WHERE DO WE GO FROM HERE? NEXT GENERATION TREATMENT INTERVENTIONS

RAY NIAURA, PHD
Outline

- Personalized treatment & personalized medicine
- Clinical algorithms
- RCTs
- Multiphase Optimization Strategy (MOST)
- Adaptive Treatment strategies
- Sequential multiple assignment randomized trial (SMART)
  - Example 1: ADHD
  - Example 2: Pharmacologic treatment for smoking in HIV+ smokers
- Analysis Approaches
Treatment Outcome: In Need of Tailoring?

Figure 2 Intent-to-treat (ITT) quit rates over 2-month, 4-month and 6-month follow-up by study condition and race/ethnic group. ME: motivationally enhanced treatment; SC: standard care treatment
LESSONS LEARNED

Tailoring – To what?

- Race/ethnicity/culture/subculture/microculture
- HIV/AIDS unique needs (what are they, compared to other chronic illnesses?)
  - Reprieve of death sentence (ART/other advances)
  - Low SES (education; income; employment)
  - Social and welfare needs (housing; access to health care; social support)
  - Psychiatric and other medical comorbidities
  - Drug/alcohol use/risky behaviors
  - Sexual orientation/sexuality
  - Low health literacy/knowledge/awareness
  - Complicated treatment regimens (e.g., many meds)
PERSONALIZED TREATMENT

What is it?

Matching patient characteristics to choice of treatment options (initial treatment selection)

Adapting treatment to interim outcomes (dynamic treatment selection)
PERSONALIZED TREATMENT

Early efforts:

- Patient-treatment matching, tailoring based on clinical information
- Stepped care
- Clinical algorithms

Personalized medicine
A medical model that proposes the customization of healthcare - with medical decisions, practices, and/or products being tailored to the individual patient.
Pharmacogenetics

- Drug metabolism (e.g., warfarin)
- Disease subsets (cancers; schizophrenias)
- Targeted therapy (cellular; molecular)
- Safety and toxicity (risk of adverse events)
- Early treatment response/failure (biomarkers: imaging; proteomics)
- Prevention (risk stratification)
Results

302 HIV+ Latinos participated (64% male). Over half of the sample was not born in the US (51%), was of Puerto Rican origin (56%), had less than a high school education (57%), and were never married (53%). Mean age was 45 ± 8 years. Retention at follow-up is depicted in Figure 1. Those who did not receive or try the patch during the intervention were more likely to drop out than those who did try the patch (p = 0.004).
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Hughes, J.R., An updated algorithm for choosing among smoking cessation treatments, Journal of Substance Abuse Treatment (2013),
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Bernard Le Foll MD PhD, Tony P. George MD
CMAJ 2007;177(11):1373-80
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PERSONALIZED TREATMENT

How do we learn how to decide?
How do we learn how to decide?

RCT’s!
(sort of)
PERSONALIZED TREATMENT: RCT’S

RCT’s are best for:

Determining whether a treatment package performs better than

• A control or comparison group (placebo; no treatment; usual care)

• An alternative intervention (comparative effectiveness)
PERSONALIZED TREATMENT: RCT’S

(Conventional) RCT’s are not as good for:

• Evaluating components in multicomponent treatments (black box treatment packages)

• Stratified effects (matching)

• Evaluating sequential treatments
MULTICOMPONENT RCT’S

An RCT that finds a significant effect DOES NOT tell us

- Which components are making positive contributions to overall effect
- Whether the inclusion of one component has an impact on the effect of another
- Whether a component’s contribution offsets its cost
- Whether all the components are really needed
- How to make the intervention more effective, efficient, and scalable
MULTICOMPONENT RCT’S

An RCT that finds a non-significant effect DOES NOT tell us

• Whether any components are worth retaining
• Whether one component had a negative effect that offset the positive effect of others
• Specifically what went wrong and how to do it better the next time
MULTICOMPONENT RCT’S

What’s the alternative?
• MOST: Preparation, Optimization, Evaluation

SCRENNING PHASE
Starting point: Components that are candidates for inclusion in an intervention
Purpose: Efficient selection of active components
Tools: Randomized experimentation via factorial ANOVA (full or fractional)

