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Personalized Organ Allocation - The Right Organ, For the Right Recipient, at the Right Time.

Brevity Matching

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Conflicts of interest.

I have no financial conflicts of interest in regards to this talk.

My fiduciary conflicts are;

- Secretary of the America Society of Transplantation
- Member of the OPTN/UNOS Membership and Professional Standards Committee
- Member of the Visiting Committee of the SRTR

So, before we begin, let's acknowledge……

Understanding SRTR's Outcome Assessment

Summarizing transplant program performance using a 5-tier system

SRTR assigns each transplant program an outcome assessment tier (1 to 5) based on how many patients remain alive with a functioning transplanted organ 1 year after transplant. The outcome assessment is displayed in the program search results, and in the more detailed results shown for the program. This guide is meant to help you understand why SRTR assigns the outcome assessment, how SRTR calculates the assessment, and how to interpret the assessment.

Table 1. Numbers of adult transplant programs in each of the 5-tier assessment system categories.

Transplant Type	Tier 1 (Worse than Expected)	Tier 2 (Somewhat Worse than Expected)	Tier 3 (Good, As Expected)	Tier 4 (Somewhat Better than Expected)	Tier 5 (Better than Expected)
Heart	8	16	44	47	8
Kidney	12	52	78	61	30
Liver	5	32	40	37	10
Lung	3	17	22	20	5

What are the challenges faced by transplant centers?

Recipient Complexity

Aging Population
Dialysis Exposure
Diabetes
Peripheral Vascular Disease
Obesity
Cardiovascular Risk

Donor Quality

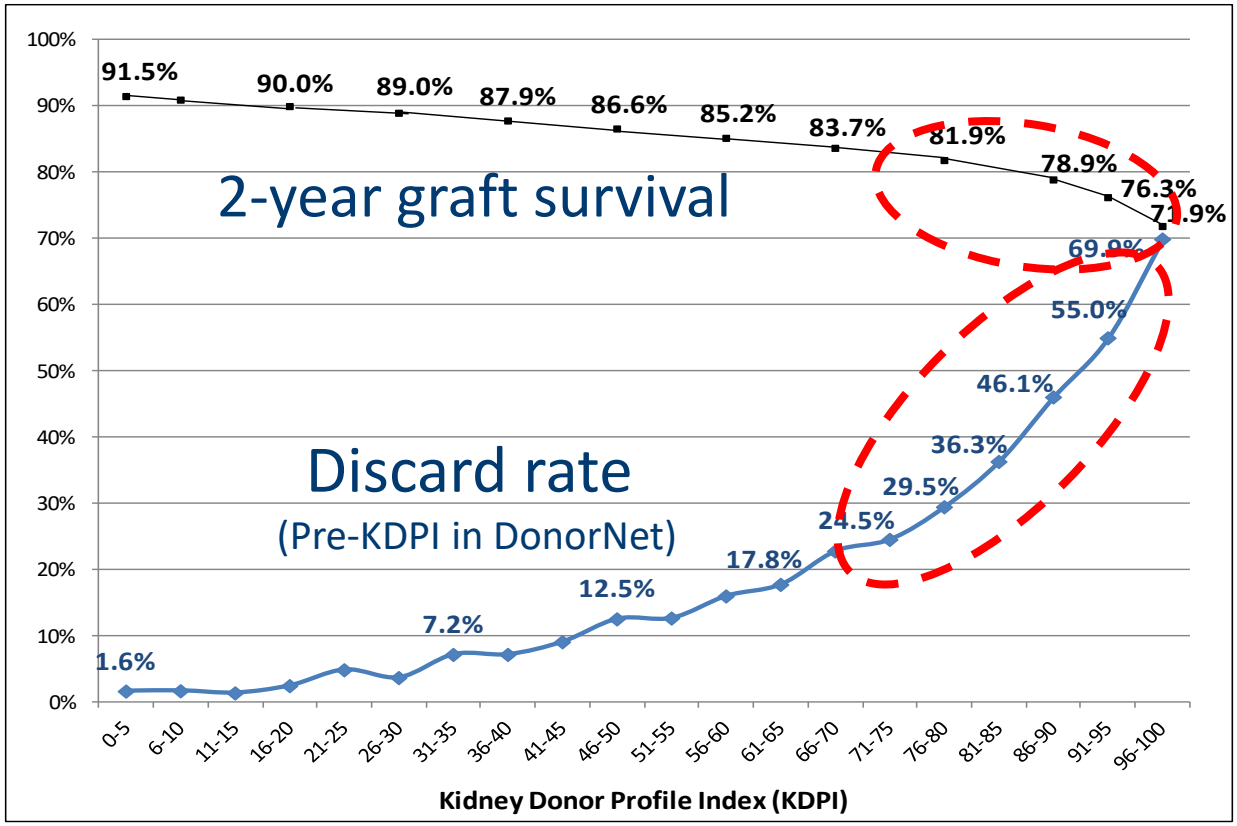
Decrease in General Population Health
Aging Population
Diabetes Prevalence
Obesity
Mode of Death – Increase in DCD Rates
Rise in PHS IR Donors

To varying degrees ***most*** of these are risk adjusted.

However, there is no risk adjustment for……

Why are we even discussing the use of high KDPI kidneys?

Because there is a disconnect, discard rates climb dramatically at higher KDPI despite acceptable 2 year graft survival rates.



Darren Stewart

Gradual decline in graft survival, yet *steep increases* in kidney discard rates.

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The new allocation system reduces the number of extreme “longevity-mismatched” transplants.

