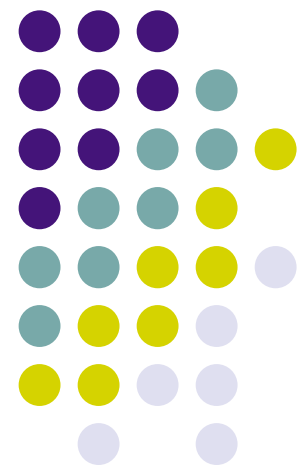


Personalized Treatment Selection Based on Randomized Clinical Trials

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Outline



- Motivation
- A systematic approach to separating subpopulations with differential treatment benefit in the absence of correct models
- Remarks
 - Evaluation of the system
 - Efficiency augmentation

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Drug Makers Fight Stimulus Provision

By ALICIA MUNDY

WASHINGTON -- The drug and medical-device industries are mobilizing to gut a provision in the stimulus bill that would spend \$1.1 billion on research comparing medical treatments, portraying it as the first step to government rationing.



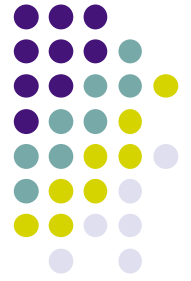
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Landov

Mr. Obama is under pressure to find long-run health-cost savings as projections show that Medicare spending is on track to severely deplete the federal budget. "Without question, we're headed for more of a public and private push for which medicines work best at the lowest cost in particular patients," said Mark McClellan, former Medicare and Medicaid chief under President George W. Bush.

Motivating Example

AIDS Clinical Trial ACTG320



- **Study Objective:** to compare the efficacy of
 - 3-drug combination therapy: Indinavir+Zidovudine/Stavudine+Lamivudine
 - 2-drug alternatives: Zidovudine/Stavudine + Lamivudine
- **Study population:** HIV infected patients with $CD4 \leq 200$ and at least three months of prior zidovudine therapy
 - 1156 patients randomized: 577 received 3-drug; 579 received 2-drug
- **Study conclusion:** 3-drug combination therapy was more effective compared to the 2-drug alternatives
- **Question:** 3-drug therapy beneficial to all subjects?

Predictor Z

Age
CD4_{wk 0}
log₁₀RNA_{wk 0}

Outcome Y

Change in CD4 from week 0 to 24

Treatment Benefit
Of 3 drug (vs 2 drug) | Z

2-drug

3-drug



Age: 12
CD4: 170
log₁₀RNA: 3.00

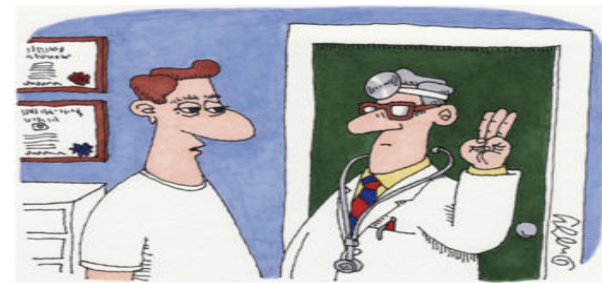


Age: 41
CD₄: 10
log₁₀RNA: 5.69

Likely to benefit from the 3-drug?
How much benefit would there be?

No ⇒ two drug
Treatment Benefit : 0 units of CD4 ↑

Yes ⇒ three drug
Treatment Benefit : 500 units of CD4 ↑



Background and Motivation



➤ Treatment × covariate interactions

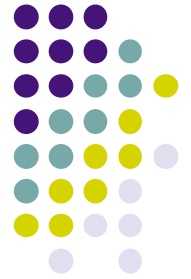
$$E(Y | \mathbf{Z}, Trt) = g\{m(\mathbf{Z}, \boldsymbol{\alpha}) + Trt \times h(\mathbf{Z}; \boldsymbol{\beta})\}$$

- Testing for $h(\mathbf{Z}; \boldsymbol{\beta}) = 0$
 - Helpful for identifying \mathbf{Z} that may affect treatment benefit
- Estimation of $h(\mathbf{Z}, \boldsymbol{\beta})$
 - Robust estimators of may be obtained for certain special cases (Vansteelandt et al, 2008)

