Bayesian Nonparametric Statistics for Fostering Innovation and Discovery in Biomedical Research

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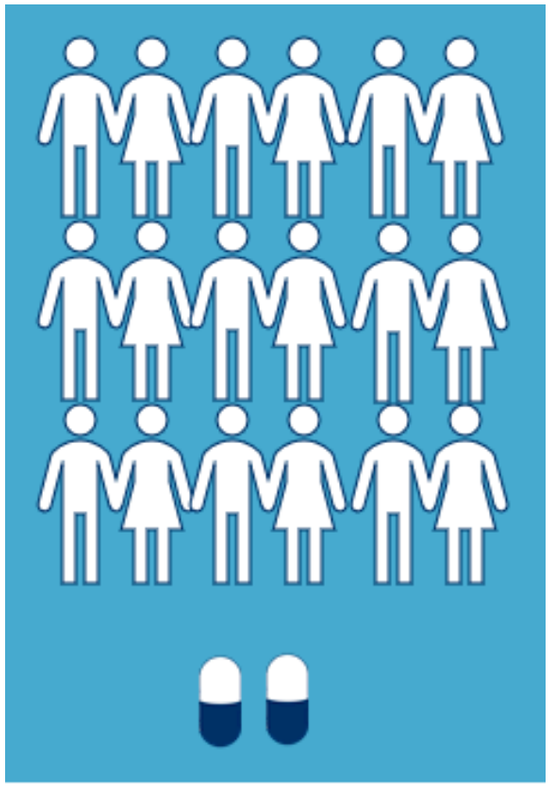
Treatment Effect

Treatment Effect

Clinical Trials



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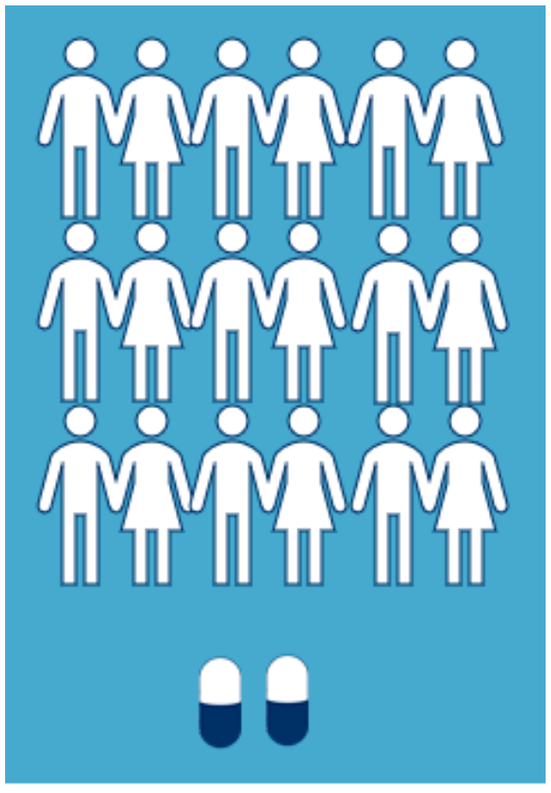

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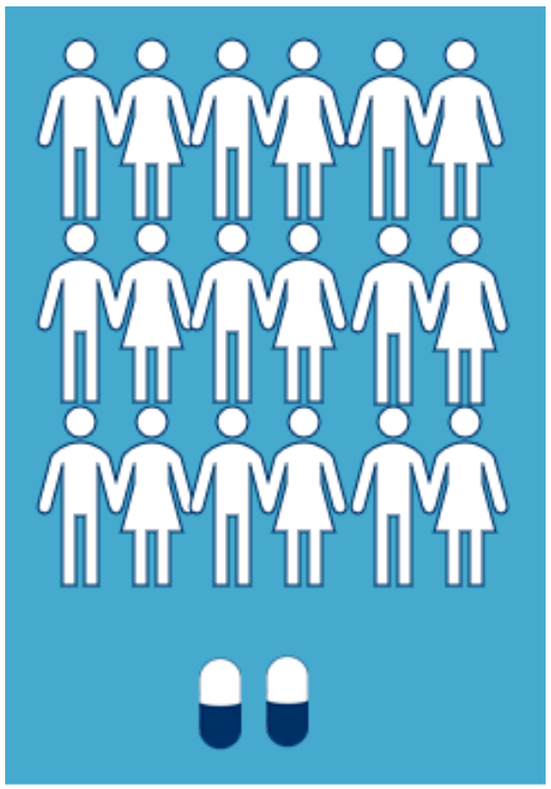
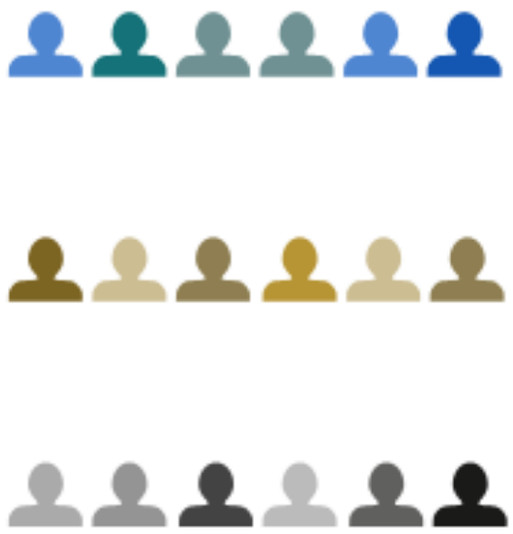


Biomarker-based Trials



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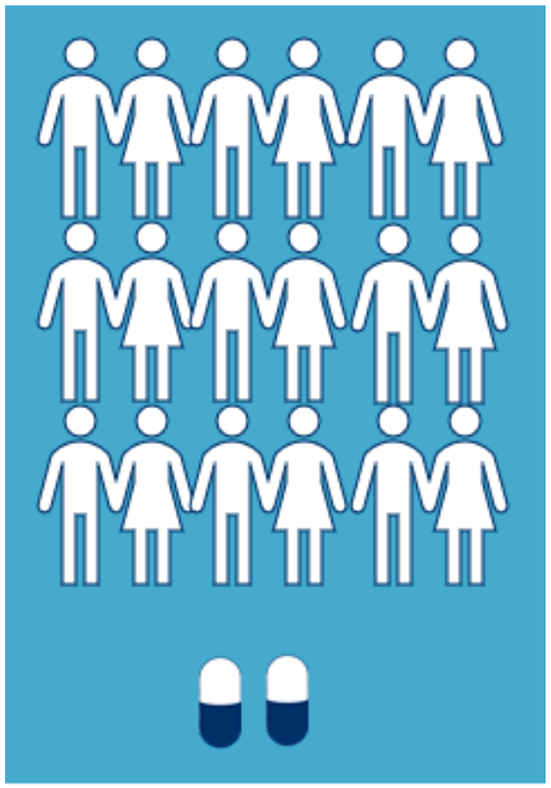

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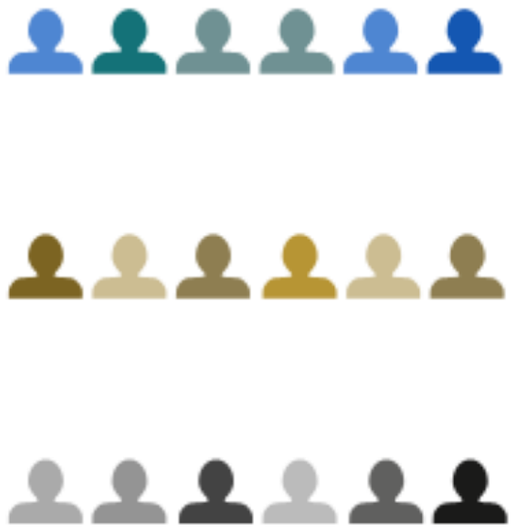

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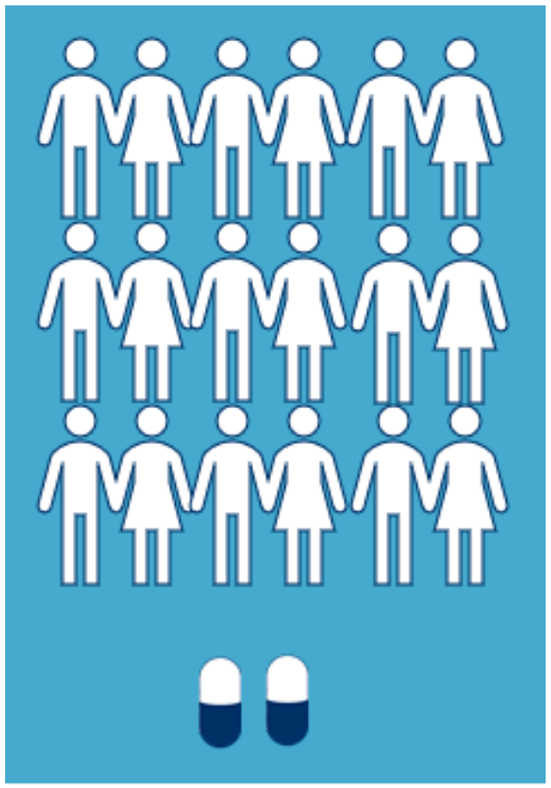

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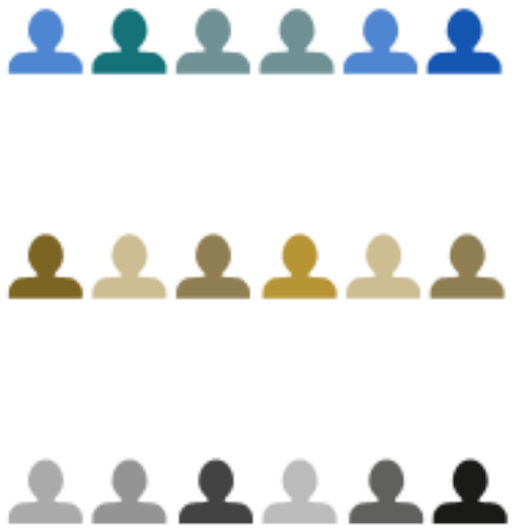

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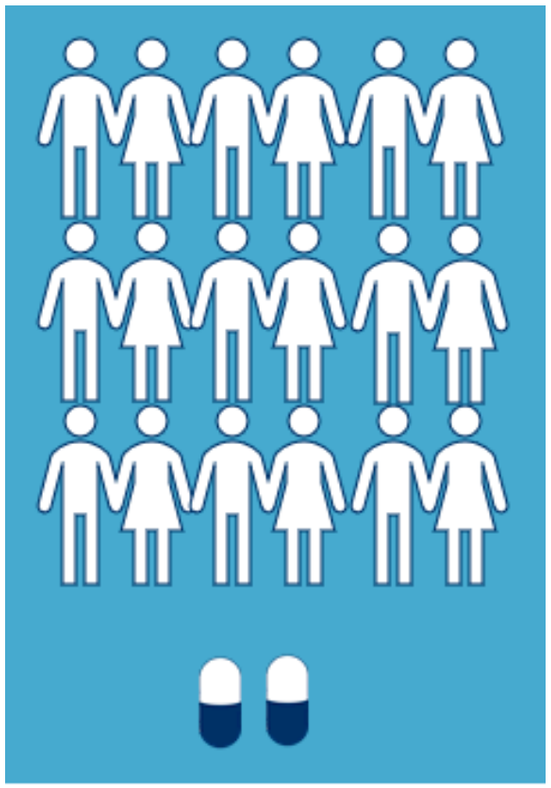

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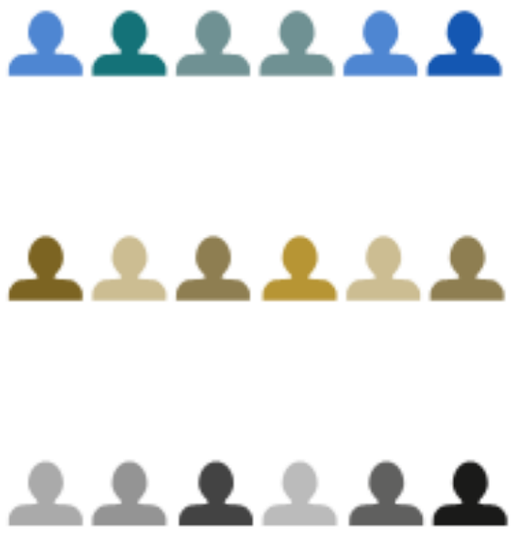

Observational Data

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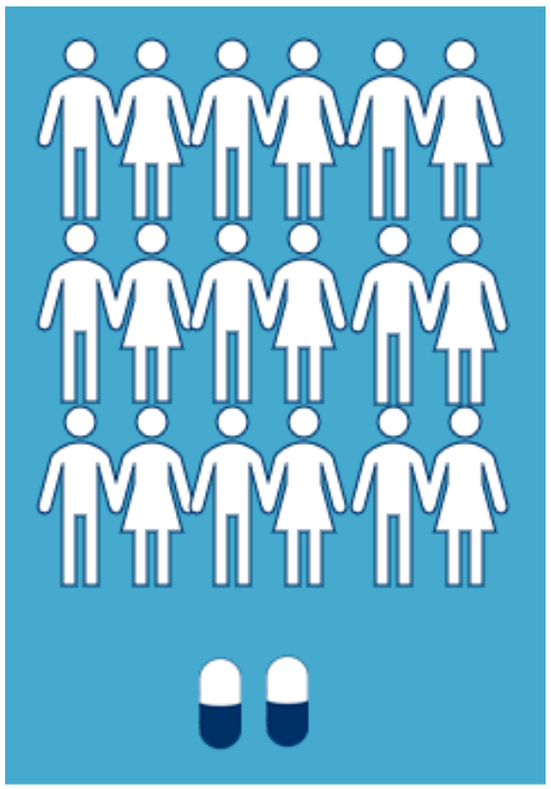

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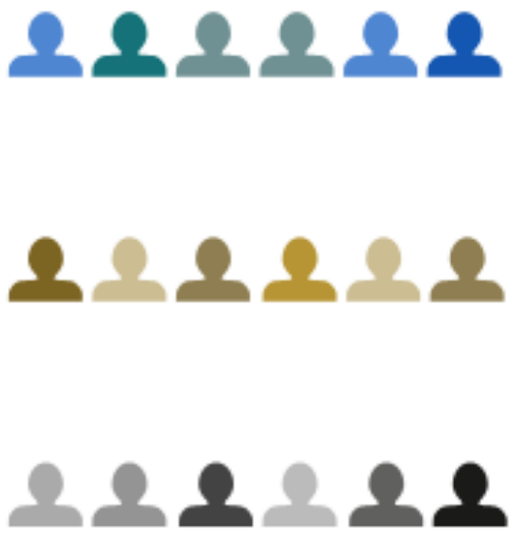

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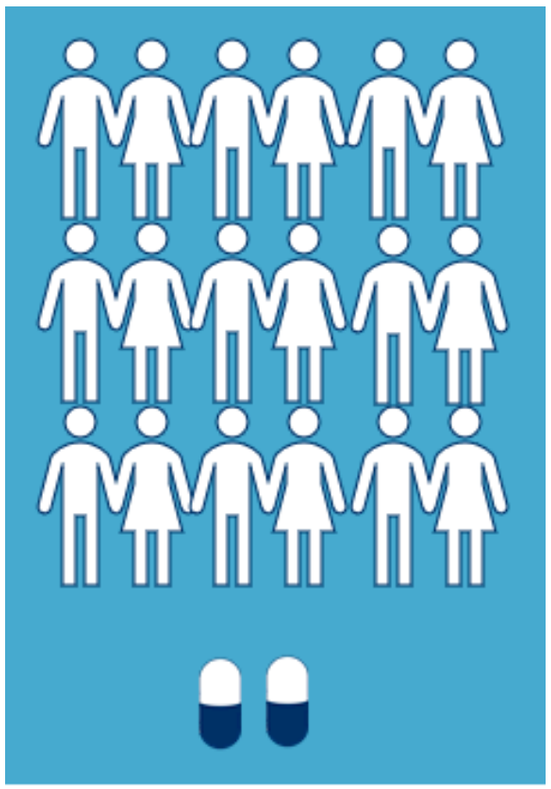

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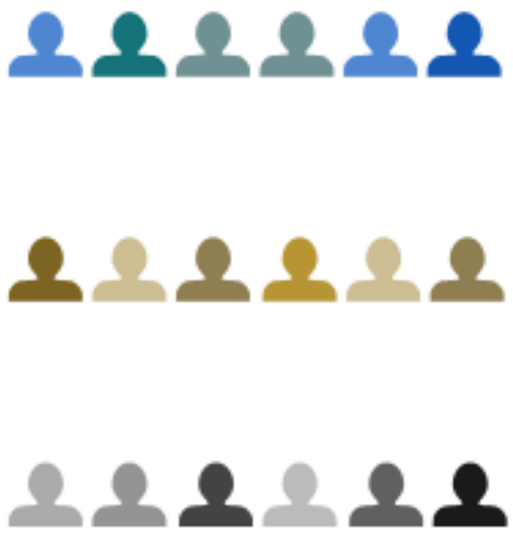

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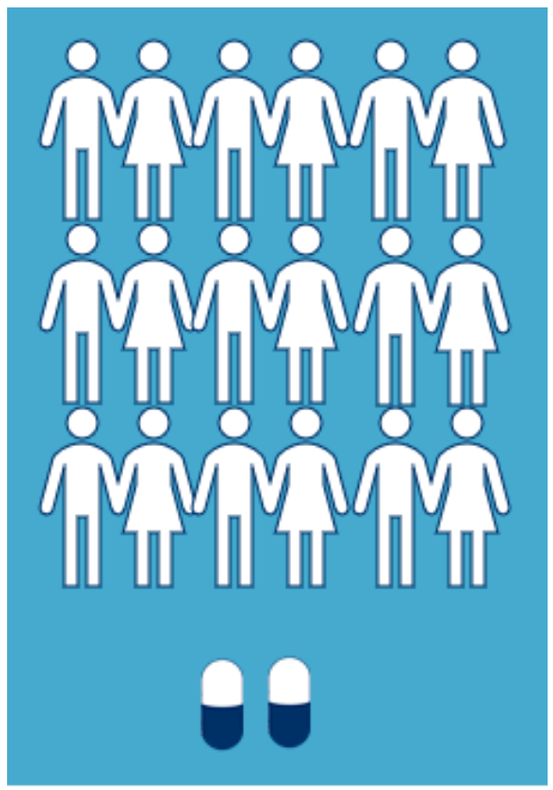

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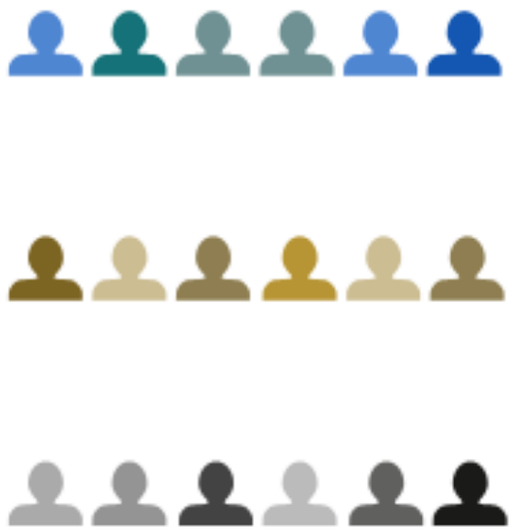

Observational Data

Population → Subgroup → Personalization

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- Homogeneous population.
- Compare survival outcomes only based on firstling therapy, ignoring the subsequent savage treatments.

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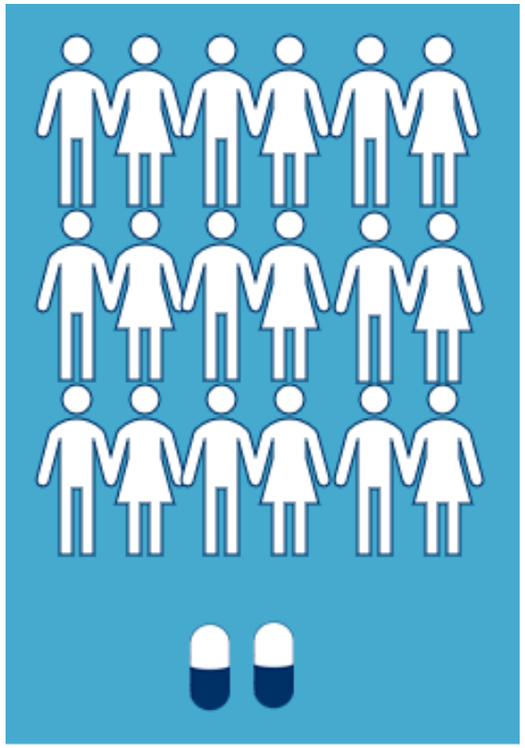

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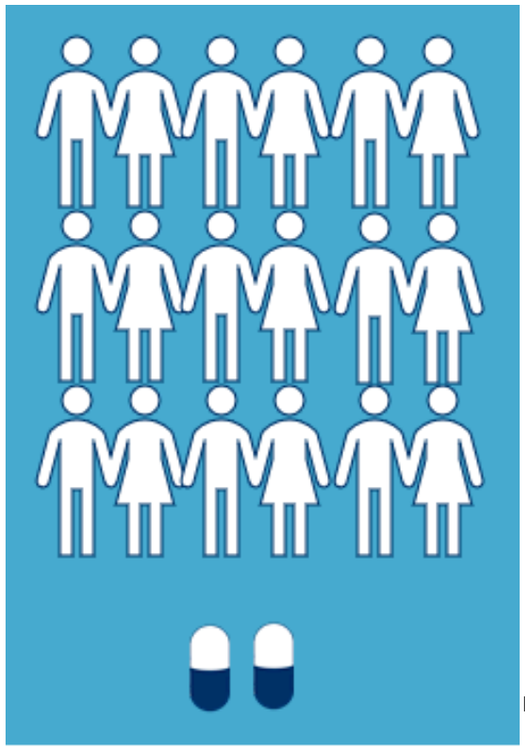
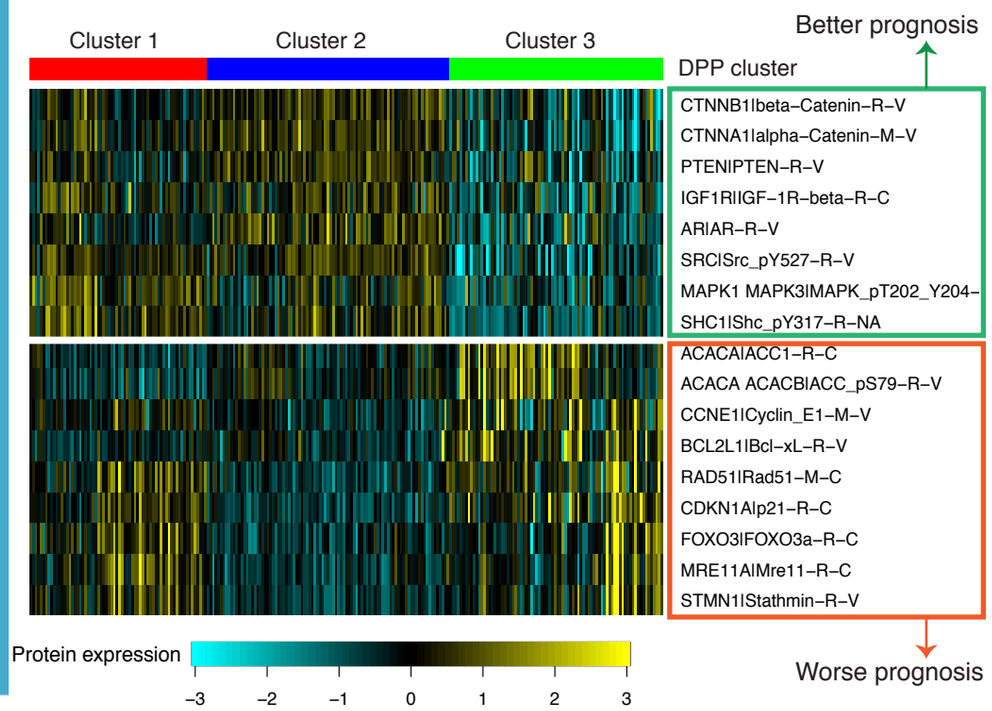


Patients clustering



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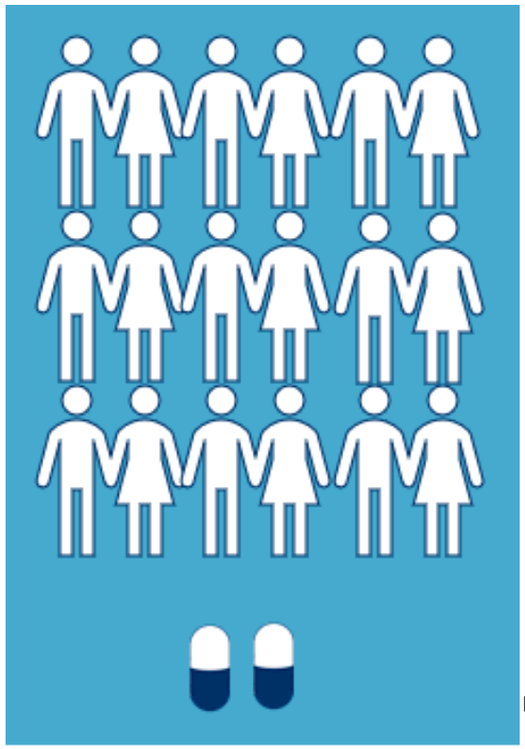

