Fred Hutch Cancer Center

A Pseudo-Value Approach to Causal Deep Learning of Semi-Competing Risks

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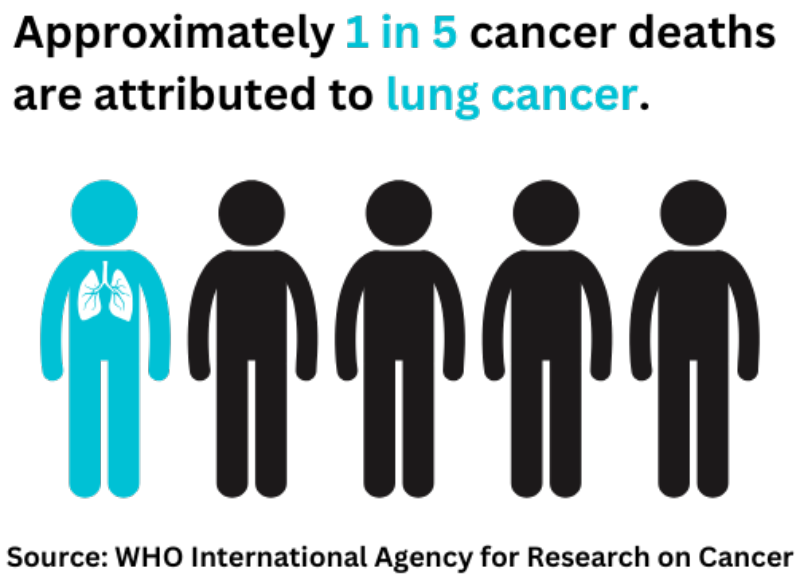
Clinical Motivation

- Lung cancer has a 5-year survival rate of **20%** [3]
- Patients can experience **recurrence**, remission, metastasis **prior to death** [8]
- **Cancer recurrence** is an important endpoint in patients who have undergone **curative treatment**
- Further understanding **patient-specific** treatment efficacy is crucial for **individualized** care [5, 2, 7]



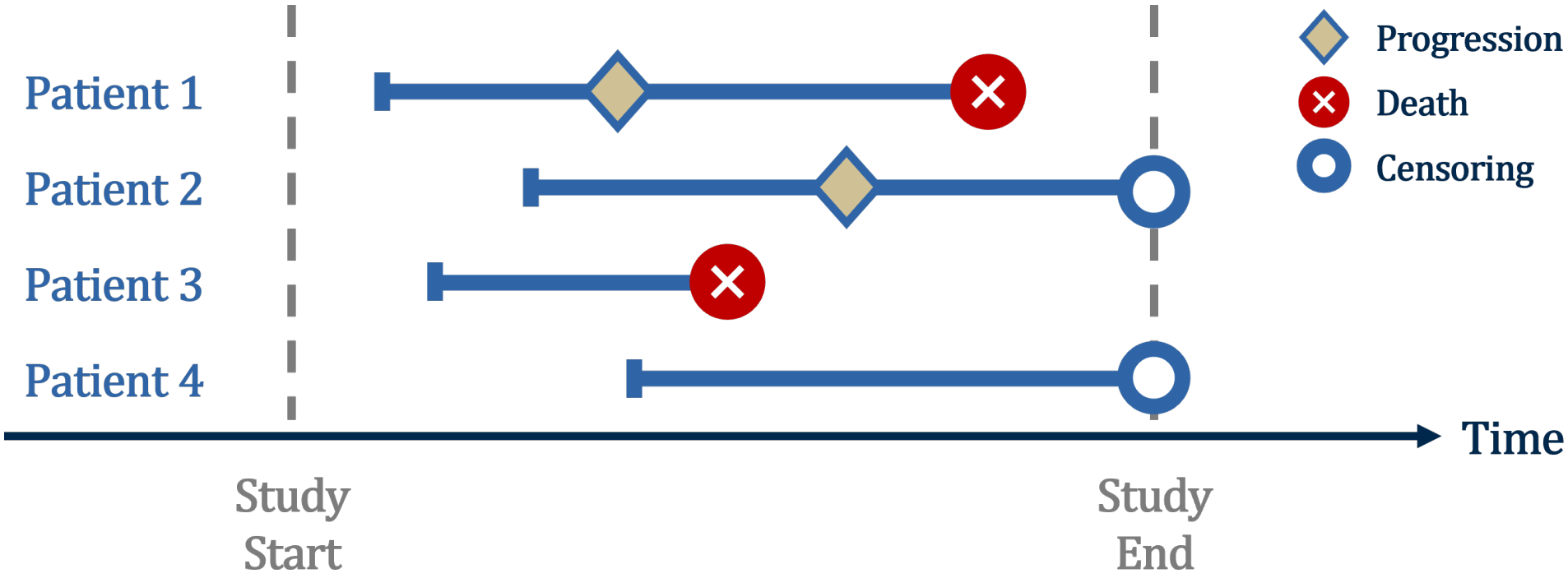
Statistical Motivation

- While **non-fatal health events** impact **treatment decisions** and disease management:
  - Overall survival is often studied without considering **competing events**
  - Composite endpoints such as **recurrence-free survival** are used [9]
  - The effects of treatments or risk factors may differ across **disease states** [1, 6]
- Data from the **Boston Lung Cancer Study**, a large cancer epidemiology cohort:
  - Observational studies provide a wealth of information on **individualized risk factors**
  - However, observational data suffer from **confounding** and **covariate imbalance**

Our Proposal

We propose a **deep learning** approach for estimating the **causal effect** of treatment on **disease recurrence** in the presence of **complex covariate relationships**

Semi-Competing Risks



Outcome Notation

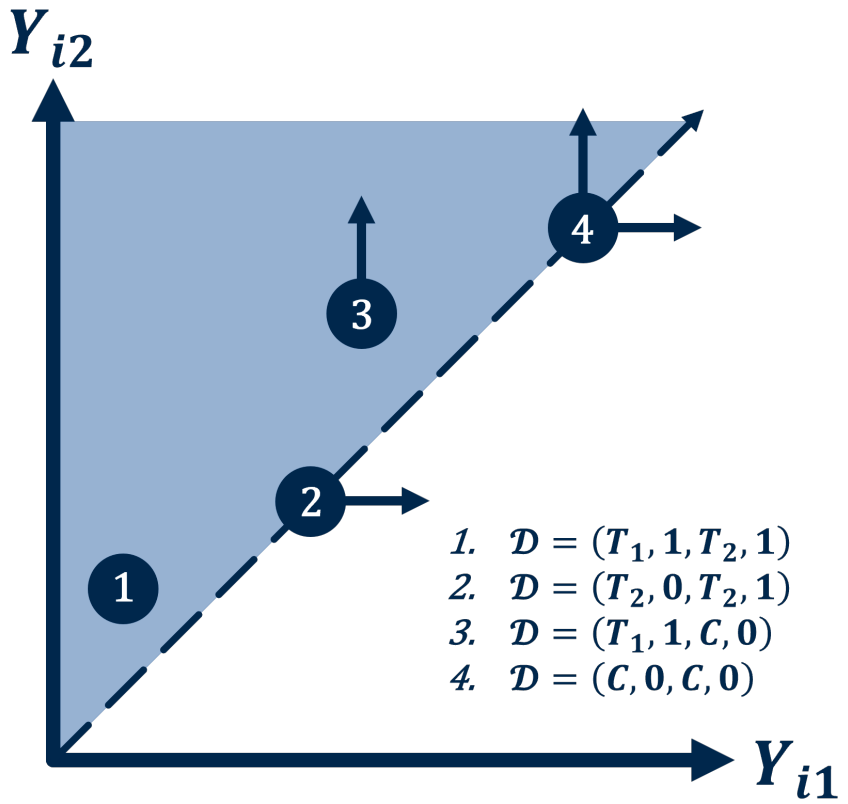
Event Times:

- T_{i1}: Time to Recurrence
- T_{i2}: Time to Death
- C_i: Censoring Time

Observable Outcomes:

- $Y_{i1} = \min(T_{i1}, T_{i2}, C_i)$
- $Y_{i2} = \min(T_{i2}, C_i)$
- $\delta_{i1} = I[T_{i1} \leq \min(T_{i2}, C_i)]$
- $\delta_{i2} = I(T_{i2} \leq C_i)$

Outcomes observable only on upper wedge:



Potential Outcomes Framework

- Z_i = Causal variable of interest ($Z_i = 1$ for surgical resection and $Z_i = 0$ for other first-line treatment options)
- X_i = p-vector of additional confounding variables
- T_{i1}^z: Potential time to recurrence had ith patient received treatment $z \in \{0, 1\}$
- Seek to estimate an **average treatment effect** (ATE; i.e., expected difference in potential outcomes)
- For time-to-recurrence, consider the average causal **risk difference** at time t:

$$\text{ATE} = \mathbb{E}\left[I\left(T_{i1}^1 > t\right) - I\left(T_{i1}^0 > t\right)\right] \tag{1}$$

Proposed Three-Stage Approach

Step 1. Estimate **survival function** for time-to-recurrence

Step 2. Calculate **pseudo-survival probabilities** at fixed times

Step 3. Train **deep neural network** to estimate **causal target** (ATE)

Step 1: Estimate the Recurrence Survival Function

- Use a **Clayton copula** to **jointly model** the survival times for disease recurrence and death:

$$S(t_1, t_2) = [S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1]^{-1/\theta}, \tag{2}$$

- Yields an expression for the **recurrence survival function** that is always **estimable**:

$$S_1(t) = [S_*(t)^{-\theta} - S_2(t)^{-\theta} + 1]^{-\frac{1}{\theta}} \tag{3}$$

Step 2: Calculate Pseudo-Survival Probabilities

- Use the estimated $S_1(t)$ to jackknife **probability of no recurrence** at fixed time points (e.g., 1, 5 years):

$$\hat{S}_{i1}(t_j) = n \times \hat{S}_1(t_j) - (n-1) \times \hat{S}_1^{-i}(t_j) \text{ for times } t_j;\ j = 1, \ldots, J$$

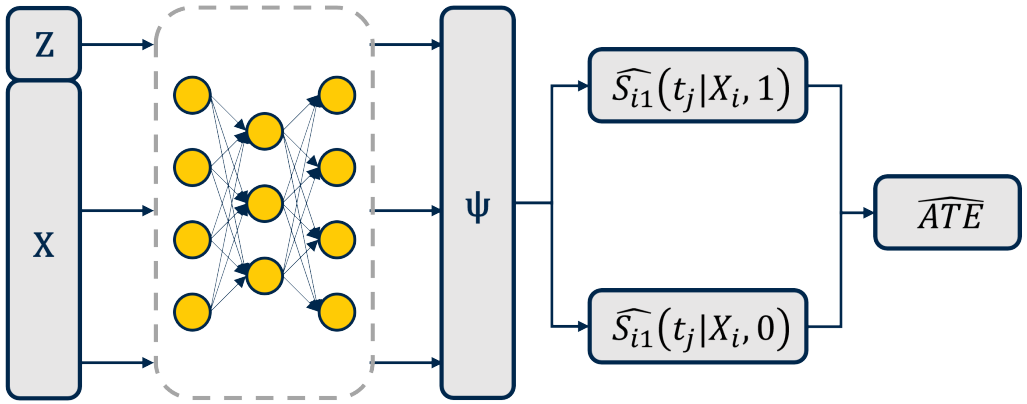
- Represents **contribution** of ith individual in estimating $\mathbb{E}[S_1(t_j)]$ in the sample of n subjects
- $S_{i1}(t_j)$ is **approximately independent** of $S_{i'1}(t_j)$ for $i \neq i'$ as $n \to \infty$
- $\lim_{n\to\infty} E[S_{i1}(t_j) \mid Z_i, X_i] = S_1(t_j \mid Z, X)$ (important for this method)

Step 3: Train Causal S-Learner

3a. **Fit** model for $S_{i1}(t \mid X_i, Z_i)$ non-parametrically with a feed-forward, fully-connected ***S*-Learner**

3b. **Predict** potential outcomes $\hat{S}_{i1}(t \mid X_i, Z_i = z); z \in \{0, 1\}$

3c. **Calculate** $\widehat{\mathrm{ATE}} = n^{-1} \sum_{i=1}^{n} \{\hat{S}_{i1}(t \mid X_i, 1) - \hat{S}_{i1}(t \mid X_i, 0)\}$



Encodes features into **lower representative space**, Ψ, w/ covariates **decorrelated** from treatment

Rationale for DNN in Causal Estimation

- Use the pseudo-survival probabilities as **targets** in a deep learning model
  - Similar to logistic model fit to $I\left(T_{i1} > t_j\right)$ if the data were **fully observed**
  - More natural to interpret than **hazards ratios**
  - No **proportional hazards** assumption
- **Binary cross-entropy loss** function, optimizing predictions for survival probabilities
- **Faster convergence** than MSE due to **steeper gradient** when prediction is far from truth

Simulation Settings

- **Setting 1: Similar Performance Expected**

  T_{i1}, T_{i2} follow **PH models** with **linear** risks, **independent covariates**, and **correlated errors**

  Risk function of 3 covariates, $Z_i \sim Bern(0.5)$, $X_{i1}, X_{i12} \sim TN(1, 0.5, 0, 2)$

- **Setting 2: Proposed Method Expected to Perform Better**

  T_{i1}, T_{i2} follow **PH models** with **non-linear** risks, **correlated covariates**, and **correlated errors**

  Risk function of 3 covariates, $X \sim TN_3(\mathbf{0}, \Sigma, \mathbf{-1}, \mathbf{1})$ where Σ is AR(1) and $Z = I(X_1 \geq 0)$, X_2 and X_3 squared

Compared **bias** and **MSE** in estimating ATE to **parametric** GEE with complementary log-log link across 50 **independent datasets**, also varying n (500 and 1,000), θ (0.5 and 2.0), and censoring rates (0% and 50%)

