# *Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer*

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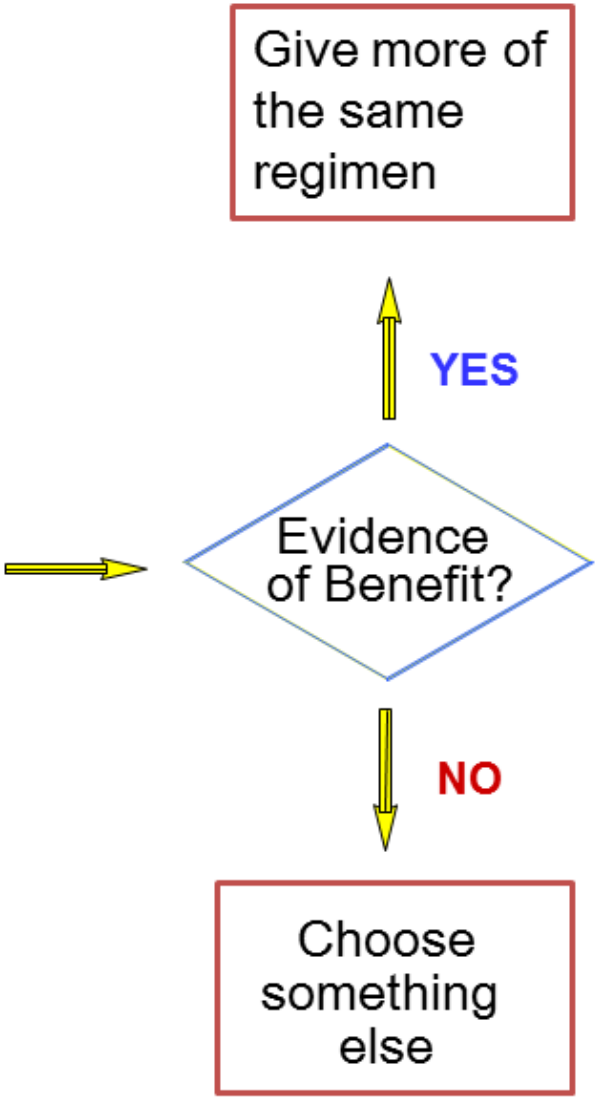
# *Dynamic Treatment Regime*

- Therapy of cancer, and many other diseases typically requires multiple stages.
  - Failure of initial trt to achieve a favorable clinical outcome
  - Recurrence, toxicity, etc
  - Therapy consists of a sequence of qualitatively different trts
- Dynamic events may affect future treatment decisions.
  - Growing back of solid tumors
  - Metastasizing to other body sites following a response of chemotherapy
  - Regimen-related toxicity

# Dynamic Treatment Practice

- Evaluate the patient's disease
- Choose a regimen
- Treat the patient




***Medical Oncology 101, According to Randy Millikan, M.D.***
***RWSL: "Repeat a Winner, Switch Away from a Loser"***

# *The AI Prostate Cancer Trial*

***Thall et al. 2007; Millikan et al. 2008***

- One of the pioneer trials designed with re-randomization (12/1998 – 01/2006 at MDACC)
- 4 chemo combinations (CVD, KA/VE, TEE, TEC) → 4x3=12 two-stage dynamic treatment strategies
- Binary "Response / No-Response" outcomes, based on drop in PSA, in each course
- Also collected survival outcome
- This study was a groundbreaking early example of a **Sequential Multiple Assignment Randomized Trial** (SMART, Murphy 2005).

## Per-Course Outcomes: (Each course is 8 weeks)

1st Success = [ **>40%** drop in PSA and absence of AD]

Repeat a successful trt, otherwise re-randomize the patient among the other 3 trts ( ***accidentally SMART*** !!! )

2nd Success = [ **>80%** drop in PSA and absence of AD]