But it does nothing to promote pairing high KDPI kidneys with older recipients.

Therefore the ad hoc approach of “Dealing from the bottom of the deck” is used.

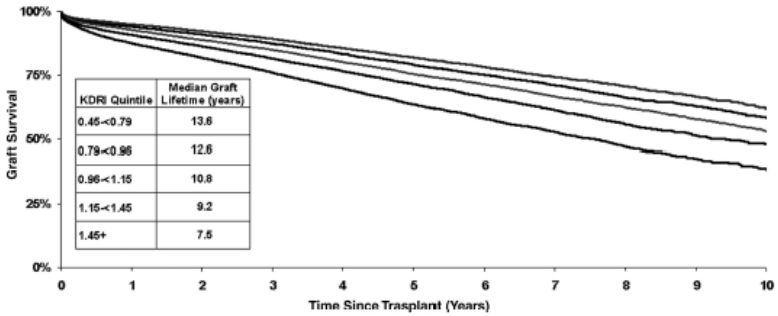
What is the Kidney Donor Risk Index (KDRI)?

TABLE 1. Donor and transplant factors and corresponding hazard ratios for graft failure

	Hazard ratio	95% Confidence Interval	*P*
Donor parameter			
Age-40 yr; applies to all ages	1.013	1.011–1.015	<0.0001
Age-18 yr; applies only if age <18	0.98	0.97–0.99	0.0033
Age-50 yr; applies only if age >50	1.011	1.005–1.016	0.0001
African American race	1.20	1.13–1.27	<0.0001
Serum creatinine-1; applies to all Cr values	1.25	1.17–1.33	<0.0001
Serum creatinine-1.5; applies if Cr >1.5	0.81	0.74–0.89	<0.0001
Hypertensive	1.13	1.08–1.19	<0.0001
Diabetic	1.14	1.04–1.24	0.0040
Cause of death: cerebrovascular accident	1.09	1.04–1.14	0.0002
Height: per 10 cm increase	0.96	0.94–0.97	<0.0001
Weight: per 5 kg increase below 80 kg	0.98	0.97–0.99	0.0003
Donation after cardiac death	1.14	1.02–1.28	0.0246
HCV positive	1.27	1.13–1.43	<0.0001
Transplant parameter			
HLA mismatch			
0 HLA-B mismatch (ref=2 B MM)	0.93	0.87–0.98	0.0111
1 HLA-B mismatch	0.94	0.90–0.98	0.0065
0 HLA-DR mismatch (ref=1 DR MM)	0.88	0.84–0.92	<0.0001
2 HLA-DR mismatch	1.08	1.03–1.13	0.0014
Cold ischemia time: per 1 hr (ref=20 hr)	1.005	1.003–1.008	<0.0001
En bloc transplant	0.70	0.57–0.84	0.0002
Double kidney transplant	0.86	0.75–1.00	0.0494

HLA, human leukocyte antigen; Cr, creatinine; HCV, hepatitis C virus.

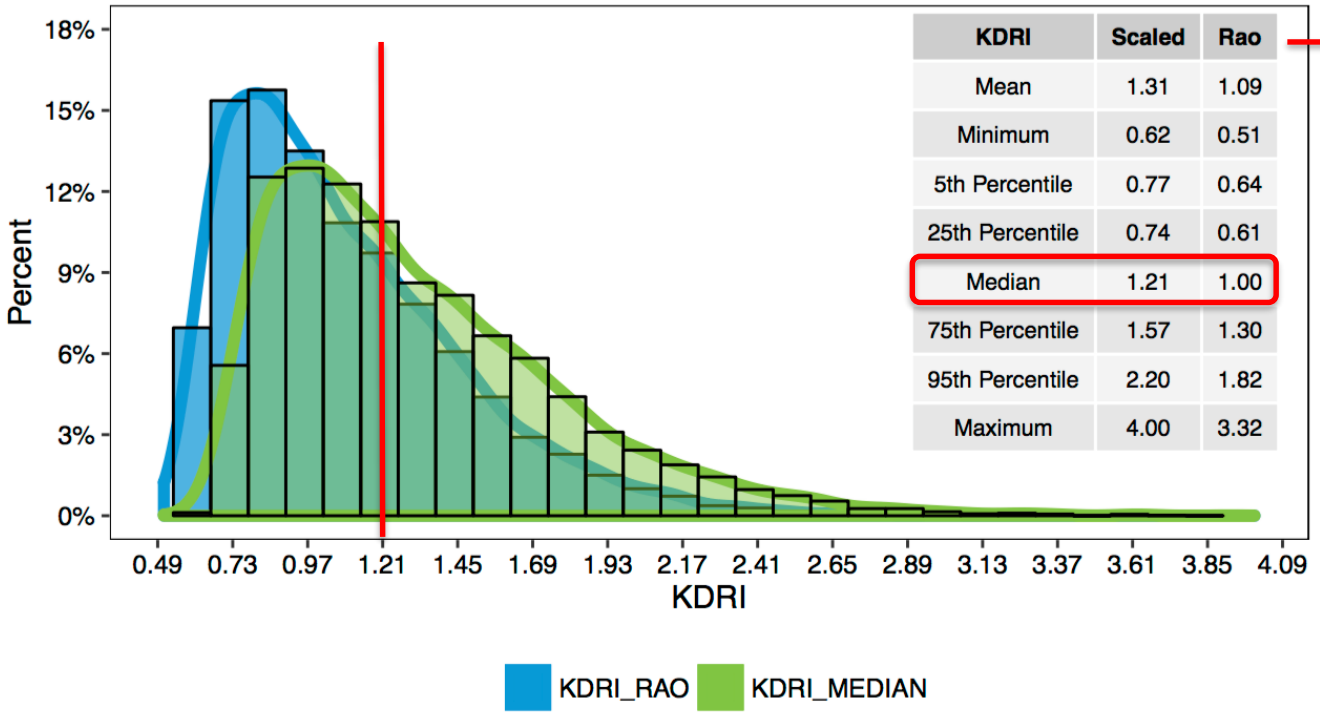
FIGURE 2. Adjusted* graft survival by kidney donor risk index (KDRI) quintile. The curves are ordered, top to bottom, as quintile 1, quintile 2, …, quintile 5. Each survival pertains to a recipient who is aged 50 years, nondiabetic, and at the reference level of all other recipient factors. Extrapolation was used for the first and second quintile. *Adjusted to a reference 50-year-old recipient.



