Estimating Individual-Level and Population-Level Causal Effects of Organ Transplantation Treatment Regimes

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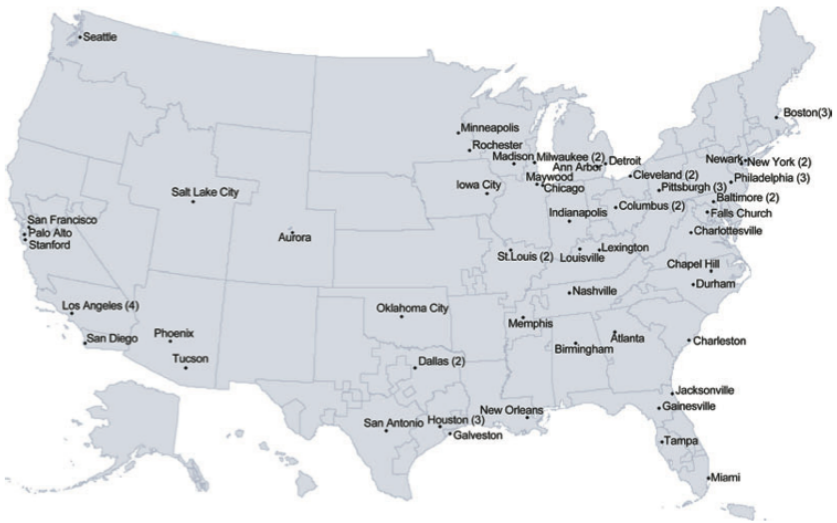
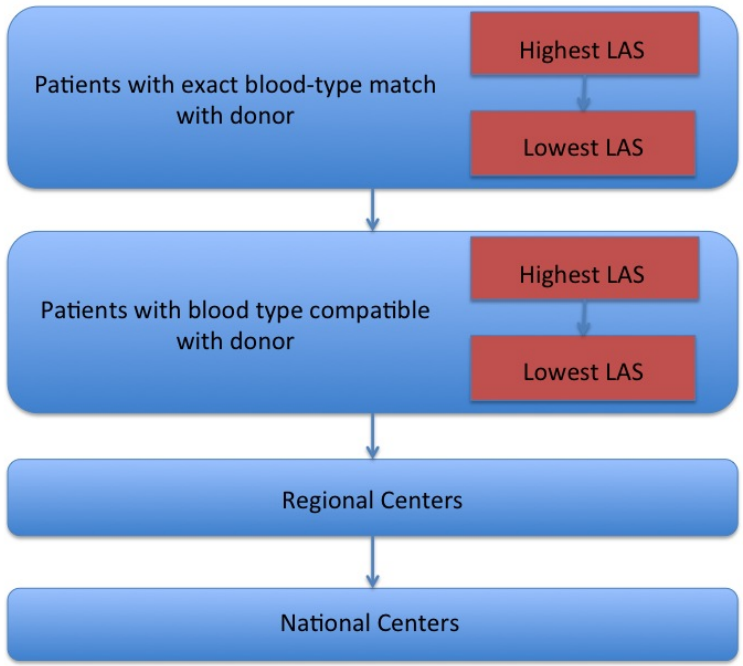
Deceased Donor Organ Offers in the United States

- More patients in need organ transplant than organs available $\rightarrow$ In 2015, 122,071 waiting at year end, 30,975 transplants performed, and 15,068 donors recovered
- United Network for Organ Sharing (UNOS) responsible for orderly offering deceased donor organs
- Order in which deceased donor organs offered to recipients a deterministic function (urgency, benefit, geography, organ quality, fairness)

Donor Lung Offers in the United States





Lung Allocation in the United States. Left figure from Colvin-Adams (2012)

Organ Acceptance

- Each time an organ is offered to a recipient it may be turned down
- Many competing factors go into organ acceptance
  1. Patient
  2. Surgeon
  3. Transplant Center
  4. Organ Procurement Organization
  5. Other Patients on Waiting List

Treatment Regimes for Organ Transplantation

Patients awaiting organ transplantation face a difficult decision if offered a low-quality organ:

- Accept the organ
- Decline the organ, hope to be offered a higher quality one in the future

Testing the effect of personalized *decision rules* (dynamic transplant regimes) would be helpful here.