## Strategy (*a, b*) :

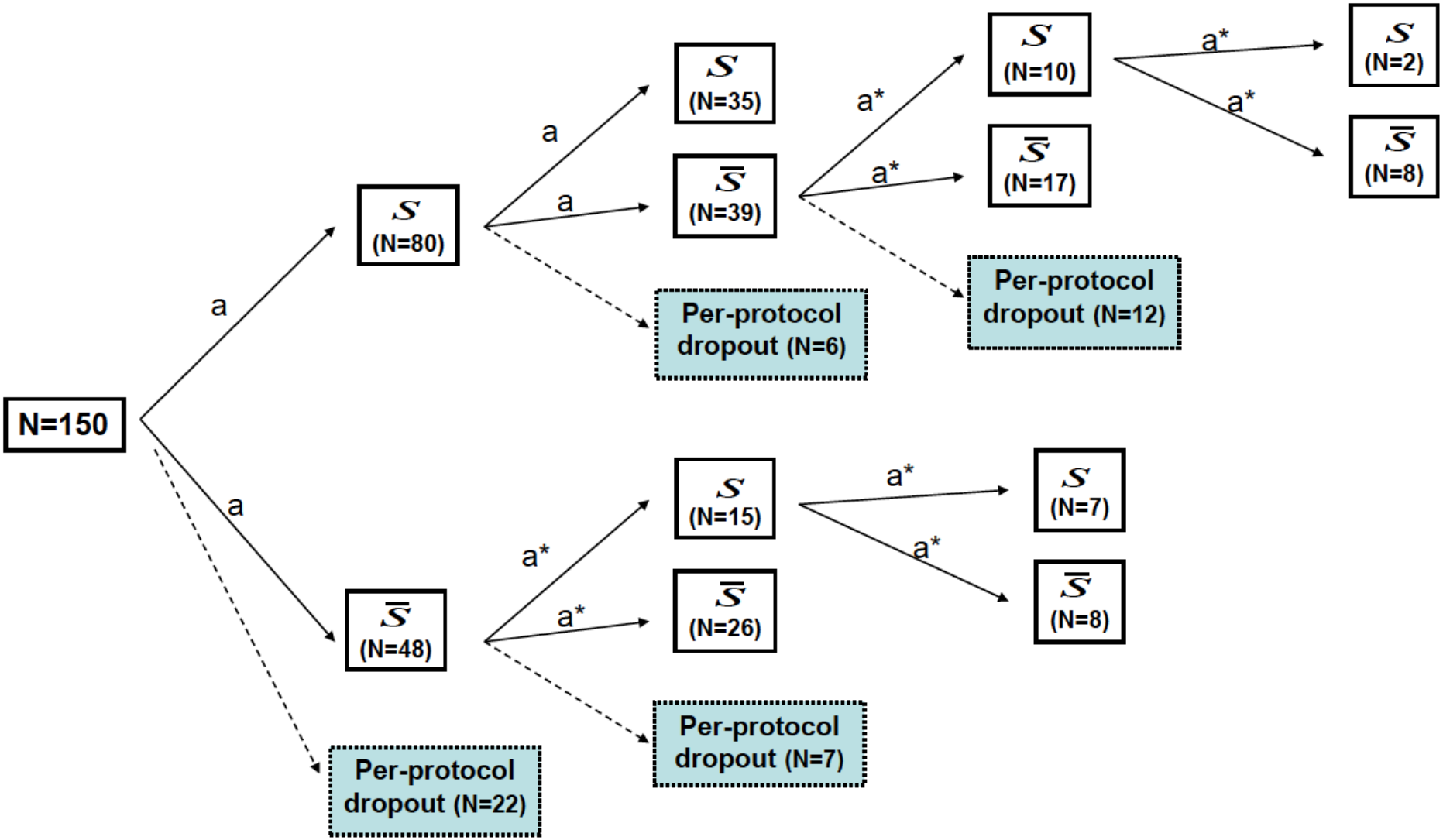
Treat with ***a*** in a course.

- Repeat the current treatment if **Success** occurs
- Switch to ***a**** if **Failure** occurs

→ Consecutive **S-S** with the same regimen → Declare victory

→ A total of 2 courses with **Failure** → Admit defeat

# *Possible Courses for Strategy (a, a*)*




*S : Per-Protocol Success;* $\overline{S}$ *: Per-Protocol Failure.*

# *Actual Trial Conduct*

***Randomize*** patients fairly among the 4 treatments

**1st Success = {>40% drop in PSA and no AD}**

Repeat a successful trt, otherwise ***re-randomize*** the patient among the other 3 (***adapt trt within the patient***)

**2nd Success = {>80% drop in PSA and no AD}**

**Patient Success** = {**2 consecutive successful courses**}

**Patient Failure** = {**A total of 2 unsuccessful courses,**

**or PD, or TOX**} →

**Stop therapy** (***an adaptive within-patient decision***)

- **Wang *et al. 2012*, Journal of the American Statistical Association. (with Discussions)**