Rao PS et al. Transplantation 2009.

What is the KDRI distribution of recovered kidneys?

Figure 2. Distribution of Kidney Donors Recovered in the U.S. in 2016, by KDRI



KDRI	Scaled	Rao
Mean	1.31	1.09
Minimum	0.62	0.51
5th Percentile	0.77	0.64
25th Percentile	0.74	0.61
Median	1.21	1.00
75th Percentile	1.57	1.30
95th Percentile	2.20	1.82
Maximum	4.00	3.32

Based on OPTN data as of April 20, 2018.

Rao PS et al. Transplantation 2009.

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https://optn.transplant.hrsa.gov/media/1512/guide_to_calculating_interpreting_kdpi.pdf

How does the KDRI become the Kidney Donor Profile Index (KDPI)?

KDRI to KDPI Mapping Table

Reference population: All deceased kidney donors recovered for the purpose of transplantation in 2017 in the U.S. KDRI scaled (normalized) such that median donor has KDRI=1.0

Based on the OPTN database as of March 09, 2018

If KDRI is Between			Then
>	<=		KDPI is
0.00000000000000	0.51097878820605	->	0%
0.51097878820605	0.58110303329243	->	1%
0.58110303329243	0.59932815069187	->	2%
0.59932815069187	0.61487566644285	->	3%
0.61487566644285	0.62713891993243	->	4%
0.62713891993243	0.63796592892641	->	5%
0.63796592892641	0.64802422439693	->	6%
0.64802422439693	0.65744958149982	->	7%
0.65744958149982	0.66680341942951	->	8%
0.66680341942951	0.67594903350827	->	9%
0.67594903350827	0.68369347347361	->	10%
0.68369347347361	0.69172749103919	->	11%
0.69172749103919	0.69940367490404	->	12%
0.69940367490404	0.70616440523059	->	13%
0.70616440523059	0.71254857052845	->	14%
0.71254857052845	0.71965222823665	->	15%
0.71965222823665	0.72601311469668	->	16%
0.72601311469668	0.73419750953865	->	17%
0.73419750953865	0.74136959452354	->	18%
0.74136959452354	0.75004295556891	->	19%

https://optn.transplant.hrsa.gov/media/2150/kdpi_mapping_table.pdf

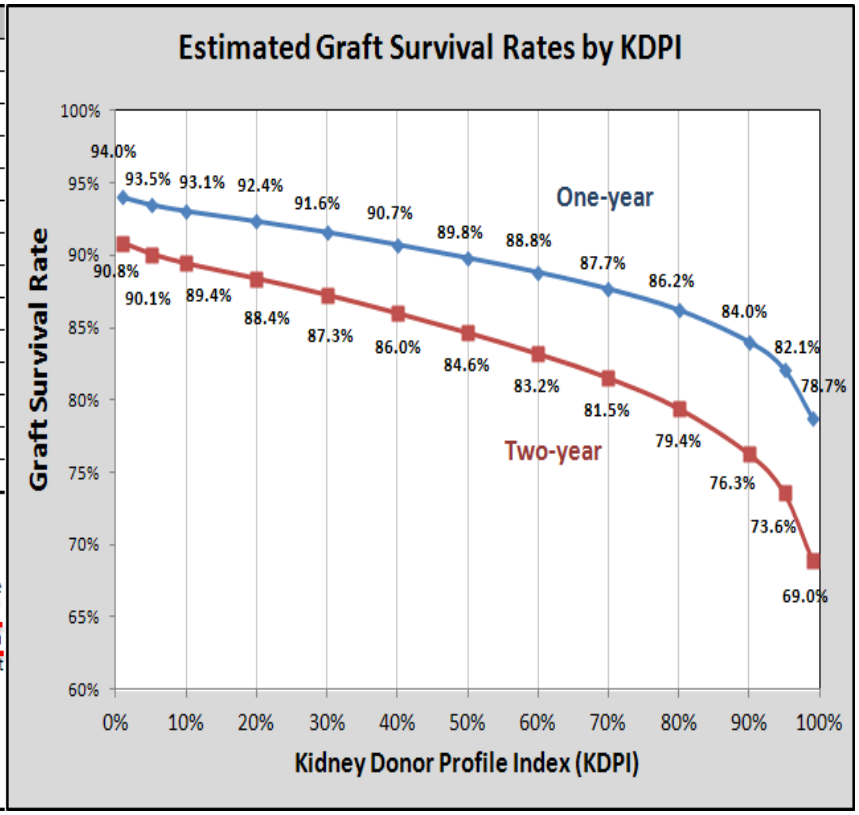
What is the Kidney Donor Profile Index (KDPI)?