➤ Issues arising from quantifying treatment benefit:

- Model based inference may be *invalid under model mis-specification*
- Fully non-parametric procedure may be *infeasible*
 - # of subgroups created by \mathbf{Z} may be large → difficult to control for the inflated type I error

Quantifying Subgroup Treatment Benefits



➤ **Notation:**

- **Z:** Covariates; **Y:** Outcome
- **Trt:** Treatment Group (independent of **Z**)
 - **Trt = 1:** experimental treatment (Y_1, \mathbf{Z}_1)
 - **Trt = 0:** placebo/standard treatment (Y_0, \mathbf{Z}_0)
- **Data:** $\{Y_{ki}, \mathbf{Z}_{ki}, i=1, \dots, n_k, k = 0, 1\}$

➤ **Objective: to approximate the treatment benefit conditional on Z:**

$$\eta_{\text{true}}(\mathbf{Z}) = E(Y_1 - Y_0 \mid \mathbf{Z}_1 = \mathbf{Z}_0 = \mathbf{Z})$$

Quantifying Subgroup Treatment Benefits



- **To approximate $\eta_{\text{true}}(\mathbf{Z})$, we may approximate $E(Y_k | \mathbf{Z}_k)$ via simple *working* models:**

$$E(Y_k | \mathbf{Z}_k = \mathbf{Z}) = g_k(\beta'_k \mathbf{Z})$$

- **Step 1: based on the working models, one may obtain an approximated treatment benefit**

$$\hat{\eta}(\mathbf{Z}) = g_1(\hat{\beta}'_1 \mathbf{Z}) - g_0(\hat{\beta}'_0 \mathbf{Z})$$

- **$\hat{\beta}_k$ is the solution to the estimating equations**

$$\sum_{i=1}^{n_k} w(\beta, \mathbf{Z}_{ki}) \mathbf{Z}_{ki} \{Y_{ki} - g_k(\beta' \mathbf{Z}_{ki})\} = 0$$

Quantifying Subgroup Treatment Benefits



- **Step 2: estimate the true treatment benefit among** $\varpi_v = \{\mathbf{Z} : \hat{\eta}(\mathbf{Z}) = v\}$

$$\Delta(v) = \mu_1(v) - \mu_0(v)$$

where $\mu_k(v) = E\{Y_k \mid \hat{\eta}(\mathbf{Z}_k) = v\} = E(Y_k \mid \mathbf{Z}_k \in \varpi_v)$

- **Estimate** $\mu_k(v)$ **non-parametrically as** $\hat{\mu}_k(v)$ **with the synthetic data** $\{Y_{ki}, \hat{\eta}(\mathbf{Z}_{ki})\}_{i=1, \dots, n_k}$ **and obtain**

$$\hat{\Delta}(v) = \hat{\mu}_1(v) - \hat{\mu}_0(v)$$

Quantifying Subgroup Treatment Benefits



- $\hat{\mu}_k(v)$ as the intercept of the solution to

$$\hat{\mathbf{S}}_{kv}(\mu, b) = \sum_{i=1}^n \begin{bmatrix} 1 \\ h^{-1} \hat{\epsilon}_{kvi} \end{bmatrix} K_h(\hat{\epsilon}_{kvi}) \{Y_{ki} - H(\mu + b \hat{\epsilon}_{kvi})\}$$

- $\hat{\epsilon}_{kvi} = \psi\{\hat{\eta}(\mathbf{Z}_{ki})\} - \psi(v)$
- $H(x) = x$ if Y continuous; $H(x) = e^x / (1 + e^x)$ if Y binary

Inference Procedures for Subgroup Treatment Benefits



- **Consistency of the estimator for $\Delta(v)$:**

$$\sup_v |\hat{\Delta}(v) - \Delta(v)| = O_p\{(nh)^{1/2} \log(n)\}$$

- $h : O(n^{-d})$ with $1/5 < d < 1/2$

- **Pointwise CI:**

$$\hat{W}(v) = (nh)^{1/2} \{\hat{\Delta}(v) - \Delta(v)\} \sim N(0, \sigma^2(v))$$