# *Actual Trial Conduct and Outcomes*

- *The RWSL algorithm as given before, but with*

  *Failure = { 2 unsuccessful courses, or PD, or TOX }*

  *→ Stop therapy*

## *The New Per-Stage Outcomes :*

*Efficacy = EFF0 if per-protocol response*

*EFF1 if no per-protocol response, but no PD*

*EFF2 if PD*

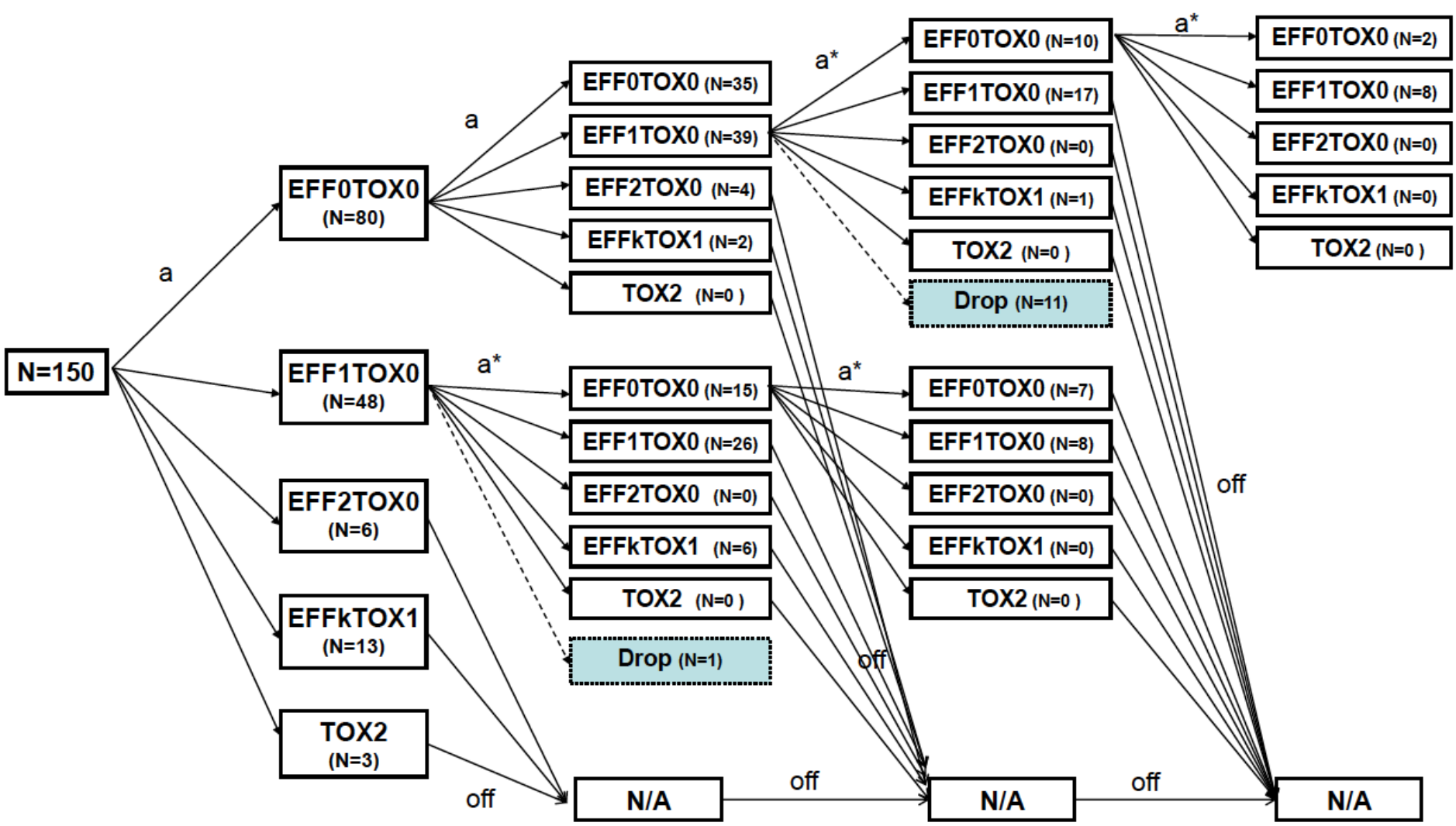
*EFF3 if inevaluable due to severe TOX*

*Toxicity = TOX0 if no TOX*

*TOX1 if treatment stopped but Efficacy evaluated*

*TOX2 if so severe that Efficacy not evaluated*

# *Possible Courses for Strategy (a, a*): Viable DTRs*




*EFFkTOX1: Toxicity at level 1 and Efficacy at any level.*

# For each patient, we have the following variables:

- Treatment Actions

  $A_j$ : the chemo received at the start of course $j$ if the patient actually received one.