KDPI Variables

- Donor age
- Height
- Weight
- Ethnicity
- History of HTN
- History of Diabetes
- Cause of Death
- Serum Creatinine
- HCV Status
- DCD Status

KDPI	Estimated Kidney Graft Survival Rates				
	1 Year	2 Years	3 Years	5 Years	8 Years
1%	94.0%	90.8%	87.8%	80.6%	68.8%
5%	93.5%	90.1%	86.8%	79.1%	66.6%
10%	93.1%	89.4%	85.9%	77.8%	64.7%
20%	92.4%	88.4%	84.5%	75.7%	61.7%
30%	91.6%	87.3%	83.1%	73.6%	58.8%
40%	90.7%	86.0%	81.5%	71.2%	55.5%
50%	89.8%	84.6%	79.7%	68.7%	52.2%
60%	88.8%	83.2%	77.9%	66.1%	48.7%
70%	87.7%	81.5%	75.7%	63.1%	45.0%
80%	86.2%	79.4%	73.1%	59.5%	40.6%
90%	84.0%	76.3%	69.2%	54.4%	34.7%
95%	82.1%	73.6%	65.9%	50.1%	30.2%
99%	78.7%	69.0%	60.4%	43.4%	23.5%

Based on OPTN data **as of April 13, 2012** including primary, solitary, adult kidney transplants from 2000-2007. These survival rates are for SINGLE kidney-alone transplants; survival rates are generally higher for en bloc or double kidney transplants. These rates were not adjusted for recipient characteristics, but instead reflect the expected survival averaged across the broad spectrum of adult recipients. The survival rates for any particular recipient will depend on specific characteristics of that recipient. Survival rates were estimated using a Cox regression model with log(KDRI) as the sole independent variable and graft failure defined as loss of graft or patient death. **Donor reference population: all kidney donors recovered in 2011.**



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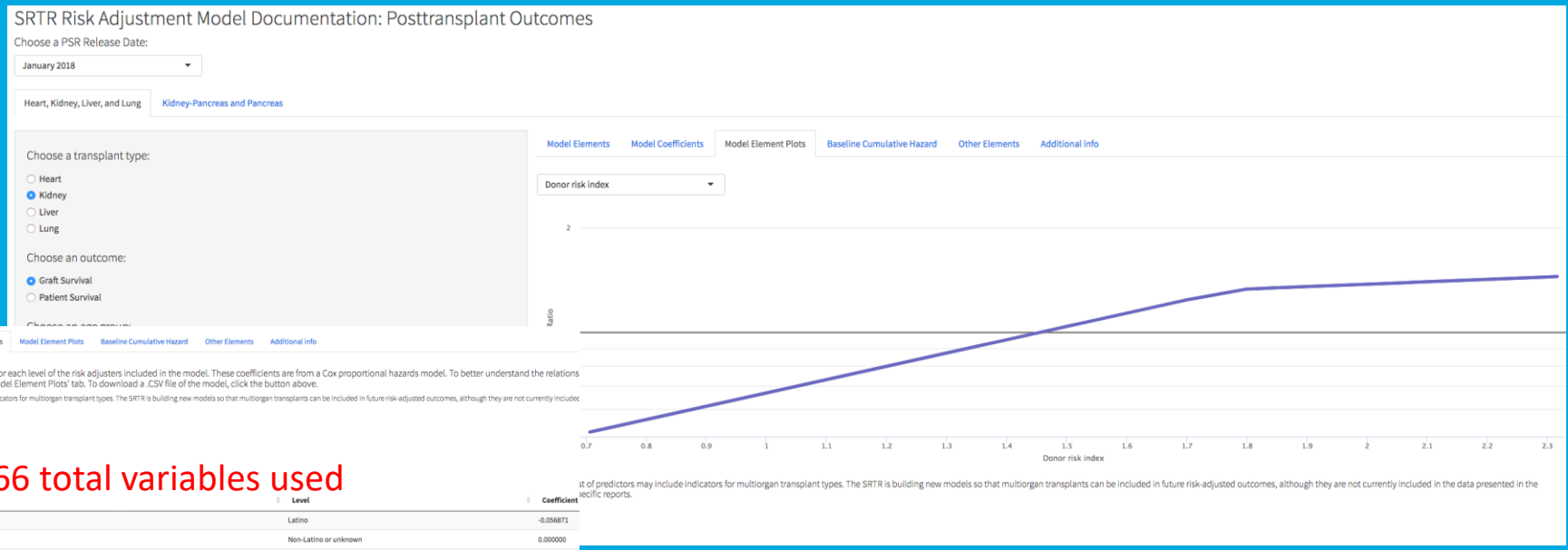
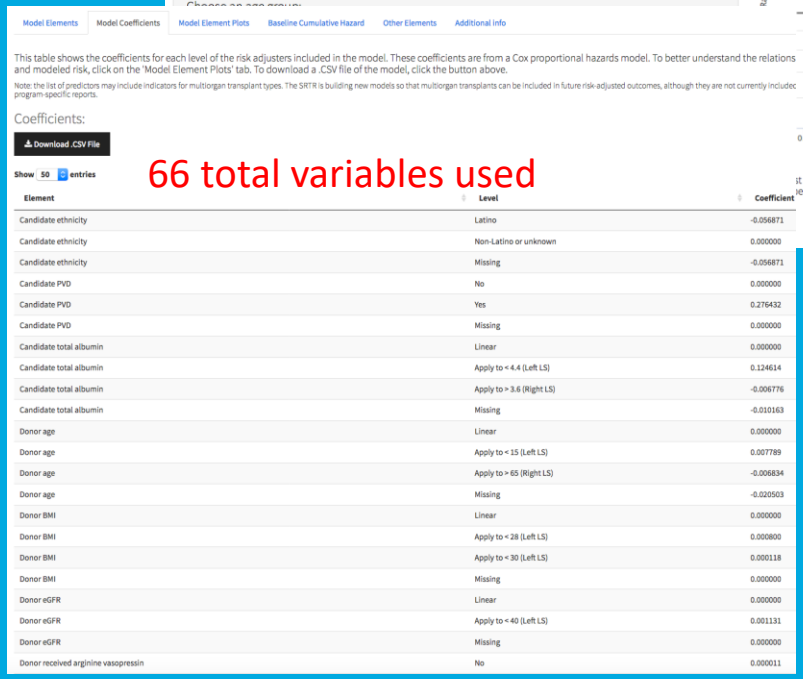
The KPDI is criticized because the “c-statistic is only 0.63.”