- **Simultaneous CI:** $\hat{S} = \sup_v |\hat{W}(v) / \hat{\sigma}(v)|$

$$P\{a_n(\hat{S} - d_n) < x\} \rightarrow e^{-2e^{-x}}$$

Selection of Bandwidth



➤ $h : O(n^{-d})$ with $1/5 < d < 1/2$

➤ Select h to optimize the estimation of

$$\Delta(v) = E\{Y_{1i} - Y_{0j} \mid \hat{\eta}(\mathbf{Z}_{0i}) = v, \hat{\eta}(\mathbf{Z}_{1j}) = v\}$$

➤ **Obtain h by minimizing a cumulative residual**

➤ under correctly model specification

$$E\left\{n_1^{-1} \sum_{i=1}^{n_1} Y_{1i} I(\mathbf{Z}_{1i} \leq z) - n_0^{-1} \sum_{j=1}^{n_0} Y_{0j} I(\mathbf{Z}_{0j} \leq z)\right\} = E[\Delta\{\eta(\mathbf{Z})\} I(\mathbf{Z} \leq z)]$$

➤ The resulting bandwidth has an order $n^{-1/3}$

Interval Estimation via Resampling Procedures



- Approximate the dist of $\hat{W}(v) = (nh)^{1/2} \{\hat{\Delta}(v) - \Delta(v)\}$ by

$$\hat{W}^*(v) = (nh)^{1/2} \sum_{i=1}^{n_1} \frac{K_h(\hat{\varepsilon}_{1vi})}{\sum_{i=1}^{n_1} K_h(\hat{\varepsilon}_{1vi})} \{Y_{1i} - \hat{\mu}_1(v)\} (N_{1i} - 1) -$$

$$(nh)^{1/2} \sum_{j=1}^{n_0} \frac{K_h(\hat{\varepsilon}_{0vj})}{\sum_{j=1}^{n_0} K_h(\hat{\varepsilon}_{0vj})} \{Y_{0j} - \hat{\mu}_1(v)\} (N_{0j} - 1) + (nh)^{1/2} \left\{ \hat{\Delta}(v; \hat{\beta}_1^*, \hat{\beta}_0^*) - \hat{\Delta}(v) \right\}$$

- $\mathbf{N} = \{N_{11}, \dots, N_{1n_1}; N_{01}, \dots, N_{0n_0}\}$ mean 1, variance 1 \perp data
- $\hat{\beta}_k^*$ obtained via perturbed estimating functions for

$$\sum_{i=1}^{n_k} w(\boldsymbol{\beta}, \mathbf{Z}_{ki}) \mathbf{Z}_{ki} \{Y_{ki} - g_k(\boldsymbol{\beta}' \mathbf{Z}_{ki})\} N_{ki} = 0$$

