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Individualized and Adaptive RT via Statistical Models

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Outline

- **Background**
- **Two Competing Outcomes: Utility Approach**
- **Directly Maximizing Expected Survival**
- **Dynamic Treatment Regimes**
- **Conclusions**

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Clinical Background

- Different clinicians often use different doses of treatment in oncology
- Any single clinician tends to use same dose
  - Little individualization

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Statistical Background

- Large literature on optimal treatment regimes
- Our setting is different
  - Two or more competing outcomes
  - Treatment variable is dose not drug A vs B
  - Not Phase I
- Available datasets from patients treated over range of dose
  - Use these to build models and optimal treatment rule

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Treatment Planning Directive

Normal Structures: (check all to be contoured)	Priority	Parameter	Goal	Notes/Comments
Lungs-GTV	1 or	Bio-NTCP (α/β=2.5)	<15% or	
Lungs-ITV		[Med Phys Consult]		
	1 or	Mean	<15.0 Gy or	
	1 or	V20.0 Gy	<35% or	
	1 or	V5.0 Gy*	<65% or	
Esophagus*	1 or	Max (0.1 cc)	<105% Rx or	
	1 or	Mean	<34 Gy or	
Heart	1 or	Max (0.1 cc)	<105% Rx or	
Pericardium	1 or	Mean	<30 Gy or	
	1 or	V30.0 Gy	<50 % or	
	1 or	V40.0 Gy	<35 % or	
SpinalCanal	1 or	Max (0.1 cc)	<45.0 Gy or	
SpinalCanal _PRV5	1 or	Max (0.1 cc)	<50.0 Gy or	
BrachialPlex_R	1 or	Max (0.1 cc)	<60.0 Gy or	
BrachialPlex_L				

Note: Limits based on RTOG 1106 or more conservative
*For IMRT/VMAT Plans

Target Coverage & Conformality Goals:				
Name	Priority	Parameter	Goal	Notes/Comments
PTV(s)	2 or	Dose covering 95% PTV	Rx Dose	
	2 or	Min Dose (0.1 cc)	93% Rx Dose	
	2 or	Max Dose (0.1 cc)	107% Rx Dose	
Conformity Index	2 or	Rx Isodose Vol/PTV	< 1.5 (If not met, consider IMRT)	

Dose Prescription:
Choose

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Individualized Treatment Planning

- Incorporate patient factors (e.g. biomarkers) into RT treatment planning
- This requires new approaches
  - Move from Dose to Expected Outcome
  - Move away from hard constraints to continuous tradeoffs
  - Make efficacy vs toxicity tradeoff explicit and quantitative

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Problems with Dose Constraints

Give max tumor dose with P(T) < 20%?

Example 1	P(E)	P(T)
Dose 1	.5	.20
Dose 2	.9	.21
Example 2		
Dose 1	.9	.05
Dose 2	.91	.20

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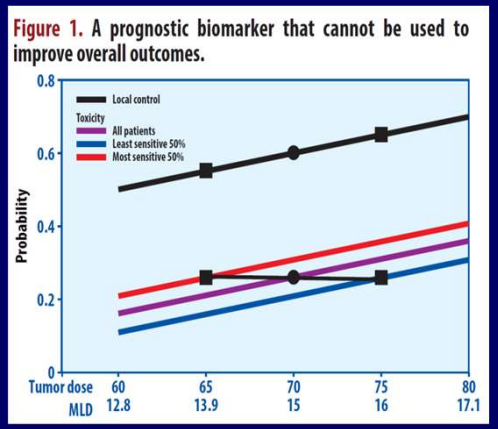
Better Models = Better Outcomes?



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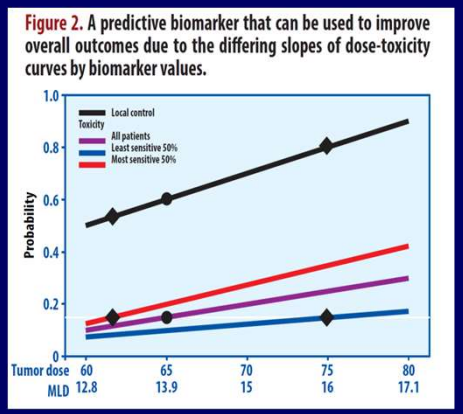
Better Models = Better Outcomes?