Transplant Regimes

Treatment regimes of interest: Rules which dictate when an offered organ should be declined
Treatment regimes for transplantation tend to be "poorly-defined":

- There is not a 1-to-1 correspondence between patient covariate history and treatment
- Transplants are not available at any time
- We cannot easily specify treatment regimes such as "Get a transplant as soon as LAS > 50" because these regimes are not clinically meaningful
- Avoid regimes which dictate if an organ should be accepted

Time-varying Treatment and Time-varying Confounding

- No randomized trials of different transplant regimes
- Necessitates the use observational datasets and appropriate methods
- Inverse probability of compliance estimators $\rightarrow$

1. Patient's follow-up time is considered only while she is "compliant" with a regime of interest
2. Once non-compliant, her follow-up time is artificially censored
3. Observations are weighted according to the inverse of probability of compliance to correct for the potential selection bias introduced by the artificial censoring

Limitations of Existing Methods

Problem:

- Anticipated survival for a given DTR depends on the quality and availability of organs, and these depend on the strategies that other patients follow to accept or decline an organ
- Patients' probability of transplant depends on regimes that other patients follow
- Conceptually similar, although not identical, to the "spillover" effect described in other contexts

Existing methods have a major limitation here:

- They estimate the causal effect of a treatment regime *for a single random participant who adopts the treatment regime*
- But the causal effect *if all patients were to adopt the treatment regime* may have more public health relevance

Goal and Outline

Develop weighted causal estimators for both cases:

- "One follows"
- "All follow"

Develop estimators:

- Assuming we have data from an observational registry
- Avoid modeling the many random processes: patient arrival, organ arrival, etc...

Potential Outcomes and Target of Interest

- $T^*(\infty)$: survival time from listing if the patient were to never receive a transplanted organ
- $T^*(b, \boldsymbol{q})$: survival time if the patient were to receive an organ b days after listing with organ characteristics $\boldsymbol{q}$
- $\boldsymbol{X}^*(b)$ to be the covariates collected b days after listing
- Inferring the distribution of $T^*(b, q)$ is not of primary interest
- $T^*(g, g')$: survival time if she followed regime g for declining offered organs and all other patients follow regime g'
- Inferring the distribution of $T^*(g, g')$ IS of primary interest

Potential Outcomes and Target of Interest

- Density of $T^*(g, g')$ ($f_{T^*(g,g')}(t)$) is a mixture distribution of well-defined counterfactual survival times

$$\sum_{\overline{x}(t)} f_{T^*(\infty)|\overline{\boldsymbol{X}}^*(t)}\left\{t|\overline{x}(t)\right\}\left[\prod_{s=1}^{t} 1-\sum_{\boldsymbol{q}} \rho^{\left(g,g'\right)}\left\{s, \boldsymbol{q}|\overline{x}(s)\right\}\right] f_{\overline{\boldsymbol{X}}^*(t)}\left\{\overline{x}(t)\right\} \tag{1}$$

$$+\sum_{b=1}^{t}\sum_{\boldsymbol{q}}\sum_{\overline{x}(b)} f_{T^*(b,\boldsymbol{q})|\overline{\boldsymbol{X}}^*(b)}\left\{t|\overline{x}(b)\right\}\left[\prod_{s=1}^{b-1} 1-\sum_{\boldsymbol{q}} \rho^{\left(g,g'\right)}\left\{s, \boldsymbol{q}|\overline{x}(s)\right\}\right] \rho^{\left(g,g'\right)}\left\{b, \boldsymbol{q}|\overline{x}(b)\right\} f_{\overline{\boldsymbol{X}}^*(b)}\left\{\overline{x}(b)\right\},$$

- $\rho^{(g,g')}\left\{b, \boldsymbol{q}|\overline{\boldsymbol{x}}(b)\right\}$: probability of receiving a transplant b days after listing with organ characteristics $\boldsymbol{q}$ given she is untransplanted $b-1$ days after listing with covariate history $\overline{\boldsymbol{x}}(b)$ and the patient follows regime g while all others follow regime g'

Transplant Regime Spillover

- "Spillover" typically refers to situations in which the distribution of well-defined potential outcomes depends on the treatment assignment of others
- Here the probability of initiating treatment depends on the treatment regime other patients follow
- Refer to this as transplant regime spillover

