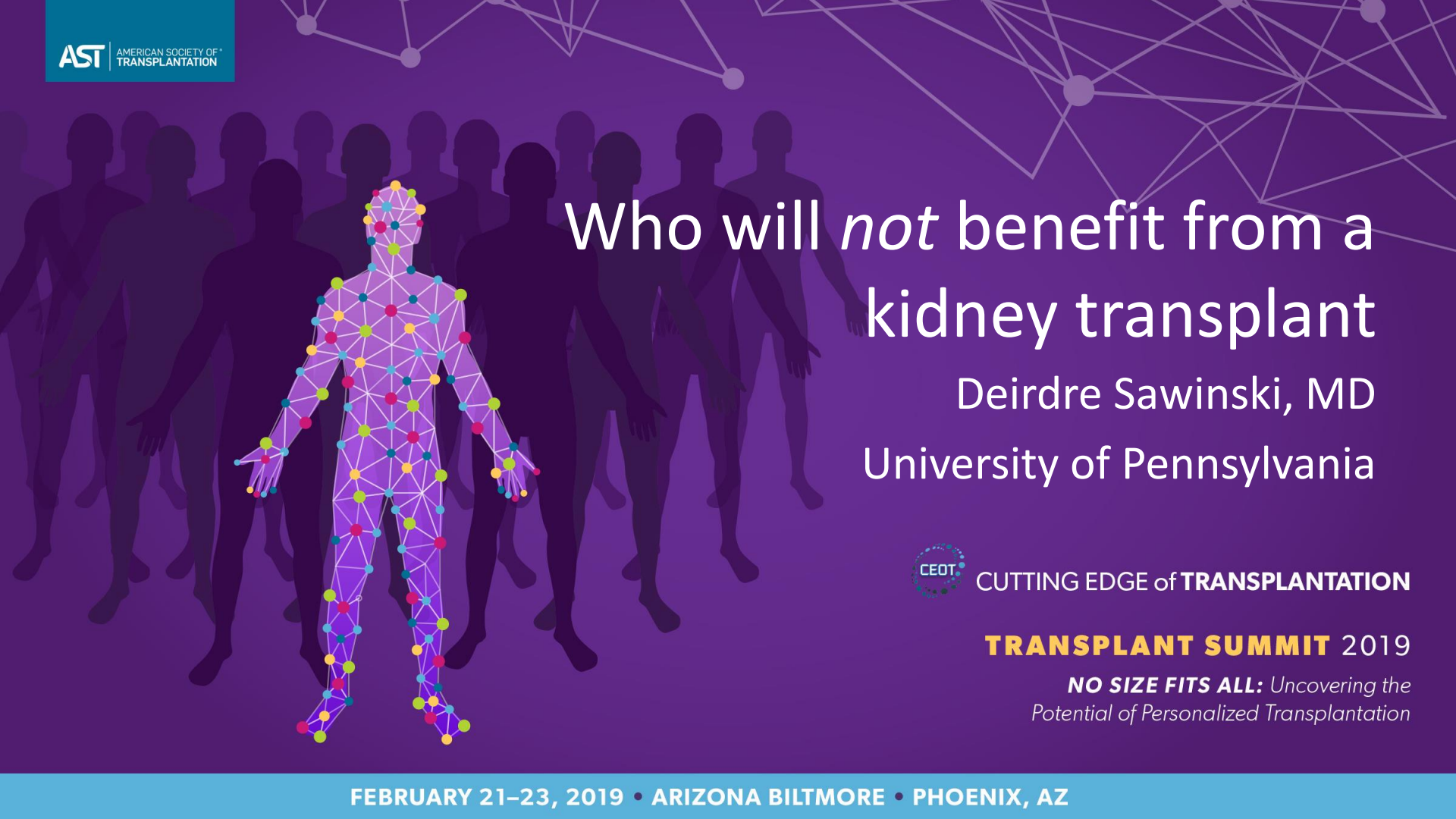
AST | AMERICAN SOCIETY OF TRANSPLANTATION



Who will *not* benefit from a kidney transplant

Deirdre Sawinski, MD

University of Pennsylvania

CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Disclosures

No financial disclosures relevant to this presentation.

I am a transplant nephrologist and I believe kidney transplantation is the best treatment for ESRD

Learning Objectives

Discuss the survival benefit associated with kidney transplantation

Explore situations where transplant may not be beneficial

Discuss statistical pitfalls in survival analyses

Who doesn’t benefit from a kidney transplant?