Simulation Setting 1

Methods Perform Similarly as Parametric Model is Correctly Specified

Average bias and MSE for estimated vs. true ATE (Setting 1)

Simulation Settings			Bias		MSE	
n	θ	Censoring	Parametric	Proposed	Parametric	Proposed
500	0.5	50%	0.0025	0.0060	0.0020	0.0063
500	0.5	0%	0.0025	0.0045	0.0022	0.0042
500	2.0	50%	0.0025	0.0057	0.0022	0.0053
500	2.0	0%	0.0018	0.0069	0.0019	0.0011
1000	0.5	50%	0.0018	0.0025	0.0013	0.0028
1000	0.5	0%	0.0023	0.0035	0.0014	0.0028
1000	2.0	50%	0.0019	0.0048	0.0014	0.0037
1000	2.0	0%	0.0018	0.0030	0.0012	0.0021

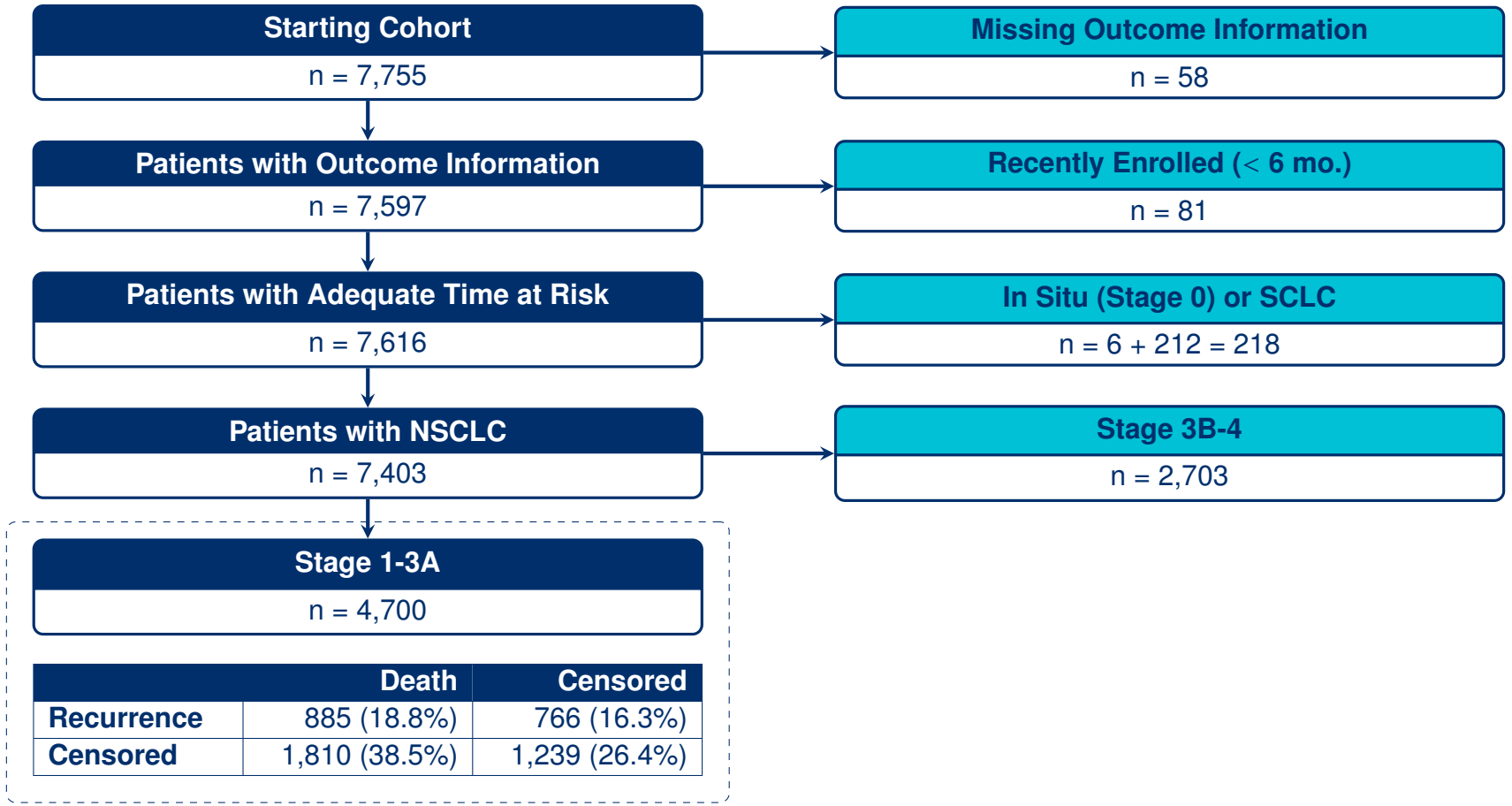
Simulation Setting 2

Proposed Outperforms Current Approach as Risk Function is Complex

Average bias and MSE for estimated vs. true ATE (Setting 2)

Simulation Settings			Bias		MSE	
n	θ	Censoring	Parametric	Proposed	Parametric	Proposed
500	0.5	50%	0.0483	**0.0043**	0.0076	**0.0032**
500	0.5	0%	0.0520	**0.0030**	0.0078	**0.0031**
500	2.0	50%	0.0444	**-0.0083**	0.0081	**0.0045**
500	2.0	0%	0.0476	**-0.0030**	0.0079	**0.0046**
1000	0.5	50%	0.0485	**-0.0043**	0.0036	**0.0028**
1000	0.5	0%	0.0518	**-0.0034**	0.0038	**0.0024**
1000	2.0	50%	0.0444	**-0.0040**	0.0046	**0.0032**
1000	2.0	0%	0.0475	**-0.0035**	0.0042	**0.0033**

BLCS Study Cohort



	Death	Censored
Recurrence	885 (18.8%)	766 (16.3%)
Censored	1,810 (38.5%)	1,239 (26.4%)