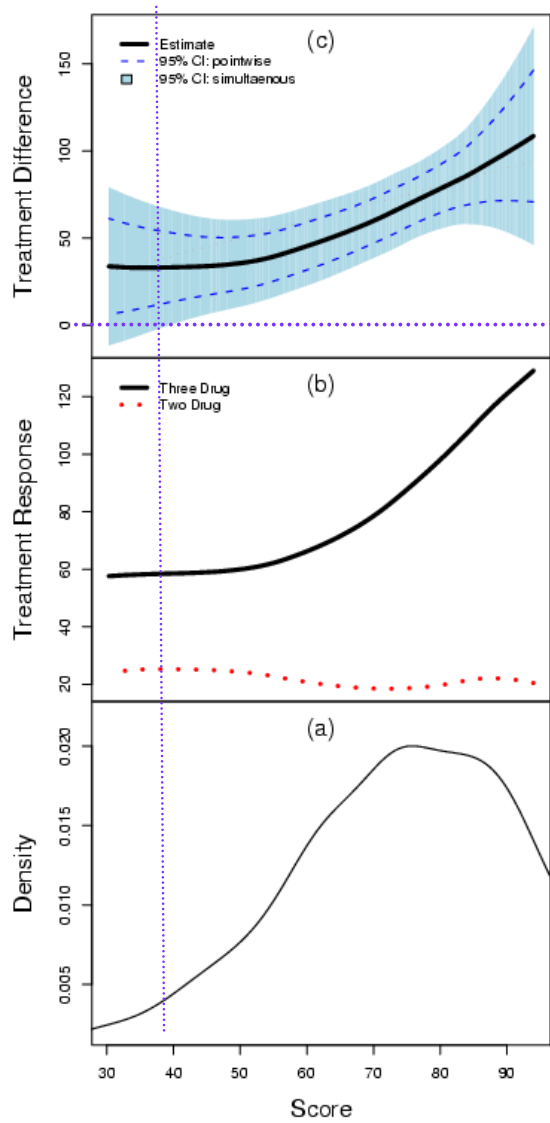
Example

AIDS Clinical Trial

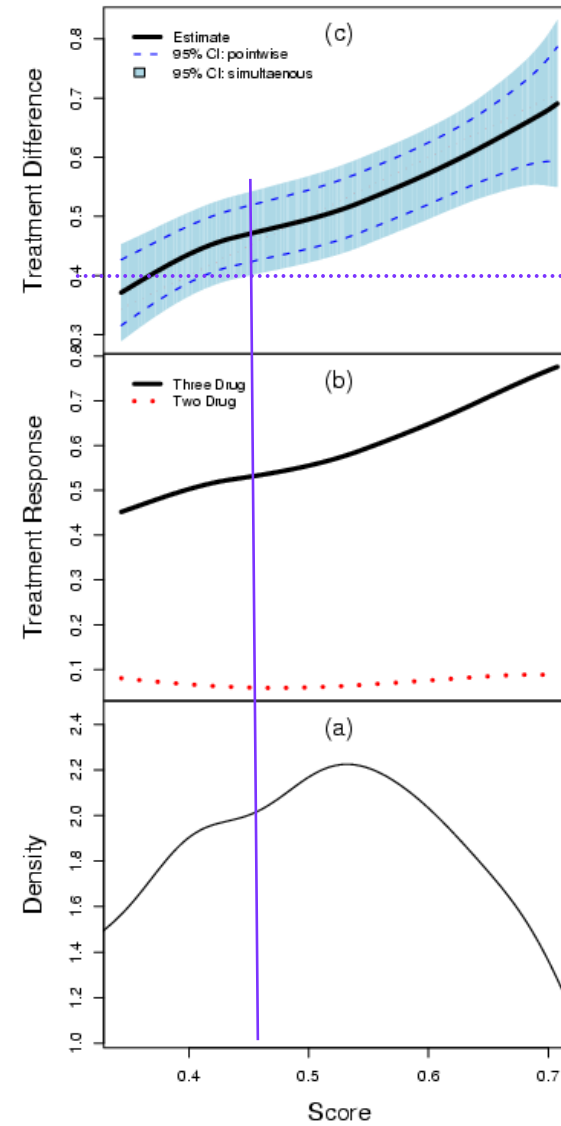


- **Objective: assess the benefit of 3-drug combination therapy vs the 2-drug alternatives across various sub-populations**
- **Predictors of treatment benefit:**
 - Age, $CD4_{wko}$, $\log CD4_{wko}$, $\log_{10} RNA_{wko}$
- **Treatment Response:**
 - Immune response (continuous)
 - change in CD4 counts from baseline to week 24
 - $E(Y | Z)$: linear regression
 - Viral response (binary)
 - RNA level below the limit of detection (500 copies/ml) at week 24
 - $E(Y | Z)$: logistic regression

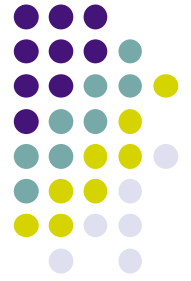
Immune Response



Viral Response



Evaluating the System for Assessing Subgroup Treatment Benefits

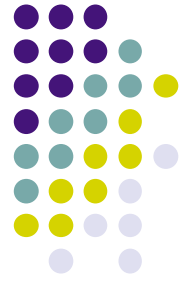


- Cumulative residual:

$$\begin{aligned} R(z) &= \int_{\mathbf{Z} \in \Omega_z} \left[E(Y_1 - Y_0 \mid \mathbf{Z}_1 = \mathbf{Z}_0 = \mathbf{Z}) - \hat{\Delta}\{\hat{\eta}(\mathbf{Z})\} \right] dF(\mathbf{Z}) \\ &= E\{Y_1 I(\mathbf{Z}_1 \in \Omega_z)\} - E\{Y_0 I(\mathbf{Z}_0 \in \Omega_z)\} - E[\hat{\Delta}\{\hat{\eta}(\mathbf{Z})\} I(\mathbf{Z} \in \Omega_z)] \end{aligned}$$

