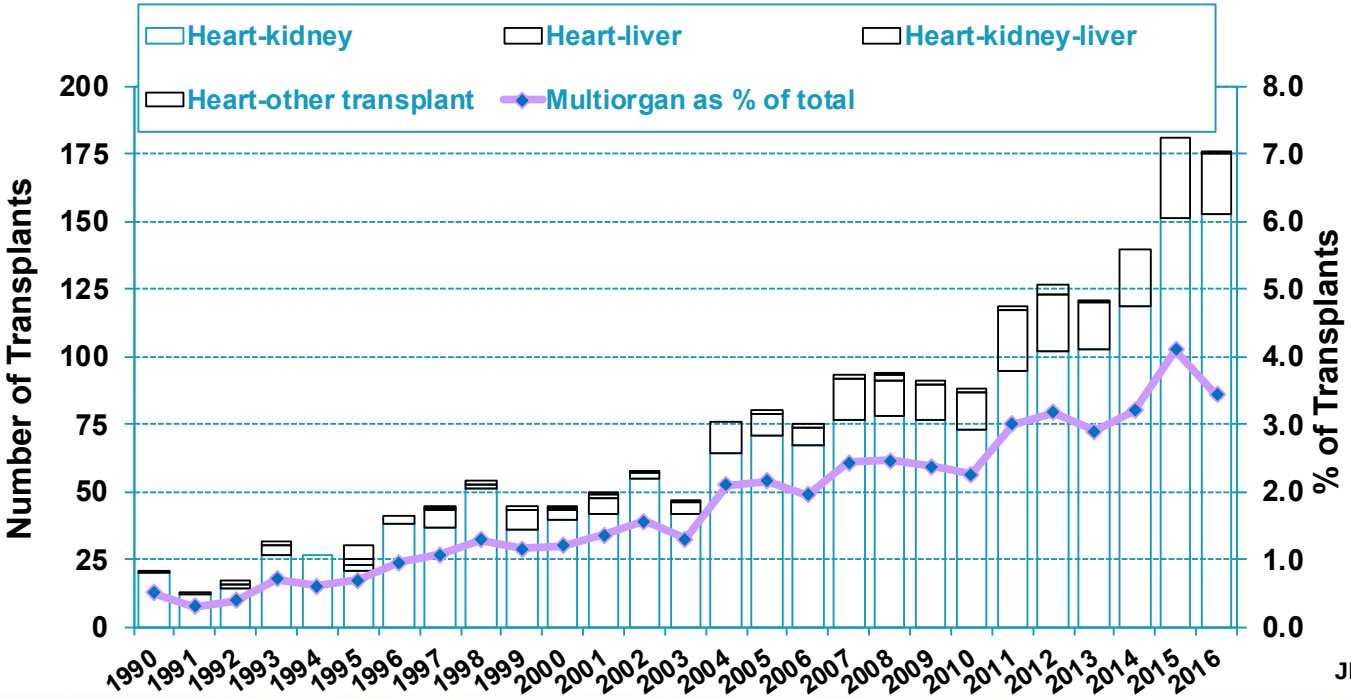
Levitsky, Baker et al. Hepatology 2014
Levitsky, Asrani et al Hepatology 2019