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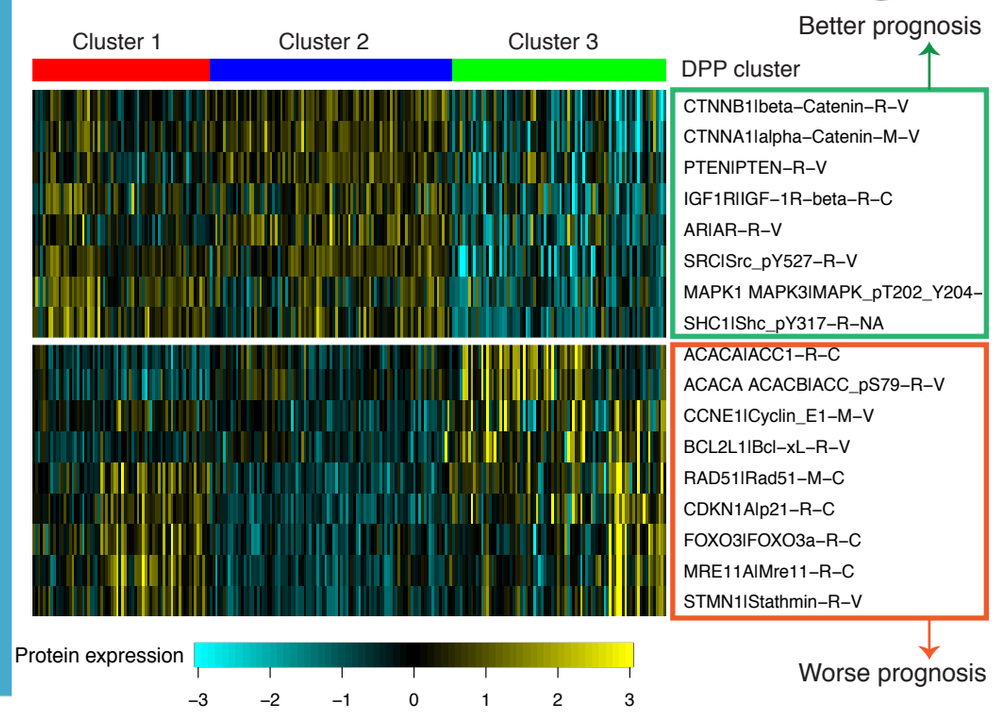
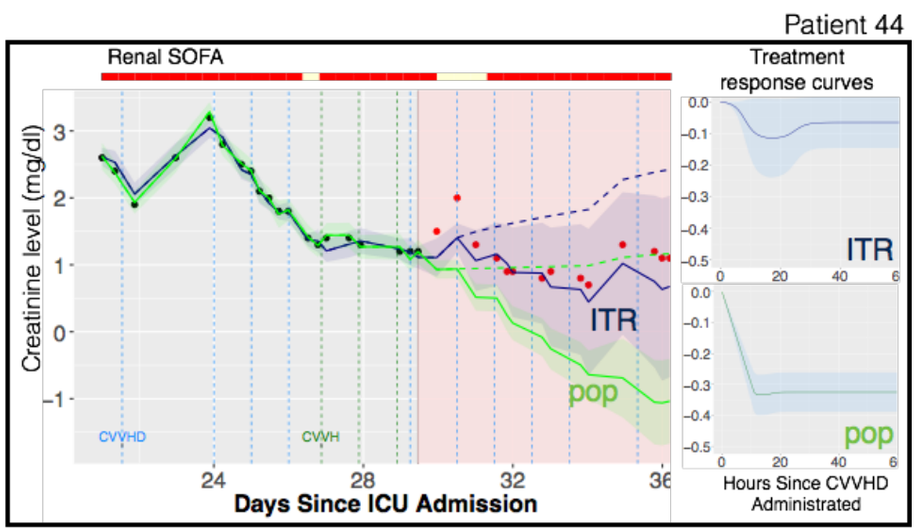


Continuous treatments



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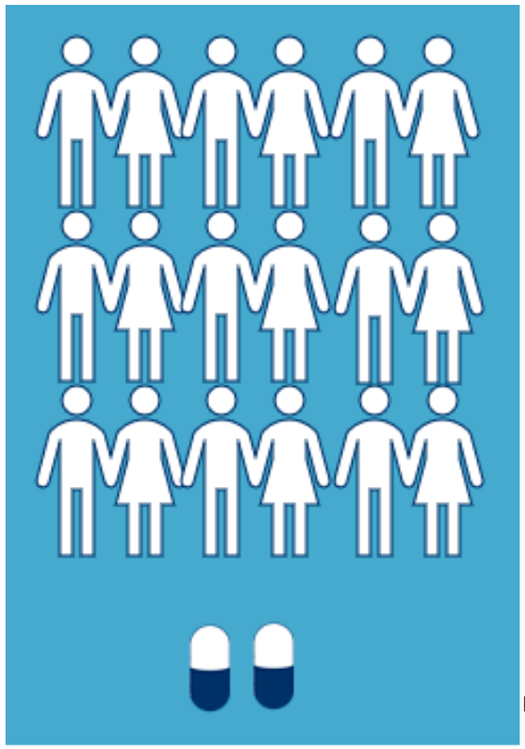

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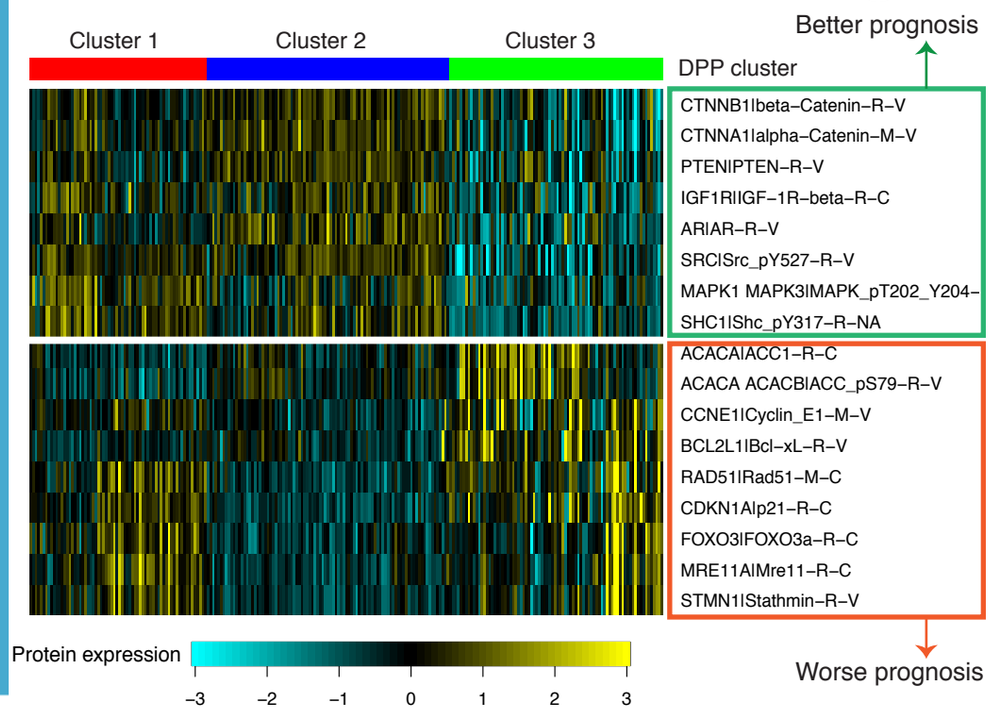

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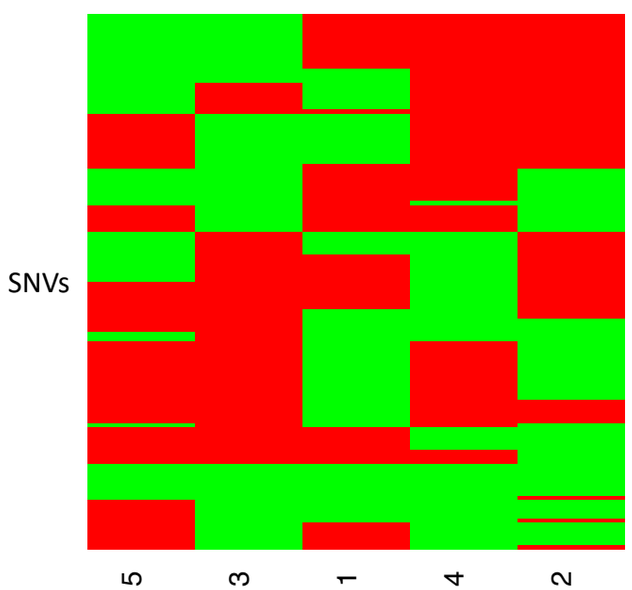

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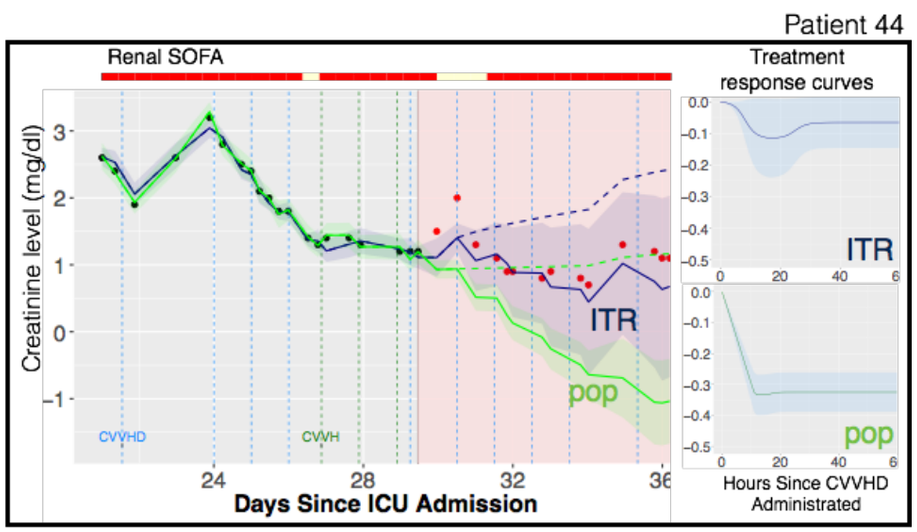

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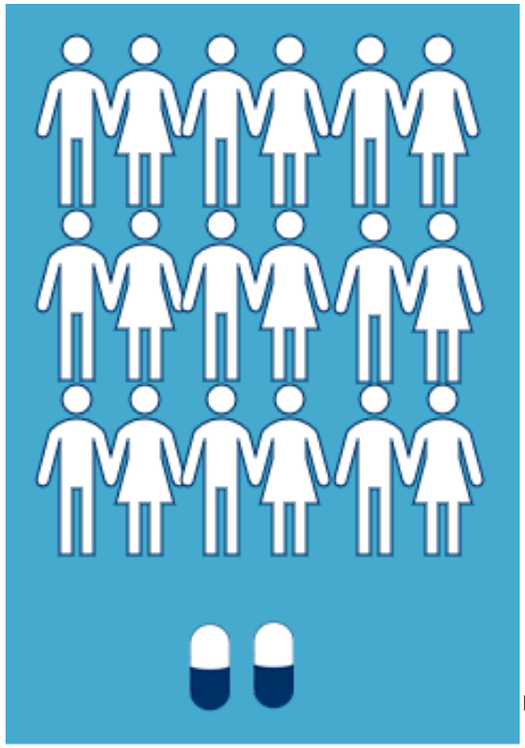

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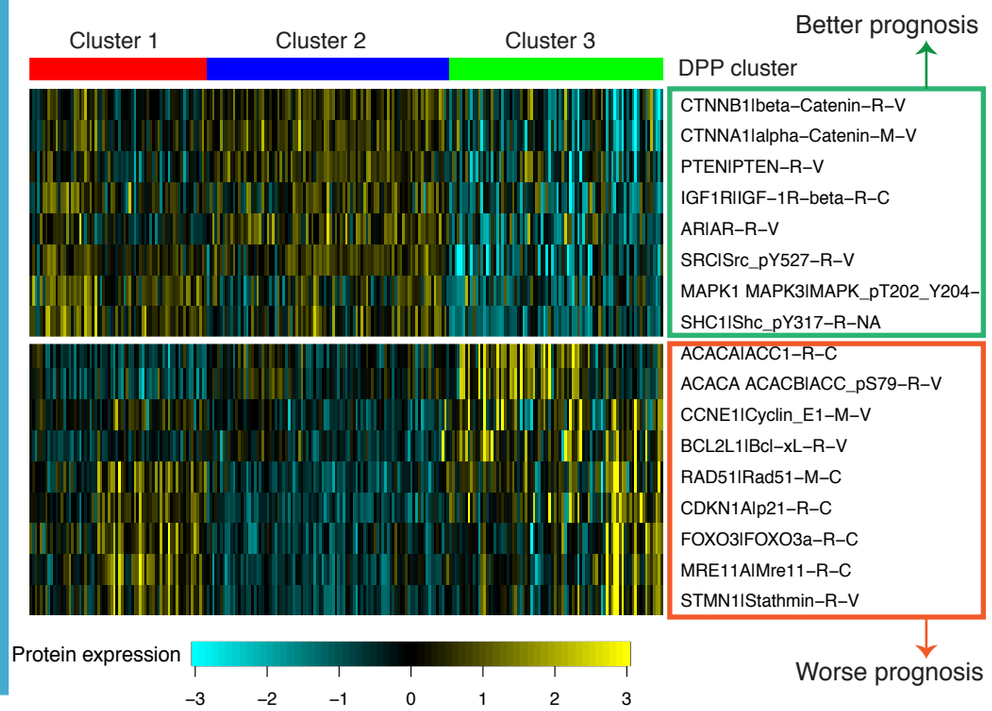
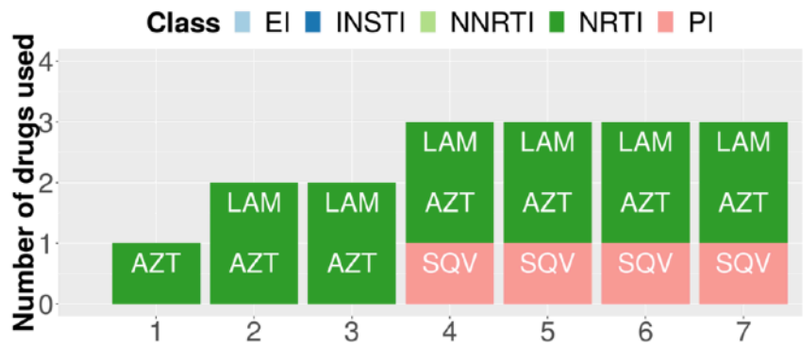


Reinforcement learning



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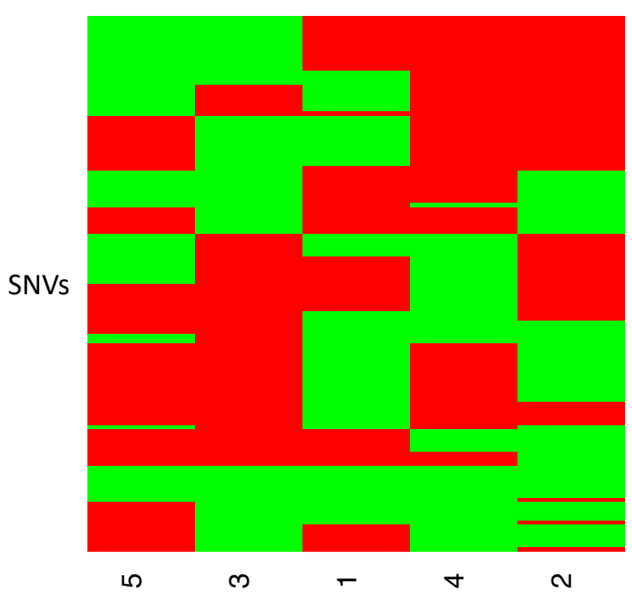

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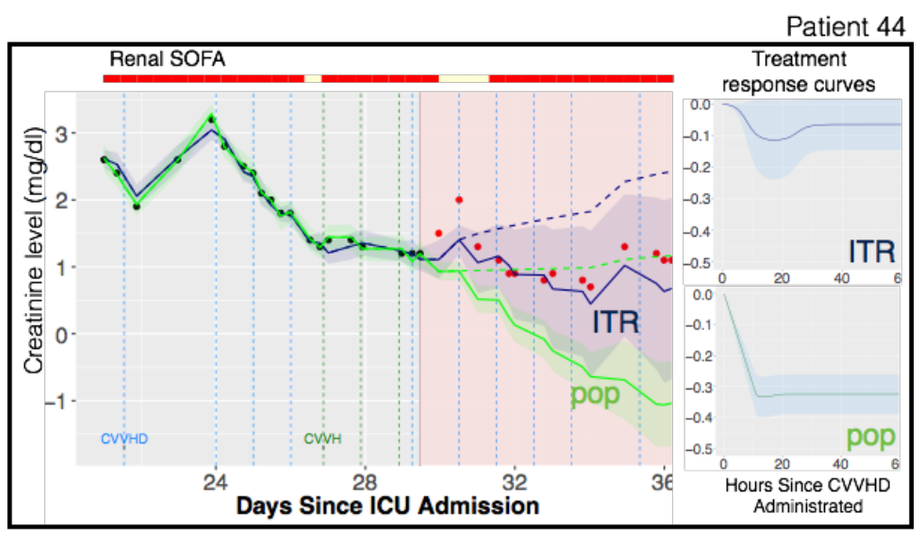

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  - **Regression** for precision dosing

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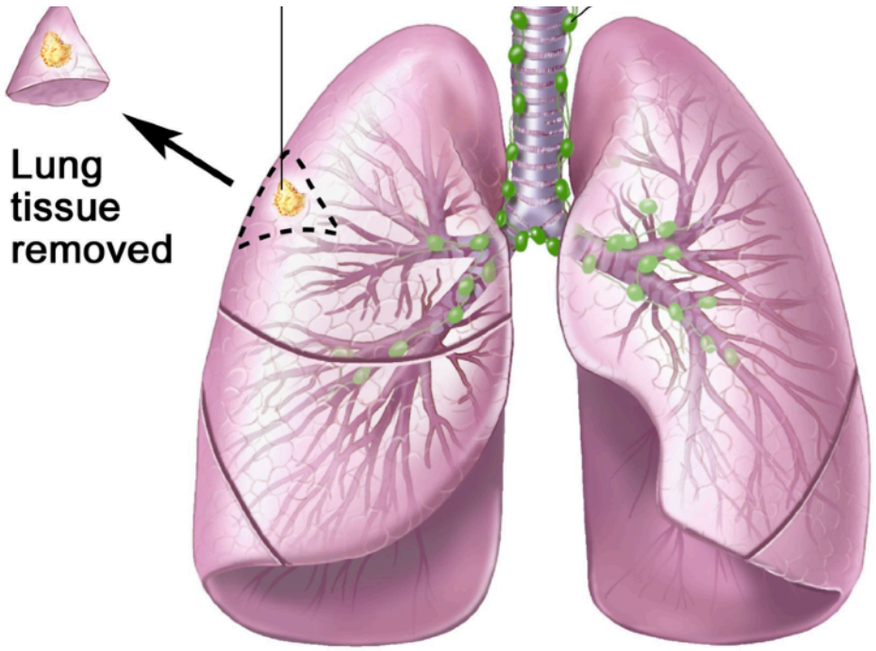
Motivating Trial

Pulmonary resection



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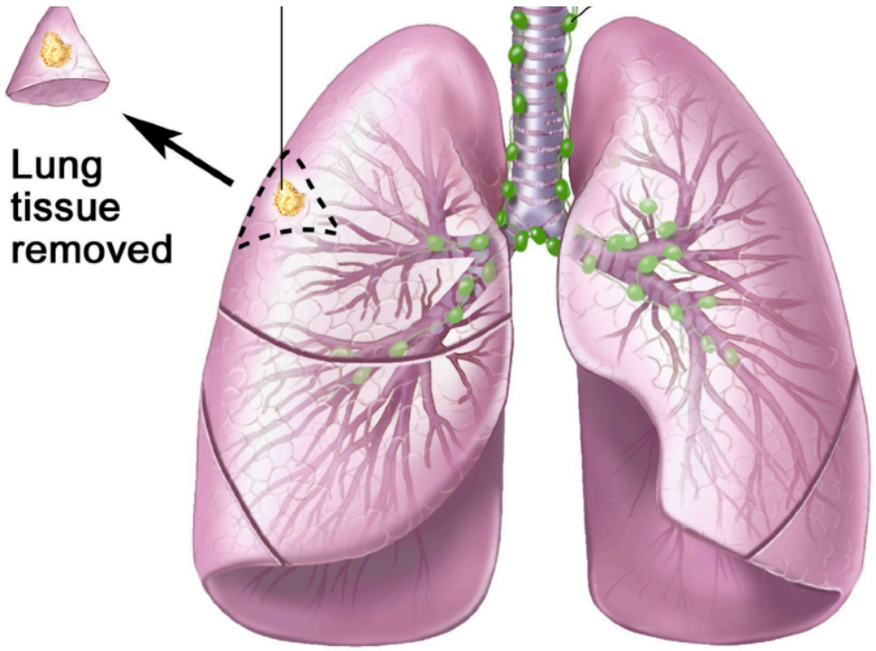

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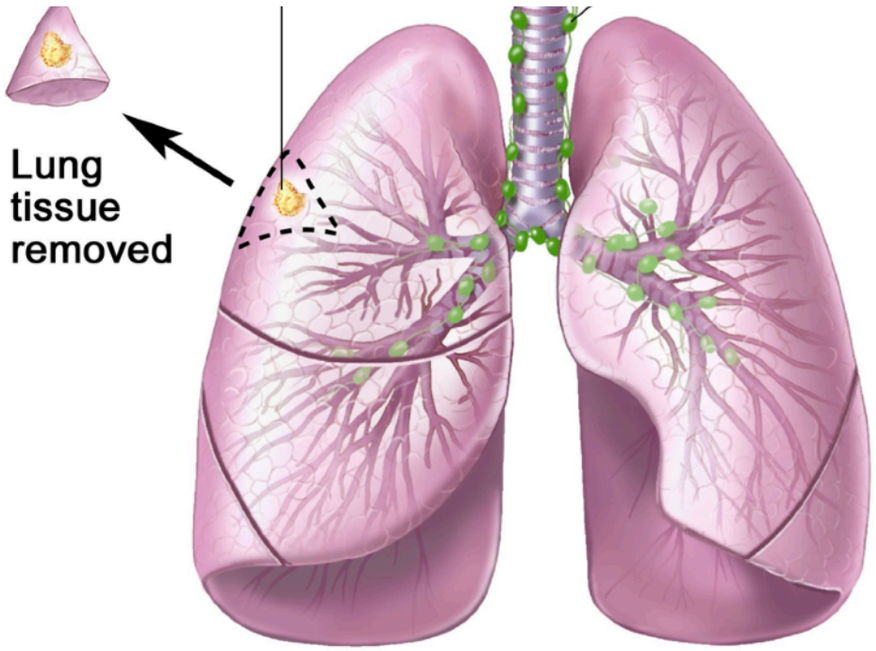

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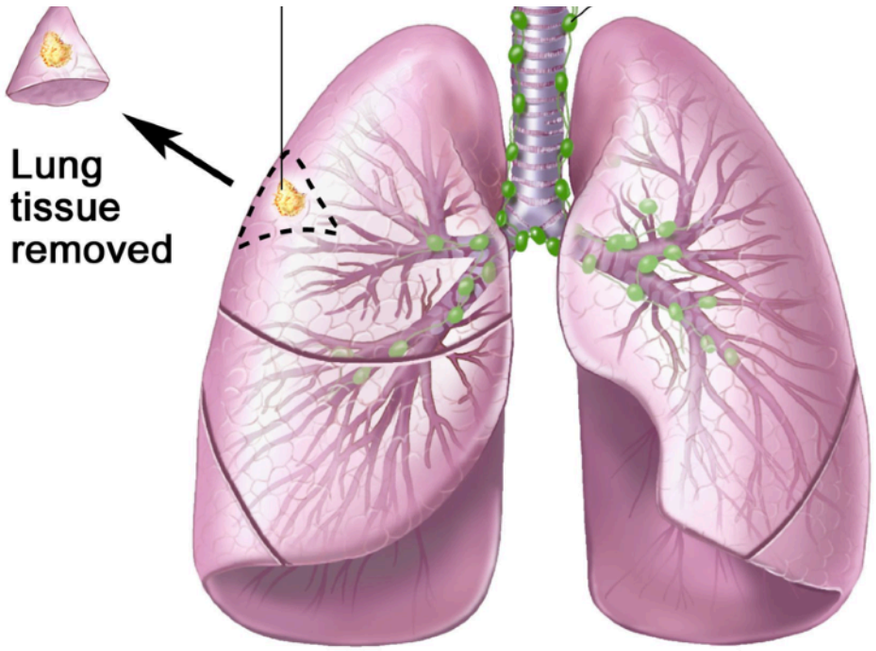

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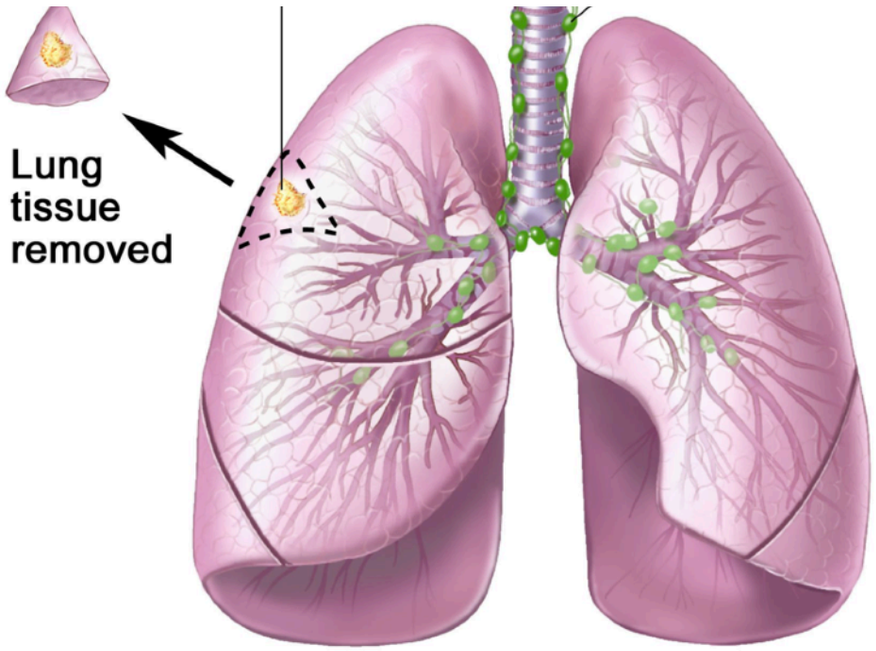

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- New way: Progel (liquid sealants)

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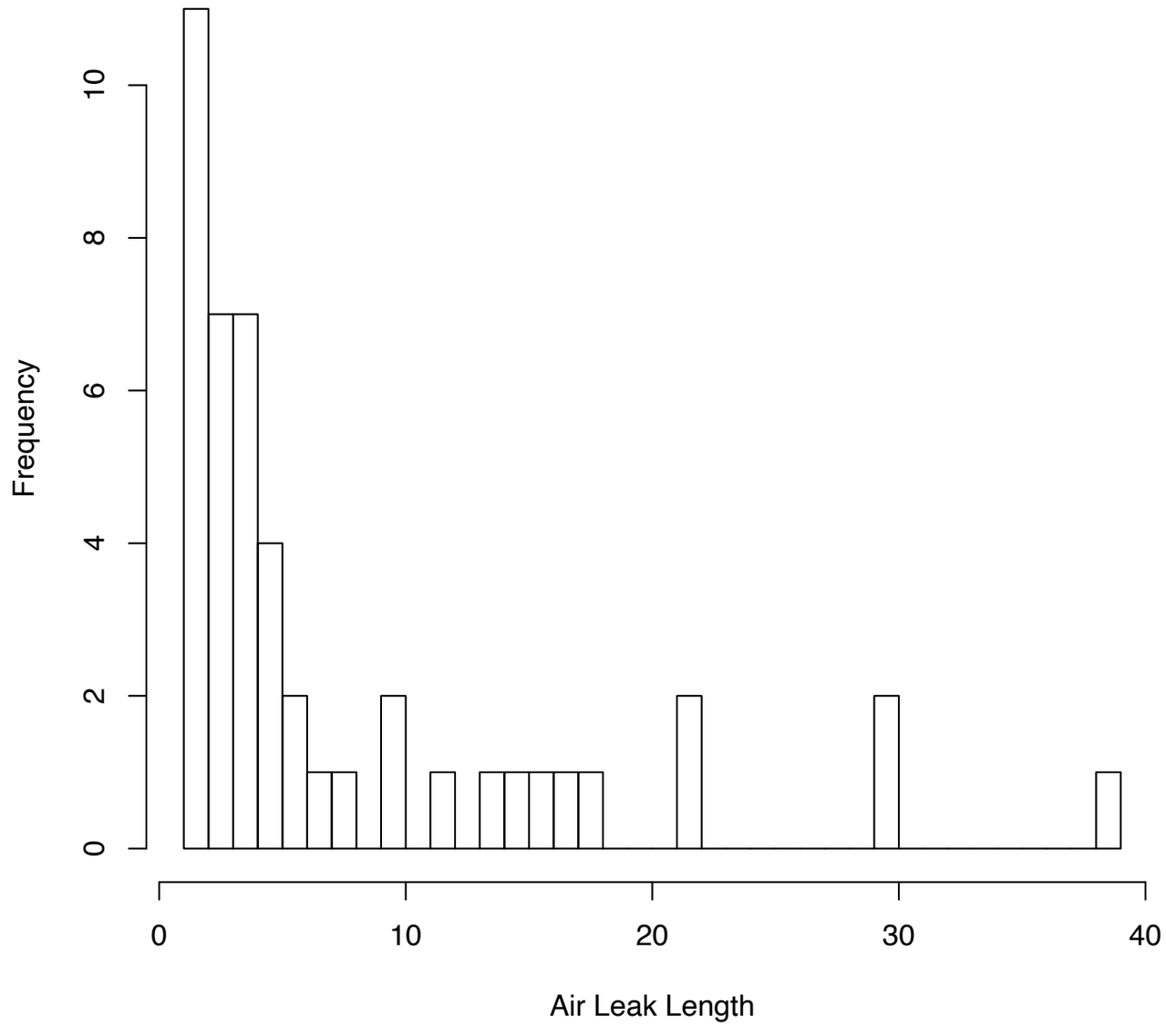