- At baseline

  $P_1$ : PSA at baseline.

  $V_1$ : indicator of high (versus low) disease volume at baseline.

- At the end of course $j-1$ and just prior to $A_j$ for $j = 2, \cdots, 5$

  $P_j$ : PSA

  $T_j$ : Toxicity

  $E_j$ : compound measure of efficacy

- Final Survival outcome: $X$

## *More Notation:*

$$L_1 = (P_1, V_1) \qquad L_j = \left(P_j, T_j, E_j, I_{(2(j-1),\infty)}(X)\right),\ j = 2, ..., 5.$$

$$S_j = I_{\{(\text{TOX0,EFF0})\}}\left[(T_j, E_j)\right] \text{ and } F_j = I_{\{(\text{TOX0,EFF1})\}}\left[(T_j, E_j)\right]$$

## *Formally Define Viable DTRs:*

$$g_{a,a^*,1}(L_1) = a, \qquad g_{a,a^*,2}(\overline{L}_2) = \begin{cases} a & \text{if } S_2 = 1 \\ a^* & \text{if } F_2 = 1 \\ \text{OFF} & \text{if } S_2 \neq 1, F_2 \neq 1, X > 2 \end{cases}$$

$$g_{a,a^*,3}(\overline{L}_3) = \begin{cases} a^* & \text{if } S_2F_3 = 1 \text{ or } F_2S_3 = 1 \\ \text{OFF} & \text{if } S_2F_3 \neq 1, \quad F_2S_3 \neq 1 \text{ and } X > 4 \end{cases}$$

$$g_{a,a^*,4}(\overline{L}_4) = \begin{cases} a^* & \text{if } S_2F_3S_4 = 1 \\ \text{OFF} & \text{if } S_2F_3S_4 \neq 1 \text{ and } X > 6 \end{cases}$$

# *Utility 1: Binary Score*

$$Y^{\text{bin}} = y^{\text{bin}}\left(\overline{L}\right) = \begin{cases} 1 & \text{if } \widetilde{S}_j \widetilde{S}_{j+1} = 1 \quad \text{for } j = 2, 3 \text{ or } 4 \\ 0 & \text{otherwise} \end{cases}$$

$$\widetilde{S}_j = I_{\{(\text{TOX0},\text{EFF0}),(\text{TOX1},\text{EFF0})\}}[(T_j, E_j)]$$

# *Utility 2: Ordinal Score*

$$Y^{\text{ord}} = y^{\text{ord}}(\overline{L})$$

$$= \begin{cases} 1 & \text{if } \widetilde{S}_j \widetilde{S}_{j+1} = 1 \text{ for } j = 2, 3 \text{ or } 4 \\ 0.5 & \text{if } \widetilde{S}_2(1 - \widetilde{S}_3)(1 - \widetilde{S}_5) = 1 \text{ or } (1 - \widetilde{S}_2)\widetilde{S}_3(1 - \widetilde{S}_4) = 1 \\ 0 & \text{otherwise} \end{cases}$$

# *Utility 3: Expert Score*

$C_j = c(E_j, T_j)$ $\qquad$ $E_j =$ Efficacy outcome

| | | EFF0 | EFF1 | EFF2 | EFF3 |
|---|---|---|---|---|---|
| $T_j =$ | TOX0 | 1.0 | 0.5 | 0.1 | X |
| Toxicity | TOX1 | 0.8 | 0.3 | 0 | X |
| outcome | TOX2 | X | X | X | 0 |

$$Y^{\text{expert}} = y^{\text{expert}}(\overline{L}) = \frac{\sum_{j=2}^{5}\{1 - I_{\{\text{OFF,N/A}\}}[A_{j-1}]\}C_j}{\sum_{j=2}^{5}\{1 - I_{\{\text{OFF,N/A}\}}[A_{j-1}]\}}$$