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

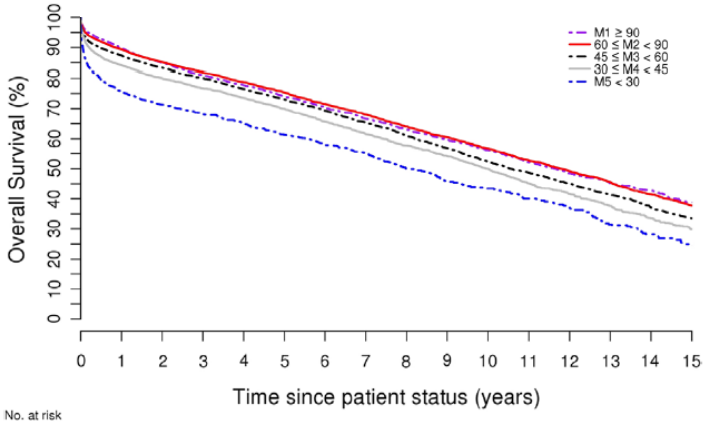


JHLT. 2018 Oct; 37(10): 1155-1206

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



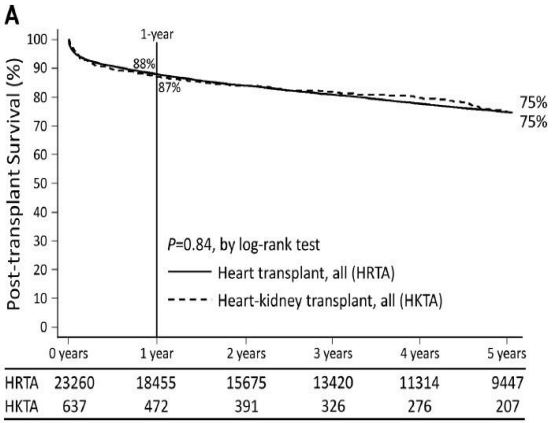
No. at risk				
M1 ≥ 90	4514	1959	790	195
60 ≤ M2 < 90	11710	5813	2644	691
45 ≤ M3 < 60	7653	3782	1574	376
30 ≤ M4 < 45	4790	2310	944	209
M5 < 30	1420	615	253	51

Adjusted mortality increases with lower eGFR (MDRD)

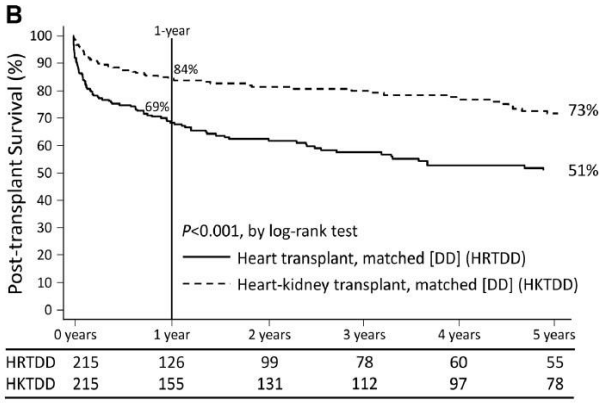
Habib PJ. J Heart Lung Transplant 2016;35:1471-1479

Survival Benefit of Heart-Kidney

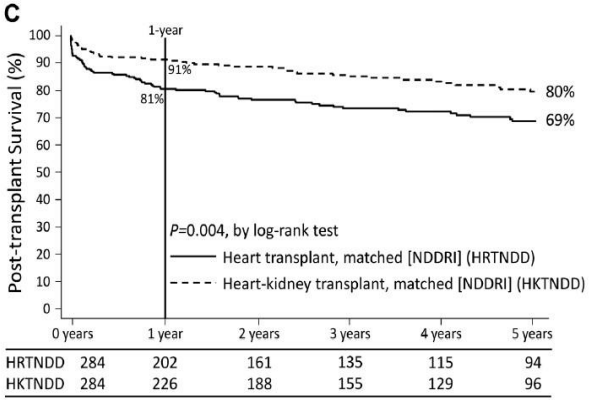
Unmatched



Dialysis Dependent (Propensity Matched)



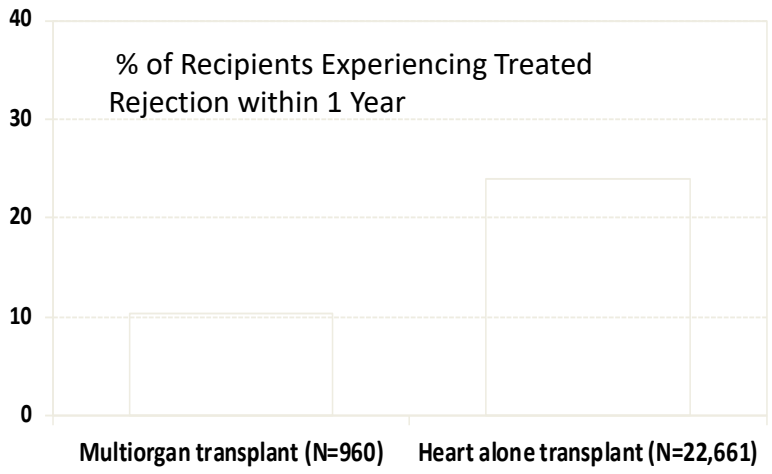
Non-Dialysis Dependent CKD (Propensity Matched)



Schaffer JM, et al. Am J Transplant 2014

Benefit of Heart-Kidney Transplant

Less ACR than OHT alone?