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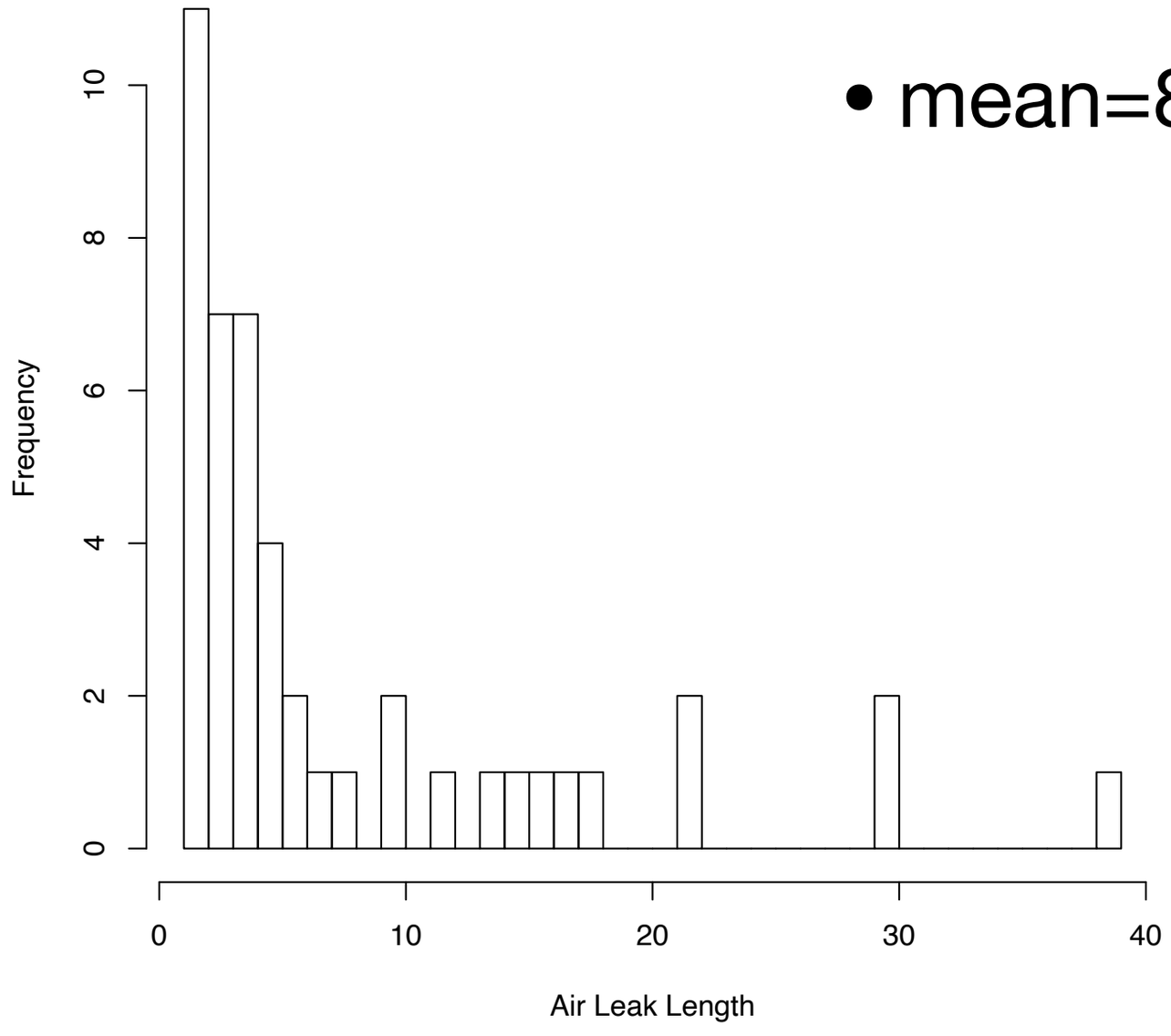

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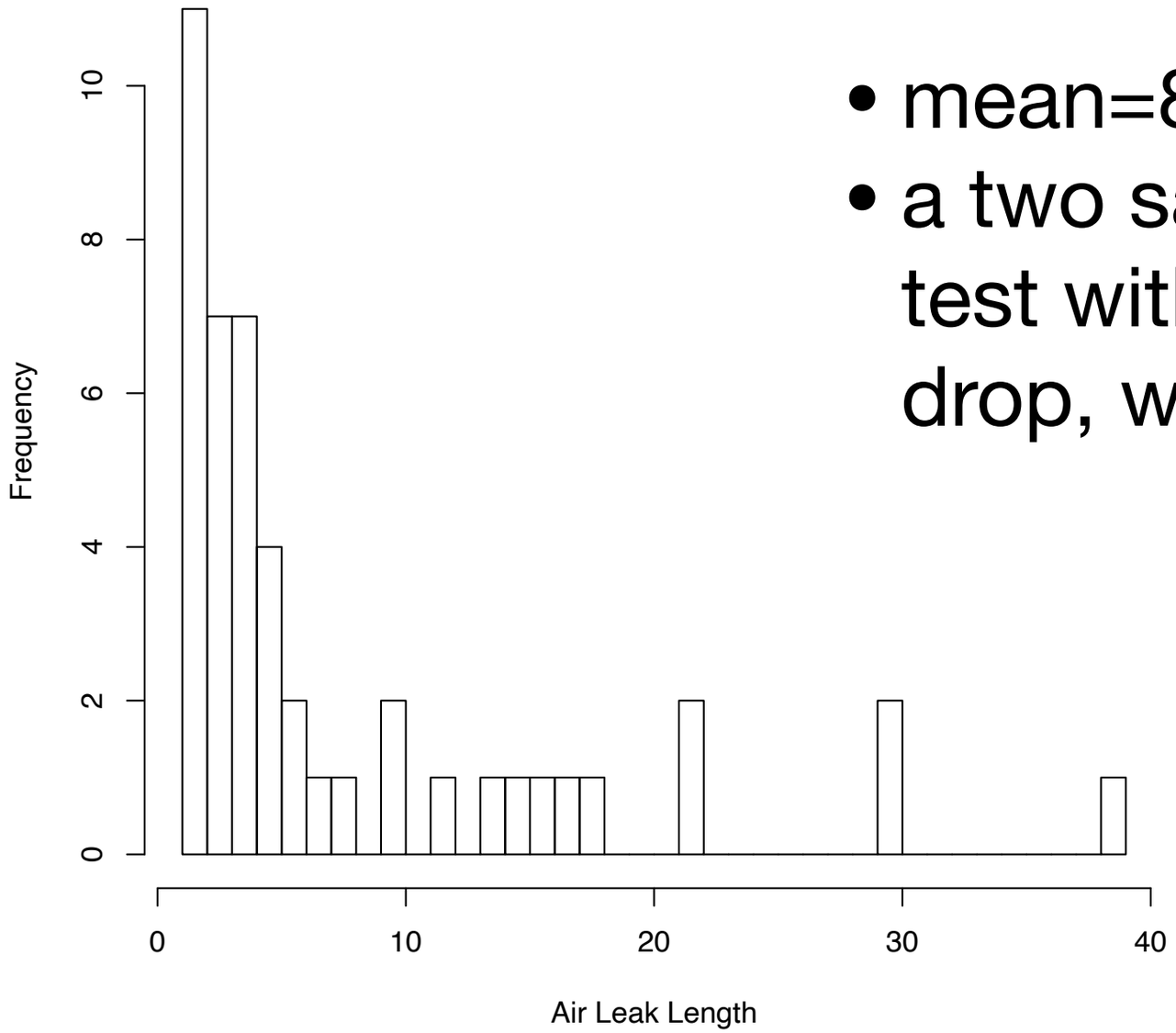

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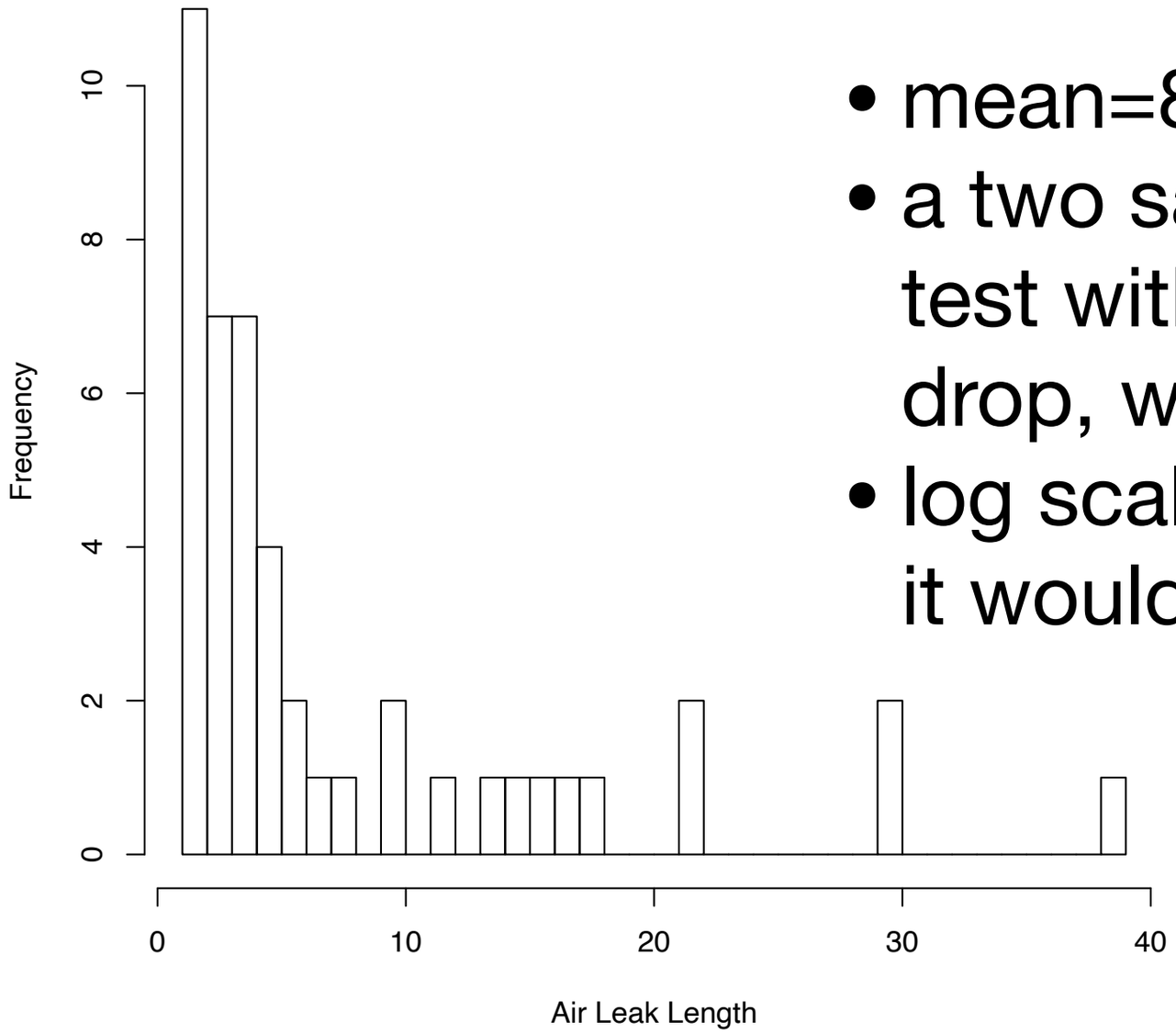

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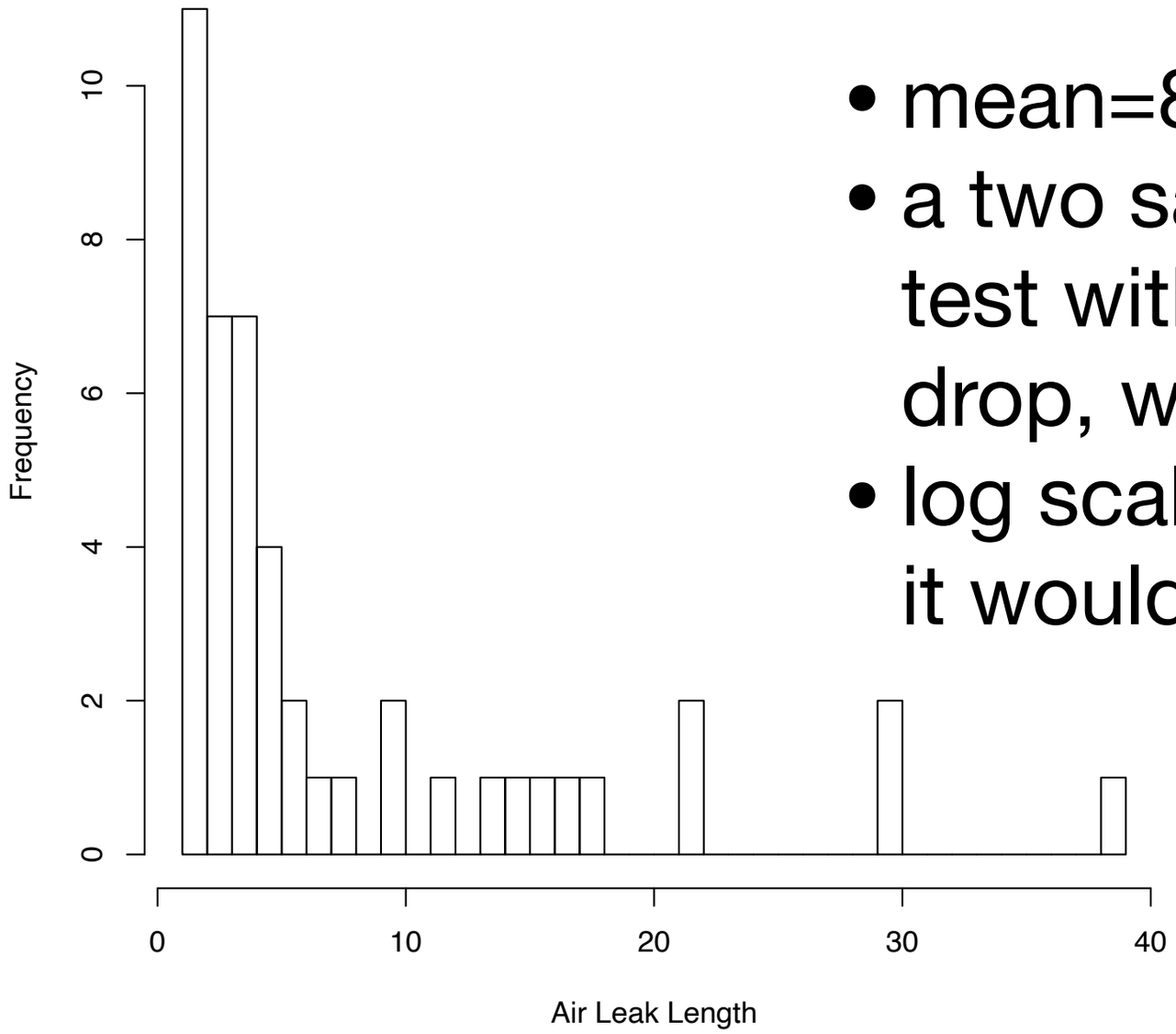

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Standard parametric model is INAPPROPRIATE!!

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- not a potential source of infection

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- Progel is inert, it cannot react chemically with the patient's lung tissue
- not a potential source of infection
- does not slow down the healing process

Modeling Considerations

- Free of air leaks immediately following surgery is possible.
- Consider the distribution of the time to resolve an air leak G_j as a mixture:

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Stochastic ordering on G_1 and G_0: Progel may be better, but not worse.

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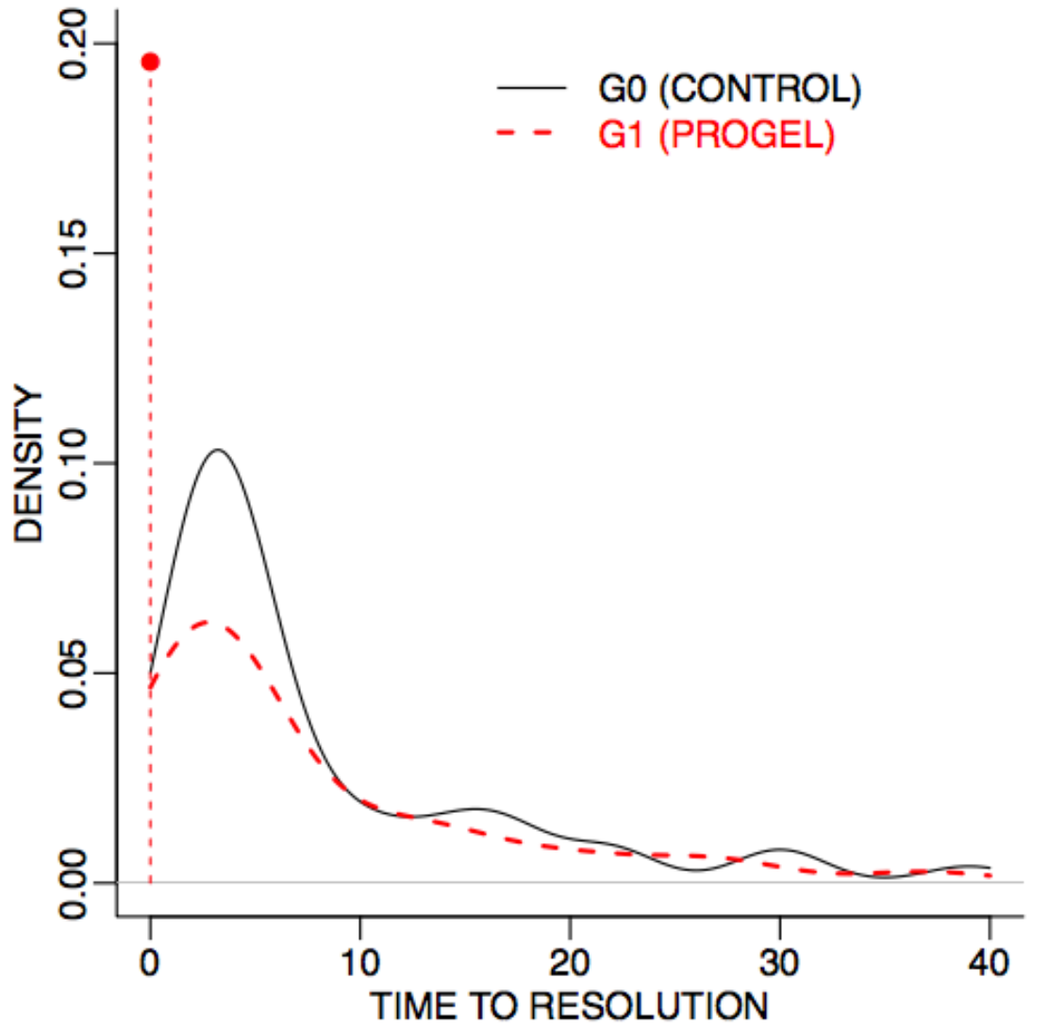

(a)

G_0 and G_1

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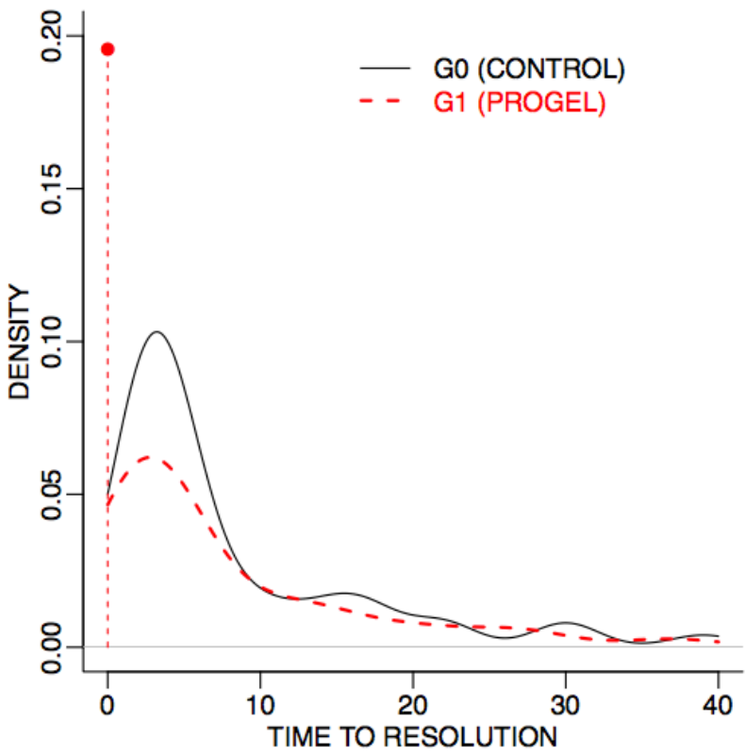
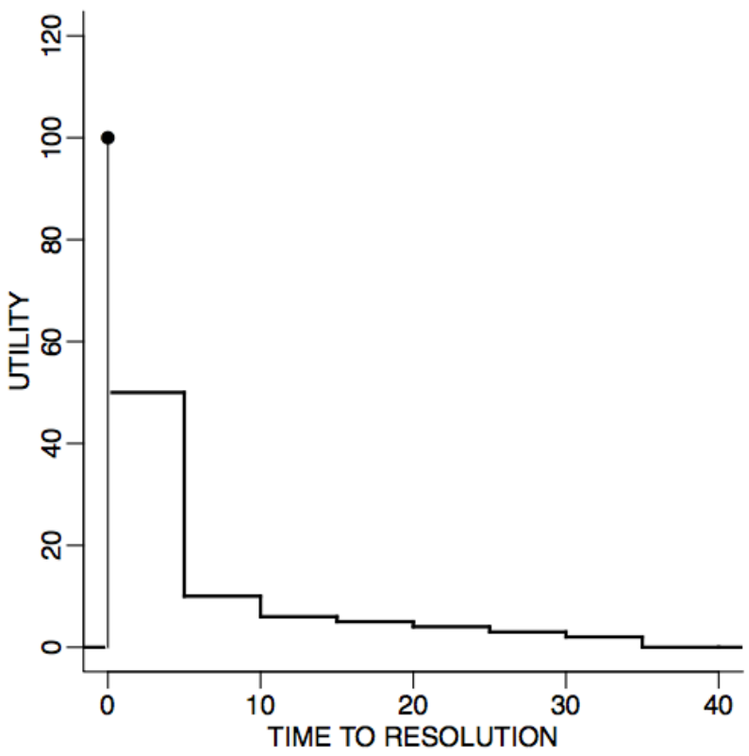
T (days)	0	5	10	15	20	25	30	35	≥ 40
Utility	100	50	10	6	5	4	3	2	0

Main Idea

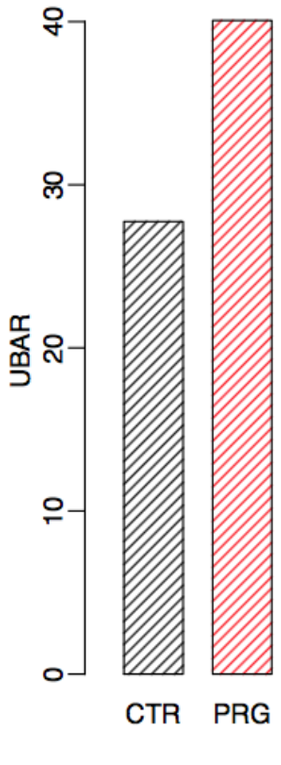
$$\bar{U}_j = \int u(Y) G_j(dY), \ j = 0, 1$$



(a)
G_0 and G_1



(b)
utilities u



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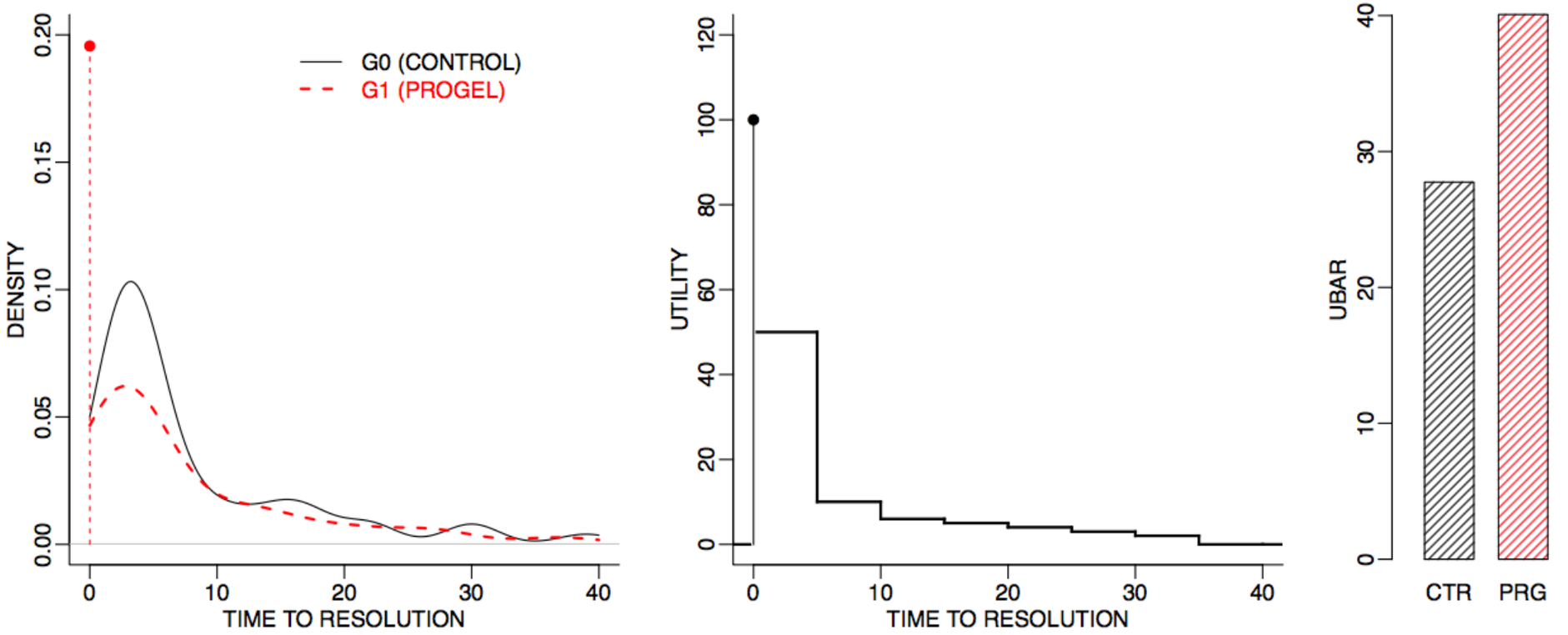

(a) G_0 and G_1 $\times$ (b) utilities u $=$ (c) $\overline{U}$.