# *Utility 4: Log-Survival*

# *Counterfactual Outcomes and Target Endpoint*

For each switch rule $g_{a,a^*}$ ,

$\overline{L}_{(a,a^*)}$ : denote the hypothetical outcome

$Y_{(a,a^*)} = y\left(\overline{L}_{(a,a^*)}\right)$ : counterfactual endpoint

$$\left(a_{opt}, a^*_{opt}\right) = \arg\max_{(a,a^*)} E\left[Y_{(a,a^*)}\right]$$

# *Saturated Marginal Structural Mean Model*

$$E\left[Y_{(a,a^*)}\right] = \sum_{a_1 \in \mathcal{A}} \sum_{a_2 \in \mathcal{A} - \{a_1\}} \beta_{a_1,a_2} I_{\{(a_1,a_2)\}}\{(a,a^*)\}$$

Inverse Probability Weighted Estimator

$$\frac{\sum_{i=1}^{n} \Delta_{a,a^*,i} \omega_i Y_i}{\sum_{i=1}^{n} \Delta_{a,a^*,i} \omega_i}$$

, where

the weights come from two sources.

$$P\left(A_j = a_j | \overline{A}_{j-1} = \overline{a}_{j-1}, \overline{L}_j, \mathcal{L}\right)$$

$$= P\left(A_j = a_j | A_j \neq \text{N/A}, \overline{A}_{j-1} = \overline{a}_{j-1}, \overline{L}_j, \mathcal{L}\right) \times P\left(A_j \neq \text{N/A} | \overline{A}_{j-1} = \overline{a}_{j-1}, \overline{L}_j, \mathcal{L}\right)$$

