Discovering and Evaluating Biomarkers for Guiding Treatment: Methodology for Precision Medicine

Module 19

July 29, 2016

Course Outline

Section I: Introduction

Section II: Developing marker-based treatment rules

Section III: Evaluating marker performance

Software and data analysis (lab format)

Section IV: Study design

Section V: Areas with evolving methodology

Section I: Introduction

- Motivation and context
- Terminology and notation
- Data examples

Biomarkers that predict treatment efficacy, a.k.a. *treatment selection / predictive / prescriptive* biomarkers, may be used to identify subjects most likely to benefit from treatment, thus sparing

- unnecessary or even harmful treatment
- associated toxicities
- cost of treatment

- E.g. when treatment is the standard of care, a biomarker may be used to identify the subset not likely to benefit, to spare unnecessary treatment (and associated cost and/or toxicity)
- E.g. when a new treatment is thought likely to benefit only some subjects, a biomarker identifying this subset can be used to recommend the intervention to them, and allow others to pursue alternatives.
- E.g. a biomarker that singles out subjects likely to experience a particular treatment-associated toxicity can be used to guide these subjects to other treatment options.

Examples of established markers

- Oncotype DX for predicting benefit of adjuvant chemotherapy to treat ER+ breast cancer
- RAS mutations for predicting benefit from anti-EGFR monoclonal antibodies for colorectal cancer
- CYP2C9 and VKORC1 genotypes for selecting dose of warfarin for preventing thrombosis/thromboembolism
- HLA-B*5701 allele for predicting hypersensitivity to abacavir for HIV treatment

- Framingham model for predicting CVD risk, to guide use of statins
- Gail model for predicting breast cancer risk, to guide use of tamoxifen

Types of biomarkers

Screening biomarkers are used to detect pre-clinical disease.

Diagnostic biomarkers are used to diagnose symptomatic subjects with a condition.

Risk prediction biomarkers are used to predict risk of a clinical outcome under standard of care. Also called *prognostic* biomarkers.

Treatment selection biomarkers are used to guide treatment decisions. Also called *predictive* or *prescriptive* biomarkers.

The last category of biomarkers is our focus.

Terminology

Biomarkers or *markers* include subject demographics, clinical characteristics, classical biomarkers, the results of genetic or proteomic analyses, and imaging test results.

Also referred to as *tailoring variables*, *covariates*, or *predictors*.

Treatment refers to some kind of experimental intervention– therapeutic or prophylactic.

Treatment rule maps the biomarker to a treatment recommendation. Also called a *treatment regime* or *treatment policy*.

Notation and setting

Our focus is the ideal setting of a randomized and controlled trial.

Subjects are randomized to treatment ($A = 1$) or standard of care ($A = 0$), which might be an alternative treatment or no treatment. $A = 0$ is also called "no treatment".

Marker X is measured at baseline. X may be univariate or multivariate.

Subjects are followed for a clinical outcome, D

- Continuous, ordinal, or binary
- Higher values of D are worse

We comment on extensions of this setting in Section V.

Data examples

- Breast cancer treatment trial*
- HIV prevention trial*
- Depression treatment trial
- Simulated data

Data are available on Dropbox:
`https://www.dropbox.com/sh/st62neevvv55ces/AAAG_t5Zx4JtOe0zL7N2NOMta?dl=0`

* Data modified for presentation and sharing.

Breast cancer treatment trial

Adjuvant chemotherapy is provided to most women with node-positive, ER+ breast cancer, despite the widespread belief that only a subset of women benefit from the chemotherapy. A biomarker which identifies women unlikely to benefit would avoid the cost and toxicity of chemotherapy for this subset.

SWOG S8814 was a phase 3 trial of tamoxifen vs. tamoxifen + chemotherapy in post-menopausal women with node-positive/ER+ breast cancer. The primary endpoint was recurrence or death within 5 years.

367 women had gene expression levels measured in the tumor tissue taken at the time of surgery (Albain et al. 2010).

The Oncotype DX recurrence score was calculated; it is a combination of expression levels of 16 cancer-related genes, currently used to guide treatment in this clinical context.

HIV prevention trial

Several recent clinical trials have demonstrated the efficacy of anti-retrovirals for HIV-prevention (PrEP) among MSM

- Downsides are cost, lack of adherence, unknown long-term safety profile

iPrEx was a phase 3 study of Truvada (FTC-TDF) as PrEP vs. placebo for HIV prevention in 2499 HIV-negative men and transgender women who have sex with men (Grant et al. 2010). The primary endpoint was HIV infection diagnosis.

Subject demographics and baseline risk behavior data may be useful for identifying the subset with the highest PrEP efficacy over 1 year, who can be targeted in rolling out the intervention.

Depression treatment trial

Chronic depression is difficult to treat. Cognitive behavioral therapy (CBT) may be more effective than pharmacotherapy, but requires as often as twice-weekly on-site clinic visits– significant time investment and monetary burden.

The Nefazodone-CBASP trial randomized 681 patients with chronic depression to Nefazodone, CBT, or the combination (Keller et al. 2000). The score on the 24-item Hamilton Rating Scale for Depression (HAMD) was the primary endpoint.

Over 50 baseline variables may be useful for identifying a subgroup for whom CBT is unnecessary, comparing the Nefazodone vs. combination therapy arms.

Simulated data

$\mathbf{X} = X_1, \ldots, X_{20} \sim$ multivariate normal. $\text{Corr}(X_i, X_j) = 0.2$.

$A \sim$ Bernoulli(0.5).

$\text{logit} P(D = 1|\mathbf{X}, A) = \gamma_0 + \gamma_1 A + \beta_0 \mathbf{X} + \beta_1 A * \mathbf{X}$.

$X_1, \ldots, X_{10}$ have neither main effects or interactions with treatment.
$X_{11}, \ldots, X_{15}$ have main effects only.
$X_{16}, \ldots, X_{20}$ have main effects and interactions with treatment.

Treatment is ineffective marginally:
$P(D = 1|A = 1) - P(D = 1|A = 0) = 0.02$.

$N = 2000$ subjects; 530 "events" $(D = 1)$.

Can $\mathbf{X}$ be used to identify a subgroup likely to benefit from treatment?

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