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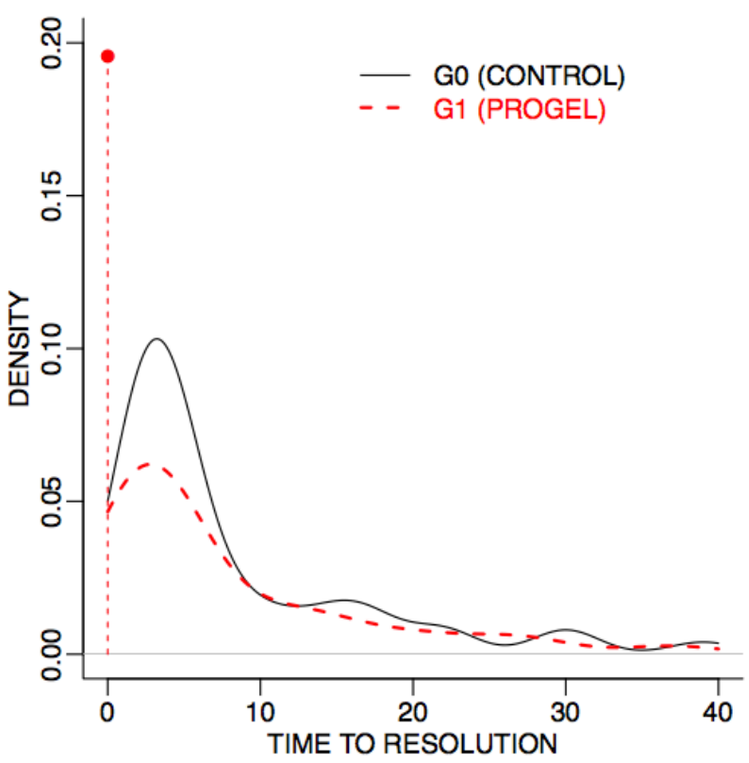

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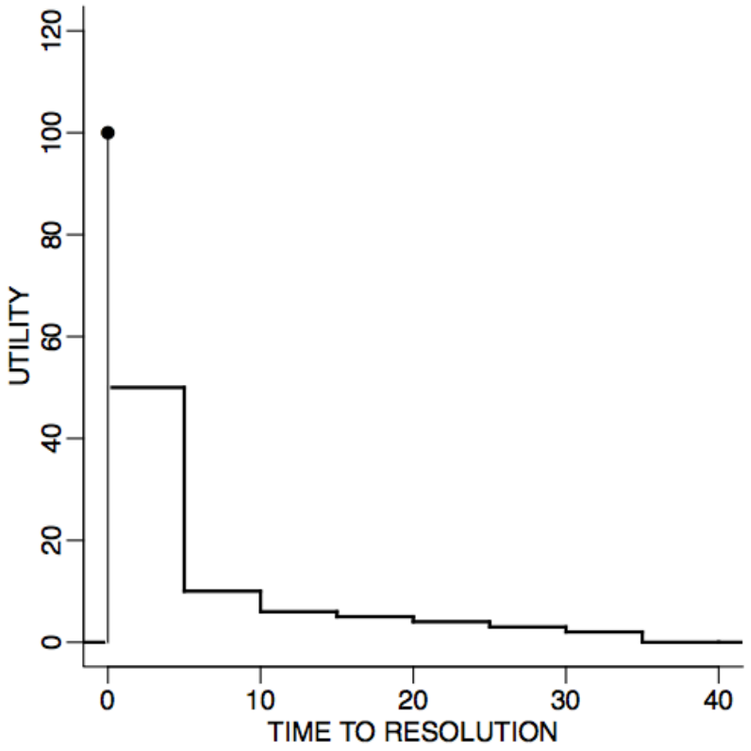

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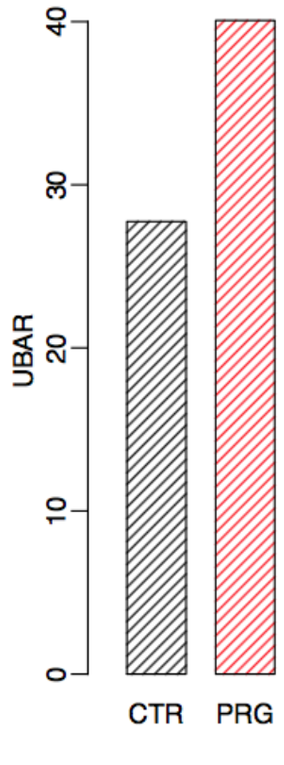

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Stick-breaking

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Posterior Inference:

- Likelihood: $p(y \mid F) = F$
- Prior: $F \sim \text{DP}(\alpha, F_0)$
- Posterior: $p(F \mid y) = \text{DP}(\alpha + 1, F^*)$ with

$$F^* = \frac{\alpha F_o + \delta_y}{\alpha + 1}.$$

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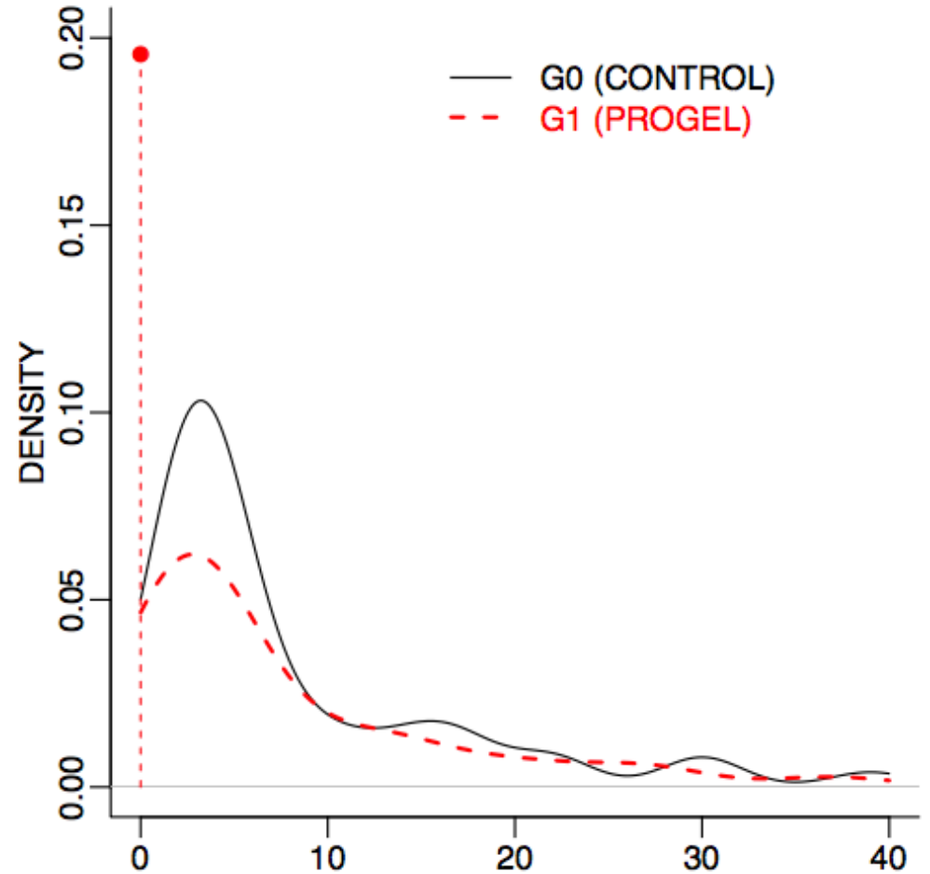

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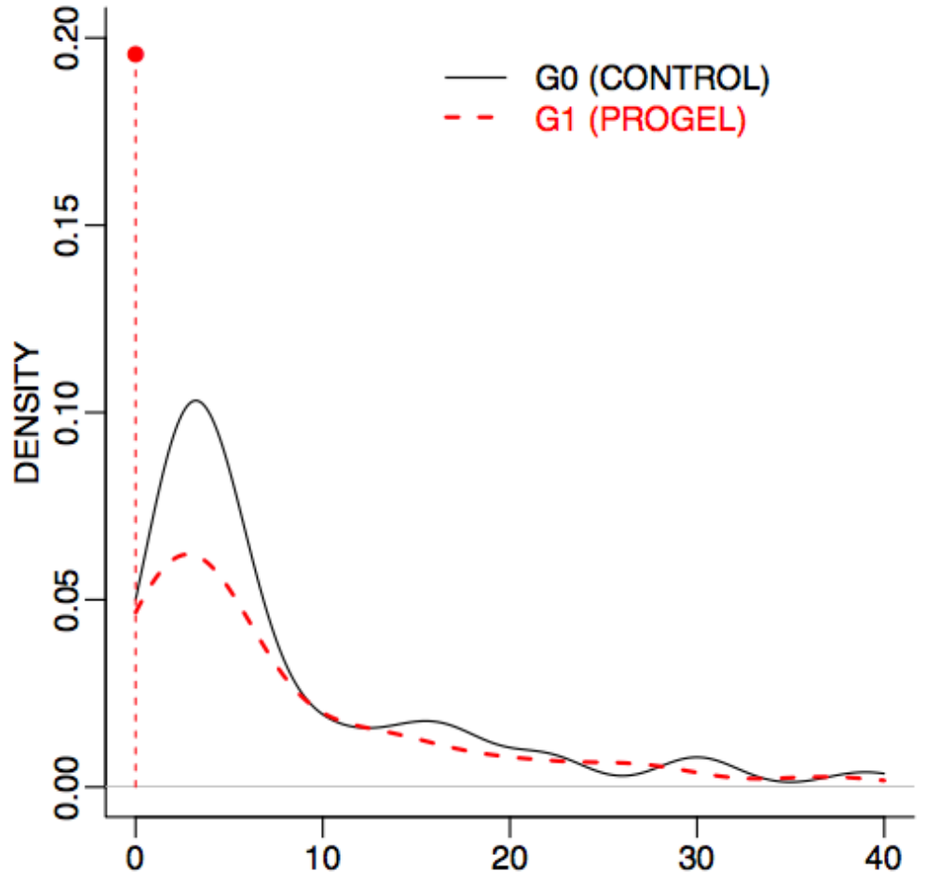

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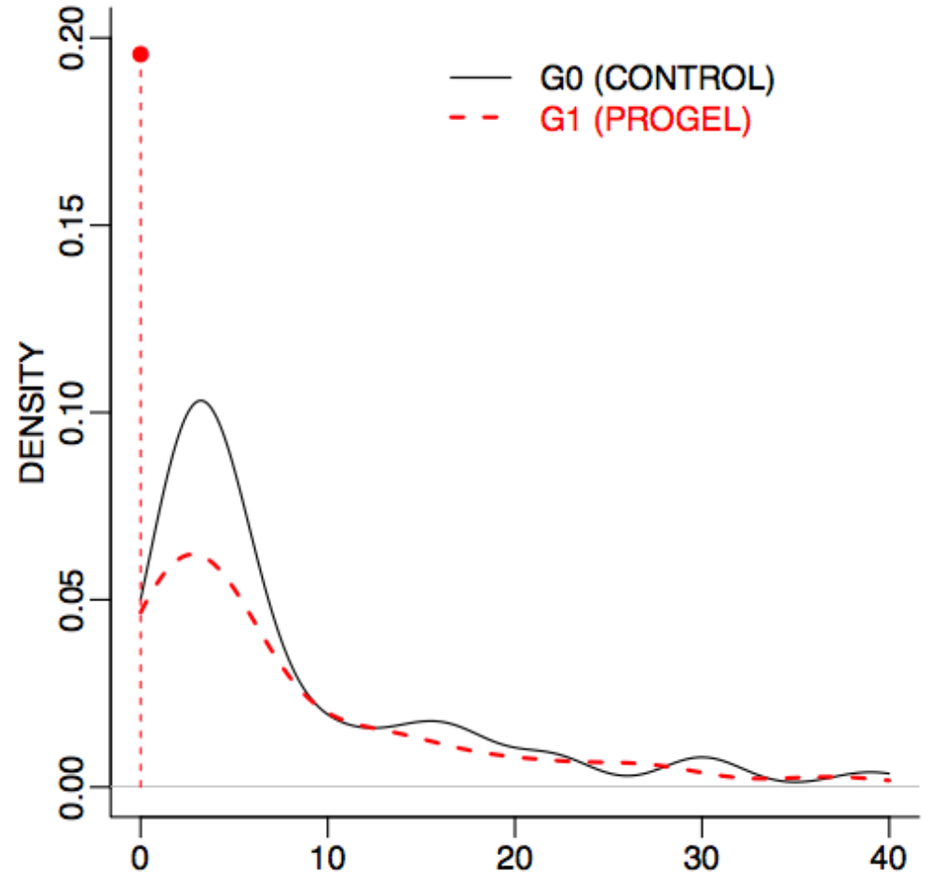

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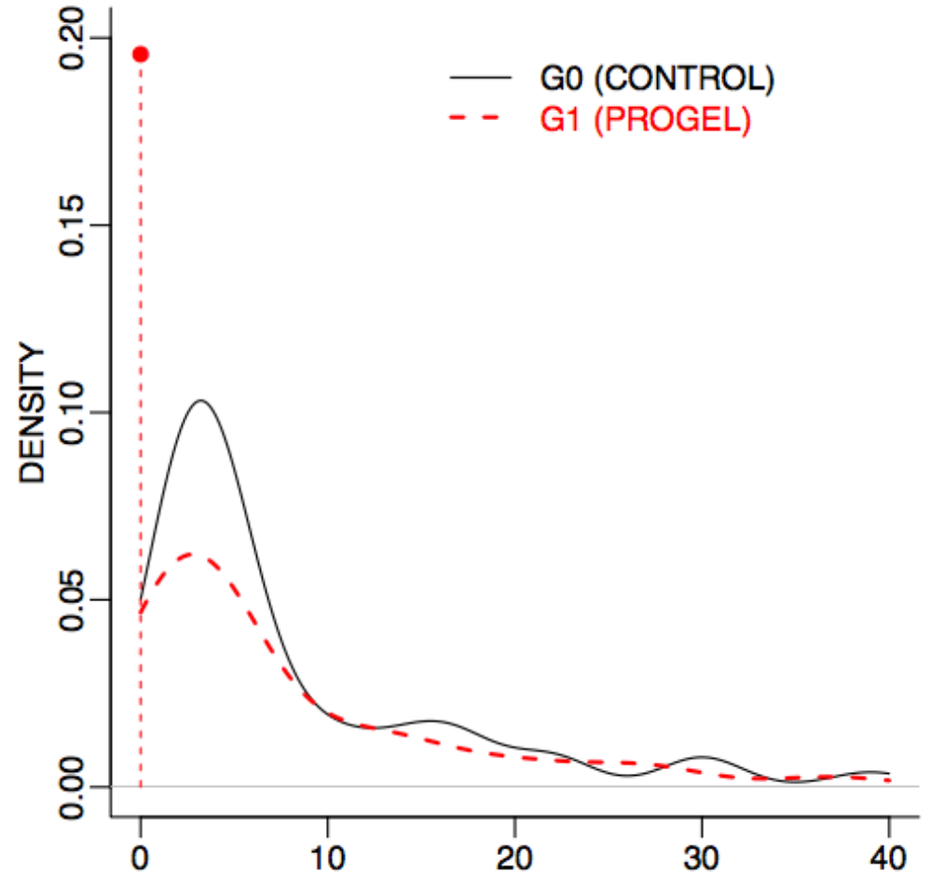

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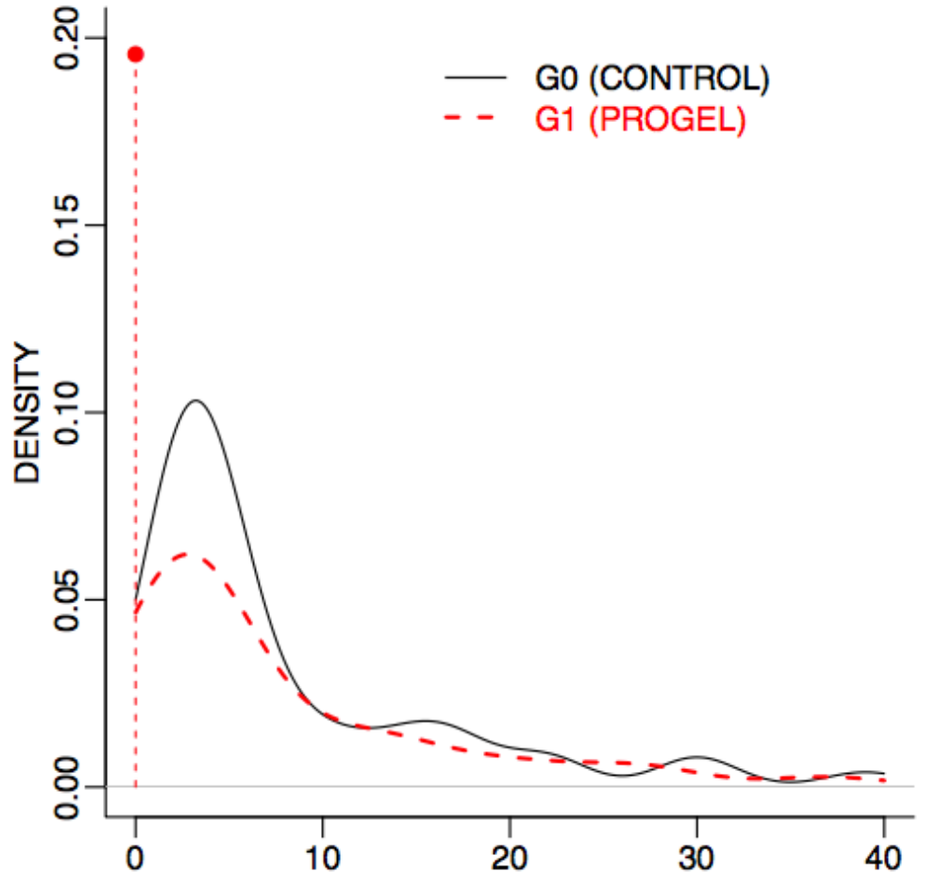

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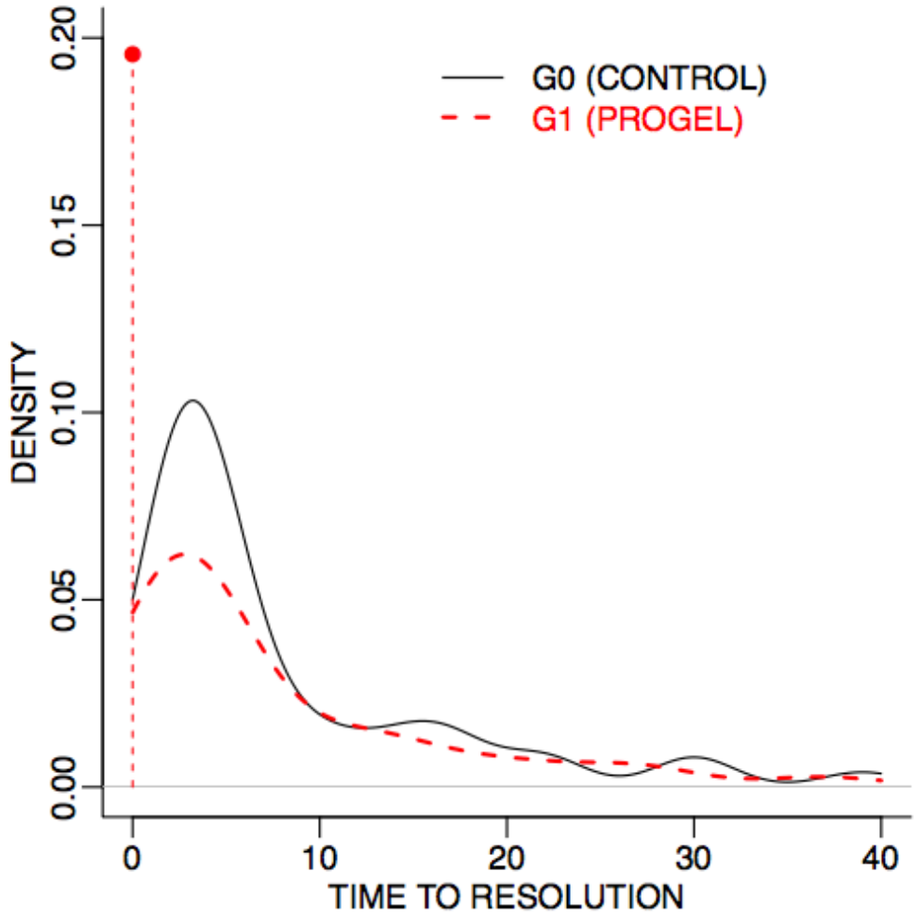

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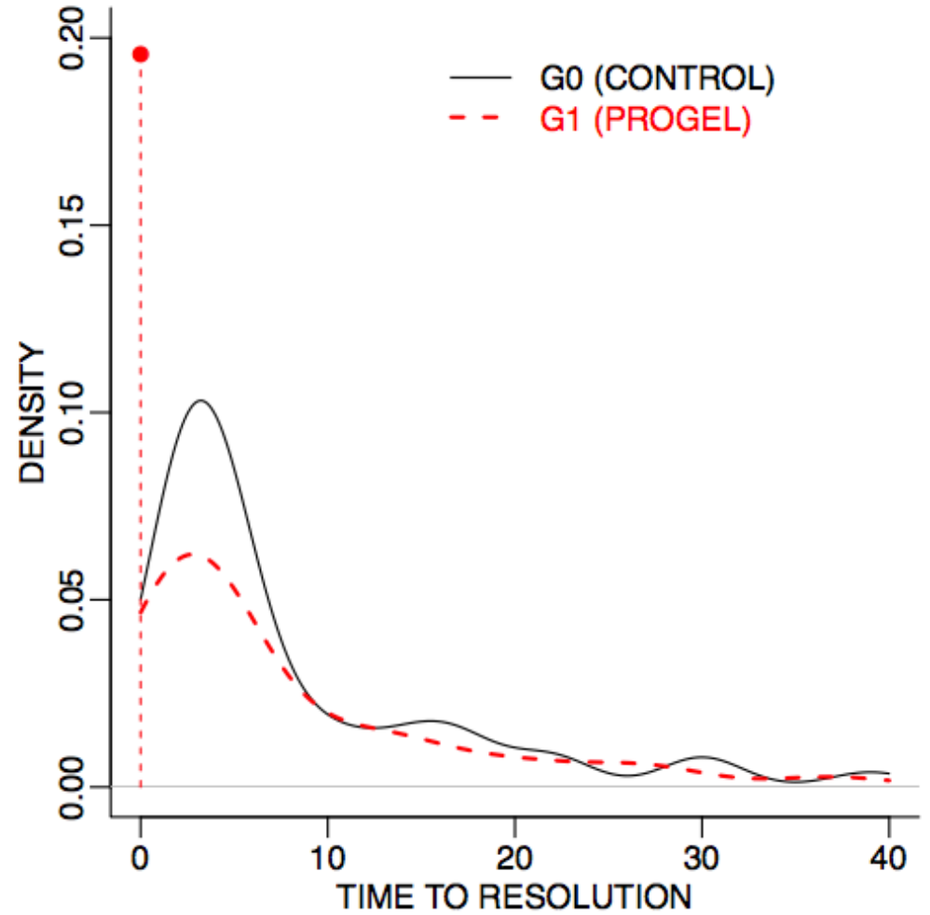

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Further prior beliefs can be added.