However, there is a strong association with 1 year graft survival in the SRTR model.





66 total variables used

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Therefore, is the flaw with KDPI itself or with how recipients are selected for a kidney with a given KDPI?

"As evidenced by its strong association in the current SRTR 1-year post-transplant graft survival model, I tend to view KDRI as a reasonably good measure of overall donor risk. However, the relatively low C-statistic means that some recipients of high-KDRI kidneys have good outcomes and some recipients of low-KDRI kidneys have poor outcomes."

-Andrew Wey, PhD SRTR Biostatistician

And the data supports not declining the offer of a high KDPI kidney for the right recipient.

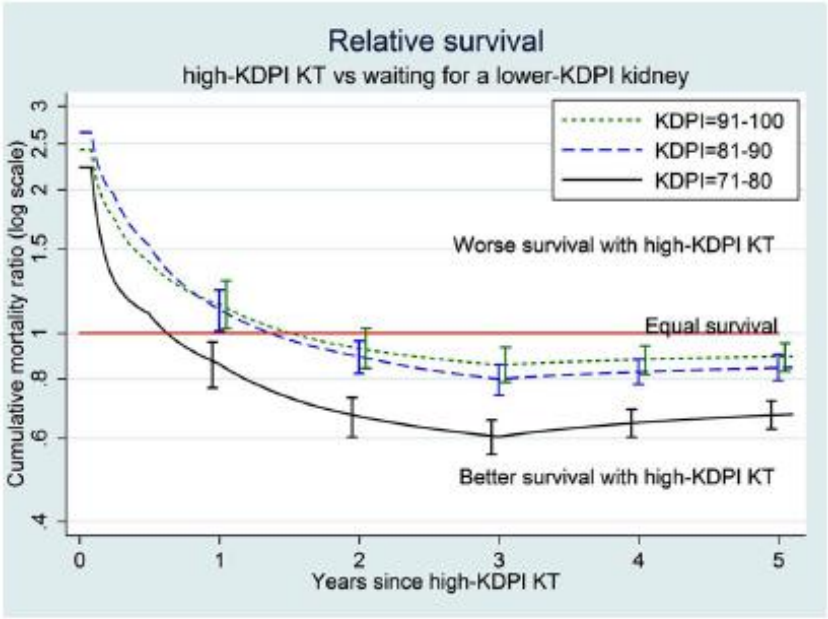


Figure 2: Plot of cumulative mortality ratio (ratio of total deaths after high-KDPI KT to deaths in the absence of high-KDPI KT) as a function of time since KT. Due to increased

Table 3: Time to equal risk, and equal survival, incurred by accepting a high-KDPI kidney transplant versus the conservative approach of waiting for a lower KDPI kidney

	Time to equal risk (months)	Time to equal survival (months)
KDPI 71–80 vs. waitlist or KDPI 0–70	1.7	7.7
KDPI 81–90 vs. waitlist or KDPI 0–80	6.0	18.0
KDPI 91–100 vs. waitlist or KDPI 0–90	7.2	19.8

KDPI, Kidney Donor Profile Index.

Massie et al AJT 2014

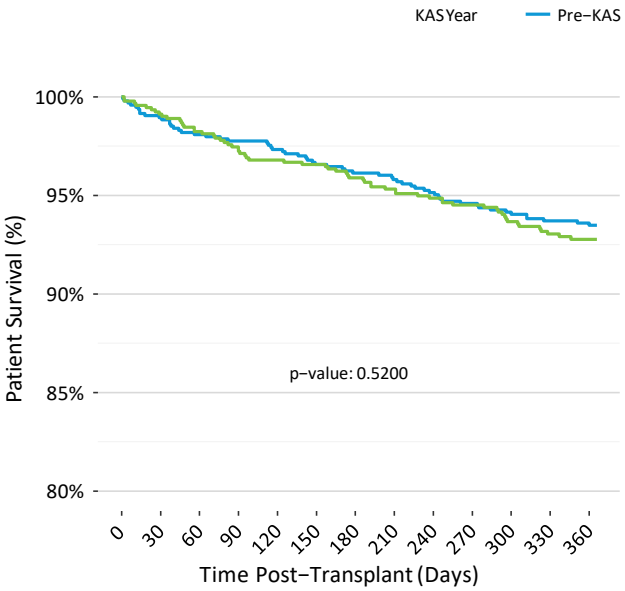
Who are the patients who benefit from receiving high KDPI kidneys?