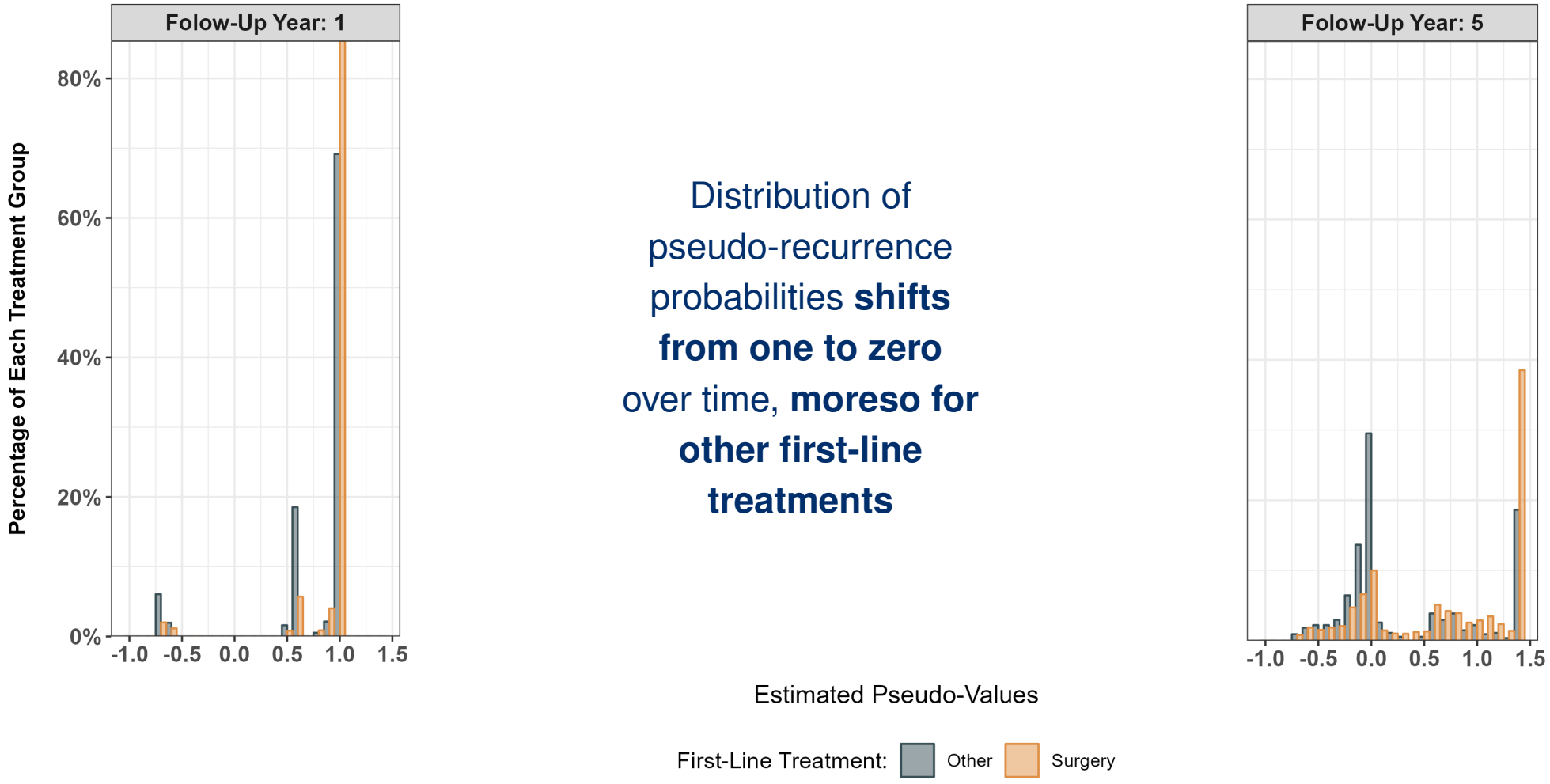
Dist. of Confounders Differs Across First-Line Trt. Groups

Characteristic*	Overall, N = 4,700[1]	Other, N = 706[1]	Surgery, N = 3,994[1]	p-value[2]
Stage at Diagnosis				**< 0.001**
Stage 1	3,007 (64%)	223 (32%)	2,784 (70%)	
Stage 2	753 (16%)	100 (14%)	653 (16%)	
Stage 3a	940 (20%)	383 (54%)	557 (14%)	
Age at Diagnosis (yrs.)	68 (61, 74)	69 (62, 77)	67 (61, 74)	**< 0.001**
Female	2,603 (55%)	367 (52%)	2,236 (56%)	0.077
Body Mass Index	26.6 (23.3, 31.1)	26.1 (22.8, 30.8)	26.7 (23.4, 31.1)	**0.013**
Smoking Status				**0.003**
Never Smoker	592 (13%)	65 (9%)	527 (13%)	
Former Smoker	2,821 (60%)	422 (60%)	2,399 (60%)	
Current Smoker	1,171 (25%)	205 (29%)	966 (24%)	
Smoker, Status Unknown	116 (2%)	14 (2%)	102 (3%)	
Pack-Years of Smoking	40 (19, 53)	40 (24, 61)	40 (18, 51)	**< 0.001**
EGFR Mutation	158 (3%)	22 (3%)	136 (3%)	**< 0.001**
Not Tested	3,805 (81%)	610 (86%)	3,195 (80%)	
KRAS Mutation	265 (6%)	17 (3%)	248 (6%)	**< 0.001**
Not Tested	3,805 (81%)	610 (86%)	3,195 (80%)	