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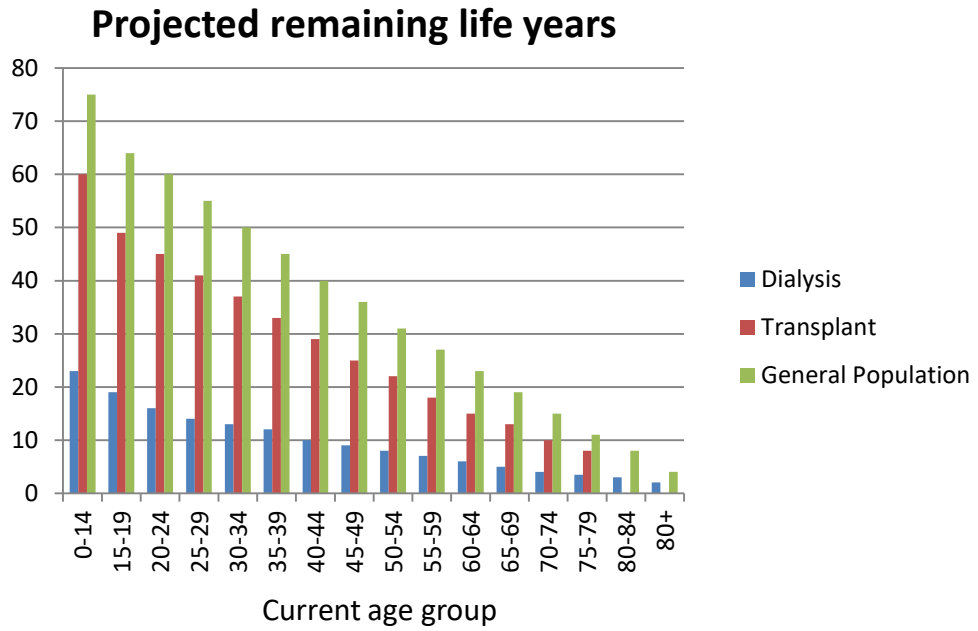
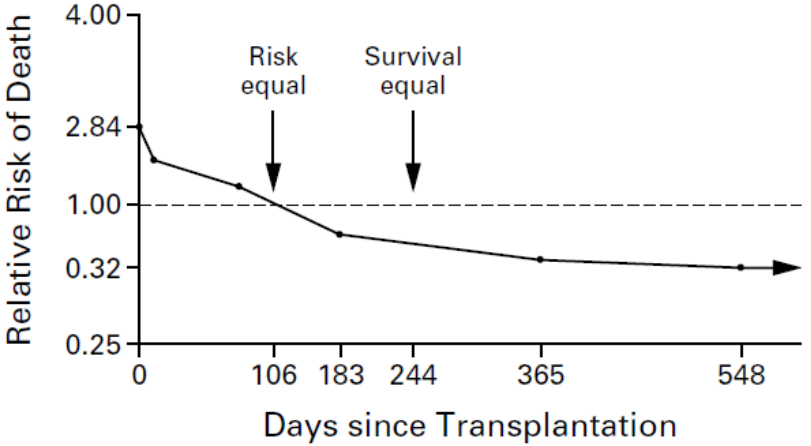
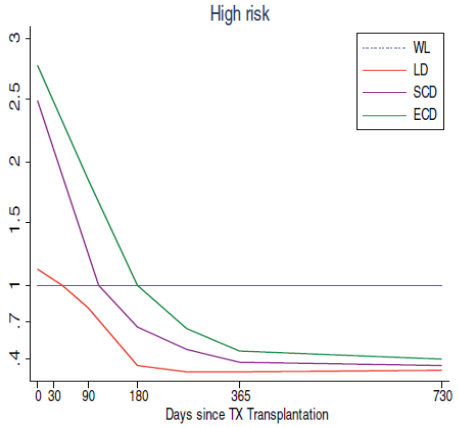
Transplant affords greater longevity than dialysis