Notation

Notation:

- L_i: listing time for ith patient
- N_{ij}, Y_{ij}: failure and at-risk indicators for ith patient on jth study day
- X_{ij}: patient characteristics including confounders
- A_{ijk}: indicator for accepting kth organ on the jth study day
- $\overline{A}_{ij}$: treatment history through the jth day
- O_{ijk}: indicator for offered kth organ on jth study
- $\overline{E}_{\cdot jk}$ to be the collection of information on all subjects prior to assigning the kth organ on the jth study day day

Causal estimand: $\lambda_t(g, g')$: hazard of death t days after entering the waiting list, and the associated survival $S_t(g, g')$

Components of the weights

$\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right) = \prod_{j'=1}^{j} \prod_{k=1}^{S_{j'}} \overline{\pi}_{ijk}^{(\emptyset,\emptyset)}\left(A_{ij'k}, E_{\cdot j'k}\right)$: The probability of the observed treatment history assuming all patients follow regime $\emptyset$ (no changes in propensity to accept or decline organs)

$\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right) = \prod_{j'=1}^{j} \prod_{k=1}^{S_{j'}} \overline{\pi}_{ijk}^{(g,g')}\left(A_{ij'k}, E_{\cdot j'k}\right)$:The probability of the observed treatment history in the counterfactual world where ith patient follows regime g and all others follow g'

Estimating $\lambda_t(g, g')$

We can estimate $\lambda_t(g, g')$ by solving the estimating equation

$$\sum_{j=1}^{m}\sum_{i=1}^{n} \frac{\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)}{\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)} \left\{N_{ij} - Y_{ij}\lambda_t(g, g')\right\} I(j - L_i = t) = 0$$

Intuition for the weights $\frac{\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)}{\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)}$:

- Similar to IPCW
- Standardize to the target population where probability of $\overline{A}_{ij}$ is different
- Mean zero estimating function $\rightarrow$ estimator for $\lambda_t(g, g')$ is CAN

Estimating $\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)$ with the Observed Data

$\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)$ is a function of the probability of being offered, and the probability of accepting if offered:

- $\Pr(A_{ij} = 1) = Pr(O_{ij} = 1) \cdot \Pr(A_{ij} = 1 | O_{ij} = 1)$
- $\Pr(A_{ij} = 0) = 1 - Pr(O_{ij} = 1) \cdot \Pr(A_{ij} = 1 | O_{ij} = 1)$

Estimating $Pr(O = 1)$ is straightforward provided I have a model for $Pr(A = 1 | O = 1)$

Estimating $\overline{\pi}_{ij}^{(\emptyset,\emptyset)}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)$ with the Observed Data

ID	LAS	A	$\Pr(A = 1 \mid O = 1)$	$\Pr(O = 1)$	$\Pr(A)$
763	52.54	0	0.563	1.000	0.437
197	43.33	1	0.339	0.437	0.148
553	41.60	0	0.302	0.289	0.913
66	33.38	0	0.160	0.202	0.968
592	33.31	0	0.158	0.169	0.973

Estimating $\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)$ with the Observed Data

This is more challenging.

The numerator is the expectation of the probability of being offered and accepting organs in the hypothetical world where all patients follow regime g' given the observed data.

$\pi_{ijk}^{(g,g')}(1, E_{\cdot jk}) = E(\pi_{ijk}^{(g,g')}(1, E_{\cdot jk}^{(g,g')})|E_{\cdot jk})$ If all patients follow

regime g':

- We don't know which patients would be on the waiting list
- We don't know what their characteristics would be
- The probability of being offered an organ can't be directly computed from the observed data
- Sample $E_{\cdot jk}^{(g,g')}$ from $E_{\cdot jk}$ – use Monte Carlo integration to evaluare expectation

Estimating $\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{.jS_j}\right)$

ID	LAS	A	$\Pr(A=1\|O=1)$	$\Pr(O=1)$	$\Pr(A)$
763	52.54	0	0.563	1.000	0.437
761	?	?	?	0.437	?
197	43.33	1	0.339	?	?
491	?	?	?	?	?
553	41.60	0	0.302	?	?
66	33.38	0	0.160	?	?
592	33.31	0	0.158	?	?