- Those who are diabetics.
- Those over 50 years of age.
- Those listed with a median waiting time of 3 years or greater.

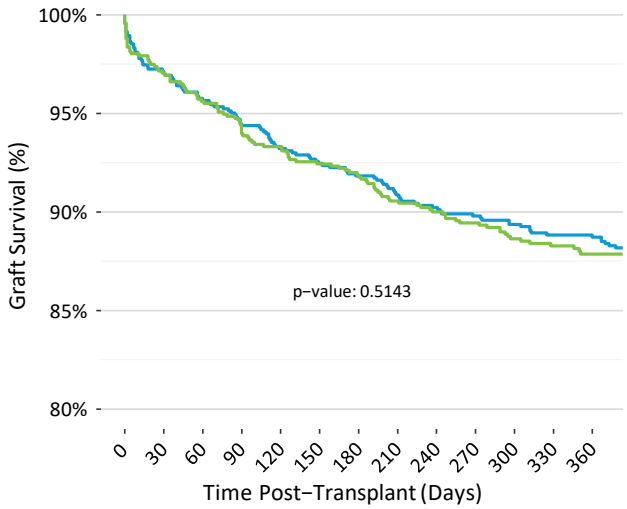
Merion et. al. JAMA 2005.

Massie et. Al. AJT 2014

And the real life patient and graft survival of kidneys KDPI > 85% is good.



Patient survival



Graft survival

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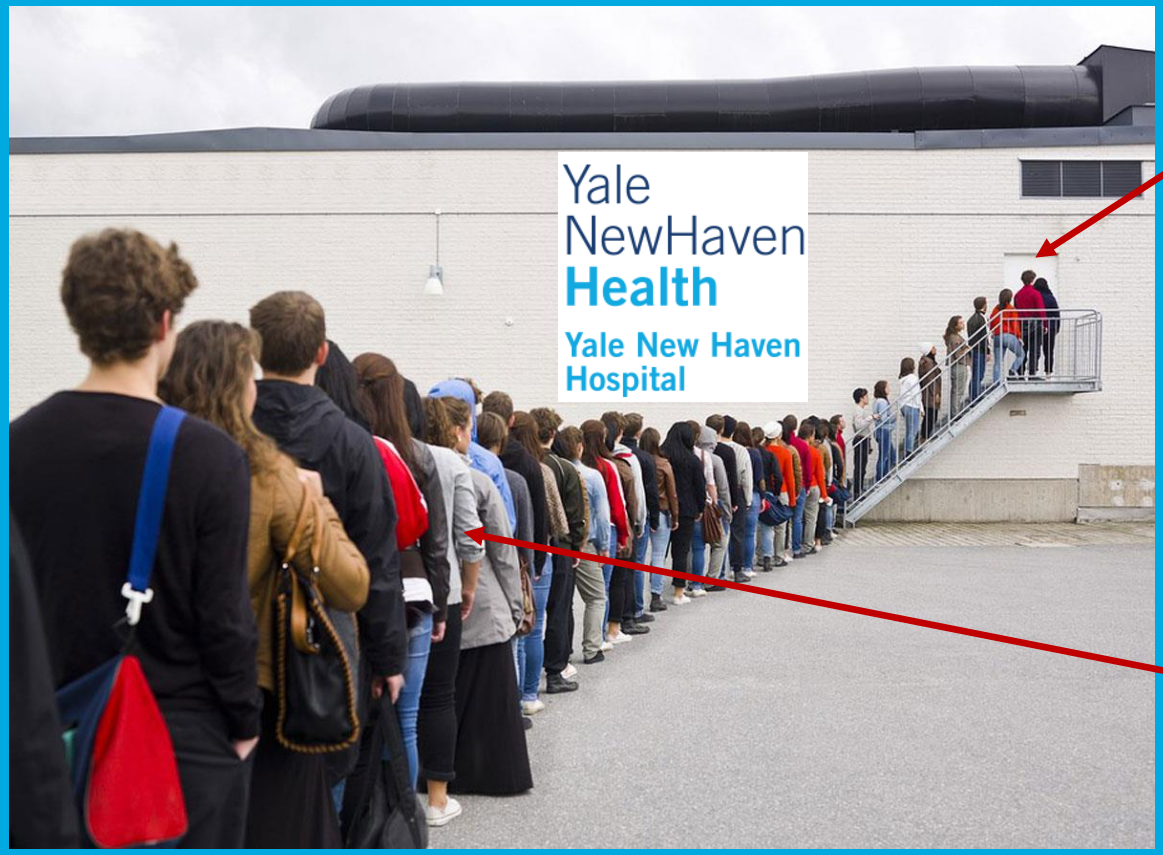
So why is there a problem with allocating high KDPI kidneys?

In clinical practice, the decision to accept a high KDPI kidney is very much dependent on the patient's position in line.



For these patients the choice is not a high KDPI kidney vs. dialysis, it is a high KDPI kidney vs. the next kidney

For these patients, the choice is a high KDPI kidney vs. prolonged dialysis exposure.

This is further complicated by avoiding “active” harm to patients and disregarding the outcome of “passive” decisions.

Often when declining a kidney offer the focus is on preventing harm done to the patient with a “bad” organ.