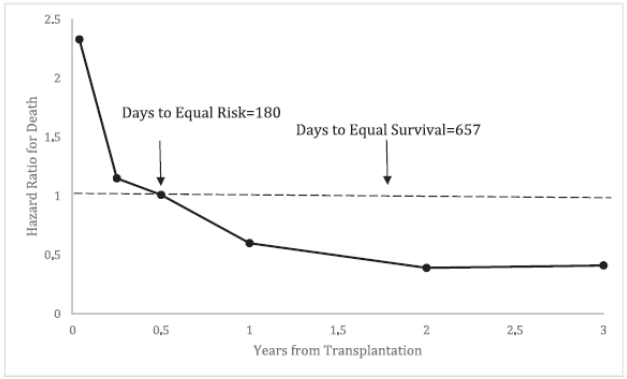
Adapted from USRDS annual data report
Wolfe et al NEJM 1999

Survival benefit even in high risk populations



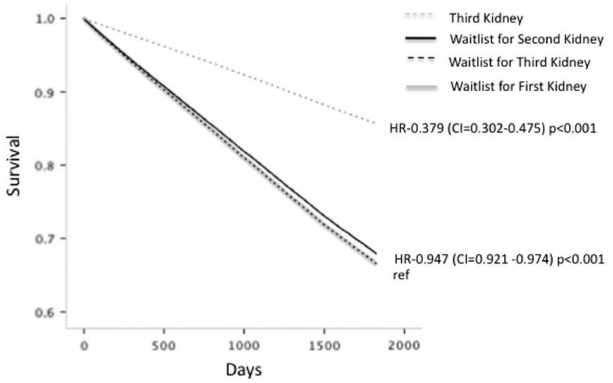
Elderly

130-521 days to benefit



Long dialysis vintage

657 days to benefit



Retransplants – 3rd KT

240 days to benefit

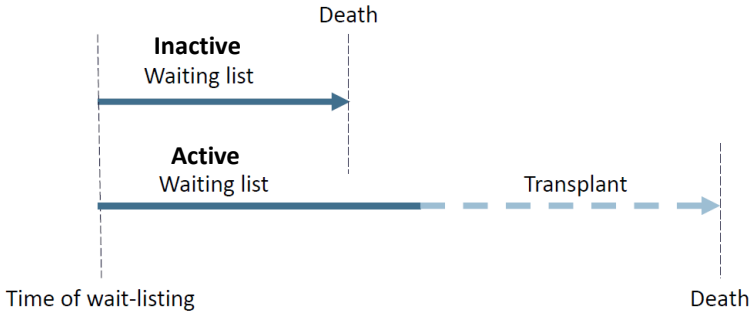
Gill et al AJT 2013; Rose et al CJASN 2017; Redfield et al Transplantation 2015

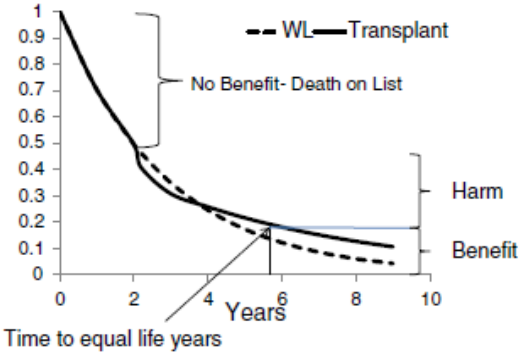
So everyone benefits, right?

- Are we using the right method?
- Are we asking the right question?

Are we using the right method?

- Population-based studies
  - Who is the reference group?
    - Dialysis patients – how counsel in clinic?
    - Are all WL patients candidates?
    - WL – *a priori* selection bias; time period?
    - Active vs inactive WL – immortal time bias
    - Inactive WL 2.2x increased risk of death
  - Registry data vs. the individual experience
    - Mortality/graft survival
    - Other outcomes – QoL, function
    - Time horizon – 1year, 3 year, longer?





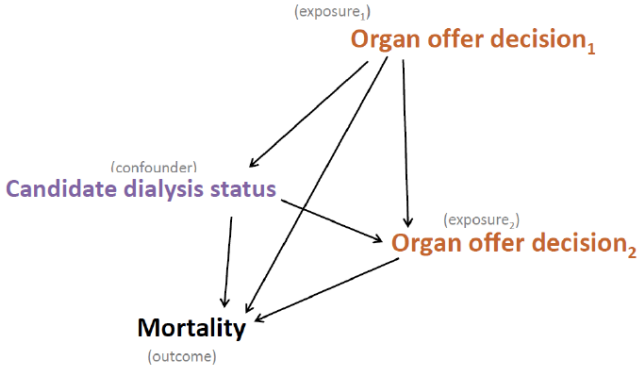
Are we using the right method?