Predictive Biomarker: used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

FDA-NIH Biomarker Working Group.

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Combining Efficacy and Toxicity

- Treatment planning must be based on toxicity and efficacy considerations
- Metrics that combine efficacy and toxicity
  - Uncomplicated control (Neither toxicity nor progression within some time interval (Ågren A et al, Red J, 1990)
  - QTWiST= Quality-Adjusted Time WIthout Symptoms or Toxicity (Jang et al, JCO, 2009, and Black et al, NEJM 2015)
  - Overall Survival
- Biomarkers are often associated with single toxicity OR efficacy outcome, not composite endpoint
  - Model outcomes separately and then combine predictions when evaluating a particular dose/plan

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Utility Approach to Optimal Dose Selection

Use this approach to tradeoff of E vs T or T1 vs T2

Select optimal dose (D) to maximize the Utility

1) U = $P(\boldsymbol{E} \mid \boldsymbol{D}, \boldsymbol{G}) - \theta * P(T \mid \mathrm{D}, \mathrm{G})$

2) **U =** $P(\boldsymbol{E} \mid \boldsymbol{D}, \boldsymbol{G}) - \sum_j \theta_j * P(T_j \mid \boldsymbol{D}, \boldsymbol{G})$

3) *U* = $P(T_1 \mid \boldsymbol{D}, \boldsymbol{G})$ **+** $\theta_2 * P(T_2 \mid \boldsymbol{D}, \boldsymbol{G})$

where G denotes covariates (age, gender, imaging metrics, biomarkers, …)

Schipper M et al, Stat Med 2014.

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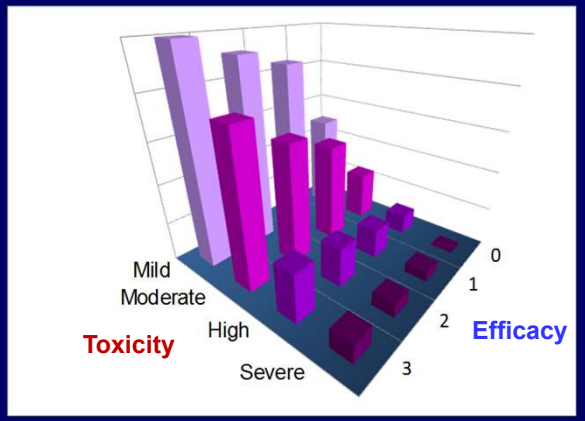
Utilities: Alternate Approach



Source: Peter Thall, UM Talk, 2014

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Choice of θ

- Elicit from clinician based on undesirability of toxicity relative to local tumor progression
  - 'How bad is the toxicity **relative to** lack of efficacy'
  - e.g 'If increasing tumor dose would increase LC from 80 to 90% how much increase in probability of G3 Pneumonitis would you take?'

Or

- As tuning parameter to control average rate of toxicity
  - As θ increases, dose and toxicity decreases

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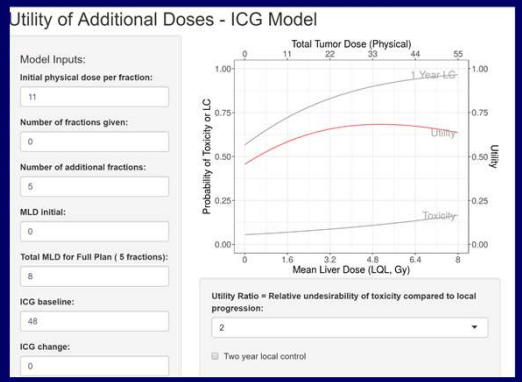
Liver Example



https://emily-morris.shinyapps.io/ExpandedApp/

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Other Applications

- Head & Neck Cancer:
  - Decision: De-escalate dose to primary tumor or individual nodes?
  - Efficacy = Local-regional control
  - Toxicity = Xerostomia, Dysphagia…
  - What is relative undesirability of G3 Dysphagia relative to local progression?