Overview

Utility **BNP**

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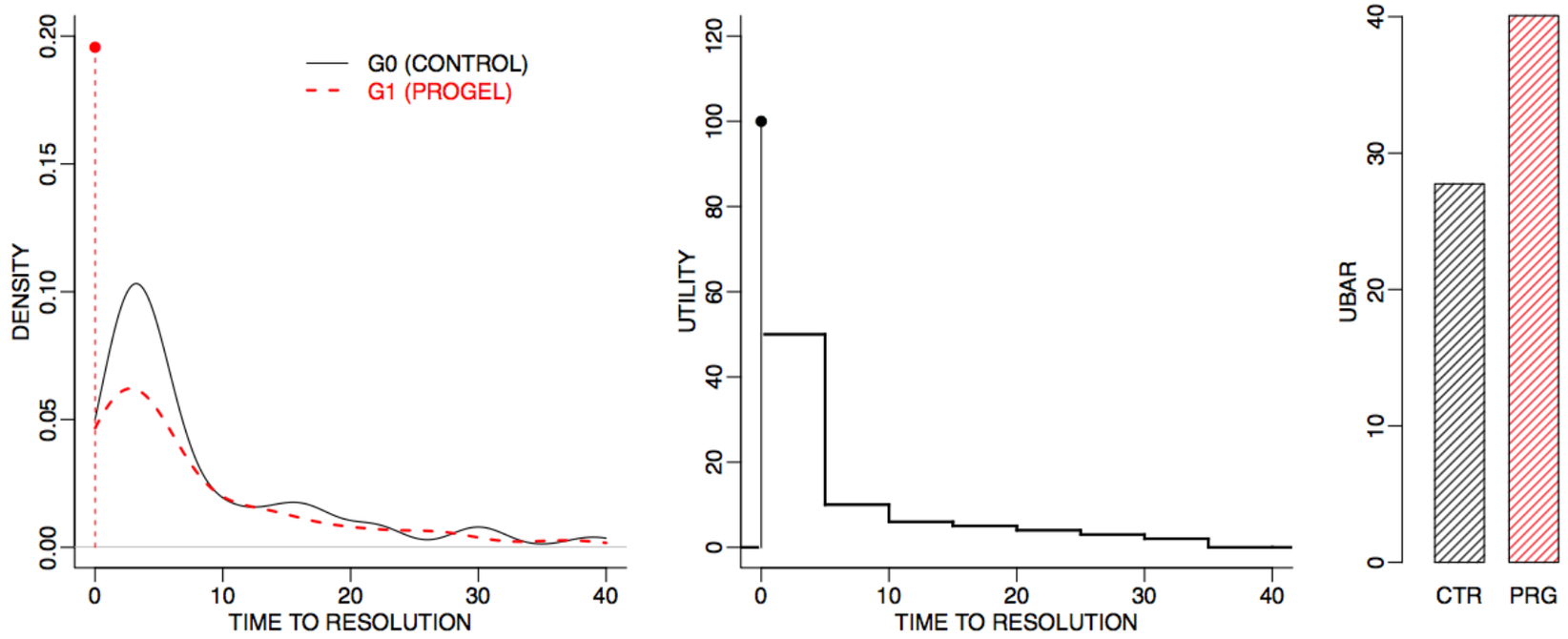

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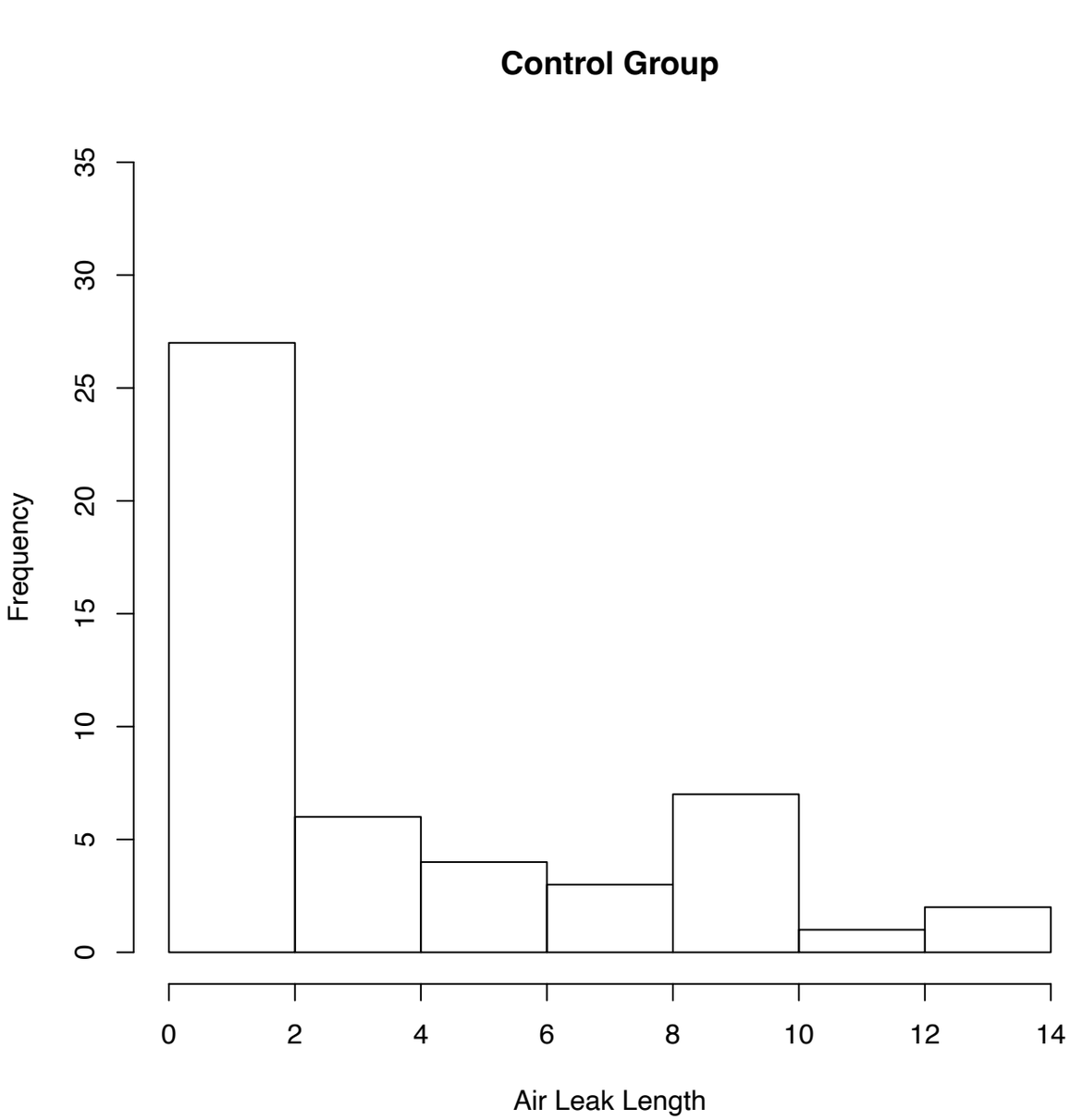
Trial Design: $Pr(\bar{U}_1 > \bar{U}_0 + \epsilon \mid \text{Data})$

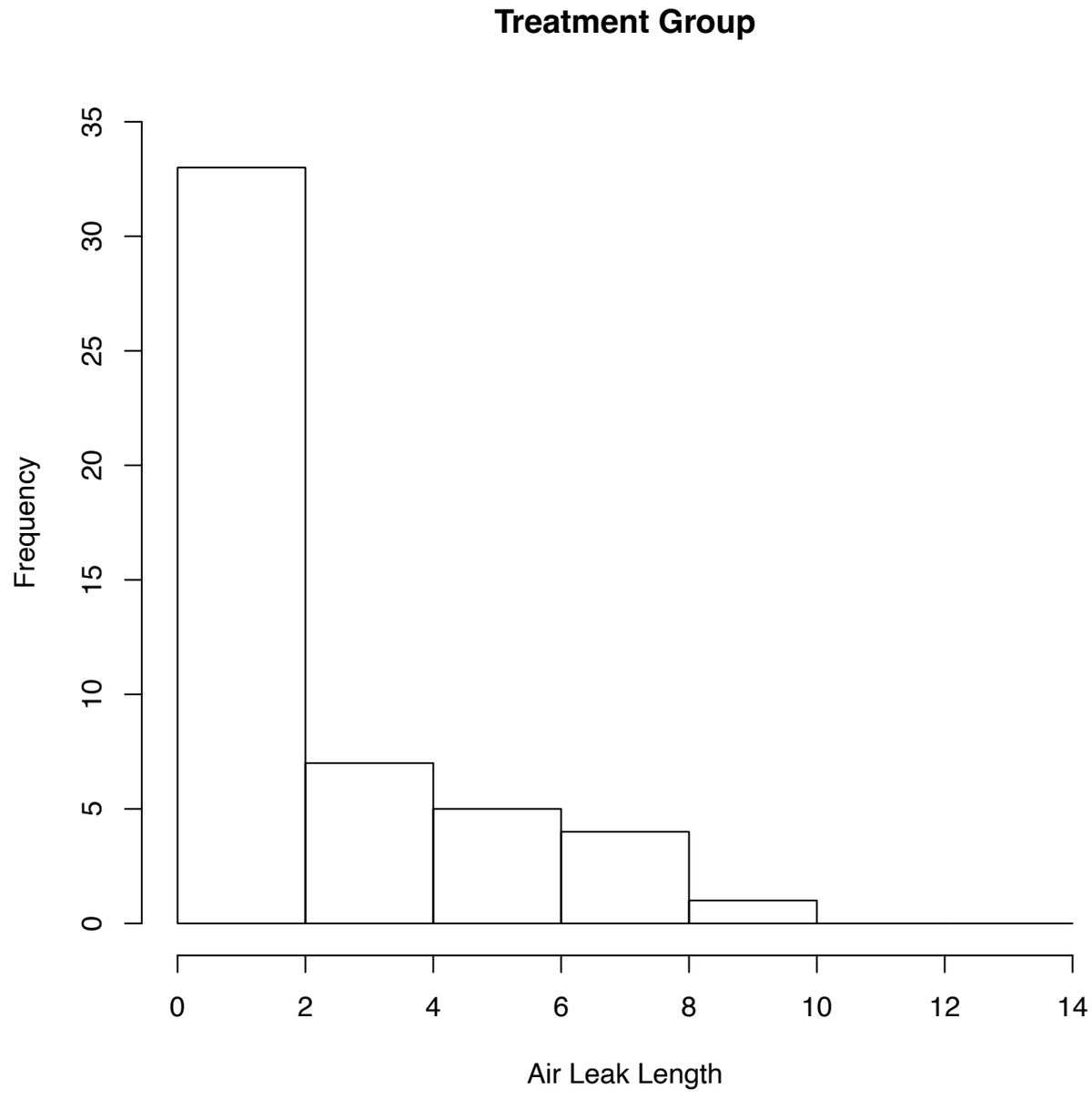
Xu et al., 2017

Simulation Study: Setup

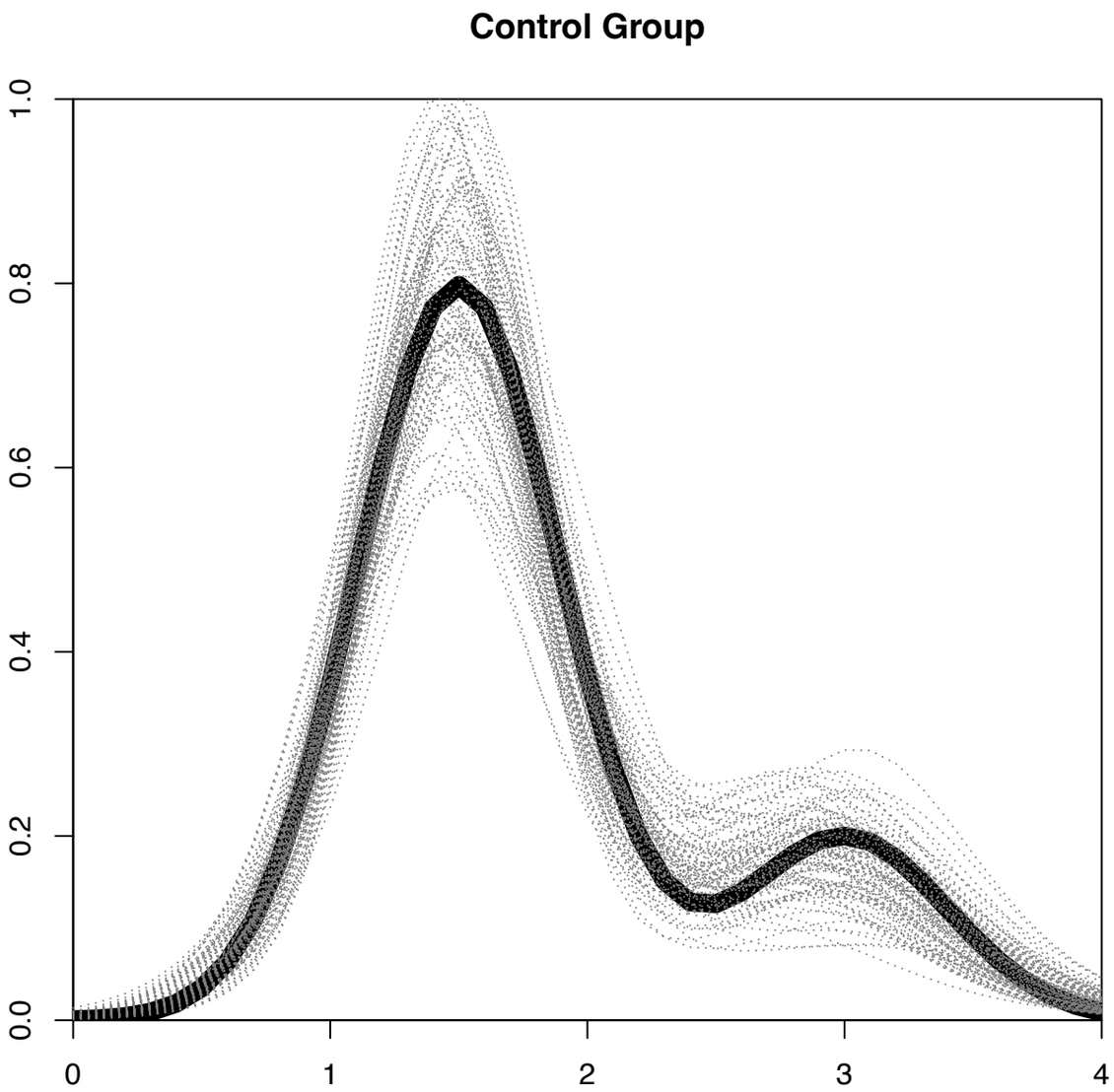
$$Y_{ji} \sim 0.8N(1.5, 0.3^2) + 0.2N(3, 0.3^2), j = 0$$

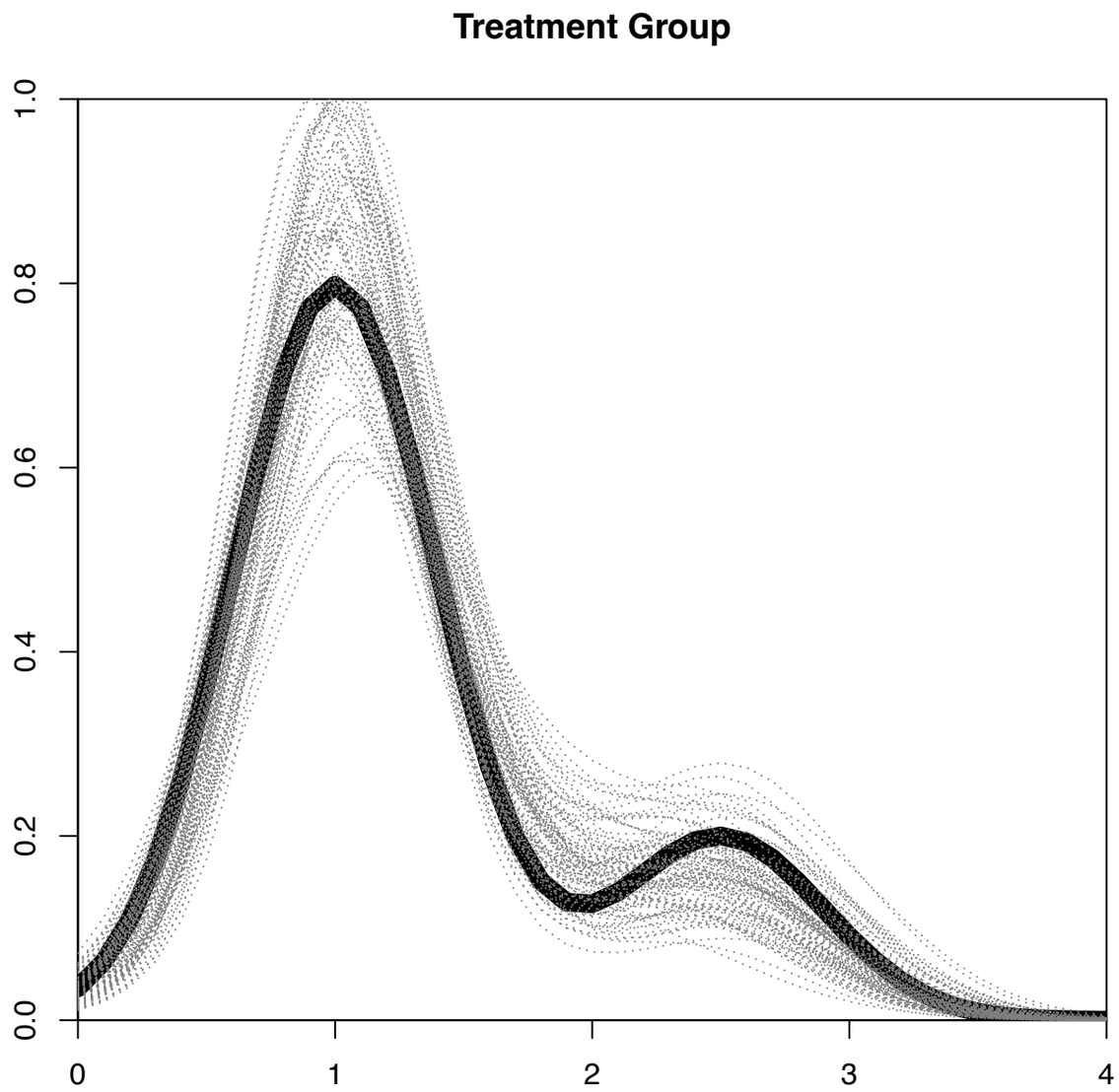
$$Y_{ji} \sim 0.8N(1, 0.3^2) + 0.2N(2.5, 0.3^2), j = 1$$





Simulation Study: Results





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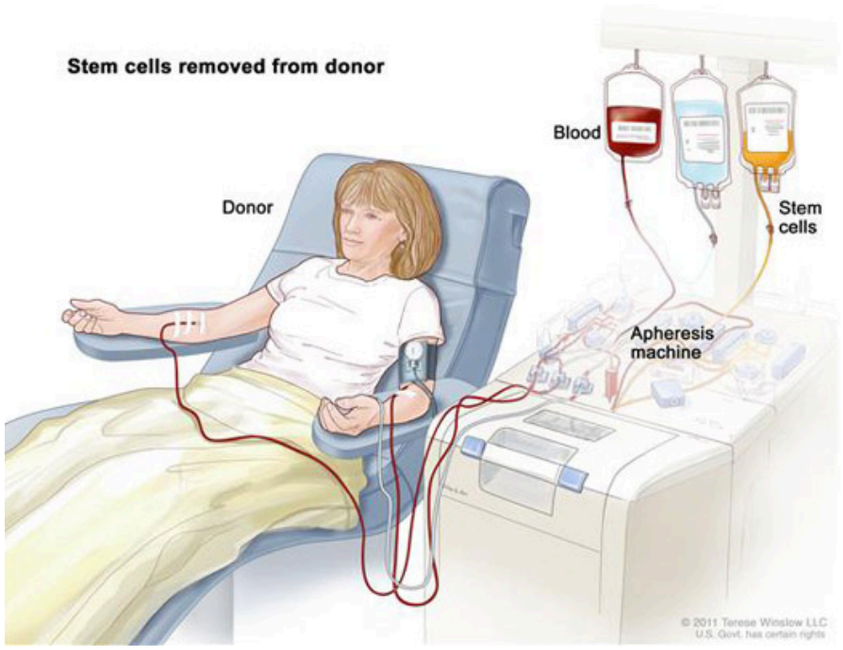
  - a convincing case for the need of a full probabilistic description of uncertainties on random probability measures

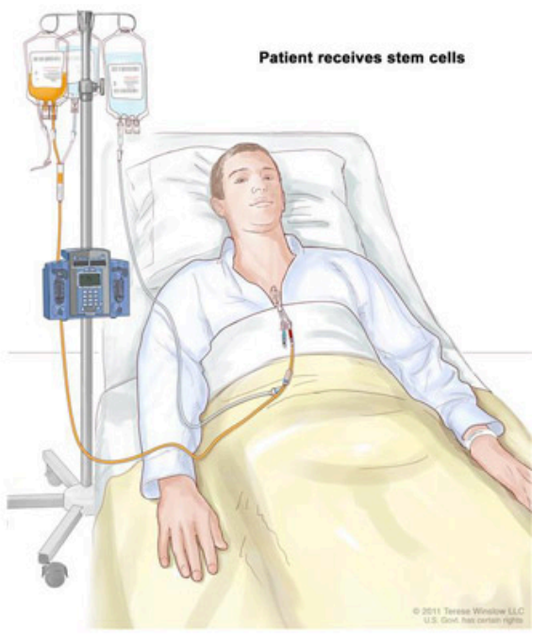
Outline

- **Part 1:** *Monday*
  - **Density estimation** for efficient clinical trial designs
  - **Regression** for precision dosing
- **Part 2:** *Wednesday*
  - **Clustering** for subgroup finding
  - **Latent feature models** for tumor heterogeneity
- **Part 3:** *Friday*
  - Estimating treatment effects from observational data

Background

Allogeneic Stem Cell Transplantation (alloSCT) is an aggressive therapy for various hematologic diseases, such as lymphocytic leukemia and non-Hodgkins lymphoma.





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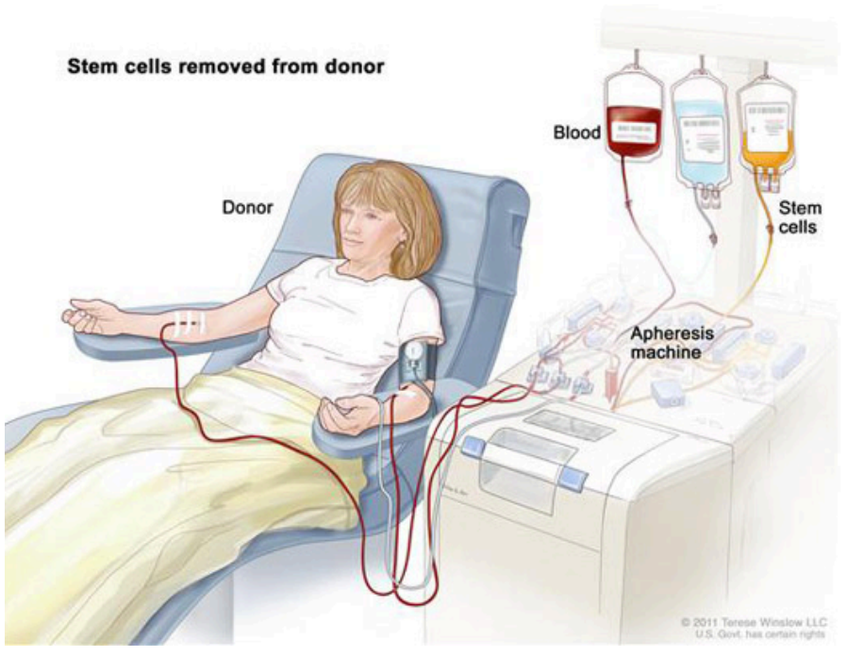

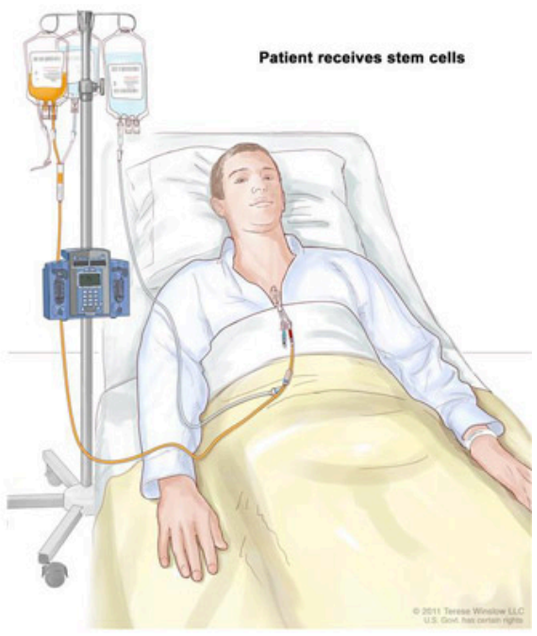

Busulfan

Background

Systemic busulfan exposure, characterized by area under the plasma concentration curve, AUC = the delivered dose, is strongly associated with clinical outcome.

- AUC too high $\Rightarrow$ High risks of severe toxicity.
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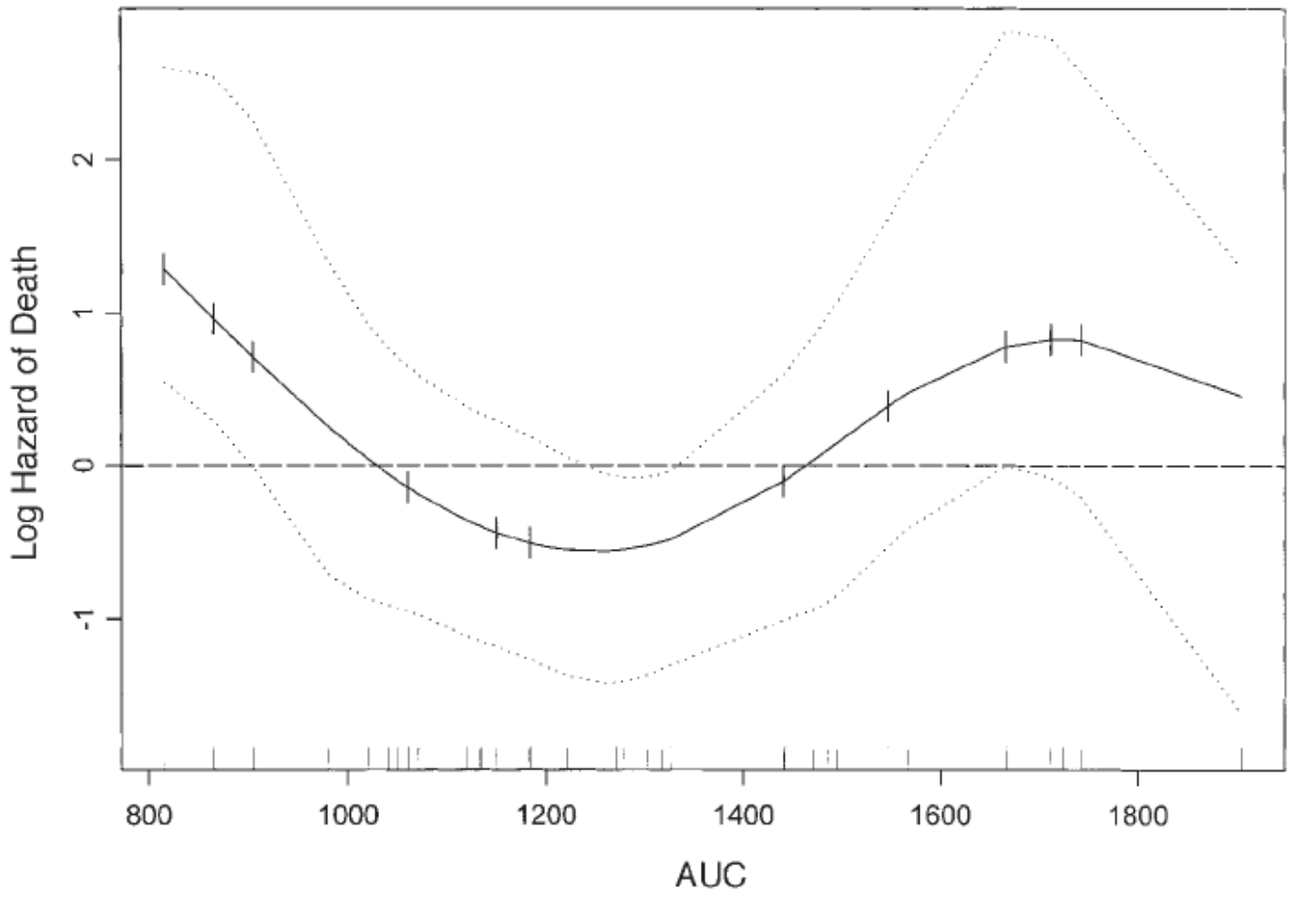
- Current practice: busulfan intravenous (IV), improving its bioavailability and delivered dosing accuracy

Background

Cox proportional hazard model (details later):