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

Less cardiac allograft vasculopathy than OHT alone?

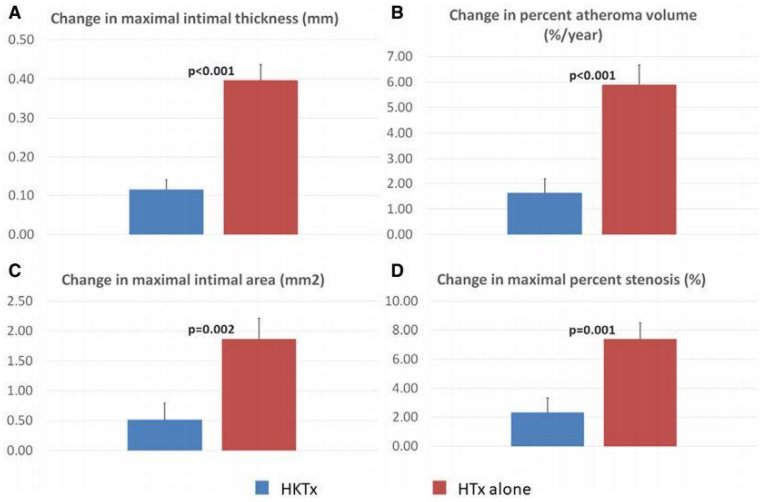


Figure 1 Change in coronary plaque between baseline and 1-year intravascular ultrasound. Change in (**a**) maximal intimal thickness, (**b**) percent atheroma volume, (**c**) maximal intimal area, and (**d**) maximal percent stenosis are compared between the patients who received heart-kidney transplantation and heart transplantation alone.

Sato T, Kobashigawa J. J Heart and Lung Transplant 2019;38(9):956–962

Consensus Conference on
Kidney Transpl

A collaborative effo
Thoracic and Critical Care Co
and the Kidney Pancreas Com

Endorsed by the *American Socie*

Chair: Jon Kobashi
Co-Chair: Darshana D
Saturday, June 1s
Boston, Massach

Information courtesy of Jon Kobashigawa

CONFERENCE OBJECTIVES

- To develop needed guidelines for the <u>interdisciplinary criteria for kidney transplantation in the combined heart/kidney transplant candidate</u>.
- 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.

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

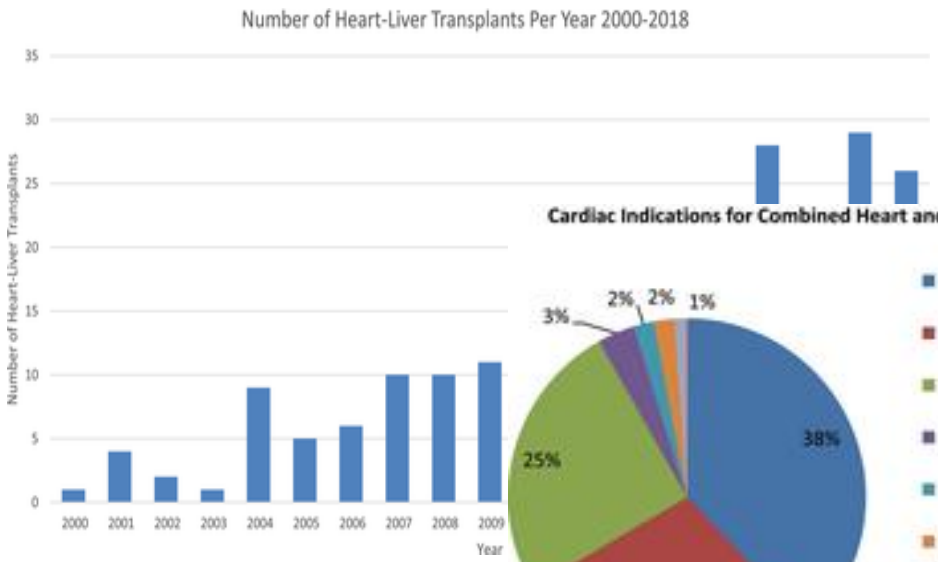
Information courtesy of Jon Kobashigawa; manuscript in preparation