- Issues in survival analysis modeling
  - Immortal time bias
  - Confounding by indication
  - Time dependent confounding

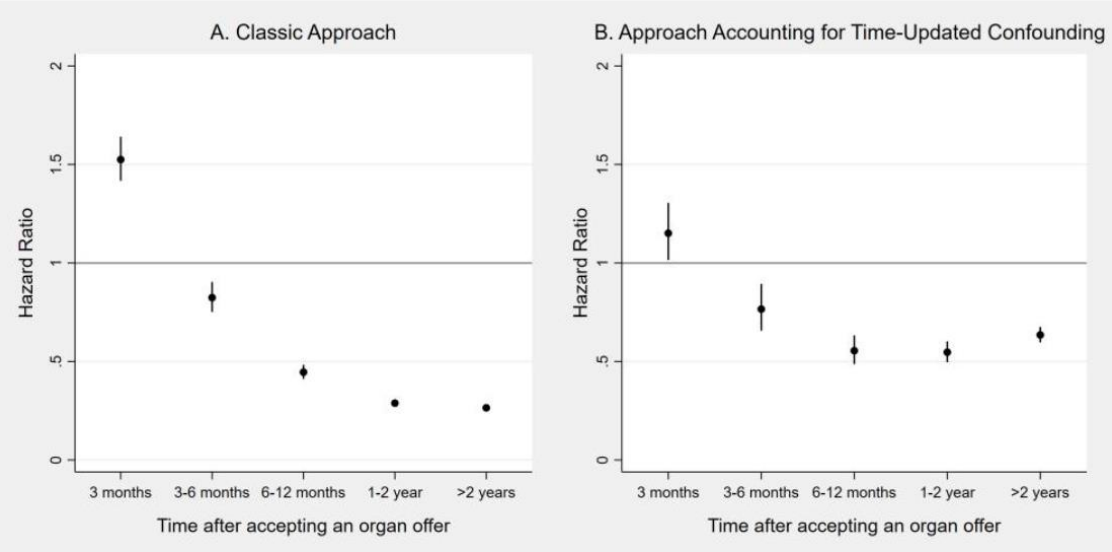
-TV cox

MSM

- Association vs. Causal models
  - Subgroup by Rx; entire population with alternates
- Marginal structural models (MSM)
  - Causal models for the marginal effect of a treatment and an outcome using time updated IPW
  - Estimate the effect of the treatment received



Are we using the right method? MSM results



UNOS match run 2007-2013
Incorporate organ offers, turn downs

Elderly, DM, long WT – benefit at 6mos

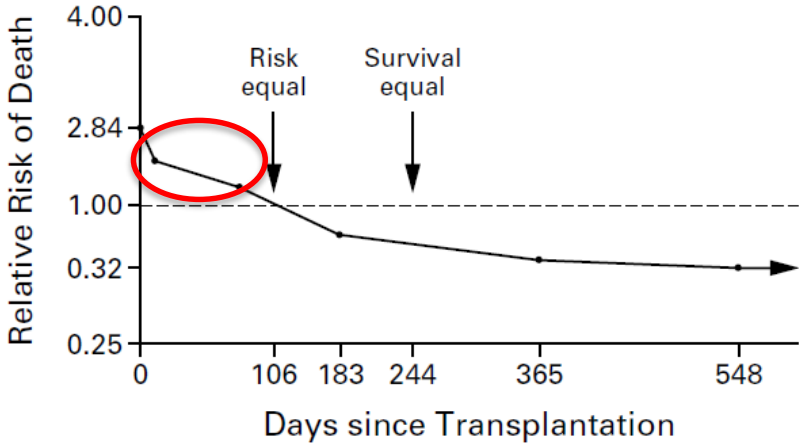
Always active HR 1.1; benefit at 3mos

Initial risk and long term benefit both attenuated

Cohen JB et al, AJT 2019

Who doesn't derive a *survival* benefit from kidney transplantation?