- Integrated sum of squared residuals $\int R(z)^2 dw(z)$ minimized under correct models

Efficiency augmentation with auxiliary variables



- Use auxiliary variables \mathbf{A} to obtain $\hat{\mathbf{e}}(v) \approx 0$ based on

$$E\{f(\mathbf{A}_1) - f(\mathbf{A}_0) \mid \mathbf{Z}_1 = \mathbf{Z}_0 = \mathbf{Z}\} = 0$$

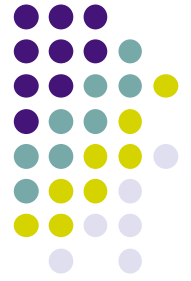
- for example:

$$\hat{\mathbf{e}}(v) = \frac{\sum_i K_h(\hat{\mathbf{e}}_{1vi}) \mathbf{A}_{1i}}{\sum_i K_h(\hat{\mathbf{e}}_{1vi})} - \frac{\sum_j K_h(\hat{\mathbf{e}}_{0vj}) \mathbf{A}_{0j}}{\sum_j K_h(\hat{\mathbf{e}}_{0vj})}$$

- Find optimal weights \mathbf{w}_{opt} to minimize

$$\text{var}\{\hat{\Delta}(v) + \mathbf{w}'\hat{\mathbf{e}}(v)\}$$

Efficiency augmentation with auxiliary variables



- Obtain optimal \mathbf{w}_{opt} based on the joint dist of $\{\hat{\Delta}(v), \hat{\mathbf{e}}(v)\}$

$$(nh)^{1/2} \{\hat{\Delta}(v) - \Delta(v)\} \approx (nh)^{-1/2} \sum_{i=1}^n E_i(v); \quad (nh)^{1/2} \hat{\mathbf{e}}(v) \approx (nh)^{-1/2} \sum_{i=1}^n \mathbf{e}_i(v)$$

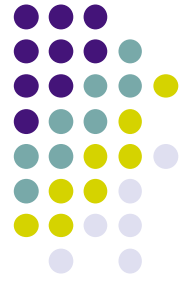
- *Regress $\{E_i(v)\}$ against $\{\mathbf{e}_i(v)\}$ to obtain \mathbf{w}_{opt} and the augmented estimator*

$$\hat{\Delta}_{\mathbf{w}_{opt}}(v) = \hat{\Delta}(v) + \mathbf{w}'_{opt}(v) \hat{\mathbf{e}}(v)$$

- *The mean squared residual error of the regression, $MRSE(v)$, while valid asymptotically, tends to under estimate the variance of the augmented estimator*

$$\text{var}\{\hat{\Delta}_{\mathbf{w}_{opt}}(v)\} \gg MRSE(v)$$

Efficiency augmentation with auxiliary variables



- To approximate the variance of $\hat{\Delta}_{\mathbf{w}_{opt}} = \hat{\Delta} + \mathbf{w}'_{opt} \hat{\mathbf{e}}$
 - *Double bootstrap: computationally intensive*
 - *Bias correction via a single layer of resampling:*

$$\text{var}(\hat{\Delta}_{\mathbf{w}_{opt}}) \approx MRSE + \text{trace}(\hat{\Sigma}_{\mathbf{we}}^2)$$

$$\hat{\Sigma}_{\mathbf{we}} = \hat{\Sigma}_{\mathbf{e}}^{-1} \frac{E\{\hat{\mathbf{e}}^* \hat{\mathbf{e}}^{*'} \hat{\varepsilon}^* | \text{Data}\}}{E\{(N-1)^3\}}$$

$\hat{\varepsilon}^*$ = residual of linear regression with $\{(\hat{\Delta}_b^* - \hat{\Delta}, \hat{\mathbf{e}}_b^*), b = 1, \dots, B\}$

# of Auxiliary Variables	5	9	17	41
Naïve	.90	.88	.87	.86
Bias Corrected	.92	.93	.93	.96

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Thank you !