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Other Applications

- Lung Cancer
  - Decision: Put more dose through normal lung or heart?
  - Give everyone same tumor dose
  - What is relative undesirability of G3 Cardiac Toxicity relative to G3 Pneumonitis?

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Other Applications

- ^{177}Lu DOTATATE for Neuroendocrine tumors
- Decision: How many cycles to give?
  - What is relative undesirability of Kidney Toxicity relative to Tumor Progression?

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Constraining Dose Effects

- Often reasonable to assume monotone effect of D on E and T
- Constrain slope of dose-efficacy and dose-toxicity curves to be non-negative for all patients

logit P(T|…) = $\beta_0 + \beta_1 X_1 + \beta_2 D + \beta_3 X_1 D$

$\frac{d}{dD} P(T) \geq 0 \Rightarrow \beta_2 + \beta_3 X_1 \geq 0$

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Constrained LASSO

In many settings, large number of potential biomarkers available

$$\boldsymbol{minimize} \; -\boldsymbol{log}\boldsymbol{L}(\boldsymbol{\beta}, \boldsymbol{X}, \boldsymbol{Y}) + \boldsymbol{\lambda}\|\boldsymbol{\beta}\|_1$$

subject to $C\beta \geq 0$

where C is a n x (2p+1) matrix

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Virtual Clinical Trials

- Simulate datasets of size N including X, D, E|X,D and T|X,D
- For each simulated dataset
  - Calculate optimal dose $d_i(X, \theta)$ for each patient
    - Using models from Forward Selection, LASSO, Constrained Lasso, fixed dose, theoretical
  - Grid search to choose $\hat{\theta}$ so that $P(T|X, \theta) = .2$
  - Calculate $P(E|X) = {}^1/_n \sum_i P(E|X_i, d_i)$

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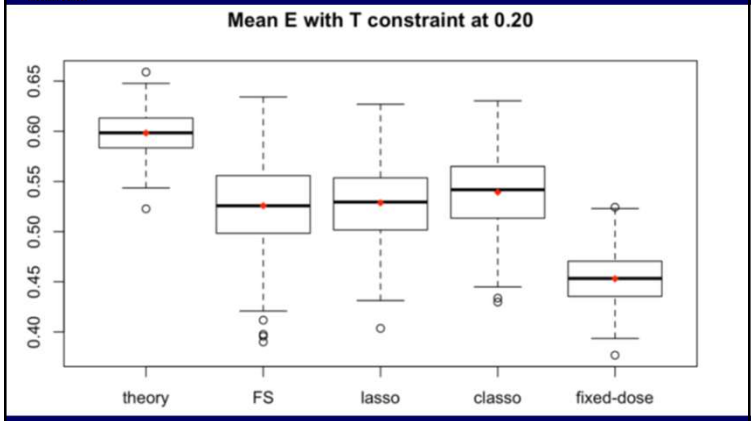
Simulation Results



Li P et al, Biometrical J. 2019

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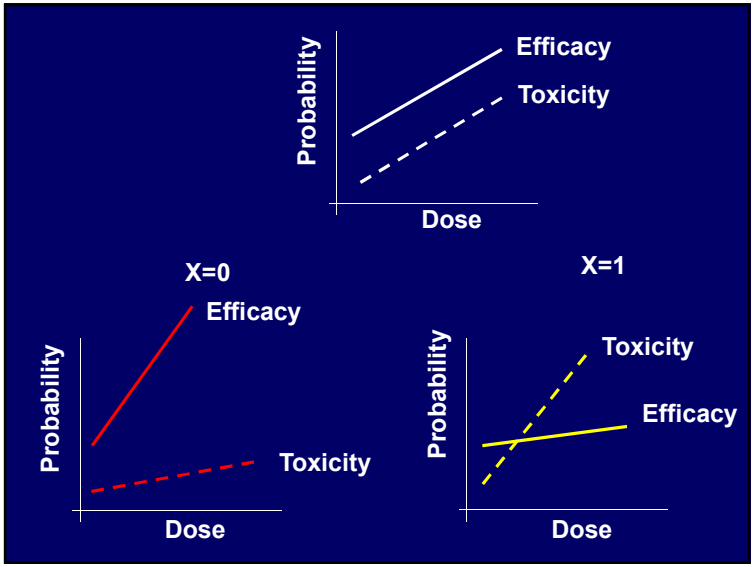