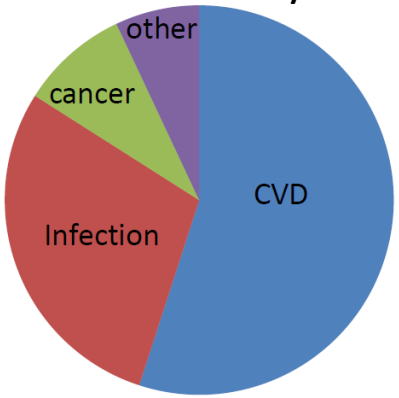
- Don't survive the index hospitalization/first year



Early posttransplant mortality

- ~5% of recipients die in the 1st year
  - Majority DWFG
  - <3mos cardiac, 3-12 mos cancer/infection
- All-cause mortality
  - Age, Caucasian race, DM, angina, PVD, longer dialysis vintage, nonpreemptive txp
- Cardiac death
  - DM, angina, PVD, CHF, prior MI
  - Age, Caucasian race, longer dialysis vintage, nonpreemptive txp, DGF, rejection, lower GFR

COD in the 1st year



Helantera et al Txp Int 2018
Gill, Pereira Transplantation 2003
Farrugia et al Transplant Int 2013

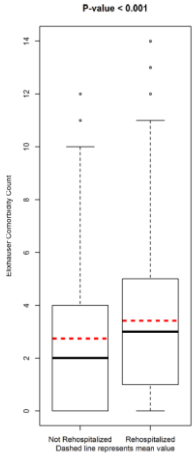
Who doesn't derive *benefit* from kidney transplantation?

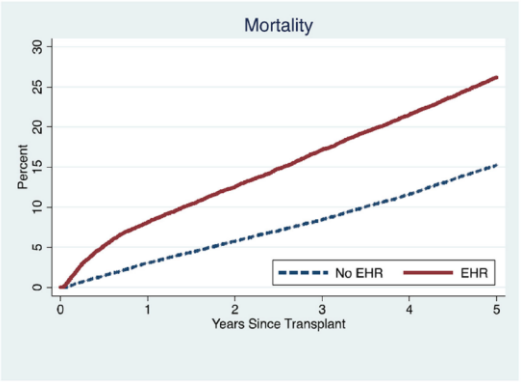
- Don't survive the index hospitalization/first year
- Experience significant complications
- Have poor allograft function
- Have poor quality of life after transplantation

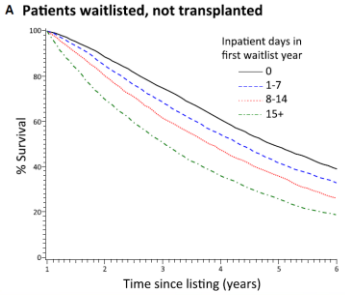
Can we identify these patients prospectively?

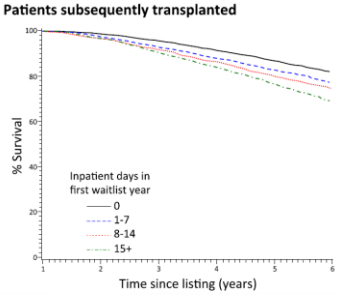
Complications – Readmissions and Frailty

- Pretransplant admissions
  - WL hospitalizations
- Early hospital readmission
  - 3-fold increase risk late readmission
  - Graft loss HR 1.43; death HR 1.50
  - Age, race, comorbidities, donor factors
  - Higher SF-36 PF score protective
- In part a function of Frailty







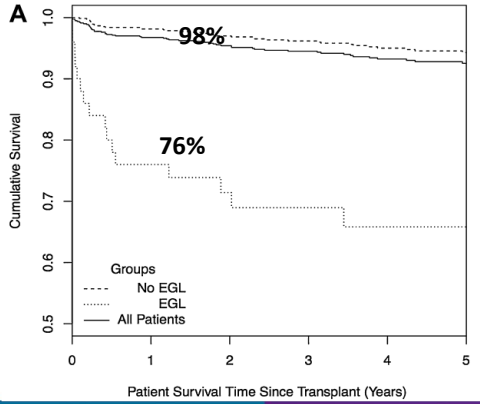


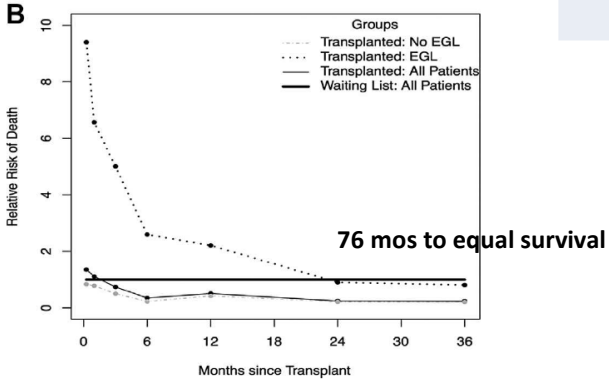
McAdams DeMarco et al AJT 2014; Lynch AJT 2017; Kutner et al CJASN 2006