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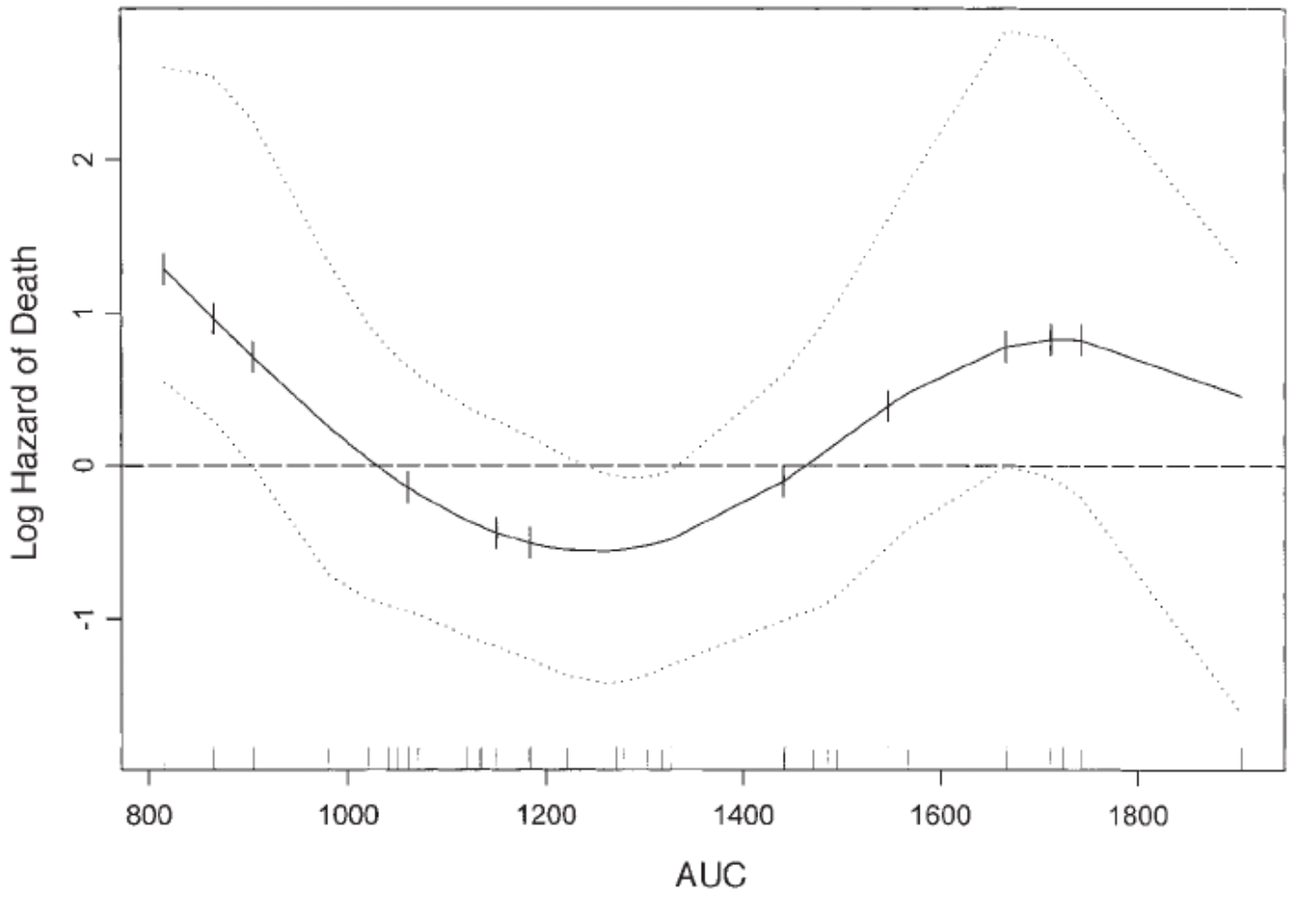

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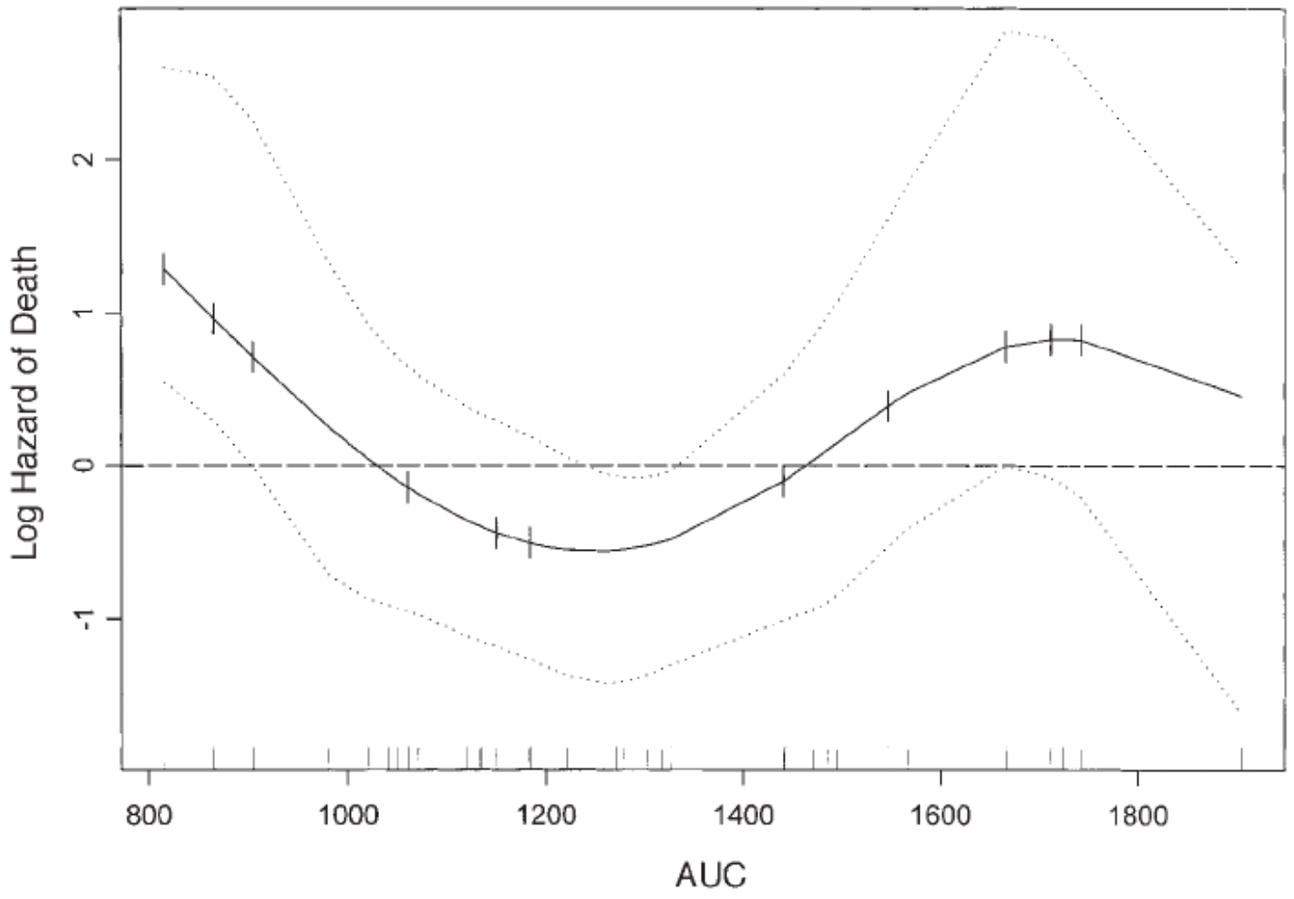

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Bartelink et al. (2016) reported an optimal AUC range (19100 to 21200 μMol-min) when treating children and young adults.

Personalizing Targeted IV Busulfan Dose

Age and **disease status at alloSCT** (CR = Complete Remission, No CR = Active Disease) are strongly predictive of T = survival time.

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Historical Data: 151 alloSCT patients who received a standard 4-day preparative regimen of IV busulfan.

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- The historical dataset has only 151 patients.

Potential Payoff of this Statistical Analysis

Challenges and Potential Benefits

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- Identifying and characterizing possibly nonlinear [Age × AUC] or [CR ×AUC] or [Age ×CR ×AUC] interactive effects on T.
- The historical dataset has only 151 patients.

Potential Payoff of this Statistical Analysis

If optimal AUC intervals based on (Age, CR) can be estimated, $E(T \mid \text{Age}, \text{CR}, \text{AUC})$ can be increased for future patients by making this personalized IV busulfan dosing in alloSCT standard clinical practice.

Traditional Survival Models

Event time data, usually involving censoring.

- Survival time: T
- Censoring time: C
- Censoring indicator: $\delta = I(T \leq C)$
- Observed data: (Y, C, δ), where $Y = min(T, C)$

Traditional Survival Models

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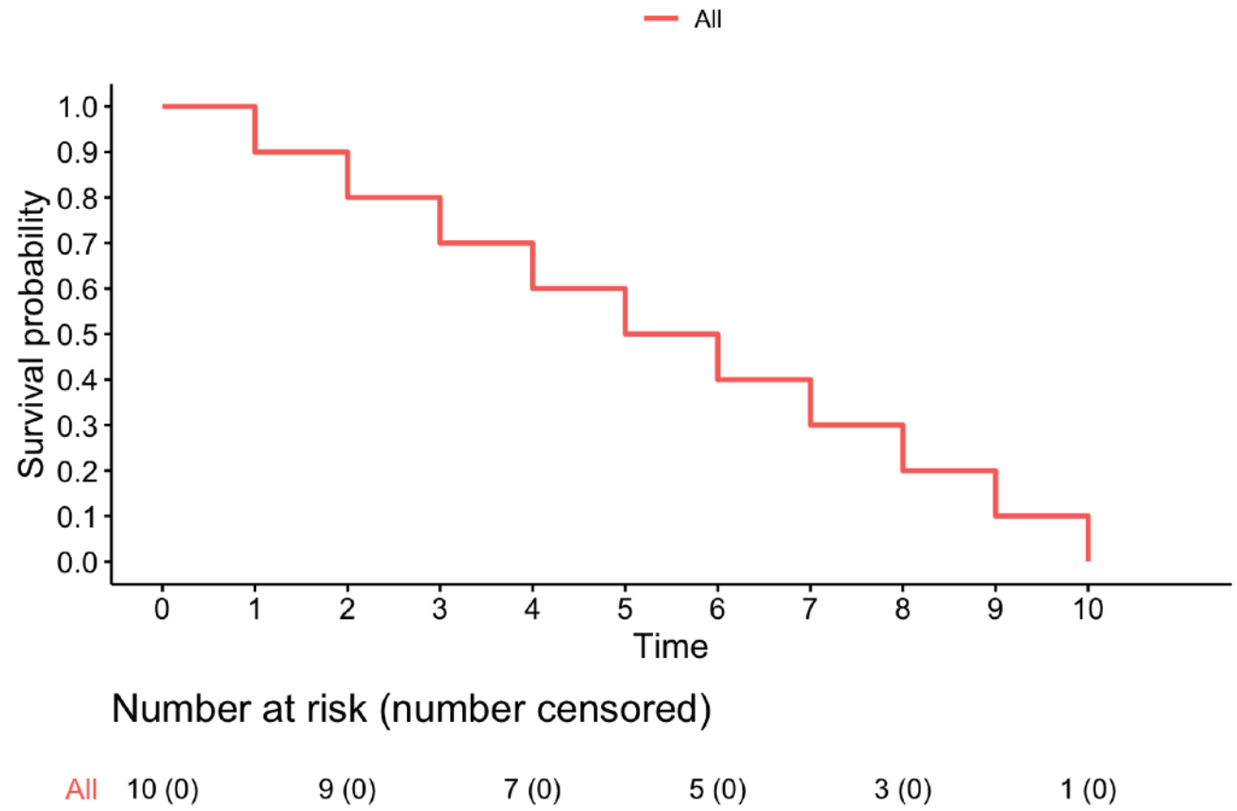
$$\Lambda(t) = \int_0^t \lambda(u)du = -\log S(t) .$$

Traditional Survival Models

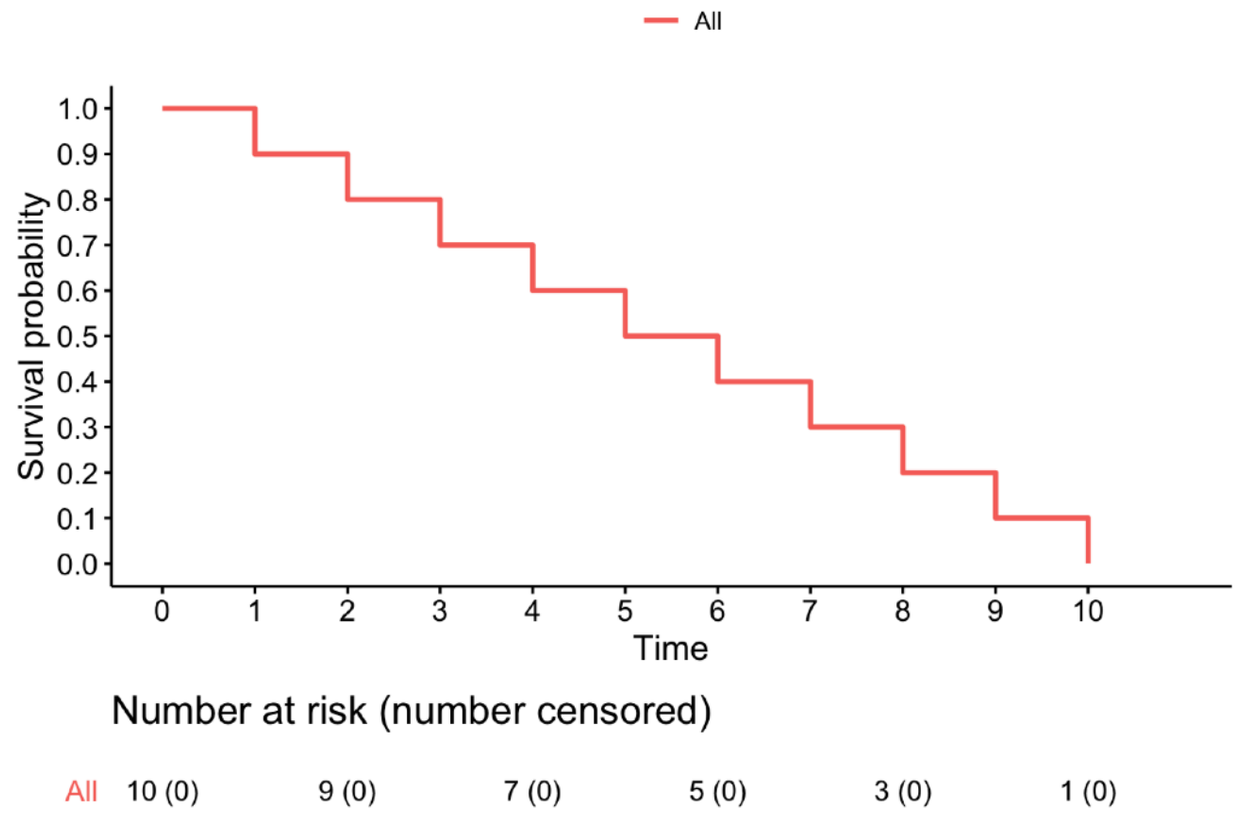
Kaplan–Meier estimator



Traditional Survival Models

Kaplan–Meier estimator

$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$



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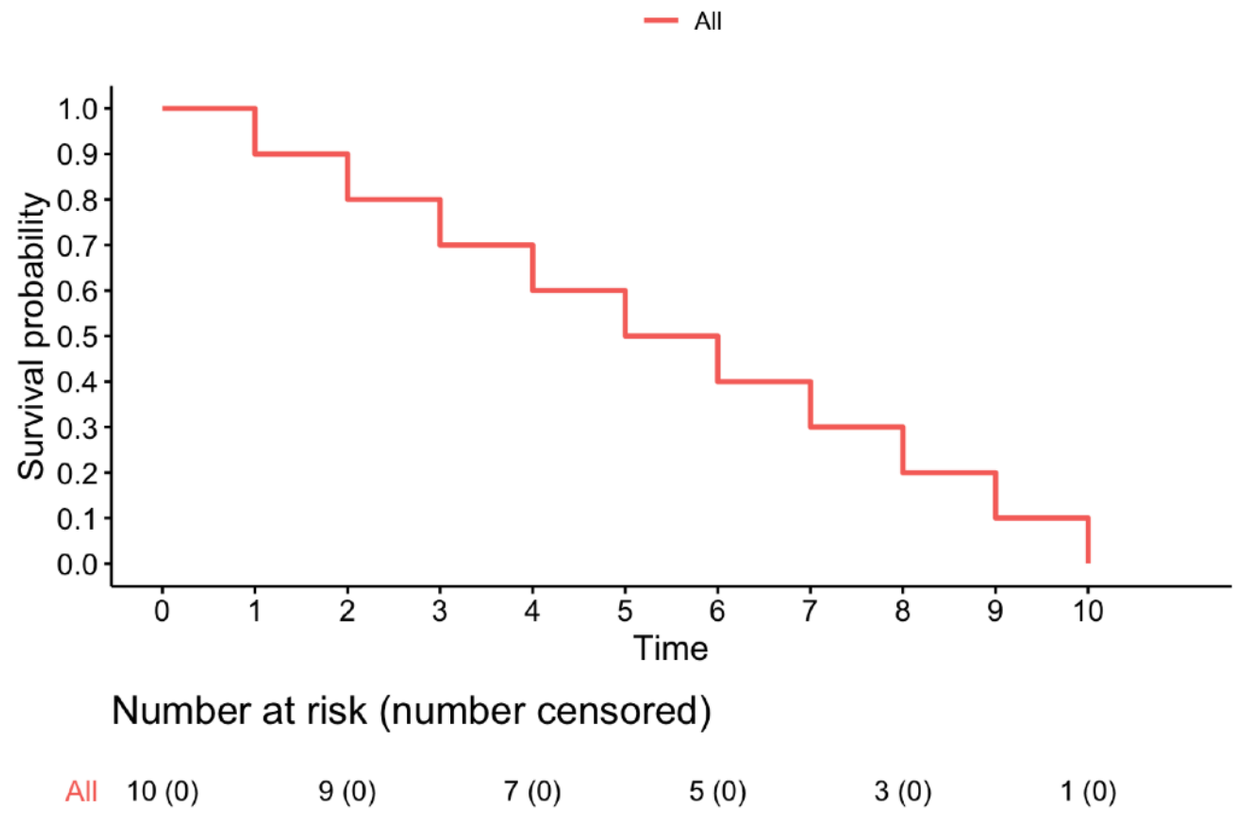

t_i: time when at least one event happened

d_i: the number of events (e.g., death) that happened at time t_i

n_i: the *individuals known to have survived* (have not yet had an event or been censored) up to time t_i

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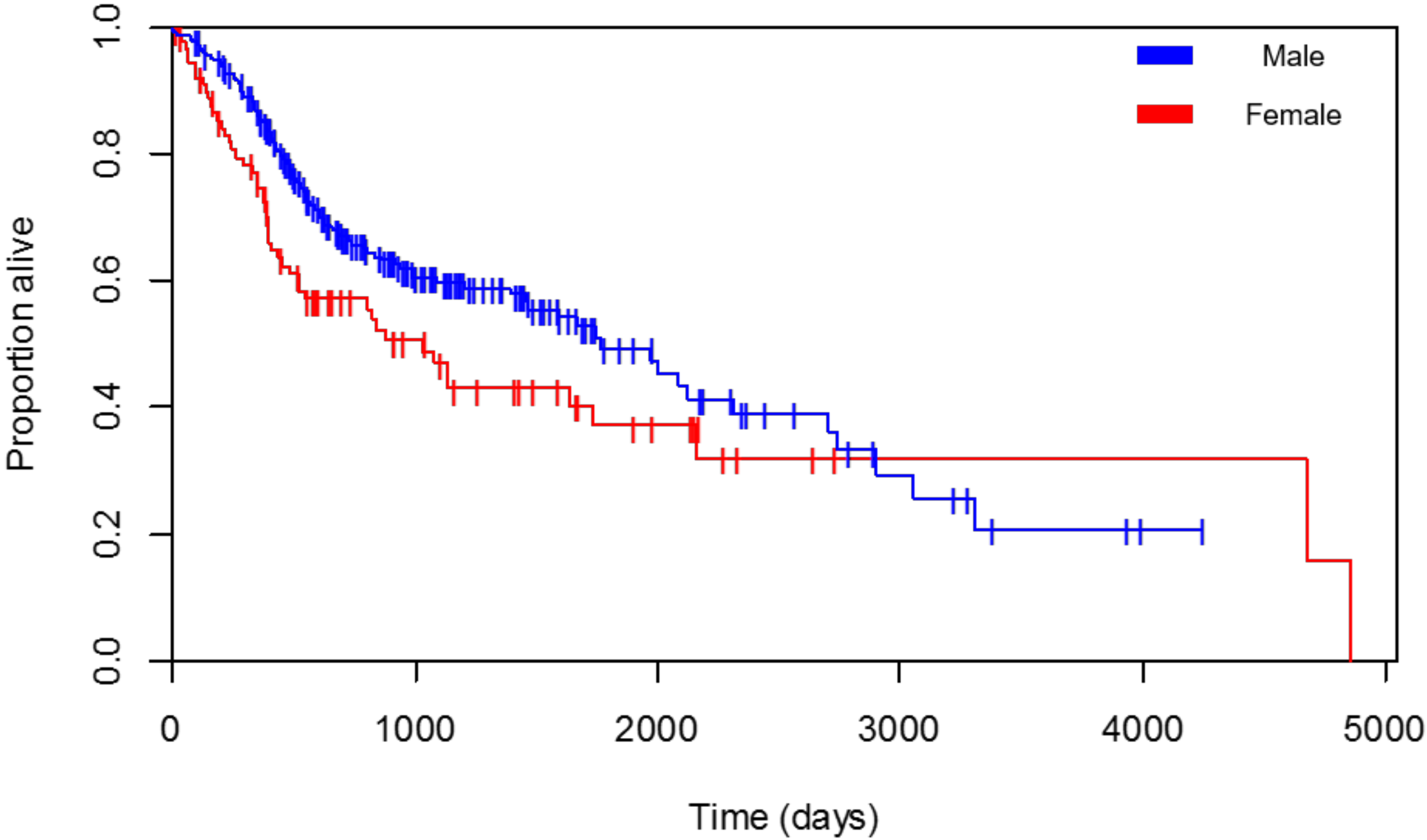
Note then that for two individuals with covariates x_1 and x_2, the ratio of hazard curves is constant, equal to $\exp((x_1 - x_2)'\beta)$, hence the name "proportional hazards."

Traditional Survival Models



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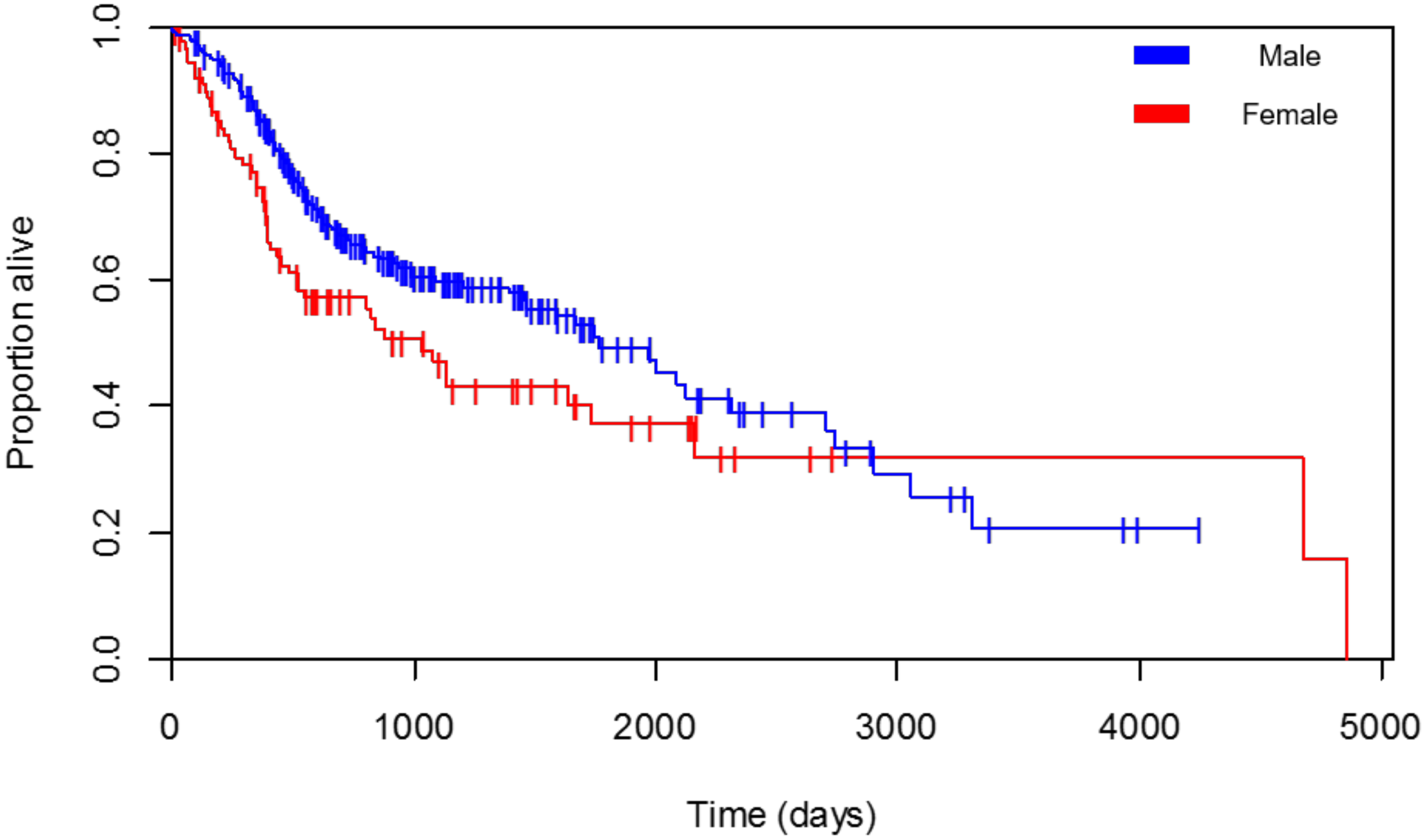

Cox Proportional Hazards (PH) model is not appropriate!