**For Treatment Assignment**

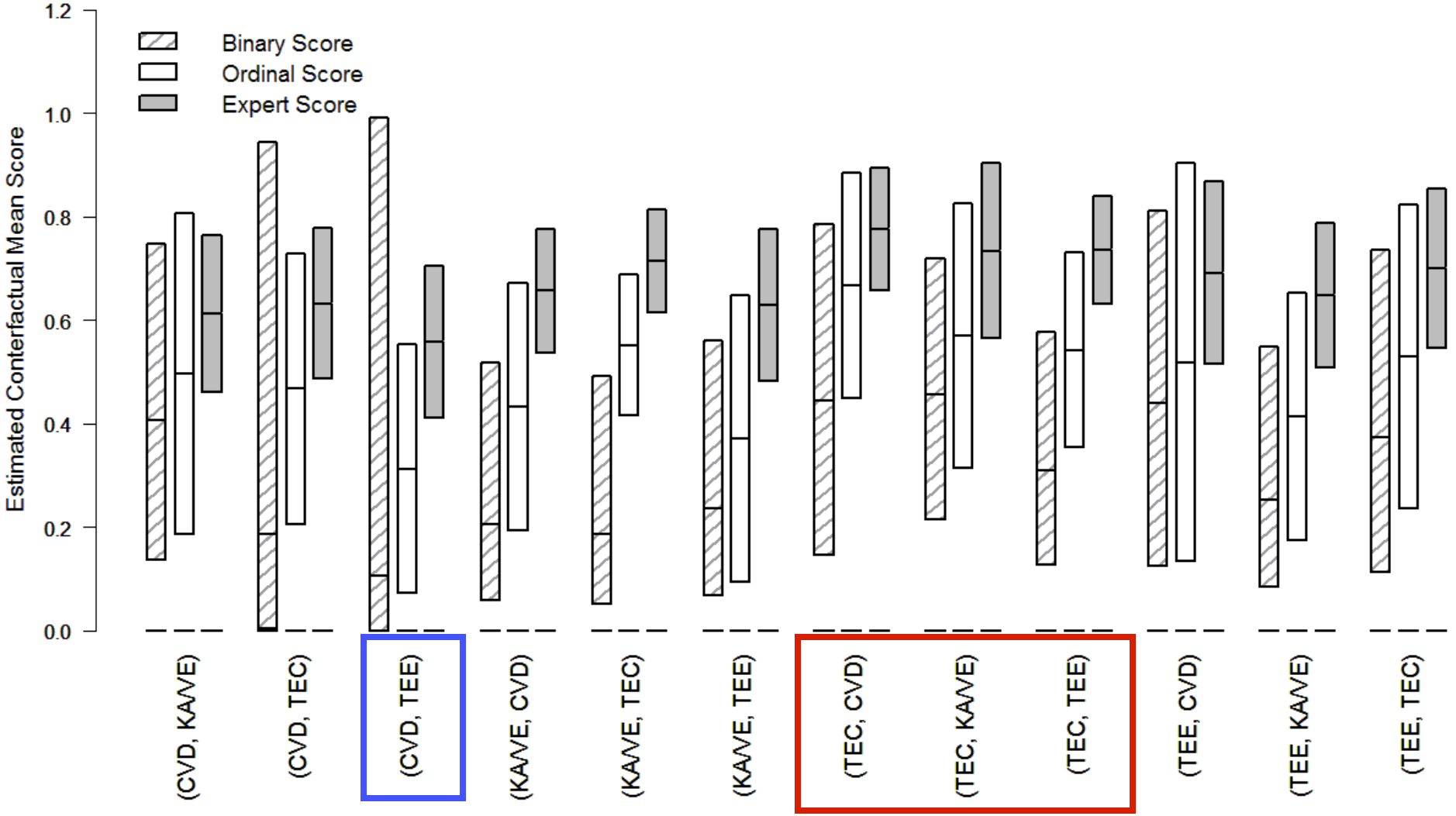
**For Patient Drop-out**

## ❖ *Inverse Probability of Treatment Weights*

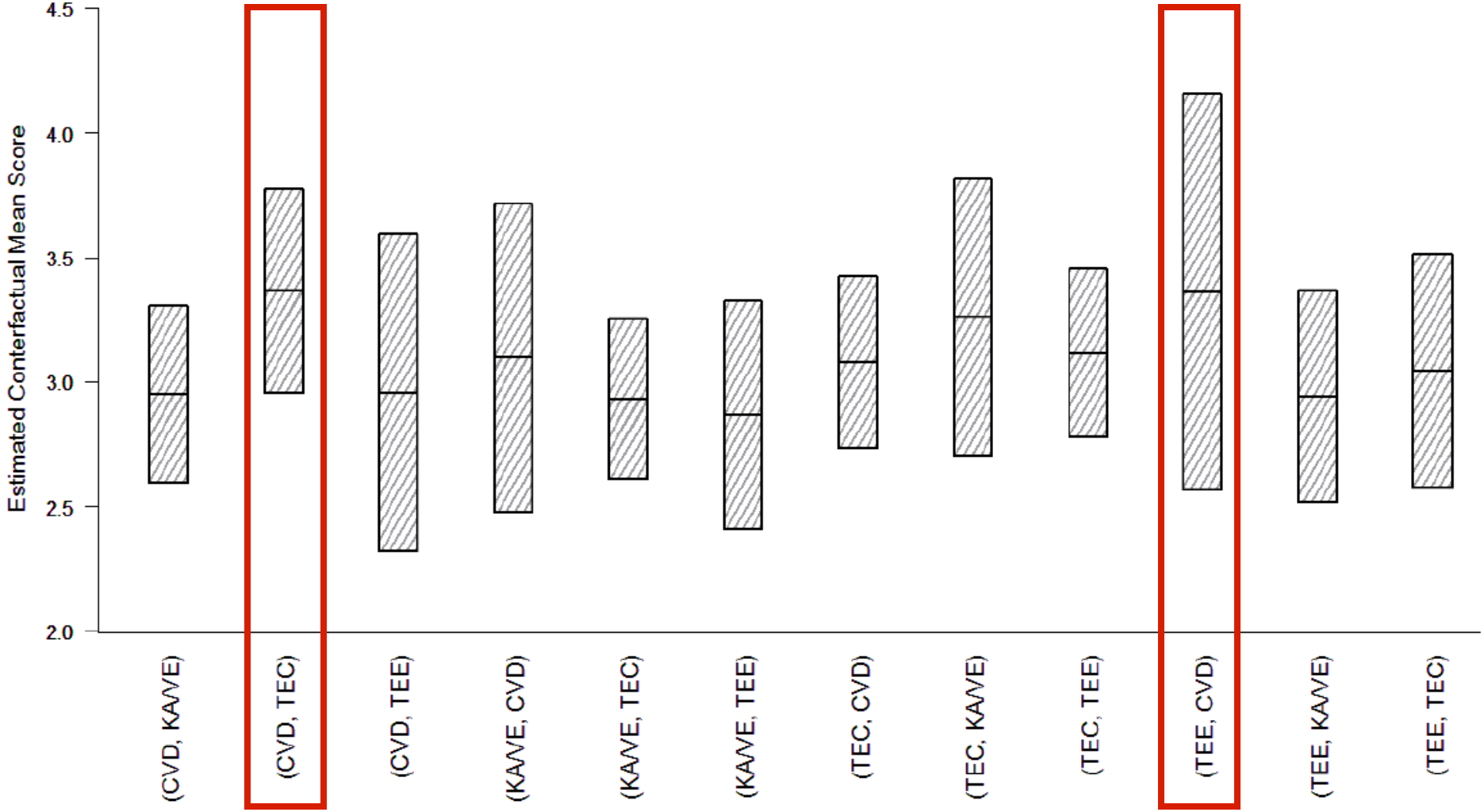
| Group | $A_1$ | $A_2$ | $A_3$ | $A_4$ | $\omega_1$ | $\omega_2$ | $\omega_3$ | $\omega_4$ | $\omega$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $a$ | OFF | OFF | OFF | 4 | 1 | 1 | 1 | 4 |
| 2 | $a$ | $a$ | OFF | OFF | 4 | 1 | 1 | 1 | 4 |
| 3 | $a$ | $a^*$ | OFF | OFF | 4 | 3 | 1 | 1 | 12 |
| 4 | $a$ | $a^*$ | $a^*$ | OFF | 4 | 3 | 1 | 1 | 12 |
| 5 | $a$ | $a$ | $a^*$ | OFF | 4 | 1 | 3 | 1 | 12 |
| 6 | $a$ | $a$ | $a^*$ | $a^*$ | 4 | 1 | 3 | 1 | 12 |