Estimating $\overline{\pi}_{ij}^{(g,g')}\left(\overline{A}_{ij}, \overline{E}_{\cdot jS_j}\right)$

Hot Deck Imputation:

- For all transplant recipients, impute missing data assuming never transplanted by borrowing data from their nearest neighbor, the "lender"
- Simulate the organ allocation when everyone follows g', assuming model for accepting organs holds
- Assume low quality organs are accepted with probability 0

We've created a hypothetical data set where all patients follow g'.

After Imputation

Assume the organ is defined as high quality under g'

ID	LAS	A	$\Pr(A = 1 \mid O = 1)$	$\Pr(O = 1)$	$\Pr(A)$
763	52.54	0	0.563	1.000	0.437
761	49.48	0	0.367	0.437	0.840
197	43.33	1	0.339	0.277	0.094
491	42.55	0	0.237	0.183	0.957
553	41.60	0	0.302	0.140	0.958
66	33.38	0	0.160	0.097	0.984
592	33.31	0	0.158	0.082	0.987

After Assigning Organ Under g, g'

Assume the organ is defined as high quality under g'

ID	LAS	A	$A^{(g,g')}$	$\Pr(A=1\|O=1)$	$\Pr(O=1)$	$\Pr(A)$
763	52.54	0	0	0.563	1.000	0.437
761	49.48		0	0.367	0.437	0.840
197	43.33	1	1	0.339	0.277	0.094
491	42.55		0	0.237	0.183	0.957
553	41.60	0	0	0.302	0.140	0.958
66	33.38	0	0	0.160	0.097	0.984
592	33.31	0	0	0.158	0.082	0.987

Simulation Study

Data Generation:

- Patient and organ arrivals: independent Poisson processes with rate parameters 0.5 and 0.32, respectively
- $b_{i0} \sim N(-1, 1)$, $b_{i1} \sim N\left(\frac{1}{365}, \frac{1}{(4 \cdot 365)^2}\right)$
- $X_{ij} = b_{i0} + b_{i1} \cdot \lfloor \frac{j - L_i}{30} \rfloor \cdot 30$, where $\lfloor \cdot \rfloor$ is the floor function, L_i is arrival time
- Organs were low-quality with probability 0.5
- Organs were accepted with probability $\left\{1 + e^{2.5 - 0.25 X_{ij}}\right\}^{-1}$

Simulation Study

Estimation:

- Estimated survival for regime g: decline all low- quality organs
- Estimated survival assuming "one follows" and "all follow"
- Hot deck imputation: lender i' for patient i selected as $\arg\min_{i'} \left(|X_{ij} - X_{i'j'}| : j - L_i = j' - L_{i'} \right)$
- Nonparametric bootstrap to estimate standard errors (SEs) and form 95% confidence intervals (CI)

Simulation Results

			Bias		CP	
Target	t	Truth	$\hat{S}_t(g,\emptyset)$	$\hat{S}_t(g,g)$	$\hat{S}_t(g,\emptyset)$	$\hat{S}_t(g,g)$
$S_t(g,\emptyset)$	180	0.785	-0.006	-0.018	0.954	0.735
	360	0.636	-0.000	-0.036	0.966	0.519
	540	0.533	0.003	-0.056	0.954	0.269
	720	0.463	0.004	-0.073	0.951	0.152
$S_t(g,g)$	180	0.770	0.009	-0.003	0.882	0.967
	360	0.599	0.037	0.001	0.333	0.978
	540	0.471	0.065	0.006	0.045	0.972
	720	0.382	0.084	0.007	0.014	0.960

Application

Data are from an observational registry maintained by the United Network for Organ Sharing

- May 4, 2005-Sept 30, 2011
- 9,091 transplants
- 13,039 patients total

Treatment regimes:

- Decline organs below pth percentile of donor quality while LAS $< M$; if LAS $\geq M$, any organ is acceptable
- p and M can both vary
- Estimated anticipated survival assuming "one follows" the regime, or "all follow" the regime.