REFINING PHASE
Starting point: Components selected in screening phase
Purpose: Fine tuning: e.g., identifying optimal dose
Tools: Randomized experimentation via factorial ANOVA (full, fractional, response surface), SMART

CONFIRMING PHASE
Starting point: Components selected in screening phase and doses established in refining phase
Purpose: Confirm efficacy of optimized intervention
Tools: Standard randomized confirmatory evaluation trial

OPTIMIZED INTERVENTION

Figure 1. Outline of the Multiphase Optimization Strategy (MOST)
ANOVA, analysis of variance; SMART, sequential multiple assignment randomized trial

PERSONALIZED TREATMENT: RCT’S

(Conventional) RCT’s are not as good for:

- Evaluating components in multicomponent treatments (black box treatment packages)
- Stratified effects (matching)
- Evaluating sequential treatments
ADAPTIVE TREATMENT STRATEGIES (ATS) AKA DYNAMIC TREATMENT REGIMES (DTR) AKA ADAPTIVE INTERVENTIONS

• Evaluating sequential treatments
**ADAPTIVE TREATMENT STRATEGIES (ATS)**

**Figure 2.** Sequential multiple assignment randomized trial (SMART) with no embedded tailoring variables.

Sequential multiple assignment randomized trial (SMART)

Small-Cell Lung Cancer

Figure 1. Sequential multiple assignment randomized trial for attention-deficit/hyperactivity disorder (ADHD) study.

Adaptive Treatment Strategies:

Are individually tailored time-varying treatments composed of:

- a sequence of critical treatment decisions
- tailoring variables decision rules, one per critical decision; decision rules input tailoring variables and output an individualized treatment recommendation.
Operationalize clinical practice:

• From the *individual/patient/client’s* point of view: A sequence of (individualized) treatments

• From the *clinical scientist’s* point of view: A sequence of **decision rules** that recommend one or more treatments at each critical decision.
Critical treatment decisions:

- How long to try the first treatment?
- How should a treatment be delivered?
- How intensive should a treatment be?
- When to stop/start treatment?
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Tailoring variables:

- severity of illness,
- presence of comorbid mental or physical conditions,
- adherence to present treatment,
- side effects resulting from present treatment,
- symptoms while in treatment.
Why Adaptive Treatment Strategies?

- High heterogeneity in response to any one treatment: What works for one person may not work for another.
- Improvement often marred by relapse.
- Lack of adherence or excessive burden is common.
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient.
Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

Treatment incurs side effects and burden, particularly over longer time periods.
Problems with adherence:
• Variations of treatment or different delivery mechanisms may increase adherence
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

Excessive treatment may lead to non-adherence

Treatment is costly (allocate resources to patients with more severe problems)

More is not always better!
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Parts of the Adaptive Treatment Strategy:

• Choice of the Tailoring Variable
• Measurement of the Tailoring Variable
• Decision Rules linking Tailoring Variables to Treatment Decisions
• Implementation of the Decision Rules
What is a sequential multiple assignment randomized trial (SMART)?

- Multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

- Goal is to inform the construction of adaptive treatment strategies.
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Subset of adaptive designs


Why not use data from multiple trials to construct the adaptive treatment strategy?

• Choose the best initial treatment on the basis of a RCT of initial treatments and choose the best secondary treatment on the basis of a RCT of secondary treatments.
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Why not use data from multiple trials to construct the adaptive treatment strategy?

Delayed Therapeutic Effects

*Positive synergies:*

- Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment.

- Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

Delayed Therapeutic Effects

*Negative synergies:*

- Treatment A may produce a higher proportion of responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond.

- Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.
Prescriptive Effects

• Treatment A may not produce as high a proportion of responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.
Sample Selection Effects

- Subjects who will enroll in, who remain in, or who are adherent in the trial of the initial treatments, may be quite different from the subjects in SMART.

e.g., maintenance and retreatment strategies in smoking cessation.
Adaptive Interventions

Behavioral interventions for prevention and treatment are an important part of the fight against drug abuse and conditions such as HIV/AIDS and mental illness. Among the challenges faced by scientists is how and when to alter the course of treatment for participants in the intervention.

