Leveraging individual subject characteristics to guide treatment decisions: Methodology for precision medicine

Module 8

July 24, 2018

Course Outline

Section I: Introduction

Section II: Building treatment rules

Software and data analysis (lab format)

Section III: Evaluating markers and treatment rules

Software and data analysis (lab format)

Section IV: Study design

Section V: Extensions

Section I: Introduction

- Motivation and context
- Terminology and notation
- Data examples

Biomarkers that predict the efficacy of treatment may be used to identify subjects most likely to benefit from treatment, thus sparing

- unnecessary or even harmful treatment
- associated toxicities and burden to the individual
- cost to the public health system

- 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

Terminology

We use the terms *biomarkers* and *markers* broadly to indicate 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, biomedical or otherwise.

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

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.

Notation and setting

We focus most on 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 dose/mode of delivery, or no treatment.

Covariate/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.

Other settings we comment on

In addition to the ideal RCT setting, we discuss other settings where X is measured at baseline and subjects are followed for outcome D:

Observational studies, where $A = 0$ for some and $A = 1$ for others, chosen at the discretion of the individual/physician

Untreated cohort studies, where $A = 0$ for all, e.g. natural history or historical studies (before advent of new treatment)

Treated cohort studies, where $A = 1$ for all, e.g. single-arm trials of an experimental treatment

Data examples

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

Data are available on Dropbox:
`https://www.dropbox.com/sh/8aab4ko1doywjq6/AACgbvBGRiRIstqCcnAevrSia?dl=0`

* Data modified for presentation and sharing.

Breast cancer treatment trial

Context: 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 that identifies women unlikely to benefit would avoid the cost and toxicity of chemotherapy for this subset.

Data: SWOG S8814, phase 3 trial (Albain et al. 2010)

- Post-menopausal women with node-positive/ER+ breast cancer
- Randomized to Tamoxifen vs. tamoxifen + chemotherapy
- Primary endpoint: recurrence or death within 5 years
- 367 women had gene expression levels measured in tumor tissue at surgery
- Oncotype DX recurrence score (RS) is a combination of expression levels of 16 cancer-related genes. RS, clinical factors, and constituent gene expression measurements may be useful for predicting chemotherapy efficacy and for guiding treatment.

HIV prevention trial

Context: 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. Targeting PrEP to high risk subgroups may be a cost-efficient strategy.

Data: iPrEx, phase 3 trial (Grant et al. 2010)

- 2499 HIV-negative men and transgender women who have sex with men
- Randomized to Truvada (FTC-TDF) as PrEP vs. placebo
- Primary endpoint: HIV infection diagnosis
- Demographics and baseline risk behavior data may be useful for targeting PrEP rollout

Depression treatment trial

Context: 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. Are there subject characteristics that can identify patients for whom CBT is unnecessary?

Data: Nefazodone-CBASP trial (Keller et al. 2000)

- 681 patients with chronic depression
- Randomized to Nefazodone, CBT, or the combination
- Primary endpoint: score on the 24-item Hamilton Rating Scale for Depression (HAMD)
- 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 not effective 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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