Application

Donor quality:

- Donor quality modeled with Cox regression
- For each transplant, donor quality was estimated for each potential recipient

Model for accepting organs:

- Logistic regression model
- Predictors: patient age, LAS, time on waiting list, native disease, patient-donor-height difference; and indicators for donor smoking ≥ 20 pack-years, donor age > 50, and their interaction

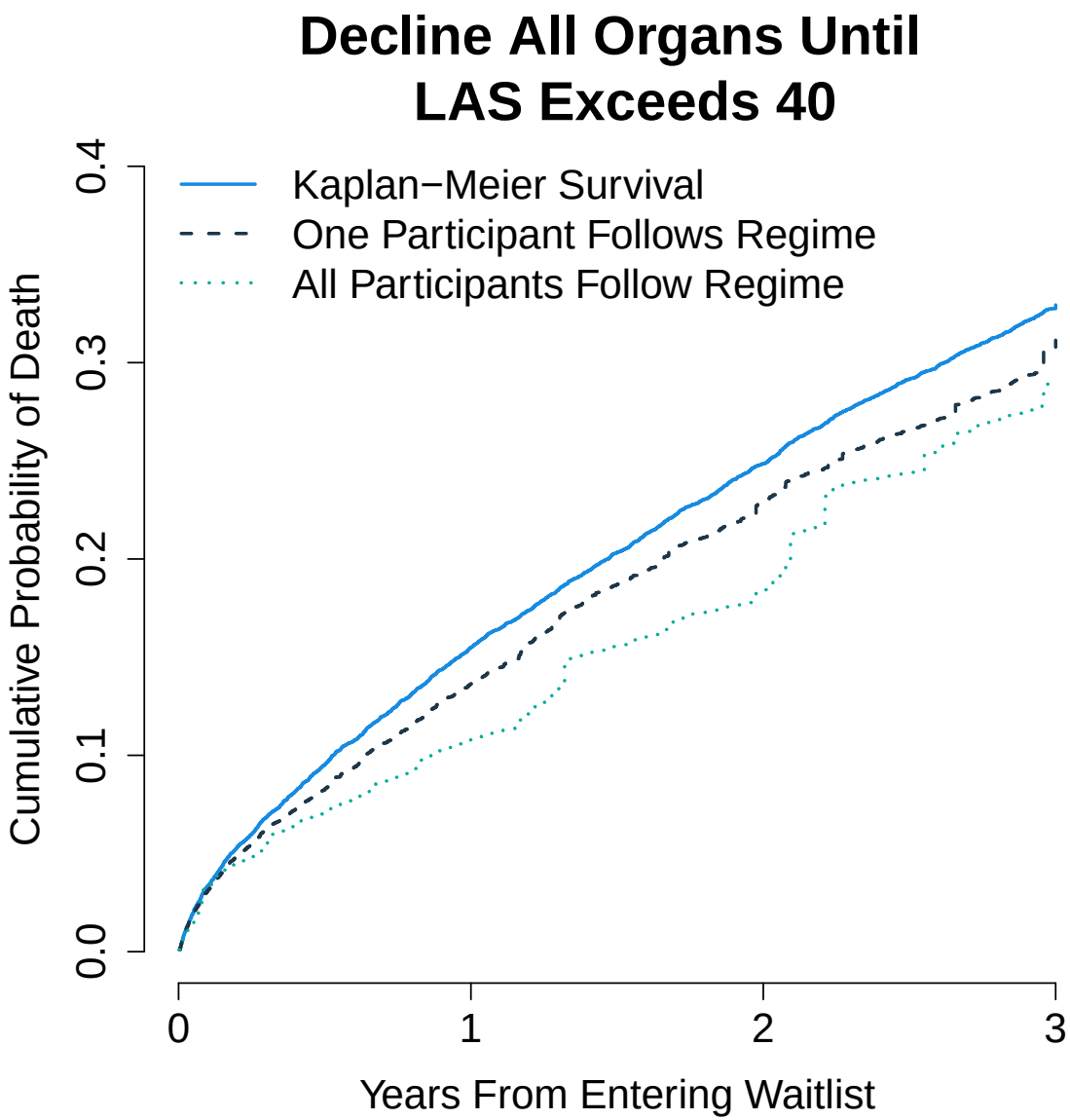
Application

Hot deck imputation for "all follow":