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- This is equivalent to a linear model for the log time-to-event T,

$$\log(T) = x'\beta + \epsilon, \text{where } p(\epsilon > \log t) = S_0(t)\,.$$

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$$C(\boldsymbol{Z}_i, \boldsymbol{Z}_\ell) = \sigma_0^2 \ \exp\left\{ -\sum_{d=1}^{D} \frac{(Z_{id} - Z_{\ell d})^2}{\lambda_d^2} \right\} + \delta_{i\ell} J^2.$$

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For right-censored survival data $D_n = \{Y_i, \delta_i, X_i\}_{i=1}^n$, the likelihood function has the usual form

$$L(\theta \mid D_n) = \prod_{i=1}^{n} \{f_{X_i}(Y_i \mid \theta)\}^{\delta_i} \{1 - F_{X_i}(Y_i \mid \theta)\}^{1-\delta_i}$$

Estimated **Optimal Targeted Intervals** of IV Busulfan AUC
Personalized For Given (CR Status, Age)

We define the predicted optimal IV busulfan targeted AUC for future patient $n+1$ with covariates $\boldsymbol{X}$ = (CR Status, Age, AUC) as

$$\widehat{AUC}_{n+1} = \text{argmax}_{AUC}\ E(Y_{n+1} \mid \boldsymbol{X}, \mathcal{D}_n)$$

Since the laboratory error in evaluation of AUC is up to about 6%, the optimal AUC interval for future patient $n+1$ is defined as

$$[\ 0.9\ \widehat{AUC}_{n+1},\quad 1.1\ \widehat{AUC}_{n+1}\ ]$$

Simulation Study: Setup

- Age: x_1 and AUC: x_2 were sampled with replacement from the actual ages and AUC values.
- CR: $x_3 \sim$ Bernoulli(0.5).
- Survival: $T \sim LN(\mu(\boldsymbol{x}_i), \sigma_0^2)$, where $\sigma_0 = 0.4$, and

$$\begin{aligned}\mu(\boldsymbol{x}_i) &= 4 - 0.1x_{i,1} + 0.7x_{i,2} + 0.3x_{i,3} - 0.07x_{i,2}^2 - 0.1x_{i,1}x_{i,2} \\ &\quad +0.2x_{i,2}x_{i,3} - 0.18x_{i,1}x_{i,2}x_{i,3}\end{aligned}$$

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Simulation Study

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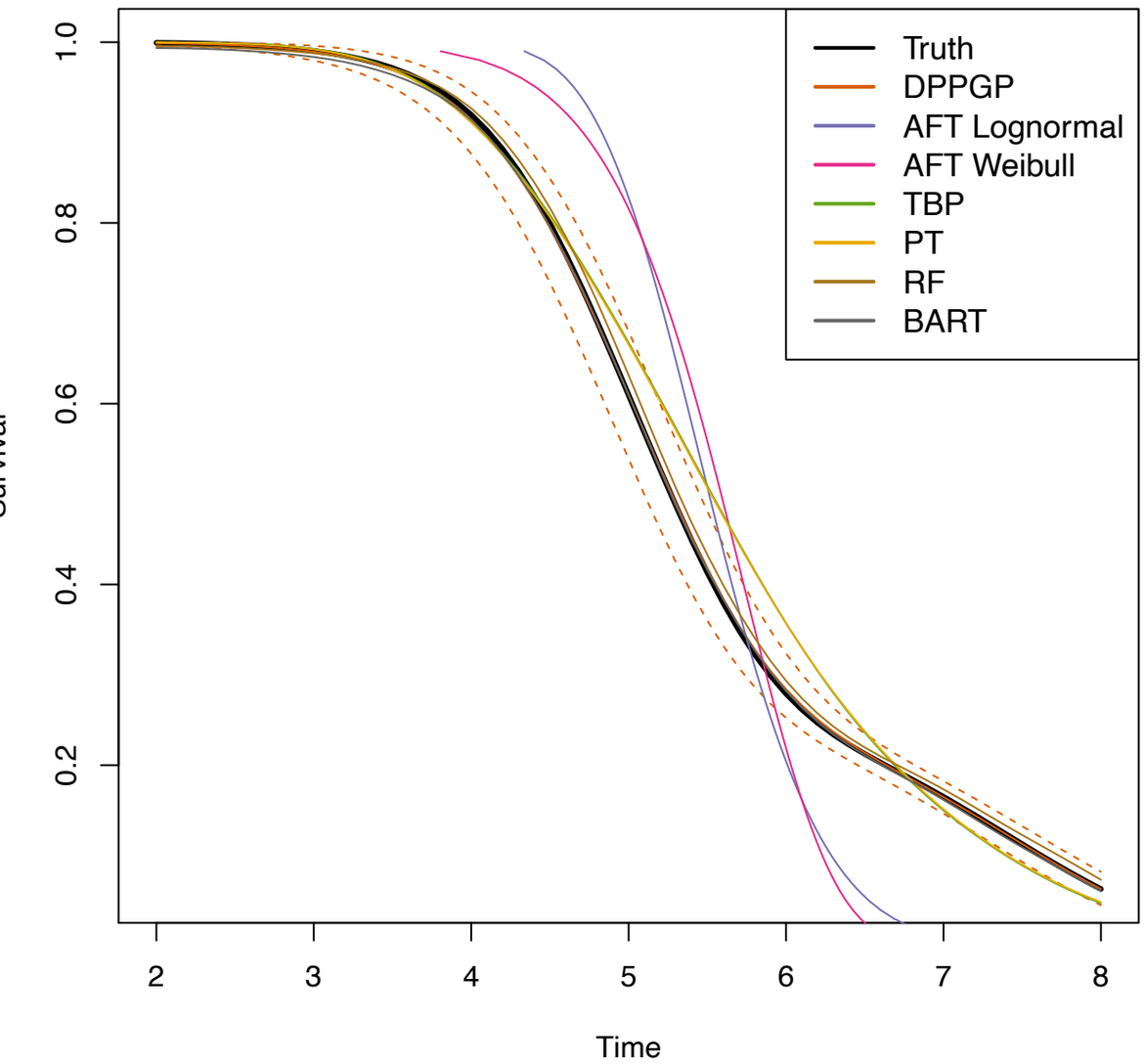
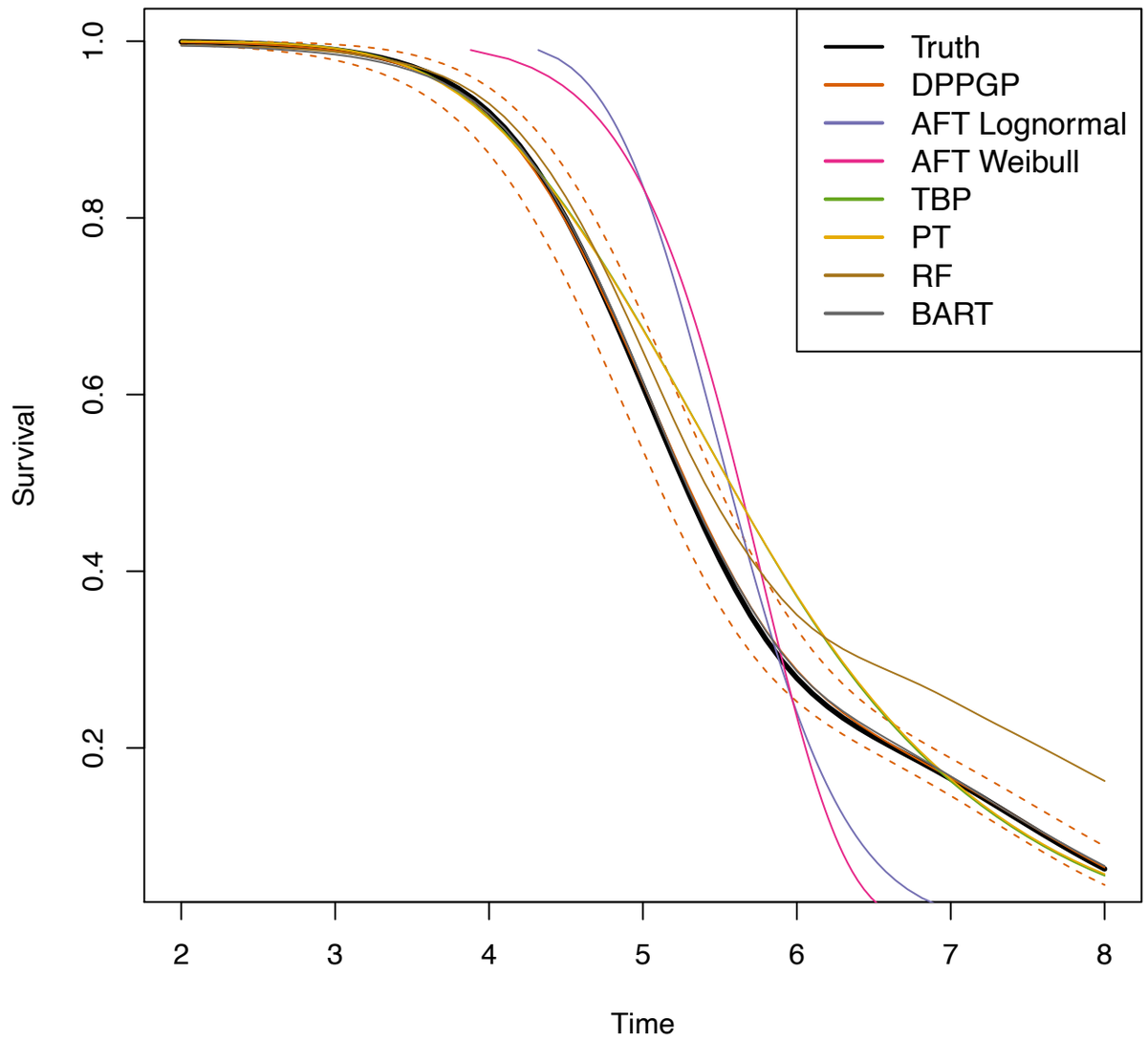


n=200 with 25% censoring



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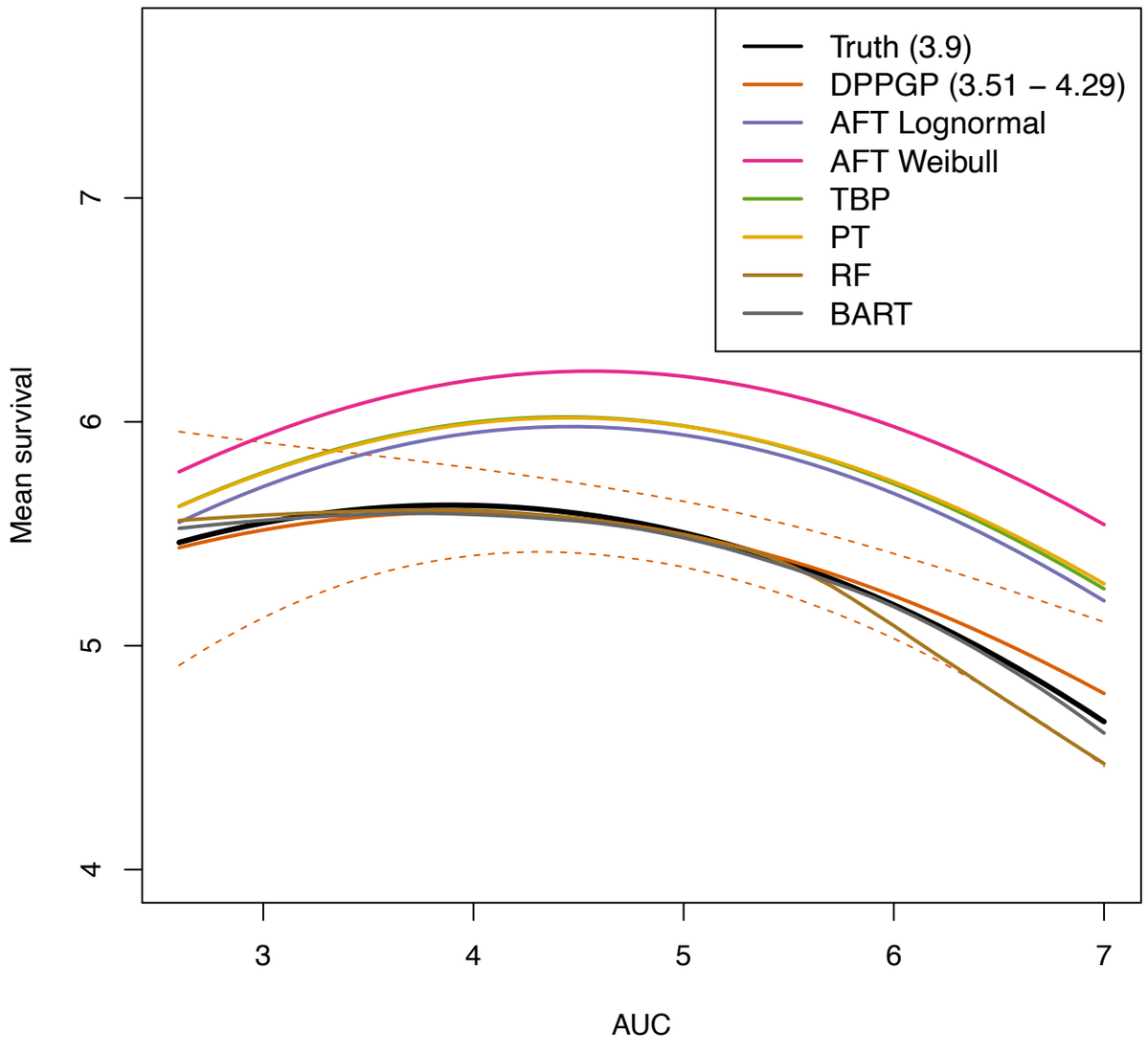
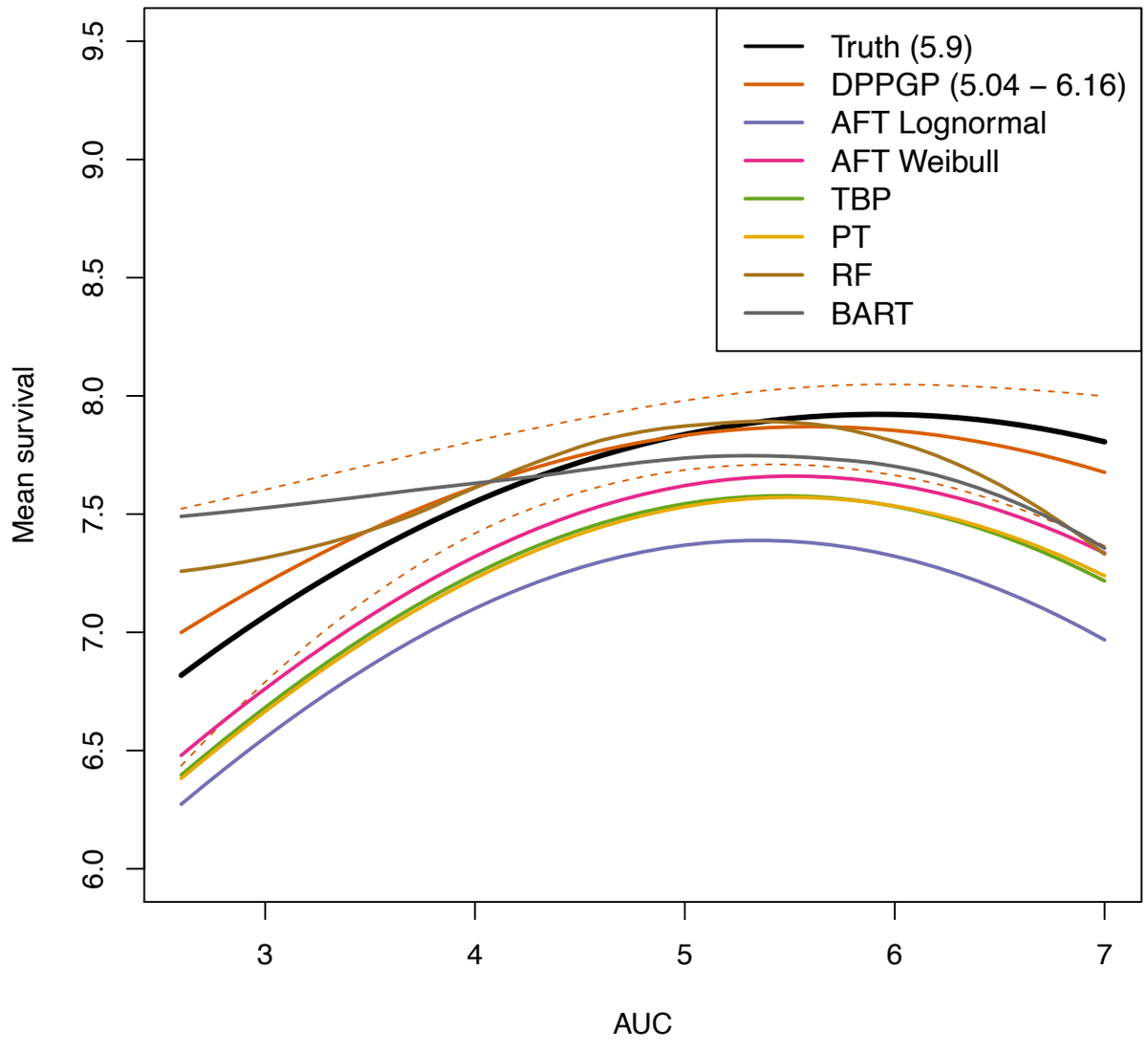