[1] n (%); Median (IQR); [2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

* Subsequent models further adjusted for race, ethnicity, and education level

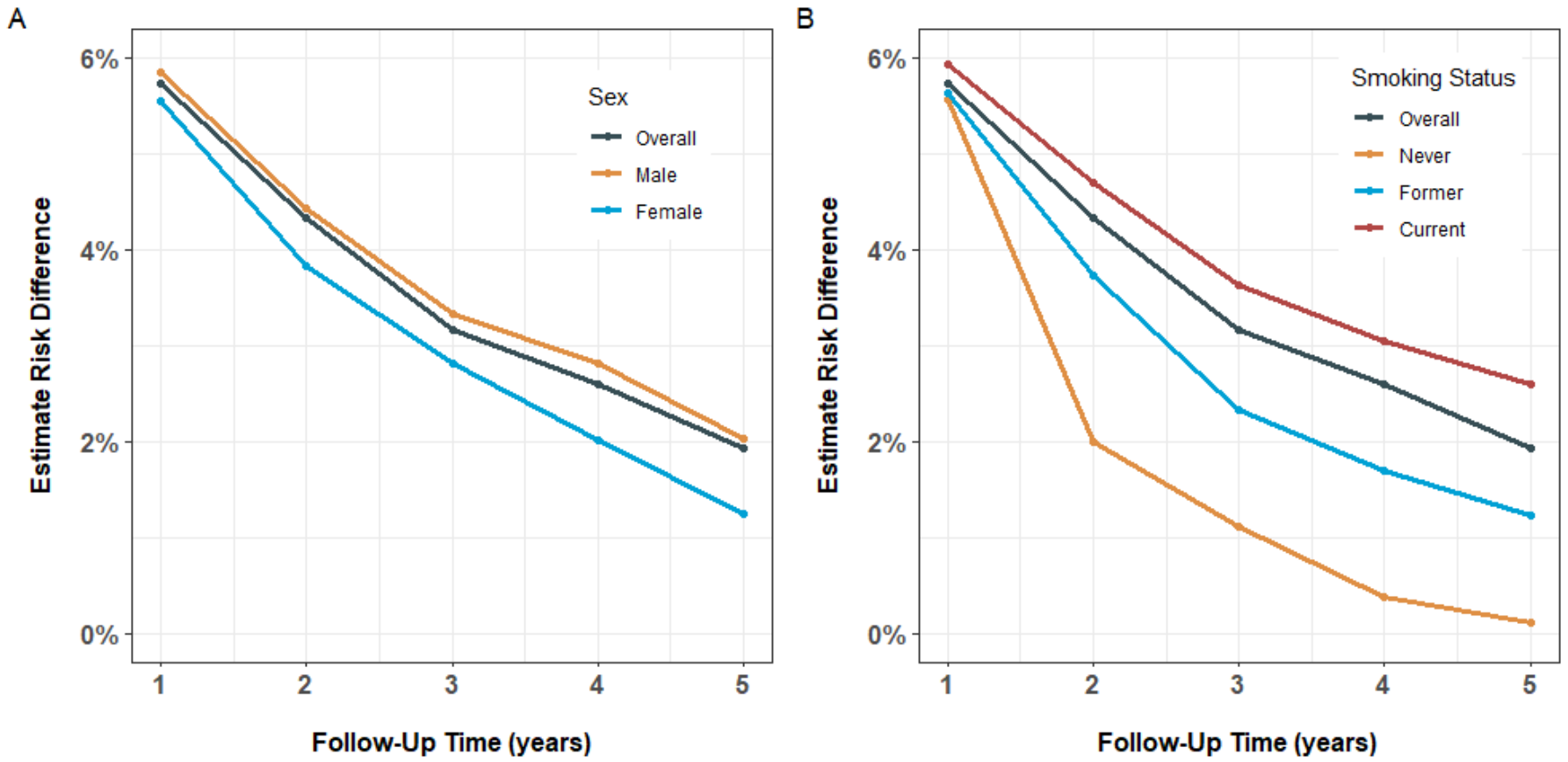
Distribution of BLCS Pseudo-Values



Distribution of pseudo-recurrence probabilities **shifts from one to zero** over time, **moreso for other first-line treatments**

Risk Difference Attenuates over Time

Differently by Patient Subgroups



BLCS Results

- **Overall difference** in risk of recurrence between first-line therapies **attenuates** over time: 5.7% at 1 year vs. 1.9% at 5 years
- Stratified by **sex** risk difference is **slightly higher** among **male** patients, attenuates similarly
- Larger differences were observed when stratifying by **smoking status**
  - Treatment **differences** slightly **higher** among **current smokers** (5.9% at 1-year vs. 2.5% at 5-years)
  - **Greater attenuation** among **former** (range: 5.6% to 1.2%) and **never** smokers (range: 5.6% to 0.1%)

Conclusions

- Method to estimate the **causal effect** of treatment on NSCLC recurrence, respecting **semi-competing risks**
- Demonstrated the **performance** of this approach on simulated and real-world data
- **Emphasized** the importance of accounting for **dependent censoring**
- **Observed** differences in the efficacy of surgical resection compared to other first-line therapies, which attenuated over time in BLCS

Planned Future Work

- Develop an approach for **quantifying uncertainty** in our estimated ATE and **drawing inference**
- Extend this method to account for other sources of **confounding** such as **immortal time bias**
- Improve the **computational efficiency** and usability of software before making it **available** via an `R` package
- Consider additional **target values** such as **restricted mean survival times**

Questions?

Thank you to my collaborators:

- My advisor: Prof. Yi Li
- My BLCS Collaborators: Dr. David Christiani, Dr. Xinan Wang, Ms. Jui Kothari

Preprint:

Slides & Code:

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Challenges We Address

1. Semi-competing risks introduce **dependent censoring**, where death **precludes** disease recurrence
2. Current approaches necessitate **complicated** loss functions or **strong assumptions** (e.g., PH)
3. Parametric or semi-parametric methods are limited in their ability to model **complex** risk functions
4. Little work integrating **causal inference** and **machine learning** in settings of **dependent censoring**

Key Assumptions

1. **Consistency**: $T_{i1} = T_{i1}^{Z_i}$ almost surely

   An individual's potential outcome under their assigned treatment group is the outcome that will be observed

2. **Positivity**: $Z_i \in \{0, 1\}\ \forall X_i$

   Every individual has a non-zero probability of being assigned to either treatment group

3. **No Interference**: T_{i1}^{z} is unaffected by the value of z for another subject, j

   The potential outcomes of one individual are not affected by the treatment assignment of other individuals

4. **Exchangeability**: $T_{i1}^{1}, T_{i1}^{0} \perp Z_i \mid X_i$

   There is no unmeasured confounding

5. **Non-Informative Censoring**: $T_{i1} \perp C_i \mid Z_i, X_i$

   Subject's censoring time is independent of their failure time given their covariates

Proposed Three-Stage Approach

Step 1. Estimate **survival function** for time-to-recurrence

Step 2. Calculate **pseudo-survival probabilities** at fixed times

- Consistent for survival probability
- Circumvents need for complex loss function
- Does not require assumptions like proportional hazards

Step 3. Train **deep neural network** to estimate **causal target** (ATE)

1. Survival Function for Time-to-Recurrence

- Assume time-to-recurrence (T_1) and death (T_2) are cont. non-negative r.v.'s with **survival functions**:

$$S_1(t_1) = \Pr(T_1 > t_1); \quad t_1 \geq 0$$
$$S_2(t_2) = \Pr(T_2 > t_2); \quad t_2 \geq 0.$$

- Distribution of T_1 is **non-parametrically identifiable** ONLY when recurrence ALWAYS precedes death

- The **joint survival function** of the event times is:

$$S(t_1, t_2) = \Pr(T_1 > t_1, T_2 > t_2)$$

Estimating $S_1(t_1)$ and θ

- Consider a **Clayton copula model** for T_1, T_2 with dependence parameter $\theta \geq 0$:

$$S(t_1, t_2) = [S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1]^{-1/\theta}, \tag{4}$$

- Given (4) and $S_2(t_2)$, $S_1(t_1)$ is **monotonic** and **estimable**:

$$S_1(t) = [S_*(t)^{-\theta} - S_2(t)^{-\theta} + 1]^{-\frac{1}{\theta}}, \tag{5}$$

  where $S_*(t)$ is the recurrence-free survival function

- $S_*(t)$ and $S_2(t)$ are **estimable via KM**, since both are **always observable**

- θ estimated via extension to concordance-based estimator of Fine et al. (2001)

Estimating θ w/o Covariates

Fine et al. (2001) proposed a **concordance**-based estimator:

$$\hat{\theta} = \frac{\sum_{i<j} W\left(Y_{ij1}, Y_{ij2}\right) D_{ij} \Delta_{ij}}{\sum_{i<j} W\left(Y_{ij1}, Y_{ij2}\right) D_{ij} \left(1 - \Delta_{ij}\right)} - 1$$

where (i, j) are independent observation pairs, and:

- $T_{ij1} = \min\left(T_{i1}, T_{j1}\right)$; $T_{ij2} = \min\left(T_{i2}, T_{j2}\right)$; $C_{ij} = \min\left(C_i, C_j\right)$
- $Y_{ij1} = \min\left(T_{ij1}, T_{ij2}, C_{ij}\right)$; $Y_{ij2} = \min\left(T_{ij2}, C_{ij}\right)$
- $D_{ij} = I\left(T_{ij1} < T_{ij2} < C_{ij}\right)$; $\Delta_{ij} = I\left[\left(T_{i1} - T_{j1}\right)\left(T_{i2} - T_{j2}\right) > 0\right]$
- $W^{-1}_{a,b}(x, y) = \frac{1}{n}\sum_i \left\{I\left(Y_{i1} \geq \min(a, x), Y_{i2} \geq \min(b, y)\right)\right\}$