- Lender i' for patient i selected as
  $\arg\min_{i'} \left(|LAS_{ij} - LAS_{i'j'}| : j - L_i = j' - L_{i'} \right)$
- LAS was only imputed variable

Nonparametric bootstrap to estimate SEs and form 95% CIs

Application Results



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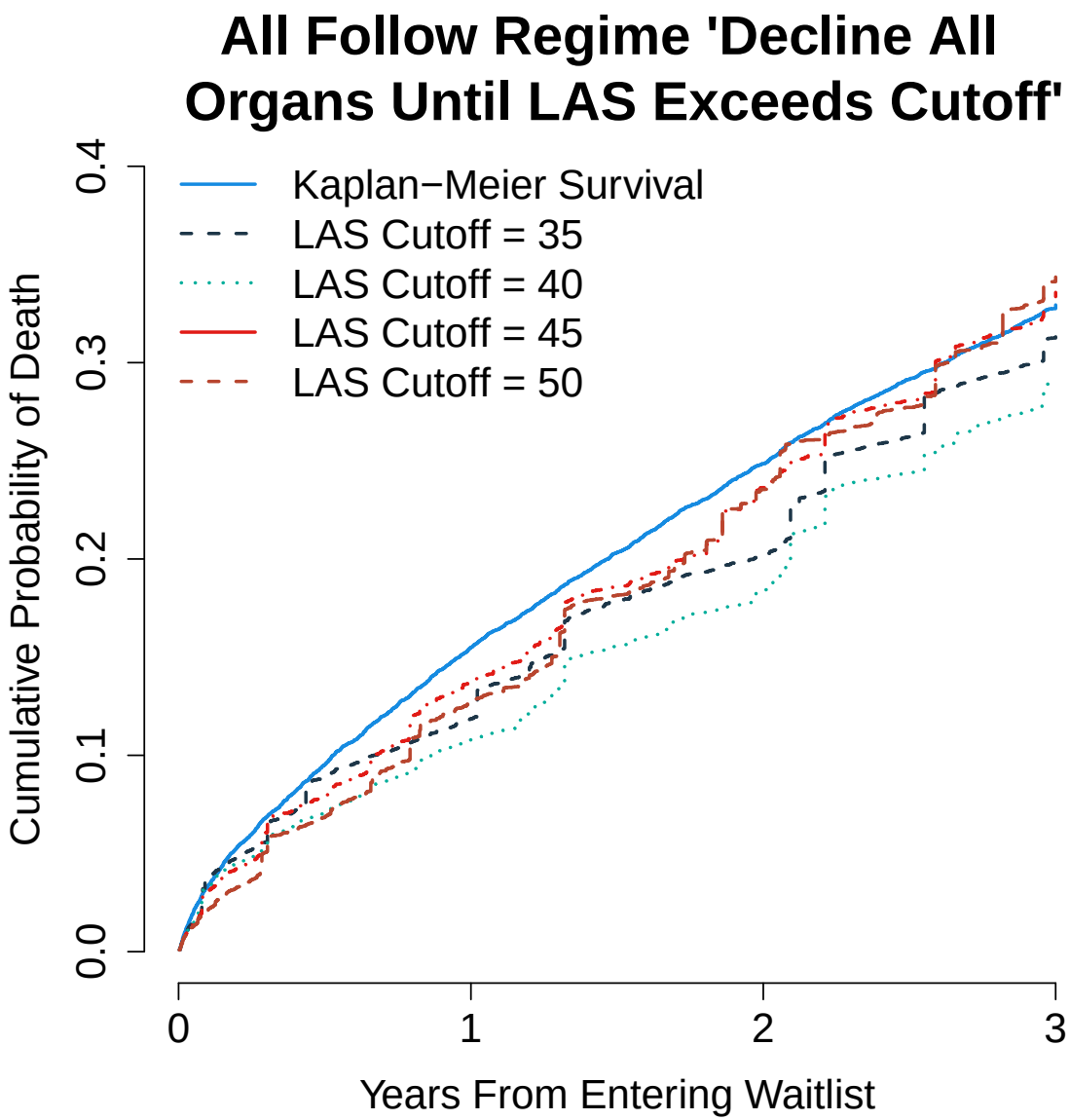