However, do we equally weight the risk of harm to the patient caused by remaining on dialysis?

vol 2 Table 5.5 Adjusted mortality (deaths per 1,000 patient-years) by age, sex, treatment modality, and comorbidity among ESRD patients and the general Medicare population, 2014

Age	Sex	Dialysis	Transplant	All Medicare	Cancer	Diabetes	CHF	CVA/TIA	AMI
65-74	Male	223	66	27	73	40	112	72	87
	Female	211	60	18	64	31	101	57	94
75+	Male	338	126	92	140	112	238	168	210
	Female	317	105	84	132	103	228	155	207

2017 USRDS Annual data report, vol. 2 chapter 5.

Brevity matching

It is necessary to develop a more rationale approach to allocating high KDPI kidneys.

- The primary benefit accrued by a patient for accepting a kidney with KDPI >.85 is a ***shortened waiting time.***

- There are ***no medical eligibility criteria*** to determine which patients are best suited for kidneys with KDPI >.85.
  - This results in...
    - Individuals who will not benefit from a high KDPI kidney being added to the list. ***Anyone can OPT IN.***
    - This causes ***delays in organ placement*** while inappropriate patients are bypassed in search of a suitable candidate.
    - ***Therefore***, inappropriate candidates on the list result in longer waiting times for suitable candidates thereby mitigating the benefit of a more rapid time to transplantation.

It is necessary to develop a more rationale approach to allocating high KDPI kidneys (2).

Therefore, if the list for kidneys with KDPI >.85 were kept ***short enough*** to minimize the waiting time *(dialysis exposure)* and populated with individuals who are ***suitable for and will benefit from*** these kidneys *(if transplanted rapidly – with a minimum of dialysis exposure)*, the following ***may occur:***

1. The ***benefit*** derived by patients from kidneys with KDPI >.85 would be realized.

2. Therefore the ***utilization*** of kidneys with KDPI >.85 would increase.

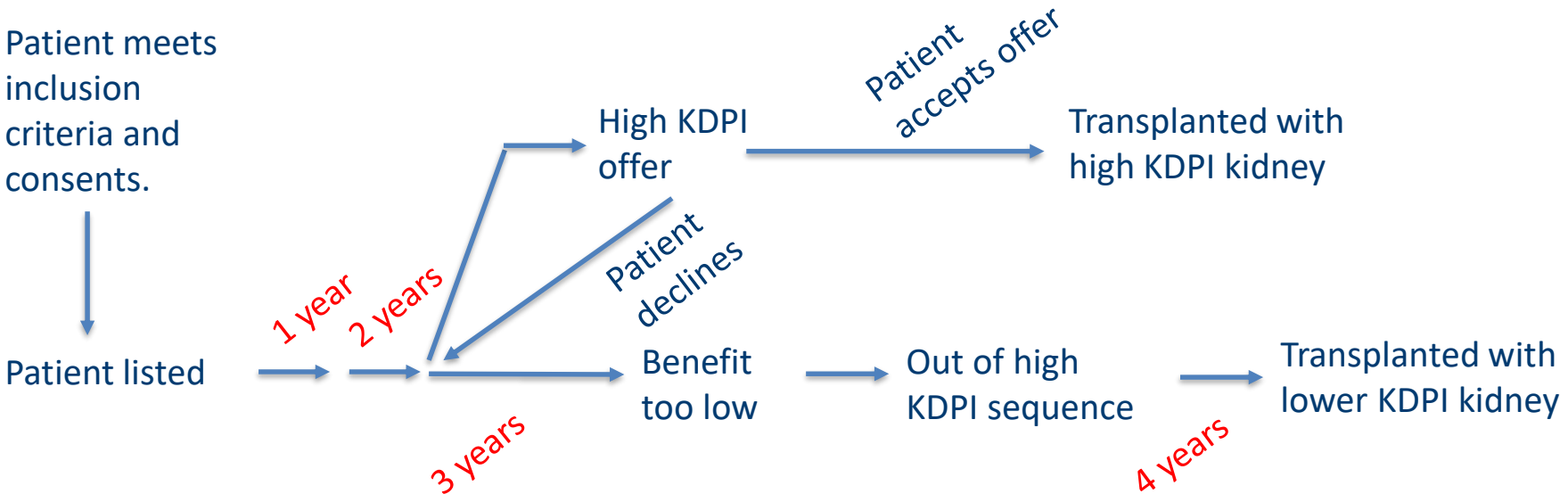
3. Resulting in a ***decrease in discards*** of kidneys with KDPI >.85.

4. Increased utilization of kidneys with KDPI >.85 would potentially result in ***OPOs pursuing more high KDPI donors.***