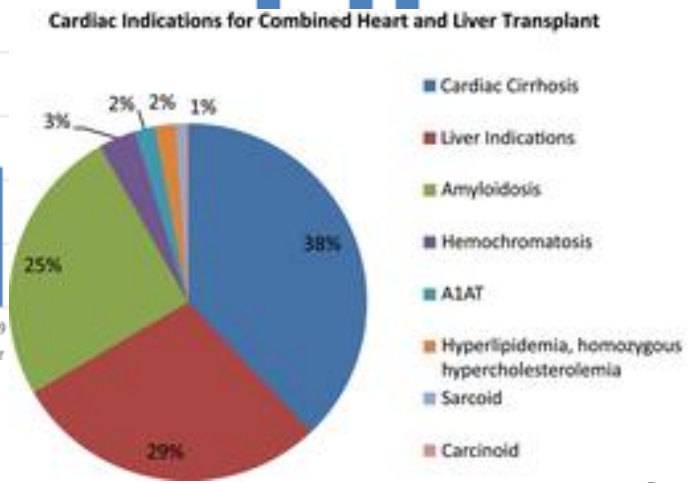
Development and implementation of candidate selection criteria

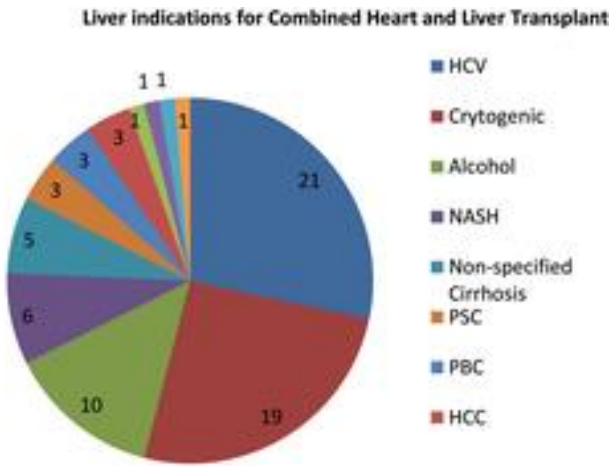
NON-KIDNEY MOT

Combined Heart-Liver Transplant

Familial amyloid and heart failure with associated cirrhosis are the most common indications