- ***Estimate the weights to improve estimation efficiency.***
- ***We further considered Inverse Probability of Missing.***

# *Estimated Regime-specific Mean Scores*



# *Estimated Regime-specific Mean Log-survival*



# *Sensitivity Analysis: using worse case and best case imputation schemes for drop-outs*

| | Expert Score[a] | Expert Score[b] | Log Survival[c] | Log Survival[d] |
|---|---|---|---|---|
| (CVD, KA/VE) | 0.62 (0.47, 0.77) | 0.62 (0.47, 0.77) | 2.93 (2.59, 3.26) | 2.92 (2.58, 3.26) |
| (CVD, TEC) | 0.63 (0.49, 0.77) | 0.63 (0.48, 0.78) | 3.28 (2.88, 3.67) | 3.27 (2.85, 3.68) |
| (CVD, TEE) | 0.57 (0.43, 0.71) | 0.57 (0.43, 0.71) | 2.93 (2.32, 3.54) | 2.92 (2.31, 3.53) |
| (KA/VE, CVD) | 0.65 (0.52, 0.77) | 0.67 (0.55, 0.80) | 3.20 (2.65, 3.76) | 3.20 (2.64, 3.77) |
| (KA/VE, TEC) | 0.70 (0.59, 0.81) | 0.73 (0.62, 0.84) | 3.05 (2.69, 3.41) | 3.05 (2.68, 3.42) |
| (KA/VE, TEE) | 0.62 (0.47, 0.77) | 0.65 (0.50, 0.80) | 3.00 (2.54, 3.46) | 3.00 (2.53, 3.47) |
| (TEC, CVD) | 0.77 (0.65, 0.89) | 0.77 (0.65, 0.89) | 3.02 (2.68, 3.36) | 3.18 (2.89, 3.47) |
| (TEC, KA/VE) | 0.72 (0.56, 0.87) | 0.72 (0.56, 0.88) | 3.13 (2.60, 3.67) | 3.31 (2.80, 3.82) |
| (TEC, TEE) | 0.73 (0.62, 0.83) | 0.73 (0.62, 0.83) | 3.03 (2.63, 3.42) | 3.17 (2.83, 3.50) |
| (TEE, CVD) | 0.65 (0.50, 0.80) | 0.68 (0.54, 0.83) | 3.06 (2.43, 3.69) | 3.02 (2.42, 3.63) |
| (TEE, KA/VE) | 0.63 (0.50, 0.75) | 0.66 (0.53, 0.79) | 2.83 (2.38, 3.28) | 2.79 (2.36, 3.23) |
| (TEE, TEC) | 0.67 (0.53, 0.81) | 0.71 (0.57, 0.84) | 2.87 (2.42, 3.31) | 2.83 (2.39, 3.27) |

[a] 1 imputed for the dropouts with CVD in the 1st course, and 0 imputed for all other dropouts.