Note: Δ_{ij} is estimable only when $D_{ij} = 1$ and a, b may be selected to dampen W for large x, y

Estimating θ w/ Covariates

With covariates Z, X, the copula model (4) is extended to

$$S(t_1, t_2 \mid Z, X) = [S_1(t_1 \mid Z, X)^{-\theta} + S_2(t_2 \mid Z, X)^{-\theta} - 1]^{-1/\theta} \tag{6}$$

- θ quantifies **correlation** of T_1 and T_2 **conditional** on Z, X
- Conditioning on Z, X, model (6) implies

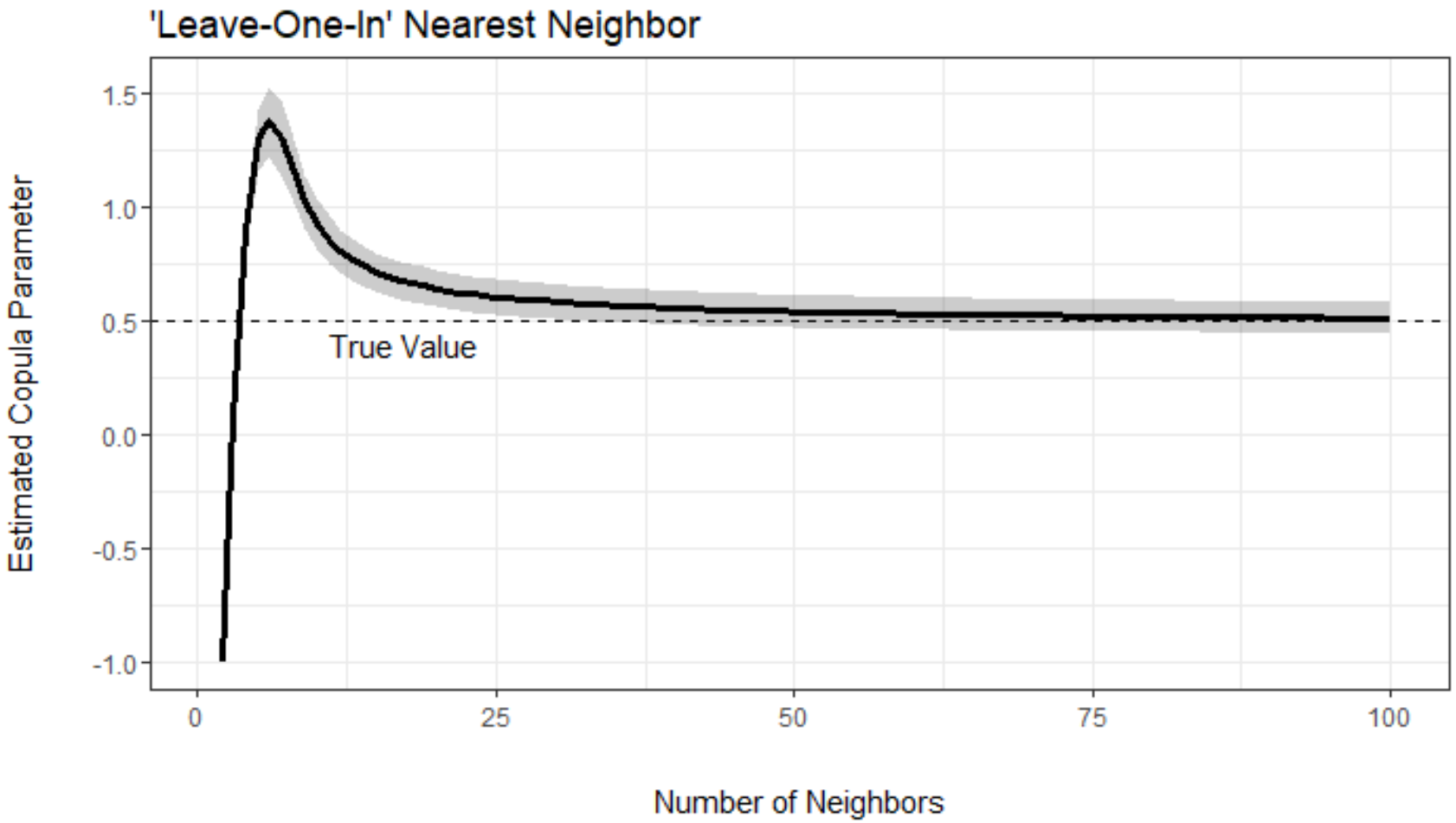
$$S_1(t \mid Z, X) = [S_*(t \mid Z, X)^{-\theta} - S_2(t \mid Z, X)^{-\theta} + 1]^{-\frac{1}{\theta}},$$

Estimating θ – 'Leave-One-In'

Propose a **conditional** $\hat{\theta}$ using nearest k neighbors to subject i:

1. Let $\tilde{X}_i = \{Z_i, X_i\}$ denote the $(p+1)$-vector of covariates for the ith patient
2. Calculate distance between $\tilde{X}_i$ and $\tilde{X}_{i'}$ for $1 \leq i \neq i' \leq n$: $||\tilde{X}_i - \tilde{X}_{i'}||_2 = \{\sum_{j=1}^{p+1} (\tilde{x}_{ij} - \tilde{x}_{i'j})^2\}^{1/2}$
3. For each i, identify k nearest neighbors, $\mathcal{N}(i,k)$
4. Estimate $\hat{\theta}^{(i)}$ based on subjects from $\mathcal{N}(i,k)$ via $\hat{\theta}^{(i)} = \frac{\sum_{j,l \in \mathcal{N}(i,k); j<l} W(Y_{jl1}, Y_{jl2}) D_{jl} \Delta_{jl}}{\sum_{j,l \mathcal{N}(i,k); j<l} W(Y_{jl1}, Y_{jl2}) D_{jl} (1-\Delta_{jl})} - 1$
5. Estimate $\hat{\theta}$ via $\hat{\theta} = n^{-1} \sum_{i=1}^{n} \hat{\theta}^{(i)}$

Example $\hat{\theta}$ Calculation



2. Pseudo-Survival Probabilities

Interested in the risk difference at **a given time point**, want a model that **reflects this**:

- Common approaches (e.g., Cox model) impose structure across **all time points** (e.g., **proportional hazards**)
- However, treatment efficacy of a may **change over time**
- **Pseudo-values** are an intuitive alternative