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Intuition

- How can Utility based dose selection increase efficacy without increasing toxicity?
  - Intuition: by 'spending' its toxicity wisely, i.e. in those patients who derive largest efficacy gain
- Ethical approach: Patients exposed to risk (P(T)) in proportion to reward (P(E))

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Conclusions

- Better models/markers can be coupled with the proposed utility approach to improve efficacy without increasing toxicity
- When fitting models where goal is personalized medicine
  - Looking for interactions with dose
  - Standard metrics (such as AUC) less relevant

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Next Steps

- Optimize full plan to directly maximize expected utility
  - Work by Dan Polan, Martha Matuszak

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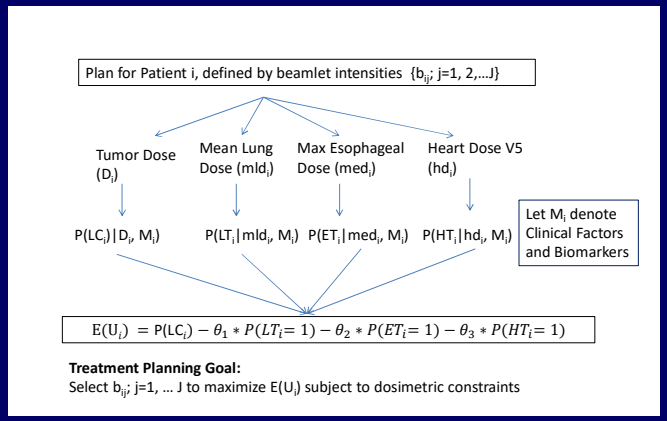
Example Schematic



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Next Steps

- Constraining risk at individual level

$$P(\boldsymbol{E} = \mathbf{1}|\boldsymbol{D}) - \boldsymbol{f}(\theta, P(\text{T=1}|\text{ D}))$$

- Compare CLASSO to machine learning methods (e.g. monotone BART)
- Joint modeling of E,T to calculate E(U)
- Involve patient when selecting θ

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Liver Dataset

Variable	Statistic	Summary
Gender Male Female	N (%)	 113 (80%) 28 (20%)
Age	Mean (sd)	65 (11)
ALBI at baseline	Mean (sd)	-2.18 (0.57)
Change in ALBI at mid-treatment	Mean (sd) [	0.20 (0.31)
MLD	Mean (sd)	13.1 (7.2)
Tumor Dose	Mean (sd)	72 (21)

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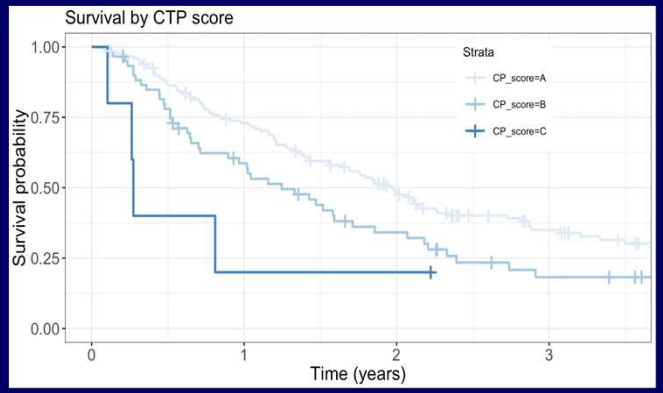
Overall Survival by CP



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OS Model

Variable	Hazard Ratio Estimate	Lower 95% CL	Upper 95% CL	P-Value
ALBI baseline	1.35	0.95	1.92	0.1
ALBI change	2.77	1.34	5.72	< 0.01
Tumor Dose (Gy)	0.98	0.96	1.00	< 0.01
MLD (Gy)	1.04	1.02	1.06	0.02

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Modeling Choices

- This model selects min or max dose as optimal for all patients
  - OS monotone function of dose
  - Not plausible
- Alternative modeling strategies
  - Cox model with quadratic dose
  - Nonparametric machine learning models

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Parametric and Nonparametric Models

- Cox Model:
  - **OS ~ ALBI baseline + ALBI change + MLD + MLD2 + D + D^2 + MLD*ALBI baseline + MLD*ALBI change + MLD^2 *ALBI baseline + MLD^2 *ALBI change**
- Bayesian Additive Regression Trees
  - Flexible approach with strong predictive performance

Sparapani RA, Logan BR, McCulloch RE, Laud PW. Nonparametric survival analysis using Bayesian Additive Regression Trees (BART). Stat Med. 2016;35(16):2741–2753.