Sequential, Multiple Assignment, Randomized Trials (SMART)

Adaptive interventions (also known as “adaptive treatment strategies” or “dynamic treatment regimes”) are individually tailored treatments. Formally, an adaptive intervention is a sequence of decision rules that specify how the intensity or type of treatment should change depending on the patient’s needs. We are developing sequential, multiple assignment, randomized trials (SMART) to enable scientists to build adaptive interventions.

Why Conduct a SMART to Build an Adaptive Intervention?

Interventions that adapt at the right times can improve participant outcomes (e.g., intensifying for people who do not respond to the initial treatment) while decreasing the cost and burden of the intervention (e.g., stepping down treatment for responsive participants). SMART designs provide the data needed to construct high-quality adaptive interventions.

Read more

Introductory Example: Using Medication to Prevent Alcoholism Relapse

Resources

- Recommended reading
- NIH PAs calling for SMART designs
- Podcast: Adaptive interventions
- Online SMART presentations

Center Collaborations

This work began as a collaboration between Susan Murphy and Linda Collins, which led to two projects: work on optimizing interventions, and SMART.

Definitions

- View All
- Adaptive Intervention
- Adaptive Treatment Strategy
- Dynamic Treatment Regime
- Treatment Policies, Inference
- Multi-Stage Decision Making
- Reinforcement Learning
- Tailoring Variable
EXAMPLE 1: ADHD

• Dynamic treatment regime for children with ADHD

• W. Pelham is the intervention scientist

Slides courtesy of Linda Collins
http://methodology.psu.edu
DYNAMIC TREATMENT REGIMES FOR CHILDREN WITH ADHD

• Two approaches to treatment of ADHD
  ◦ Behavior modification (BMOD)
  ◦ Medication

• They can be combined into a dynamic treatment regime

• What is the best set of decision rules?
DYNAMIC TREATMENT REGIMES FOR CHILDREN WITH ADHD

Research questions that must be addressed for optimization:

◦ Is it better to start with BMOD or medication?
  • Note: BMOD much more expensive
◦ For those who do not respond to initial treatment, is it better to
  • Remain with the same strategy but enhance?
  • Augment with the other strategy?
◦ What is the best overall strategy?
SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART)

- **Medication**
  - Response → Continue Med (SG1)
  - Non-Response → Enhance (SG2)

- **BMOD**
  - Response → Augment (SG3)
  - Non-Response → Continue BMOD (SG4)

- Enhance (SG5)
- Augment (SG6)
QUESTIONS WE CAN ADDRESS WITH SMART

Is it better to start with BMOD or MED?

• \((SG1+SG2+SG3)\) vs. \((SG4+SG5+SG6)\)
• Medication vs. BMOD
  ◦ Averaging over subsequent treatment
QUESTIONS WE CAN ADDRESS WITH SMART

Is it better to Enhance or Augment for non-responders?
• (SG2+SG5) vs. (SG3+SG6)
• Enhance vs. Augment
QUESTIONS WE CAN ADDRESS WITH SMART

• What is the best overall strategy? There are FOUR embedded here:

Stage 1 = {MED},
   IF response = {NO}
   THEN stage 2 = {AUGMENT}
   ELSE continue stage 1

Stage 1 = {MED},
   IF response = {NO}
   THEN stage 2 = {ENHANCE}
   ELSE continue stage 1

Stage 1 = {BMOD},
   IF response = {NO}
   THEN stage 2 = {AUGMENT}
   ELSE continue stage 1

Stage 1 = {BMOD},
   IF response = {NO}
   THEN stage 2 = {ENHANCE}
   ELSE continue stage 1
Example 2: Pharmacologic treatment for smoking in HIV+ smokers

## Smoking Cessation: What Works?

**Pharmacotherapies**

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<th>Comparison</th>
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</table>
(1) What does one do when smokers fail to quit or relapse?

(2) What does one do when smokers quit?
(1) What does one do when smokers fail to quit or relapse?