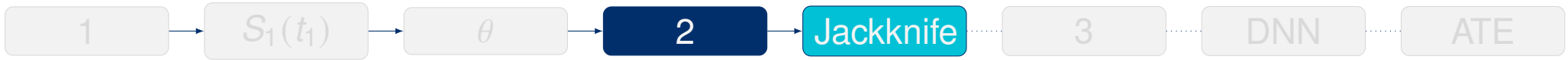
Jackknife Pseudo-Values

- Probability of **no recurrence** by time t_j, $j = 1, \ldots, J$, is $S_1(t_j) = \Pr(T_1 > t_j)$
- **Pseudo-survival probability** for ith individual at time t_j:

$$\hat{S}_{i1}(t_j) = n \times \hat{S}_1(t_j) - (n-1) \times \hat{S}_1^{-i}(t_j)$$

  where $\hat{S}_1(t_j)$ and $\hat{S}_1^{-i}(t_j)$ are estimates of $S_1(t_j)$ using all n subjects and excluding the ith subject

- Represents contribution of ith individual in estimating $\mathbb{E}[S_1(t_j)]$ in the sample of n subjects
- $\hat{S}_i(t)$ then used as **response**, similar to logistic model fit to $I(T_{i1} > t_j)$ if the data were **fully observed**



Example Calculation

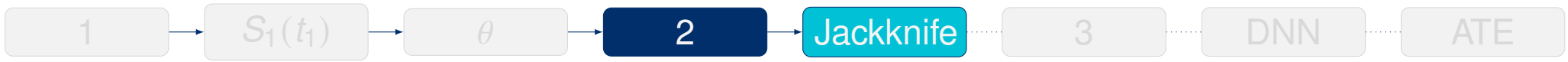
Example pseudo-values for two individuals.

Observation		Simulated Outcomes				Treatment	Estimated
ID	t	Y_{i1}	D_{i1}	Y_{i2}	D_{i2}	Z_i	Pseudo-Values
1	0.2	0.3991	1	0.4054	1	0	1.0302
1	0.4	0.3991	1	0.4054	1	0	-0.3260
1	0.6	0.3991	1	0.4054	1	0	0.1765
1	0.8	0.3991	1	0.4054	1	0	0.0968
1	1.0	0.3991	1	0.4054	1	0	0.0496
2	0.2	1.0401	0	1.0401	0	1	1.0302
2	0.4	1.0401	0	1.0401	0	1	1.1761
2	0.6	1.0401	0	1.0401	0	1	1.3082
2	0.8	1.0401	0	1.0401	0	1	1.4430
2	1.0	1.0401	0	1.0401	0	1	1.5688

Some Useful Properties

1. **Survival probabilities** are more natural to interpret than **hazards ratios**
2. $S_{i1}(t_j)$ is **approximately independent** of $S_{i'1}(t_j)$ for $i \neq i'$ as $n \to \infty$
3. $\lim_{n\to\infty} E[S_{i1}(t_j) \mid Z_i, X_i] = S_1(t_j \mid Z, X)$ (important for this method)

- With (2) and (3), these pseudo-values can be used as a **response variables** in a **deep learning framework**
- Imputed outcome is **more efficient** for deep learning



3. Deep Learning

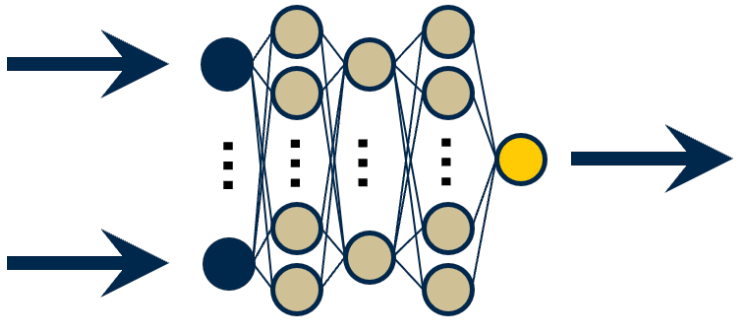
Deep learning mirrors how the brain functions:

- **Neurons** connected in a network of L layers, with k_l neurons in the lth layer
- Predictions based on L-fold **composite**:

$$F_L(\cdot) = f_L \circ f_{L-1} \circ \cdots \circ f_1(\cdot) \text{ where } (g \circ f)(\cdot) = g(f(\cdot))$$

$$f_l(x) = \sigma_l\left(\mathbf{W}_l x + \mathrm{b}_l\right) \in \mathbb{R}^{k_{l+1}}$$

where σ_l is an activation function, $\mathbf{W}_l$ are weights, and b_L are biases

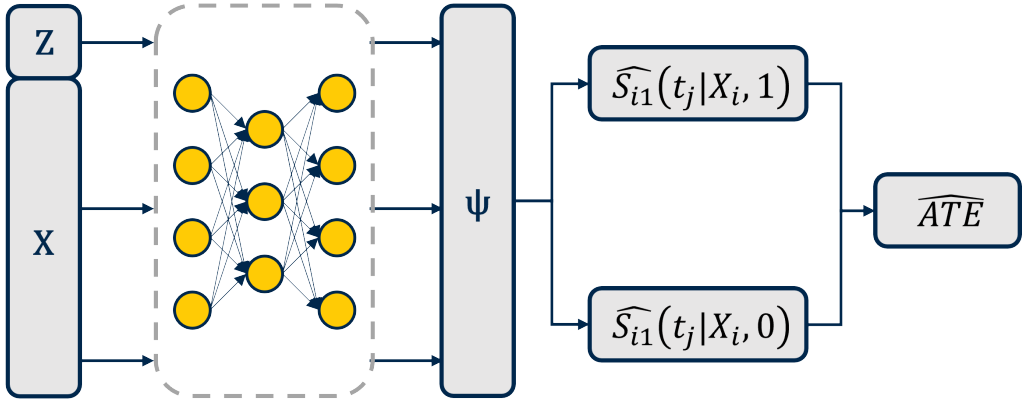


> Allows for ***non-parametric*** estimation of risk functions

> Circumvents the ***curse of dimensionality*** [4, 10]

Causal S-Learner

1. **Fit** model for $S_{i1}(t \mid X_i, Z_i)$ non-parametrically with a feed-forward, fully-connected ***S*-Learner**
2. **Predict** potential outcomes $\hat{S}_{i1}(t \mid X_i, Z_i = z); z \in \{0, 1\}$
3. **Calculate** $\hat{\text{ATE}} = n^{-1} \sum_{i=1}^{n} \{\hat{S}_{i1}(t \mid X_i, 1) - \hat{S}_{i1}(t \mid X_i, 0)\}$