Poor allograft function

- Early graft loss
  - 3% of KT - DWGF, thrombosis, AR, PNF
  - DCD, donor age, VTE, ischemic time
- EGL affects patient survival

	Thrombosis	PNF	AR
Recipient	Male	Female Non DM	Age Prior KT BMI WT
Donor	BMI CIT	Age BMI ECD WIT/CIT	Age ECD

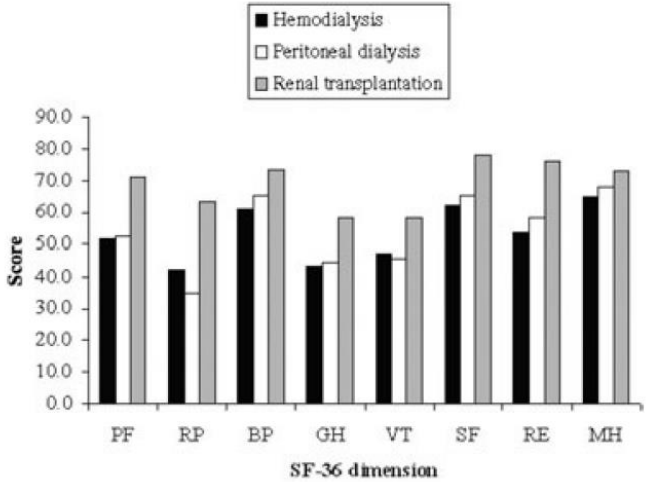


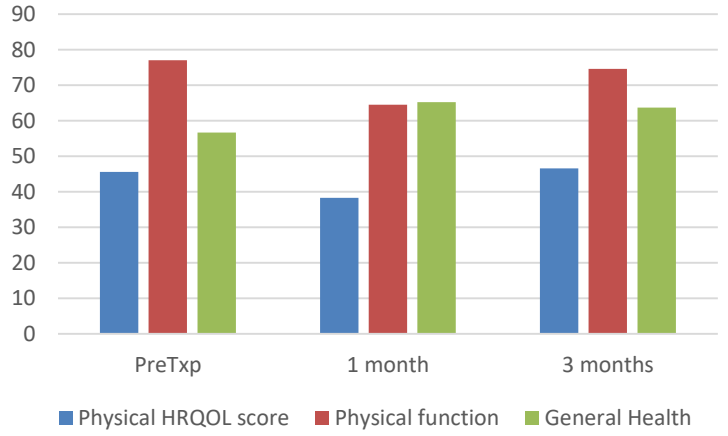


Hamed AJT 2015;
Brooks Trends in Txp 2017

Post transplant health-related quality of life

- HRQoL assessments – no uniform standard
- Generally assumed – HRQoL increases with transplant

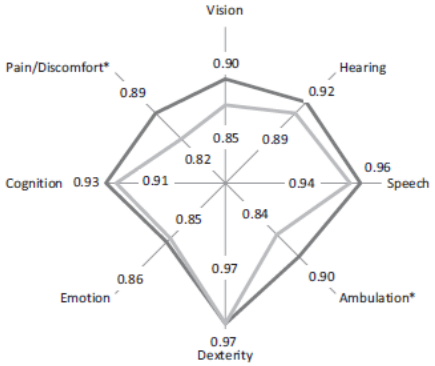




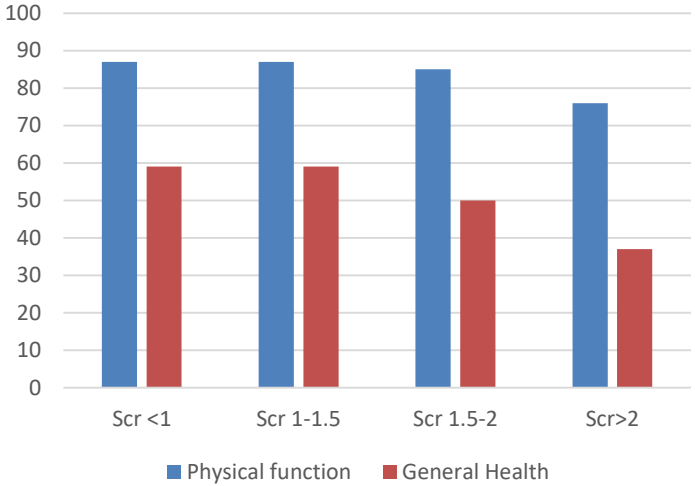
Maglinte et al Clin Epi 2012; McAdams DeMarco Transplantation 2018