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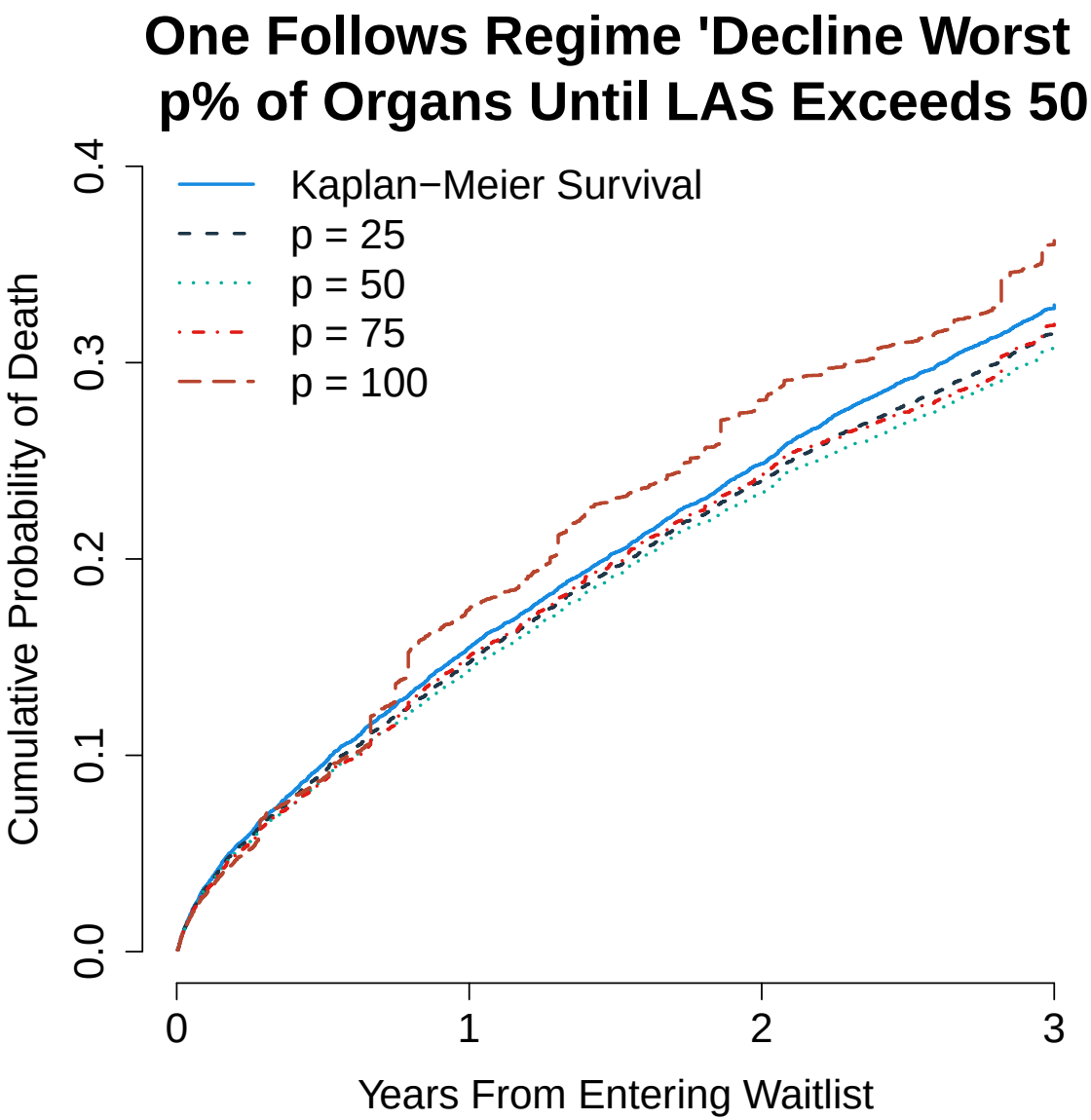

Summary

Simulation shows:

- Estimators have little bias for their target
- Causal estimand must be specified with care

Application

- "One follows" and "all follows" are different
- Patients may gain a modest increase in survival probability by declining transplantation while LAS is low
- Effect may be greater if the entire population adopts the strategy

Summary

Thank you!