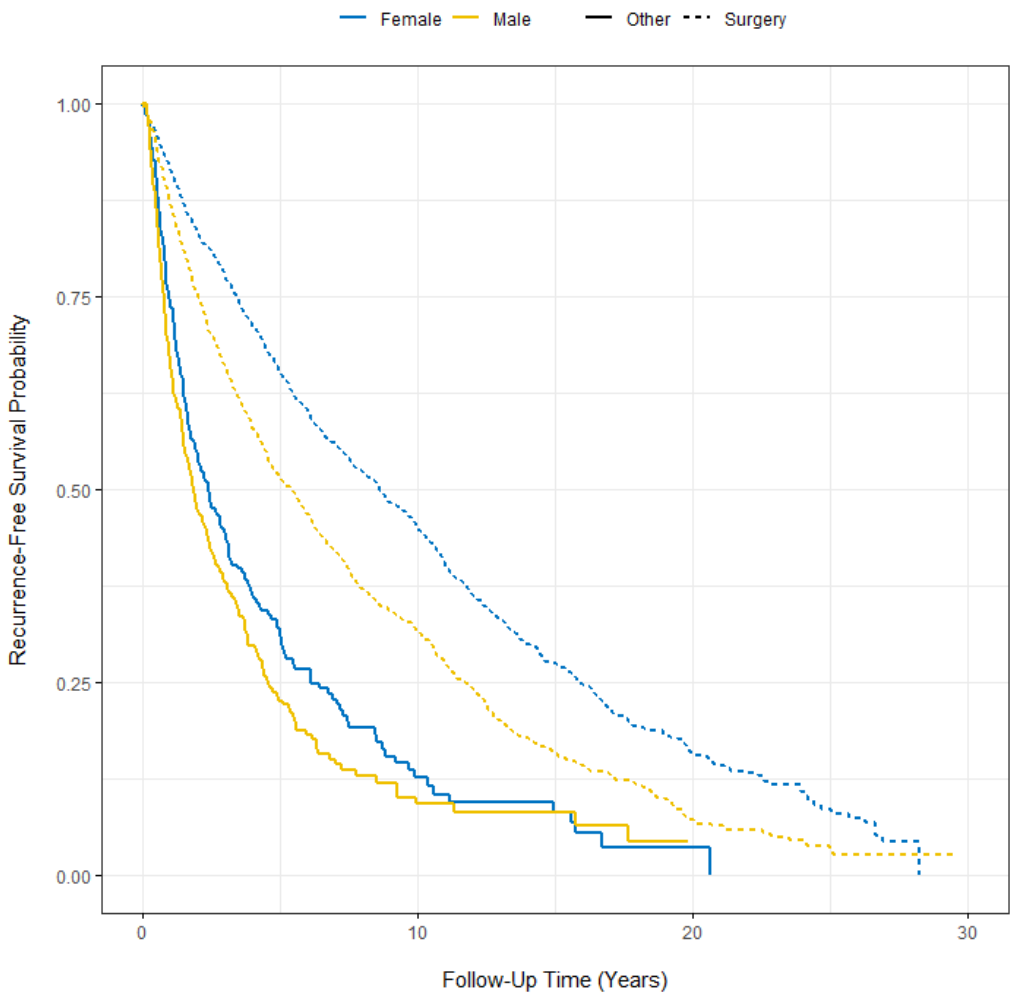


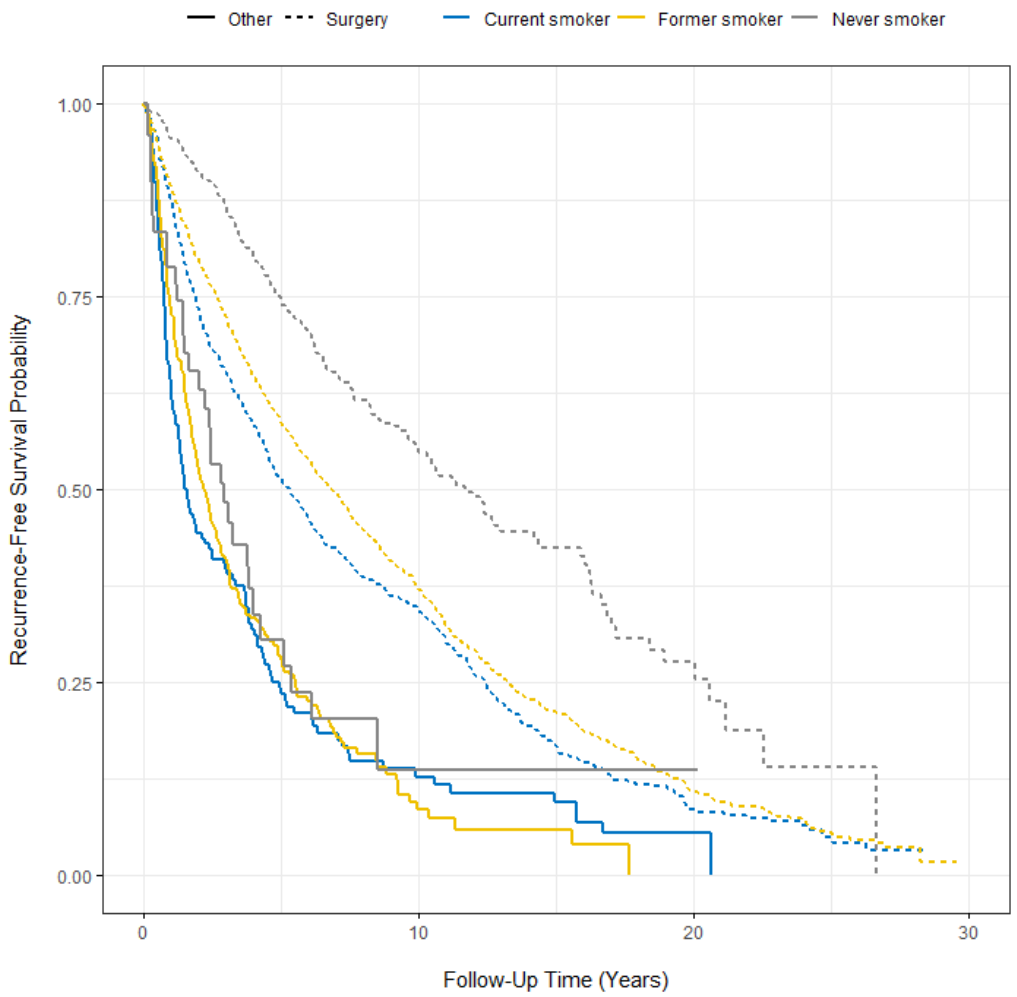
1 → $S_1(t_1)$ → θ → 2 → Jackknife → 3 → DNN → ATE

Advantages of Causal S-Learner

- DNNs encode **informative** features into lower **representative spaces**
- These **embeddings** make downstream supervised learning tasks easier
- S-Learning for causal estimation outputs Ψ, which produces a **representation** of the covariates **decorrelated** from the treatment
- For our **pseudo-value** approach, network output optimized under the **binary cross-entropy loss** function
  - **Faster learning rate/convergence** than MSE due to **steeper gradient** when prediction is far from truth
  - More natural **interpretation** than common loss functions in survival analysis

BLCS KM-Estimated Recurrence-Free Survival





BLCS Estimated θ

- Estimated θ using **'leave-one-in' extension** to the concordance-based estimator
- Among **all patients**, estimated $\hat{\theta} = 5.60$, corresponding to a Kendall's τ value of 0.737
  - This suggests a **high degree of correlation** between recurrence and death
- Stratified estimates of θ **differed across subgroups**
  - E.g., by **sex**, estimated θ **higher among females** (5.93; $\tau = 0.748$) than males (4.85; $\tau = 0.708$)