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Virtual Clinical Trial

- Split the data into testing and training datasets
- Using the training set
  - Fit model for OS(X,D)
  - Use this model to define ODR
- Using the validation set
  - Fit model for OS(X,D)
  - Use this model to calculate OS(D_i^{opt}, X_i) for patients in training set
- Repeated 10 times and average OS(D_i^{opt}, X_i)

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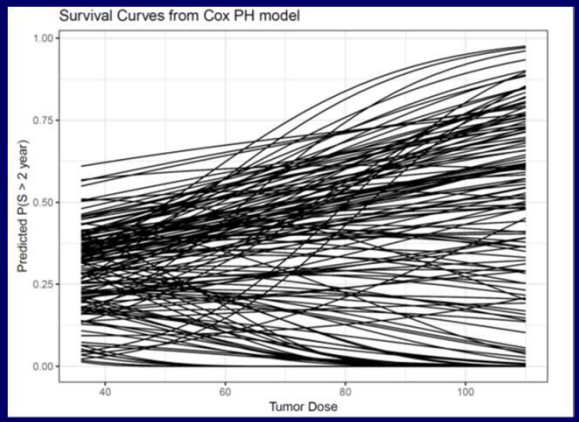
Individual OS vs D Curves



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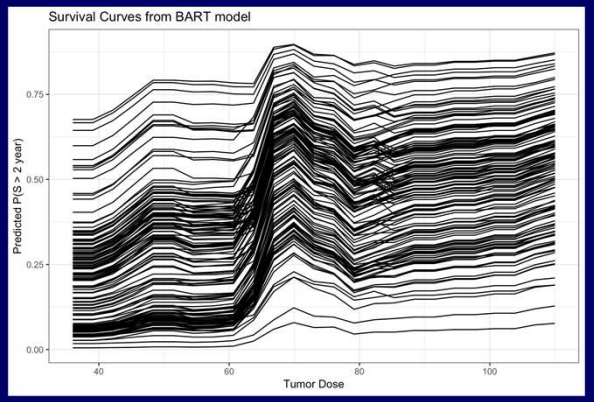
Individual OS vs D Curves



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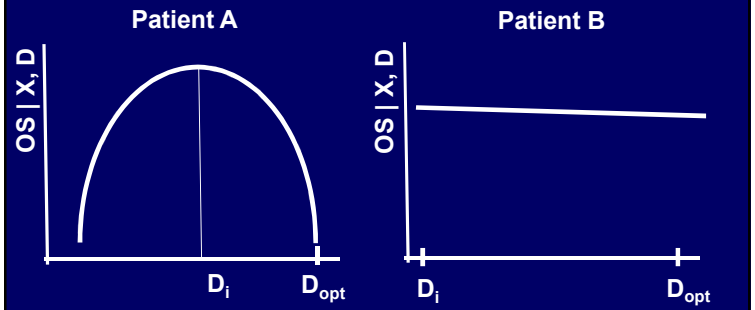
Shrinkage Estimator of Optimal Dose



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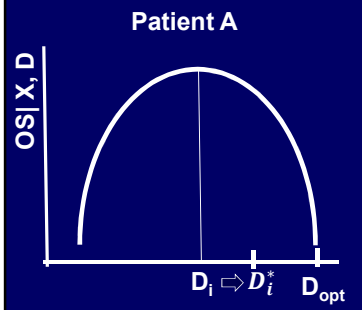
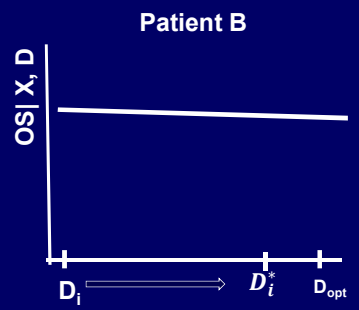
Shrinkage Estimator of Optimal Dose