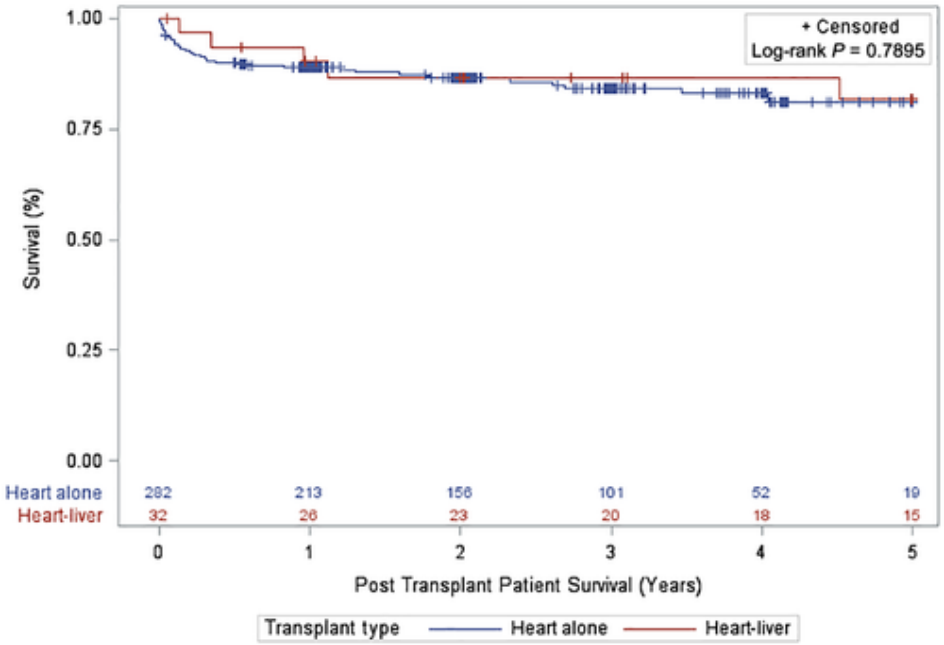






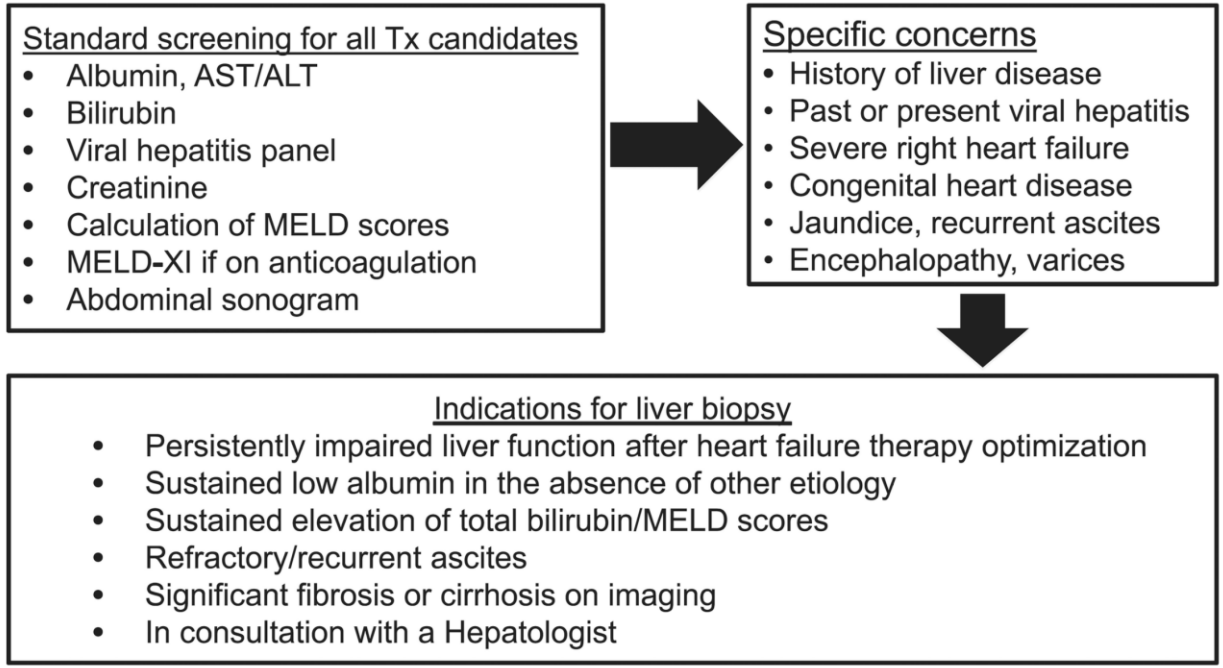
Beal EW, et al. Transplantation 2016; Zhao K et al CLD 2019

Combined Heart-Liver Outcomes: Similar to Heart Alone



Zhao K et al CLD 2019

Indication for Liver Biopsy in Heart Transplant Candidates



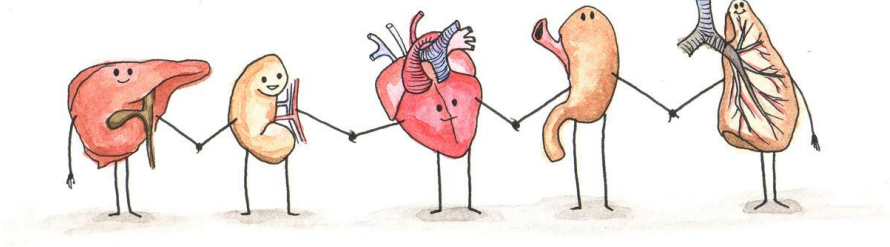
Farr M, et al JHLB 2015

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

Farr M, et al JHLB 2015

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