Poor post transplant HRQoL

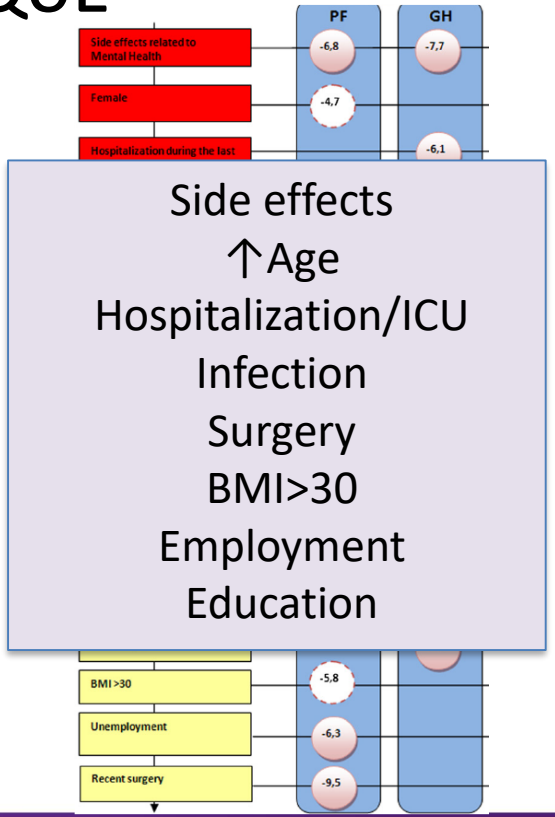
- Effect modification by comorbidities



Diabetes



Renal Function

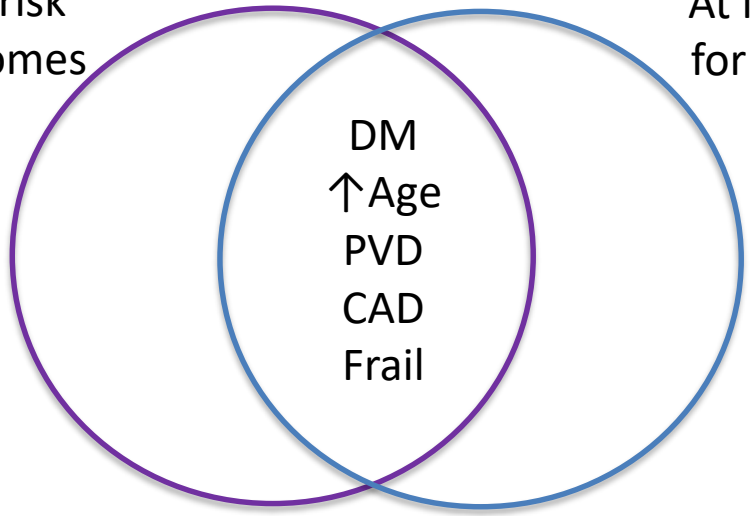


Side effects
↑Age
Hospitalization/ICU
Infection
Surgery
BMI>30
Employment
Education

Dukes et al Clin Transpl 2013; Fujisawa Urology 2000; Gentile Health and QOL Outcomes 2013

Conundrum

At increased risk for poor outcomes

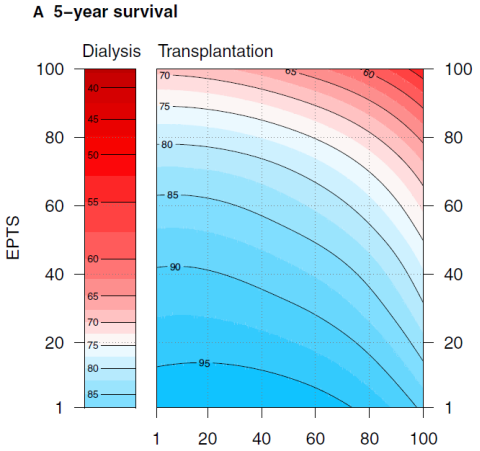


At increased risk for death on WL

We need better tools to separate the two groups

How can we better predict patient outcomes?