- Continue same treatment
- Re-treat: Switch or augment

(2) What does one do when smokers successfully quit?

- Monitor progress
- Relapse prevention intervention
- Continue to treat (maintenance treatment)
(1) What does one do when smokers fail to quit or relapse?

  - Re-treat: Switch or augment

(2) What does one do when smokers successfully quit?

  - Monitor progress
  - Relapse prevention intervention
  - Continue to treat (maintenance treatment)

How do you test these strategies?

The SMART way
Example

O1: Tailoring variables (e.g., prior tx response; adverse events; depression)

A2: Initial treatment

O2: Initial response (e.g., withdrawal symptoms; side effects; lack of efficacy; lack of adherence)

A2: Choice of next treatment based on O2 – better drug or behavioral tx?

Y: Outcome (quit or relapse)
Tailoring variables:

- severity of illness
- presence of comorbid mental or physical conditions
- adherence to present treatment
- side effects resulting from present treatment
- symptoms while in treatment
Analysis Approaches:

IPTW; G-computation

Q-learning (Watkins, 1989; Murphy, 2005)
Popular method from computer science.
Regression-based:
Sequence of regressions
One regression for each stage
Rationale:
Base your decision on what you know up to that point
Assume best future decisions

Package ‘qLearn’

February 15, 2013

Type  Package

Title  Estimation and inference for Q-learning

Version  1.0

Date  2012-03-01

Author  Jingyi Xin, Bibhas Chakraborty, and Eric B. Laber

Maintainer  Bibhas Chakraborty <bc2425@columbia.edu>

Description  Functions to implement Q-learning for estimating optimal dynamic treatment regimes from two stage sequentially randomized trials, and to perform inference via m-out-of-n bootstrap for parameters indexing the optimal regime.
AFTER THE SMART

Results of analyses will be used to decide on best decision rules, i.e. optimized intervention

This does not tell us whether the optimized intervention has a statistically significant effect as compared to a control

Must move to the evaluation phase for that: (RCT)
It's Challenge Time
CHALLENGE ACCEPTED
THANK YOU
**Figure 1**

The longitudinal phase-based model of tobacco use initiation and cessation.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Exemplar challenges</th>
<th>Exemplar intervention components</th>
<th>Exemplar measures of mechanism</th>
<th>Exemplary treatment selection measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4. Lack of support</td>
<td></td>
<td>4. Self-efficacy</td>
<td></td>
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<tr>
<td></td>
<td>2. Withdrawal and craving</td>
<td>2. Behavioral intervention to reduce smoking contingencies,</td>
<td>2. Smoking rate and contingencies</td>
<td>2. Number of days smoking early in attempt</td>
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<tr>
<td></td>
<td></td>
<td>make practice quit attempts, practice coping, lifestyle changes</td>
<td>(cue exposure)</td>
<td></td>
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<tr>
<td></td>
<td>3. Coping skill practice</td>
<td>3. Motivational and supportive counseling</td>
<td>3. Practice quit attempts and coping and symptomatic reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Decline in positive affect</td>
<td>2. Supportive counseling</td>
<td>increase and trajectory</td>
<td></td>
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<tr>
<td></td>
<td>3. Smoking cues</td>
<td></td>
<td>2. Positive affect</td>
<td>2. Number of days smoking early in attempt</td>
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<tr>
<td></td>
<td>4. Lapses</td>
<td></td>
<td>3. Perceived support</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>(buffered temptations and stressors)</td>
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<tr>
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<td></td>
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<td></td>
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<tr>
<td>Maintenance</td>
<td>1. Lapses</td>
<td>1. Medication (extended)</td>
<td>1. Medication use</td>
<td>1. Lapses and lapse latency</td>
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<tr>
<td></td>
<td>5. Declines in motivation</td>
<td></td>
<td>5. Lapse response</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>(self-efficacy, motivation, craving)</td>
<td></td>
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<tr>
<td></td>
<td>7. Non-adherence</td>
<td></td>
<td>6. Perceived support</td>
<td></td>
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<td>7. Response to smoking</td>
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