[b] 0 imputed for the dropouts with TEC in the 1st course, and 1 imputed for all other dropouts.

[c] Maximum of the survival time in reference group imputed for dropouts with KA/VE in the 1st course and 1/2 of the minimum remaining survival time imputed for all other dropouts

[d] 1/2 of the minimum remaining survival time in reference group imputed for dropouts with CVD or TEE in the 1st course and Maximum of the survival time imputed for all other dropouts

# *Some Closing Thoughts on This Trial*

1. Re-randomization design using "repeat a winner" and "switch-away from a loser" rules is a good idea.

2. Limitations of this study
   - Moderate sample size
   - Conservative simultaneous confidence intervals

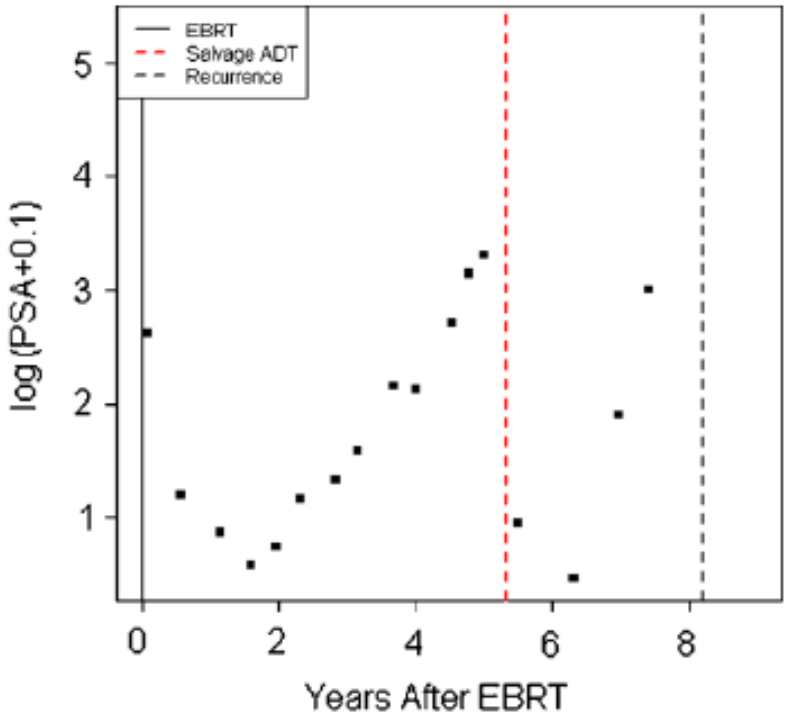
3. Make sure you define patient outcome carefully. It is seldom binary or simple, and it should reflect actual clinical practice.

4. Cute DTR and IPW methodologies are the right thing to do, but they are of little use without intelligent medical collaborators.

# *SMART → Observational Data*

## Prostate Cancer Recurrence Management

- Prostate cancer recurrence need to be managed after initial treatment (EBRT).
- PSA is measured over time as an indicator for increasing risk of recurrence.
- Salvage treatment decision need to be made dynamically to prolong the recurrence free survival




**When would be the best time to initiate salvage treatment?**

# *Some Ongoing Research*

- The proposed method provides reasonable amount of robustness for the problem
  - Random Forest to provide more robustness and flexibility model for weight estimation.
  - Non-parametric survival estimation without any assumption like proportional hazard.
- Random Survival Forest (Bou-Hamad, 2011) could be more reasonable estimation for the weights
- More efficient maximization method is needed for higher dimension $\mathbf{b}$, e.g. Adaptive grid approach (Leary, 2001)

# *Dynamic Treatment Regime*

## *Ultimate Goals:*

- *Personalized Health Care*
- *How to tailor diagnosis and treatment based on individual's information?*
- *How to better characterize each patient?*

# *Eyeball Test*


***Empirical Data +***
***Novel Statistical Methodology***
***Better Prognostic Tools***

- Patient satisfaction and personalized care
- Allocation of scarce and expensive resources (e.g. liver transplantation and HCV treatment)
- Survival improvement
- Guidance on adaptive treatment strategies for patients

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