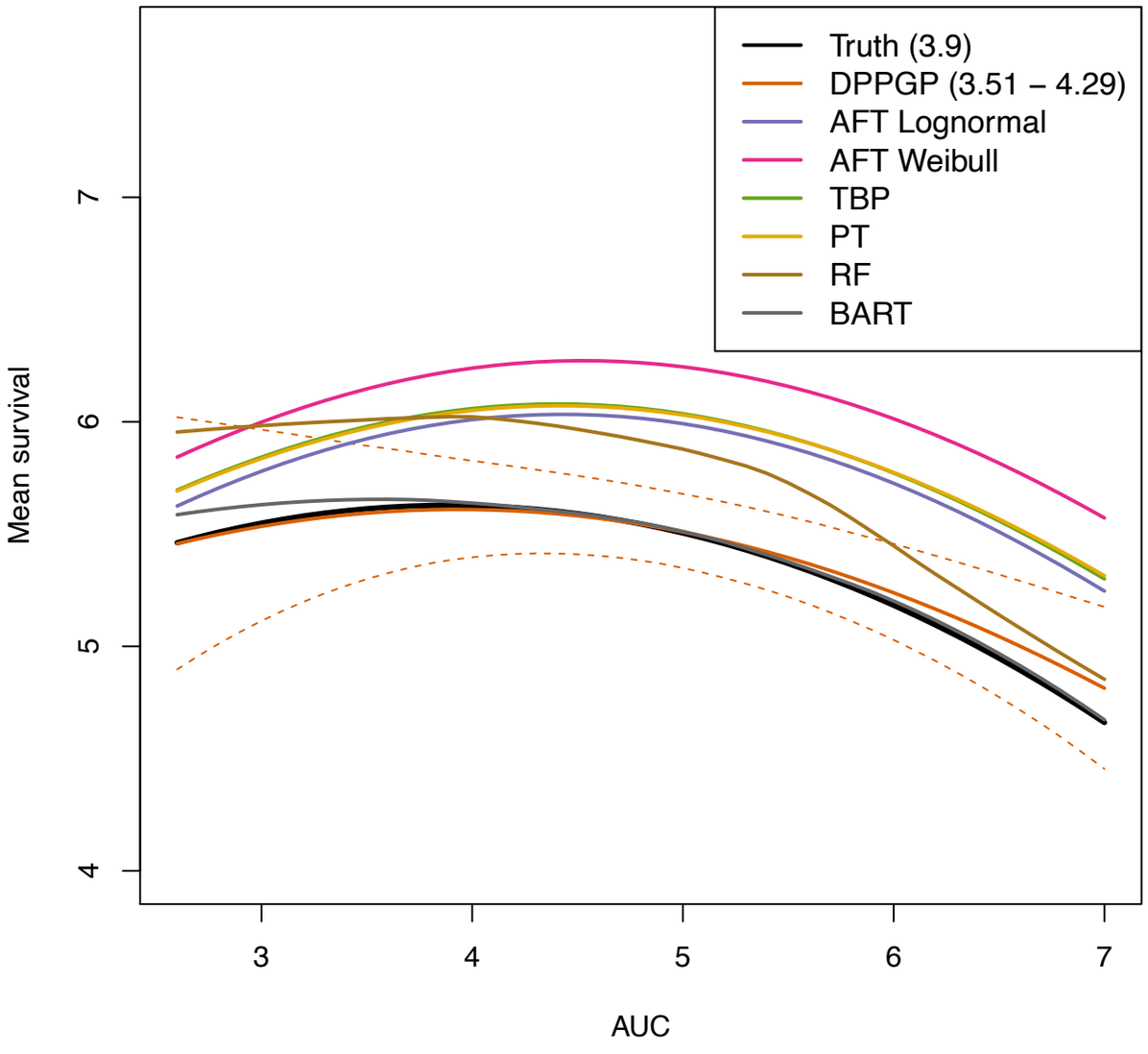
CR=0



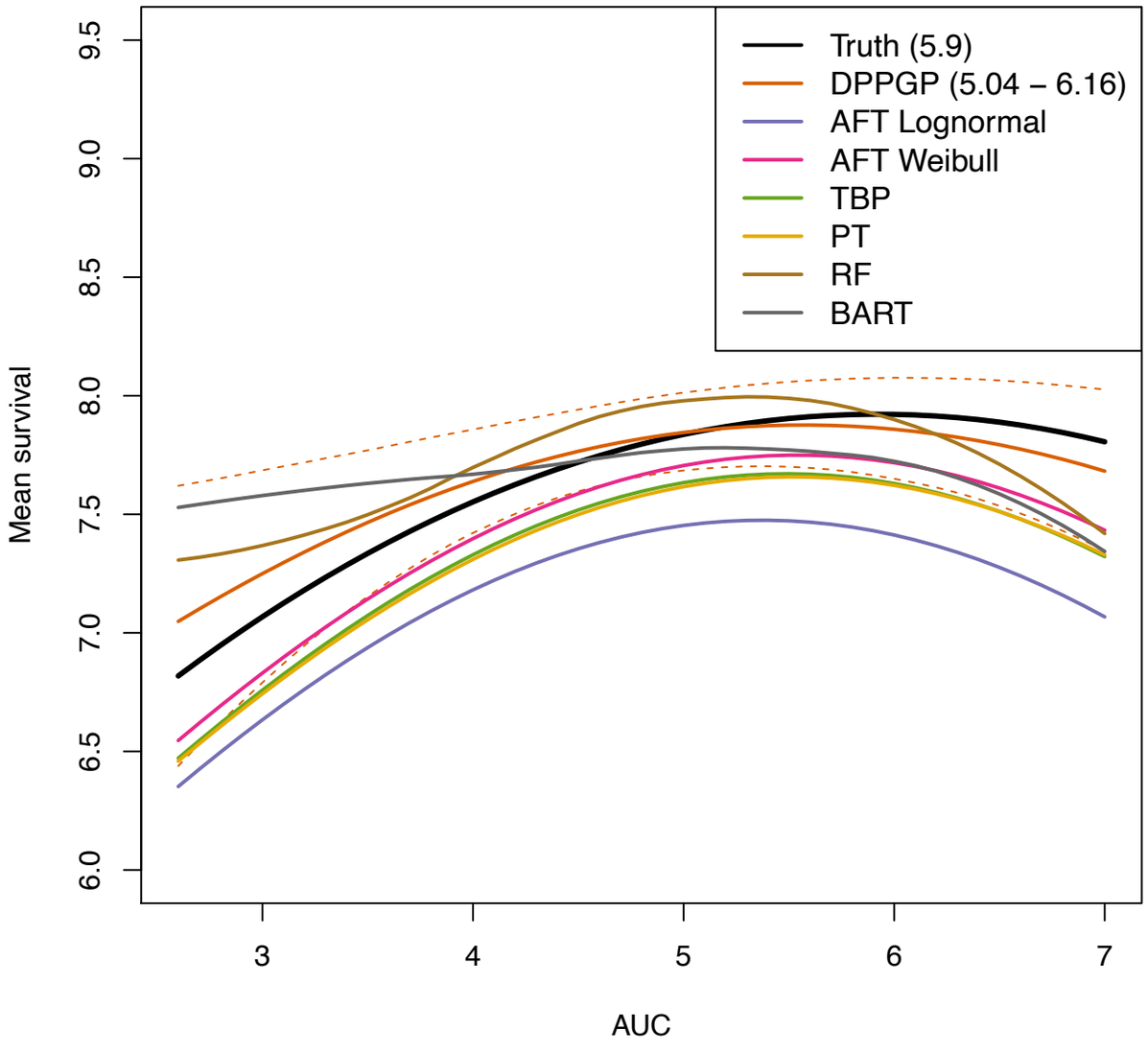
CR=1

Simulation Study

n=200 with 25% censoring

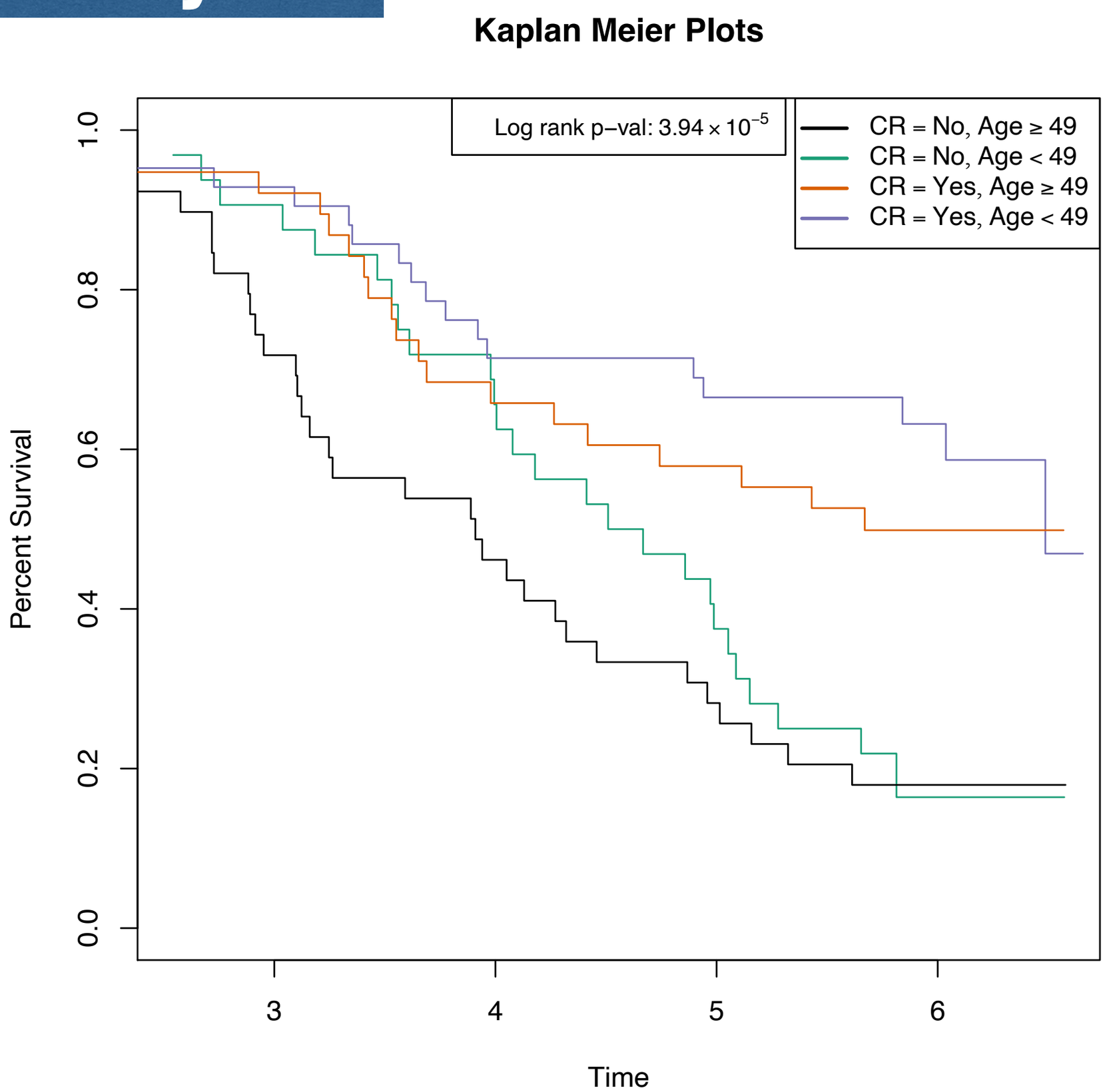


CR=0



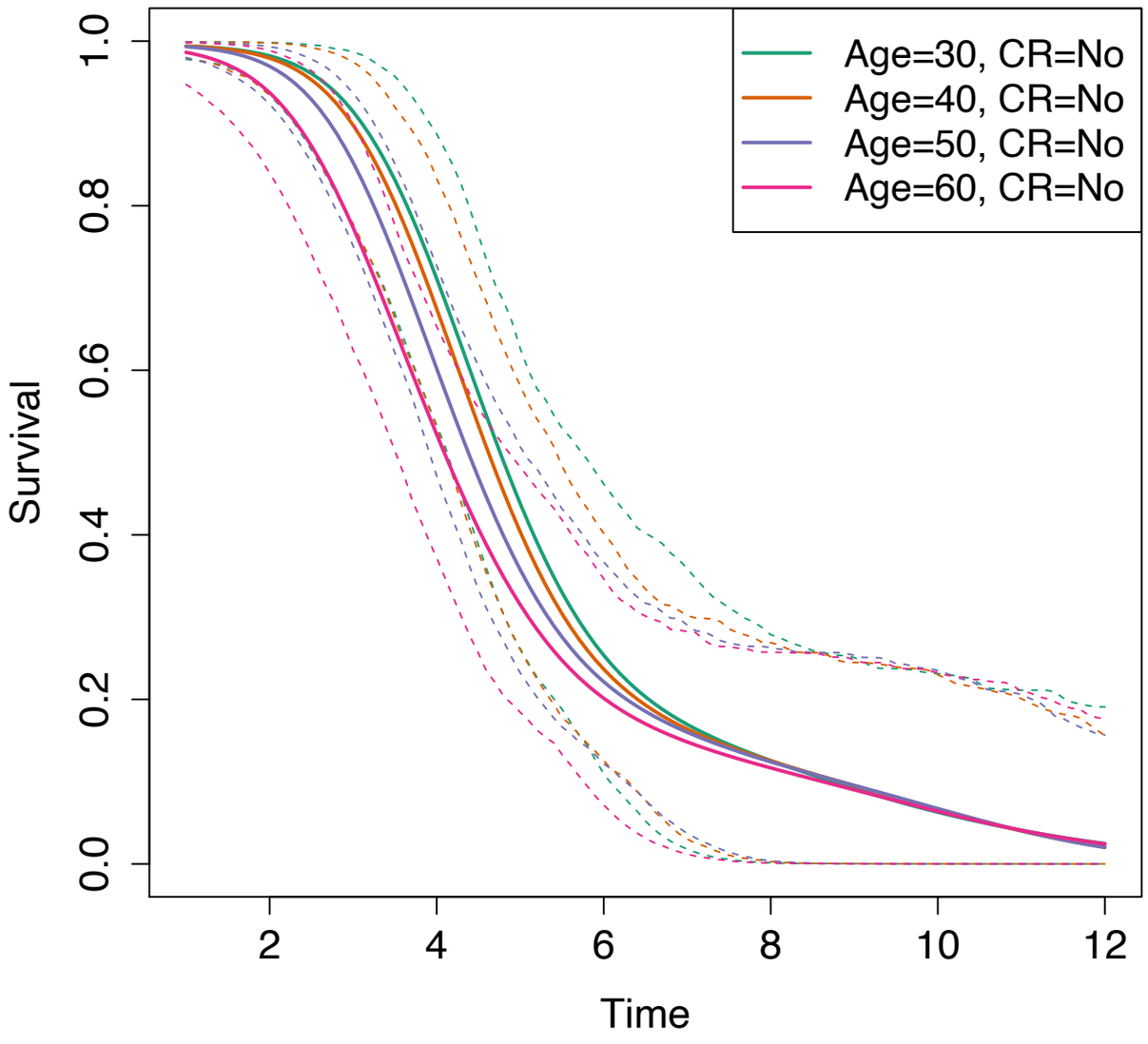
CR=1

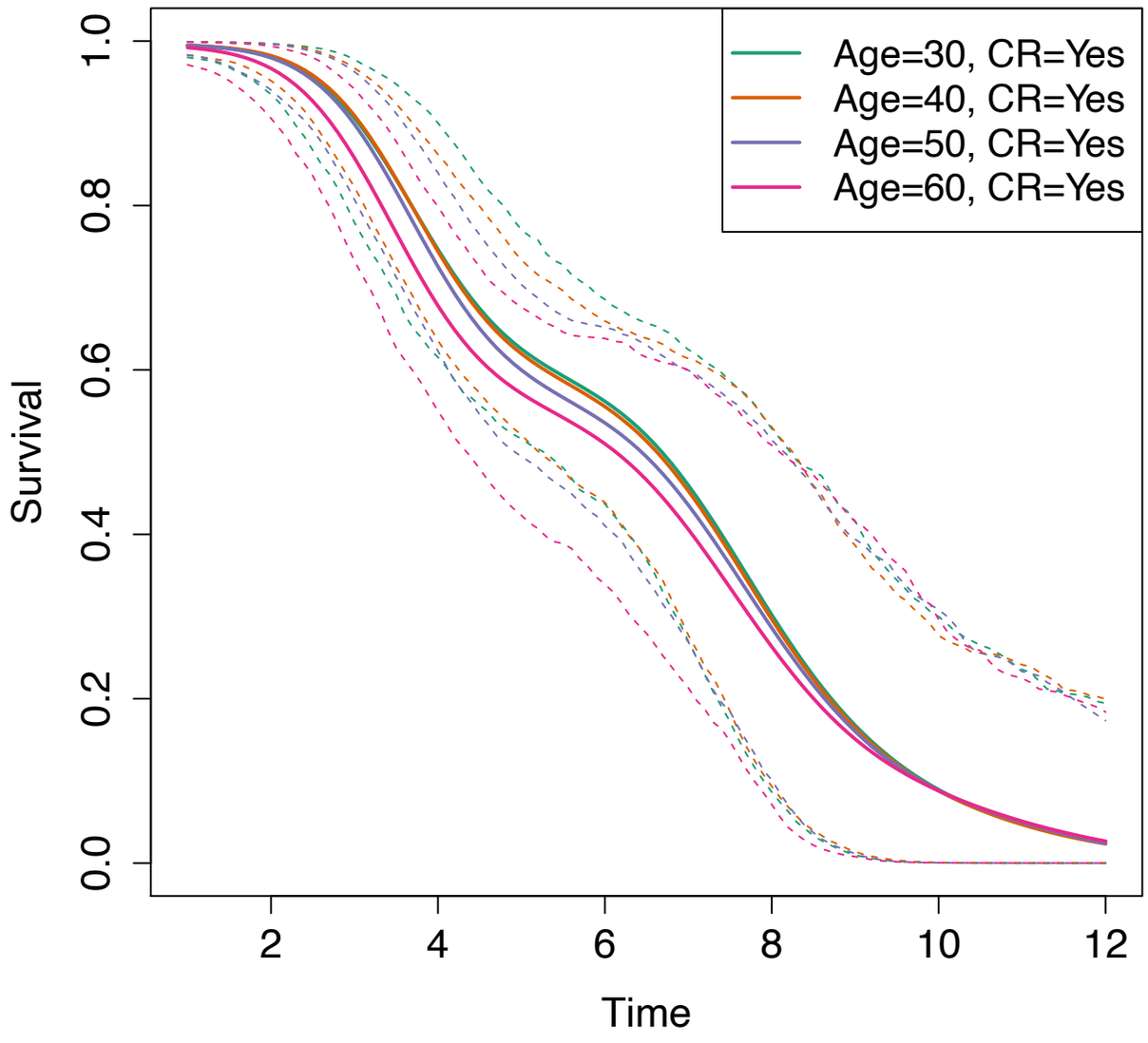
Data Analysis



Data Analysis

AUC=5





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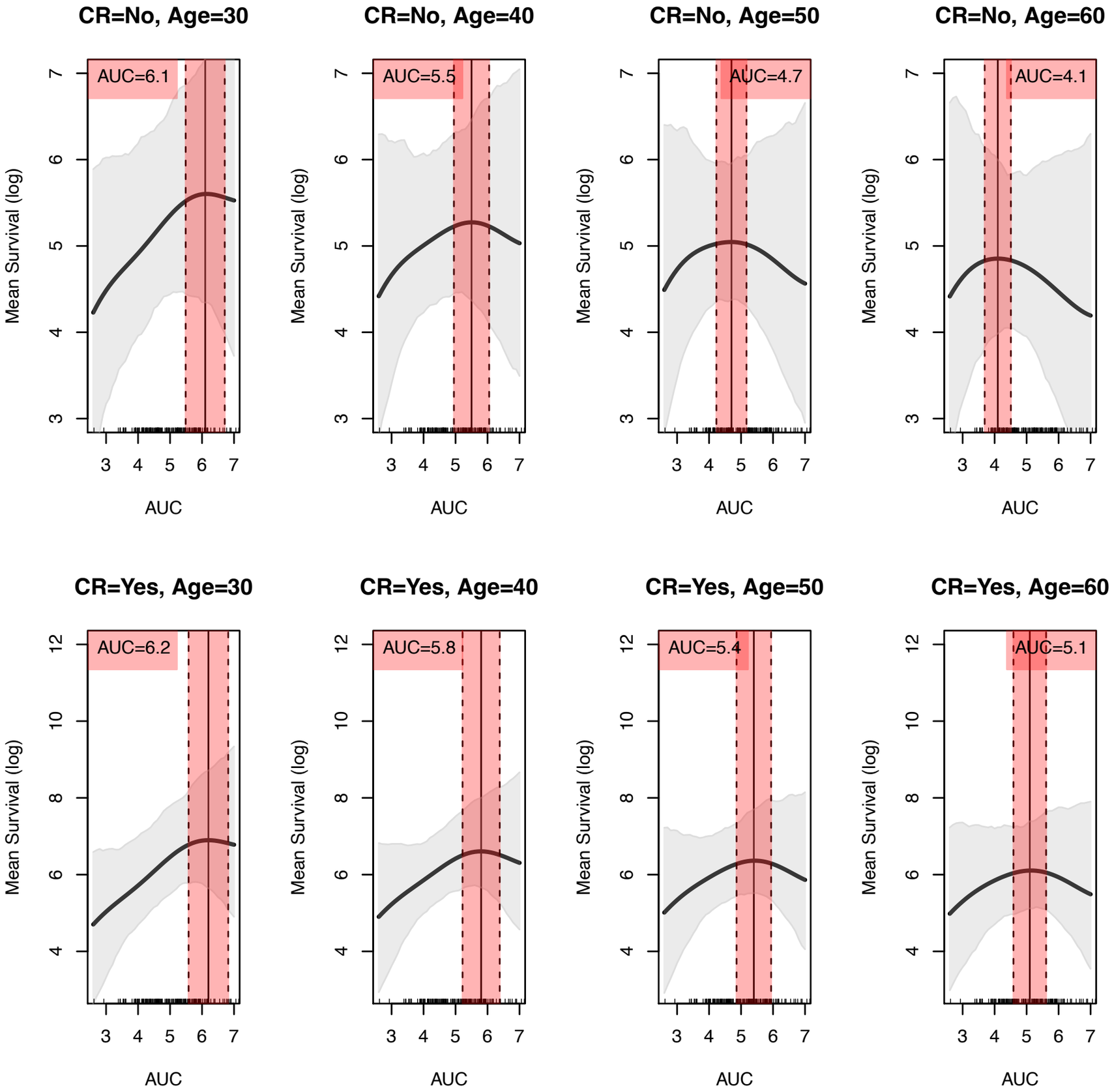

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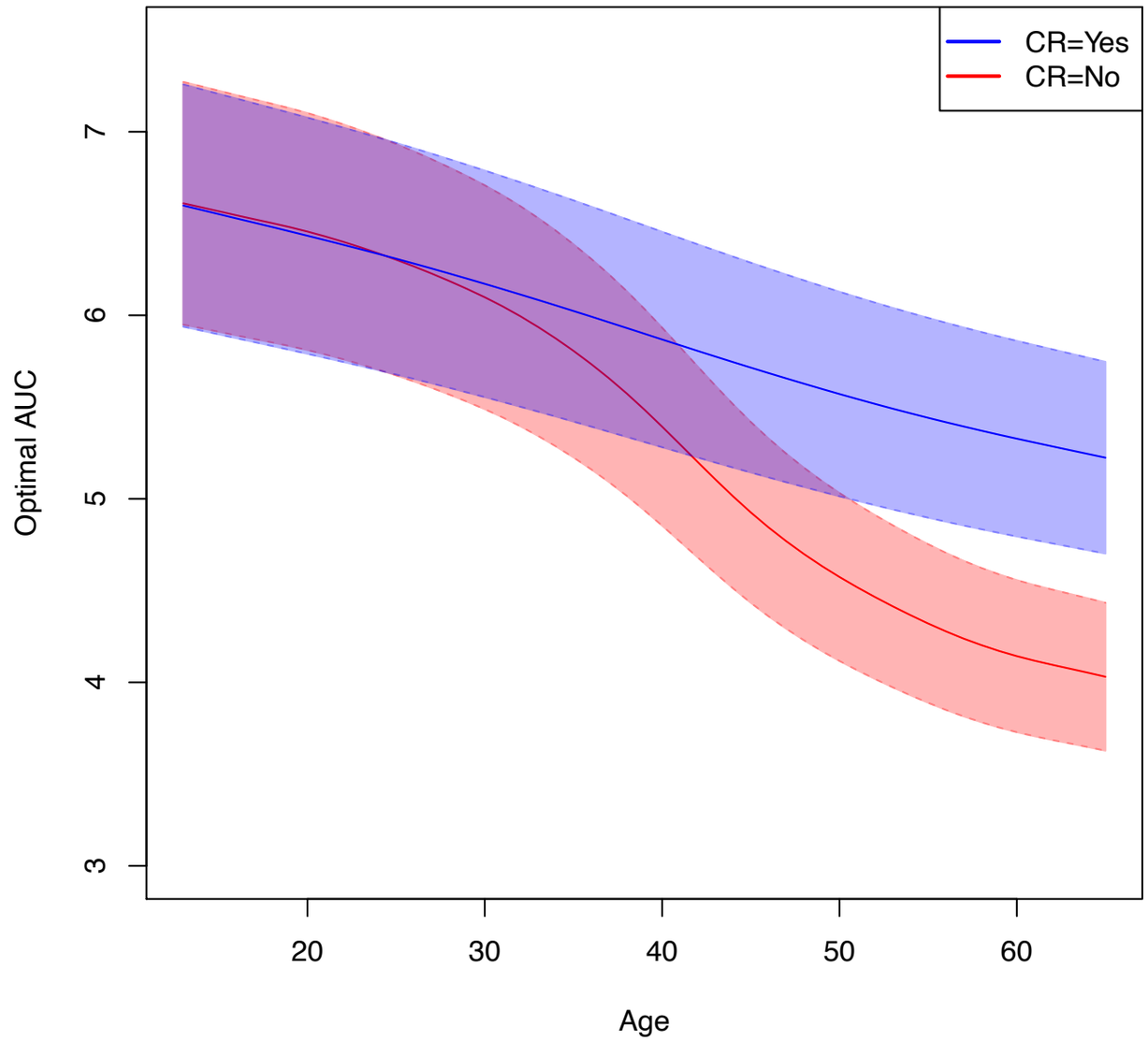

Xu et al., 2019

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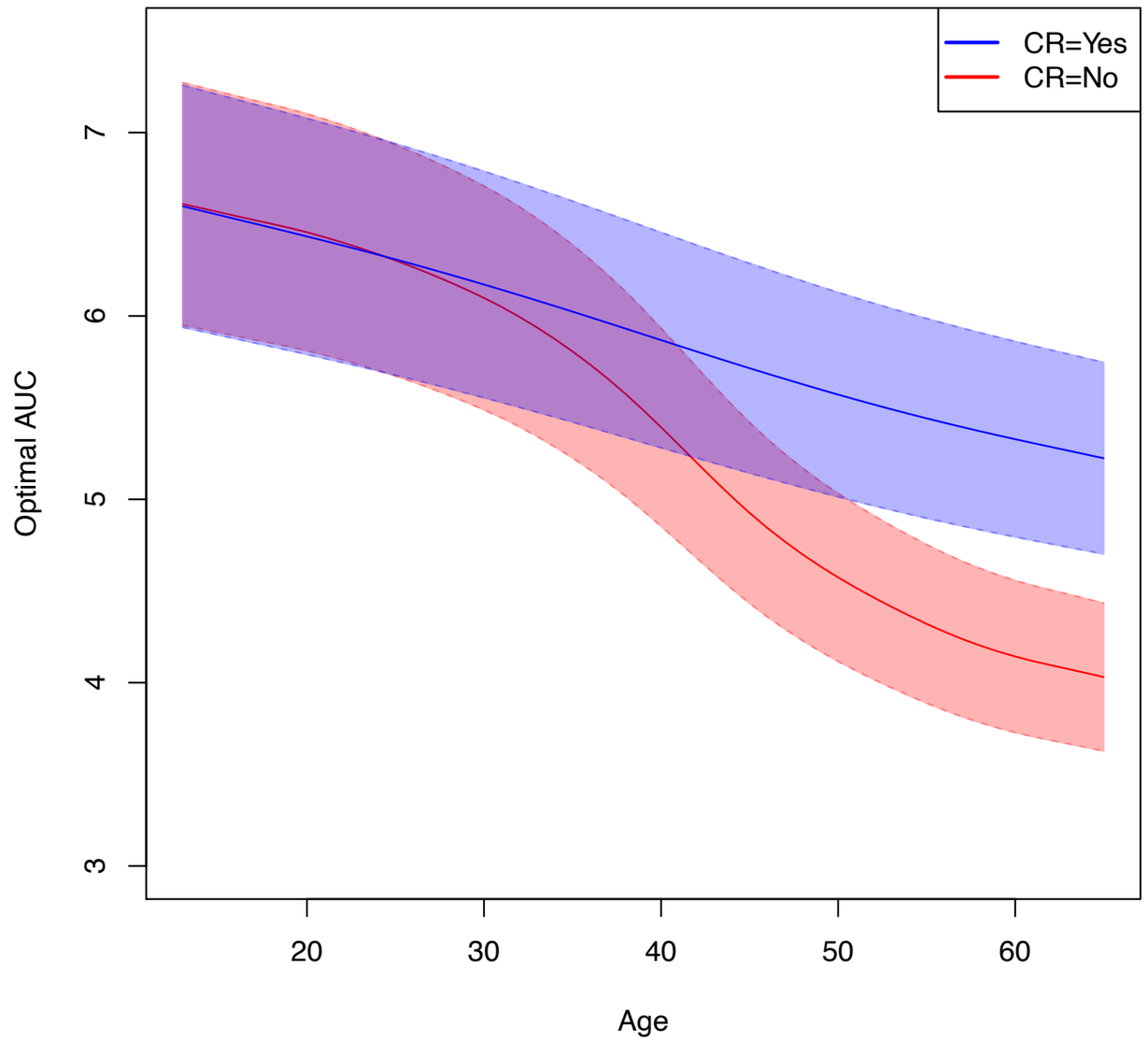

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Xu et al., 2019

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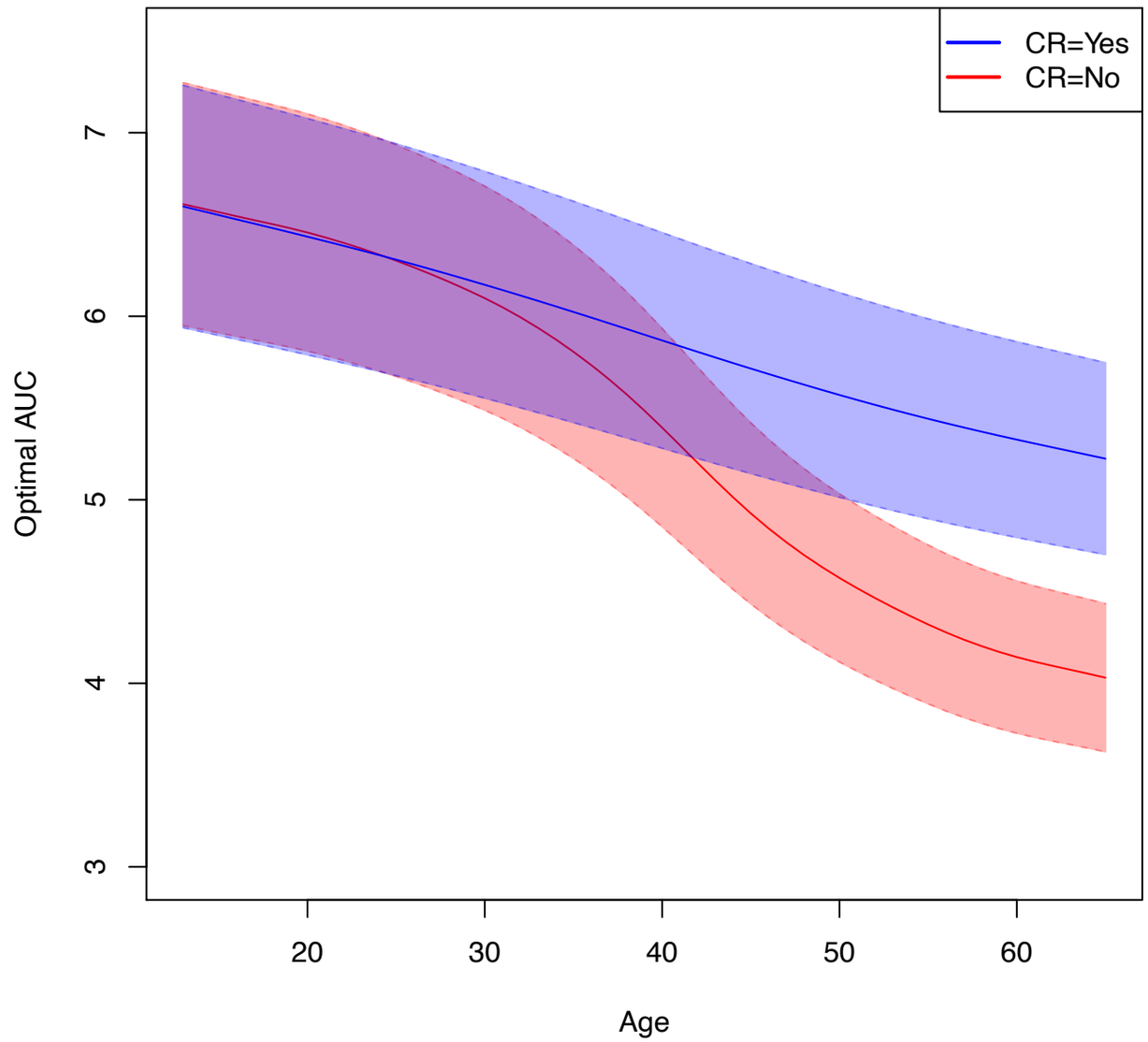

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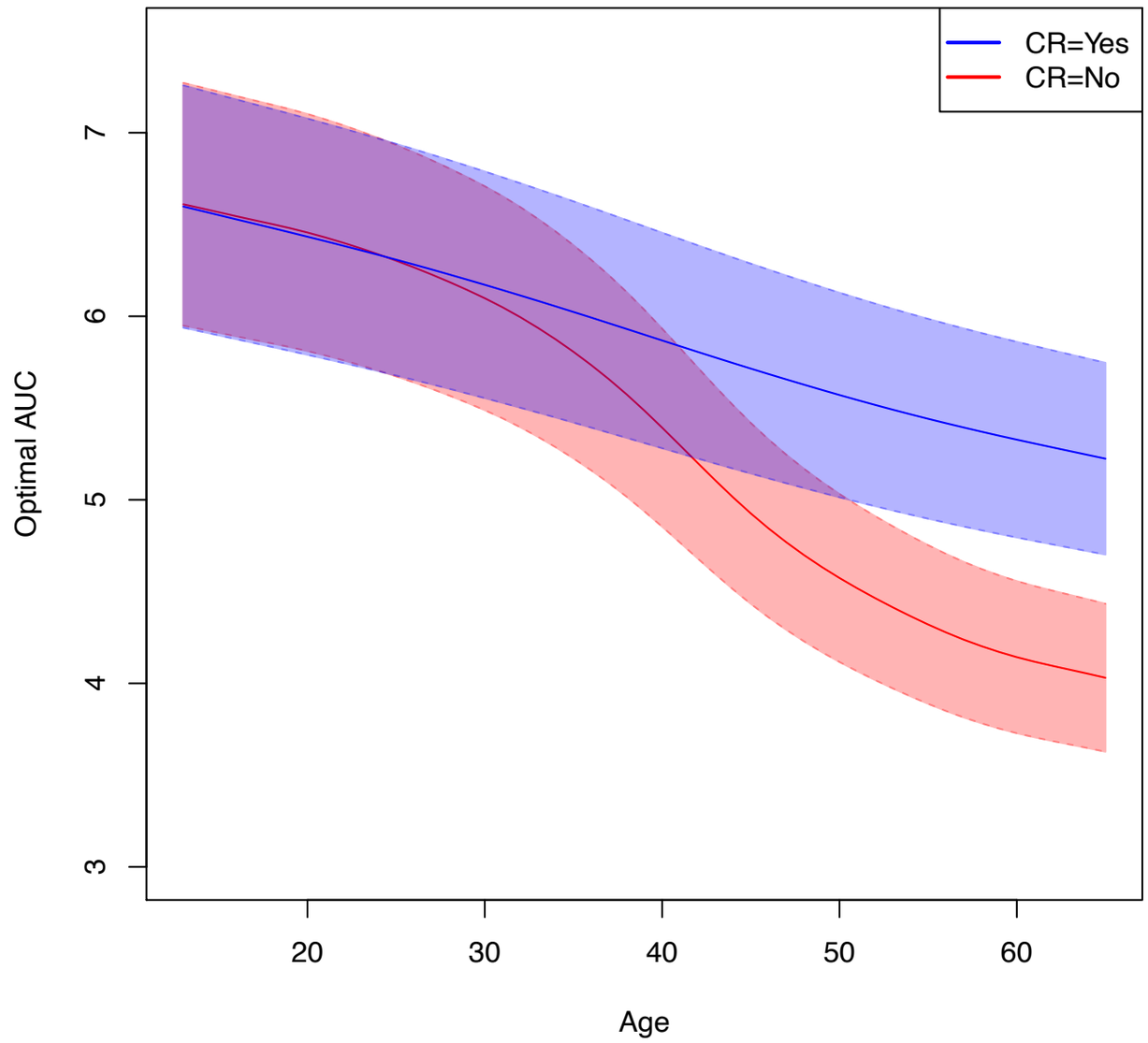

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Xu et al., 2019

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The R package DDPGPSurv can be downloaded from

https://cran.r-project.org/web/packages/DDPGPSurv/index.html