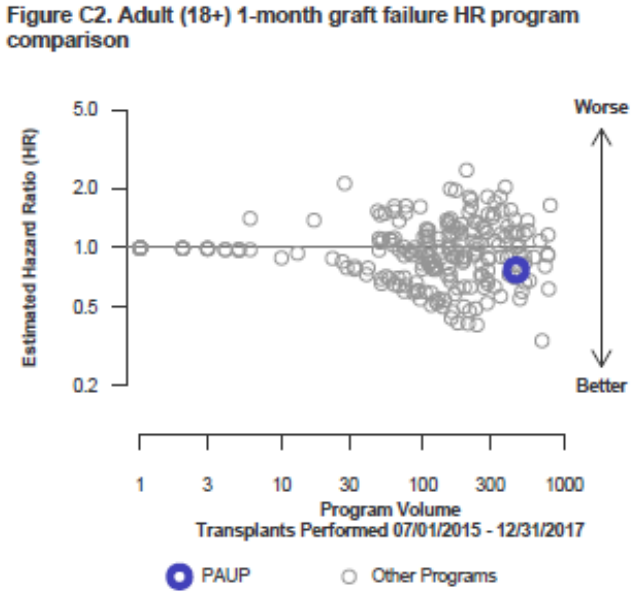
- Better quality data
  - granularity
  - Better reporting of time dependent covariates
  - Collection/availability of time dependent confounders
- Predictive vs Explanatory models
  - iBOX
    - IFTA/injury/eGFR/proteinuria/DSA; C statistic 0.83 (0.78-0.87)
- Advanced statistical techniques
  - Joint models
  - Machine learning



Loupy A et al AJT 2017; Bae et al AJT 2019

Who else doesn't benefit from poor outcomes?

- Transplant center
  - Graded on 1 and 3 year outcomes
- Insurers
  - Financial break even point – 3 years
  - DM, CHF, CAD, PVD, obesity cost more
  - Readmissions, complications add to expense
- Donor families



Nassir et al Transplantation 2015; Held AJT 2016 ; Axelrod AJT 2017

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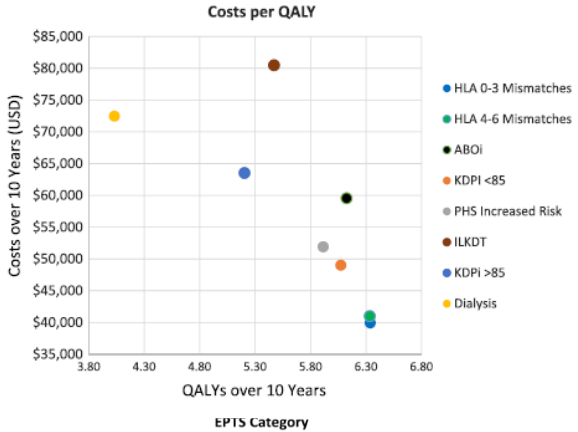
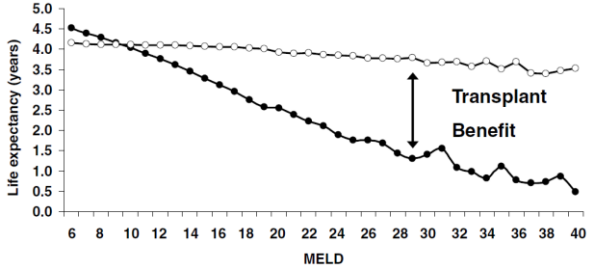
Dialysis survival	Total dialysis cost	Transplant survival	Total transplant cost
≤1 yr	$121K	≤1 yrs	$233K
≤2 yrs	$242K	≤2 yrs	$265K
≤3 yrs	$363K	≤3 yrs	$293K
≤4 yrs	$484K	≤4 yrs	$329K



Nassir et al Transplantation 2015; Held AJT 2016 ; Axelrod AJT 2017

In kidney allocation should the question be who benefits more?

- LAS
  - LAS= transplant benefit – 2(WL survival)
- Liver
- Kidney
  - Survival prediction models exist but accuracy probably insufficient for making allocation decisions
  - “lower risk” doesn’t mean no risk of WL mortality



Schaubel et al AJT 2009

Summary/Conclusions

- Imperfect data suggests a survival benefit with transplantation for all sub-populations studied
- Certain subgroups may be at risk for poor outcomes that can limit that benefit
- Current models cannot accurately predict an individual patient's likelihood of success
- On overhaul of current data collection practices will be required to improve predictive accuracy