$$D_i^* = w_i * D_i + (1 - w_i) * D_{pop}$$

$$w_i = \frac{E(OS|D_i) - E(OS|D_{pop})}{SE[E(OS|D_i) - E(OS|D_{pop})]}$$

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Virtual Trial: Results

Dose Selection Method	OS(2 Years)
Fixed: 8Gy X 5 (EQD2=60)	0.36
Fixed: 10Gy X 5 (EQD2 = 83)	0.43
Nonlinear Cox PH model	0.45
Nonlinear Cox PH model: shrinkage estimator	0.48
BART	0.46
Observed	0.44

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Dynamic Treatment Regimes

- A dynamic treatment regime (DTR) is a sequence of decision rules, one per stage, that map time-varying state of an individual to recommended treatments:
  - Aim to optimize some cumulative clinical outcome.
- Key: Heterogeneity in responses
  - Across patients: what works for one may not work for another.
  - Within a patient: what works now may not work later.

Zhao YQ, Laber EB. Estimation of optimal dynamic treatment regimes. *Clin Trials*. 2014

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How can we estimate a DTR?

- Best: Run a SMART trial
- Or, analyze existing data

Chapter 4: SMART design, conduct, and analysis in oncology
Peter Thall

Wang L, Rotnitzky A, Lin X, Millikan RE & Thall PF. Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer, JASA, 2012

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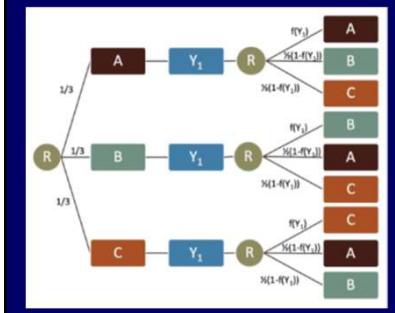
SMART Trials



- Current SMART literature: Categorical Treatment and Binary outcomes

Sample Sequential Multiple Assignment Randomized Trials with Continuous Outcomes. JSM, 2019. Hartman H, Schipper M, Kidwell K

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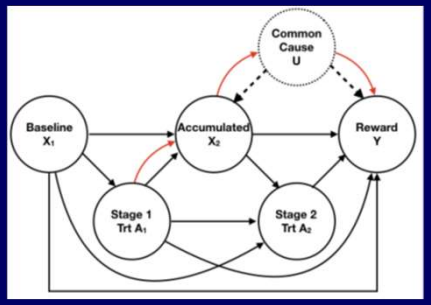
Estimating DTR from Observational Data



Result of time-varying confounding: collider-stratification bias (Berksons fallacy)
Traditional regression methods fail

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Adaptive RT: Dynamic Treatment Regimes

- Large statistical literature on DTRs
- Mostly focused on binary outcomes (not survival)
- Mostly focused on categorical treatment options (not dose of RT)

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Options for Clinical Trial

- Conduct a 'standard' SMART trial with no covariate based randomization
- Conduct a randomized Ph II trial comparing outcomes between
  - Previously estimated DTR vs Standard
- Hybrid

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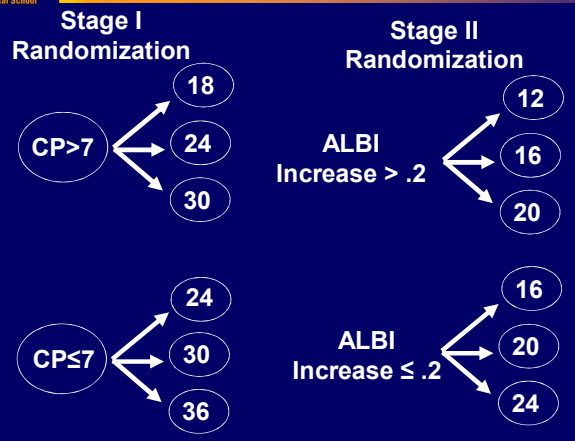
Hybrid SMART



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m1 mjschipp, 7/11/2019

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Questions?