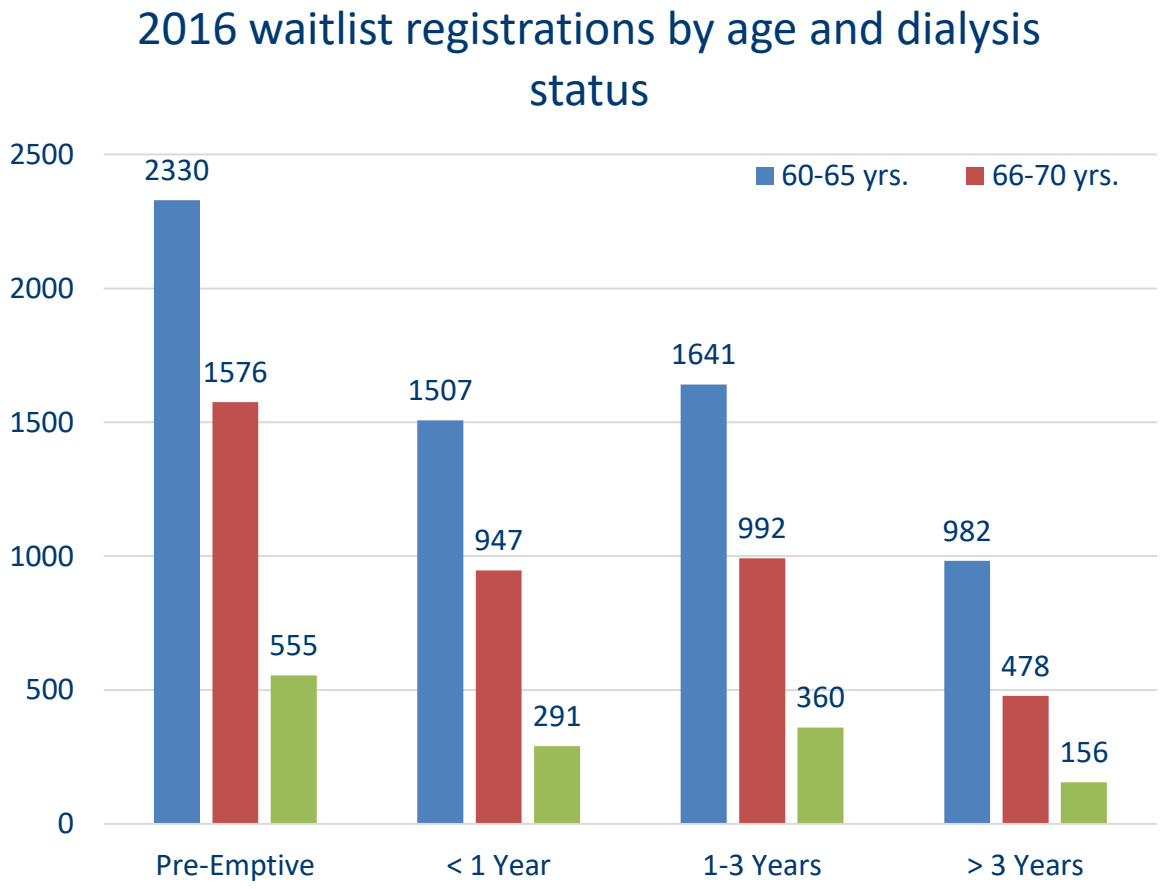
We need to develop a better way to allocate high KDPI kidneys.

- Define a population of patients that will benefit from earlier transplant with a high KDPI kidney. They will receive a new allocation score.
  - Similar to patients in the top 20% EPTS receiving the top 20% KDPI kidneys. It will be a time dependent metric.
  - Population needs to be kept ***small enough*** to allow for timely transplant.
- Only those ***meeting medical criteria***, can be placed on the high KDPI list.
  - Patient must **opt in** and consent.
  - Patients not meeting the medical criteria ***can not*** be entered.
- The new score ***changes with age and time on dialysis*** just like EPTS. As time elapses, if not transplanted the patient will eventually sun set out of the sequence.
- At some point in time, it is ***better for the patient to wait longer*** for a low KDPI kidney.

A proposed model.



Who would qualify for this allocation sequence?



Totals
60-65 -- 6460
66-70 -- 4020
71-75 -- 1360

Pre-Emptive to 1 year
60-65 -- 3837
66-70 -- 2523
71-75 -- 846

Pre-Emptive to 3 years
60-65 -- 5478
66-70 -- 3515
71-75 -- 1206

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Not every older patient will accept a high KDPI kidney.

Current waitlist registrations by age and willingness to accept KDPI > 85%.

Age	Willingness to accept KDPI > 85%	
	Yes	
	N	%
60 – 65 yrs.	10112	52
66 – 70 yrs.	8253	59
71 - 75 yrs.	3570	65

Therefore ~ 2857 potential candidates per year.

How many how KDPI kidneys are available?

Sequence A KDPI <=20%	Sequence B KDPI >20% but <35%	Sequence C KDPI >=35% but <=85%	Sequence D KDPI>85%
Highly Sensitized 0-ABDRmm (top 20% EPTS) Prior living donor Local pediatrics Local top 20% EPTS 0-ABDRmm (all) Local (all) Regional pediatrics Regional (top 20%) Regional (all) National pediatrics National (top 20%) National (all)	Highly Sensitized 0-ABDRmm Prior living donor Local pediatrics Local adults Regional pediatrics Regional adults National pediatrics National adults	Highly Sensitized 0-ABDRmm Prior living donor Local Regional National	Highly Sensitized 0-ABDRmm ***Local Brevity Matching***

This was 2014 kidneys in 2016

Is this approach plausible?

In 2016…

# of patients registered age 66-75 = *5380*

→ # of patients registered pre-emptive to <3 yrs HD = *4721*

→ # of patients willing to accept* KDPI > .85 = *2832*

*~60%

→ # of patients listed <u>active</u>[&] = *2156*

[&]75% based on 2016 OPTN data

2014 kidneys to allocate.

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Some provocative concluding thoughts in lieu of a summary slide.

I think we need to change our frame of reference in regards to donor recipient matching from thinking we protected someone from a "bad" offer, to considering the harm done by not using that organ and causing someone to die on the list with out a transplant.

I consider the popular mantra that physician clinical decision making is paramount in accepting an organ to be false, it ultimately does more harm. *(Weekend effect – Mohan KI 2016, biopsy)*

I believe that organ allocation policy should be reconfigured to promote the best societal outcome as opposed to the best individual outcome. *(We are rationing a societal resource)*

I would add both incentives to accept offers *(altering the definition of non function to include poor function or extending the duration beyond 90 days)* and disincentives to decline offers *(loss of some allocation points)*.


THE
END