Adaptive Treatment Strategies

- “...are individually tailored sequences of treatments, with treatment type and dosage adapted to the patient.”

- “Adaptive”
  - Decisions are tailored to individual patients at the time of treatment

- “Strategy”
  - A sequence of treatment decisions unfolding over time
Adaptive Treatment Strategies?

- Sounds like “Clinical Practice”
  - Doctors tailor treatments to individual patients, and often have a long-range strategy in mind.
- We want to operationalize this
  - We can then construct adaptive treatment strategies from data.
Why Adaptive Treatment Strategies?

- When do doctors use them? Chronic illness.
- Adaptive (tailoring)
  - What works for one patient may not work for another.
- Strategy (sequencing)
  - What works now may not work later.
  - There may be cycles of remission/relapse.
- **Treatments provide both therapeutic and diagnostic benefit.**
Example: Depression*

- Provide Citalopram for up to 12 weeks.
  - If the patient **remits**, defined by a QIDS-SR depression rating score $\leq 5$, continue to provide Citalopram and **monitor**.
  - Otherwise if the patient **does not remit**,
    - If the patient’s QIDS-SR score is $> 15$, switch treatment to **Bupropion**.
    - If the patient’s QIDS-SR score is $\leq 15$, switch treatment to **Venlafaxine**.

- Here, treatments are **adapted** using QIDS-SR as a tailoring variable, and the **strategy** has up to two treatments

*I am not a psychiatrist! This is a made-up example. Don’t try this at home.*
Provide CITalopram for up to 12 weeks.

- If the patient *remits*, defined by a QIDS-SR depression rating score $\leq 5$, continue to provide CITalopram and monitor.

- Otherwise if the patient *does not remit*,
  - If the patient’s QIDS-SR score is $> 15$, switch treatment to BUPropion.
  - If the patient’s QIDS-SR score is $\leq 15$, switch treatment to VENlafaxine.
How would we develop such a treatment strategy?

- **From Data**
  - Longitudinal data collected from patients as they follow different paths through a proposed set of possible treatment strategies

- **Sequenced Multiple Assignment Randomized Trials**
  - Pinpoint a *small number* of critical decisions per patient to investigate
  - A randomization takes place at each critical decision (multiple randomizations for each patient)
  - Goal is to inform the construction of an adaptive treatment strategy.
SMART Design Principles

- At each stage, restrict class of treatments only by ethical, feasibility or strong scientific considerations. **Use a summary instead of complicated intermediate outcomes** to restrict class of next treatments.

- **But collect intermediate outcomes** that might be useful in ascertaining for whom each treatment works best. This information might enter into the adaptive treatment strategy.
How might we arrive at this strategy?
How might we arrive at this strategy?

- Run a randomized trial
- Start at the end of the study
- Identify the best final treatment
- Work backwards in time toward the beginning of the study
- Analyses can use patient characteristics/outcomes to provide evidence for a more sophisticated adaptive treatment strategy.
Remission → Monitor

CIT

No Remission

Remission

SER

No Remission

Remission

BUP

VEN

Monitor

BUP

VEN
CIT

Remission → Monitor

No Remission → BUP if QIDS > 15

QIDS ≤ 15 → VEN

SER

Remission → Monitor

No Remission → BUP if QIDS > 15

QIDS ≤ 15 → VEN
CIT

Remission → Monitor

No Remission → BUP

SER

Remission → Monitor

No Remission → BUP

QIDS > 15 → Monitor

QIDS <= 15 → BUP

QIDS > 15 → BUP

QIDS <= 15 → VEN

? → VEN
CIT

Remission

No Remission

? (Decision Point)

QIDS > 15

QIDS <= 15

Monitor

BUP

VEN
Run a randomized trial

- Start at the end of the study
- Identify the best final treatment
- Work backwards in time toward the beginning of the study
- Analyses can use patient characteristics/outcomes to provide evidence for a more sophisticated adaptive treatment strategy.
Analyses To Date

- STAR*D: Sequenced Treatment Alternatives to Relive Depression
  - NIMH-funded, ~4000 patients, ~4 stages of treatment
- CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness
  - NIMH-funded, ~1600 patients, ~3 phases of treatment

Both of these predate SMART, and are quite complicated.

We have done preliminary analyses of these studies.
Ongoing Research

- How do we know if we’ve really constructed a good strategy?
  - Eric Laber and I are working on measures of confidence for strategy quality.

- Can the data inform us about which quantities are useful for selecting treatments?
  - Peng Zhang is working on selecting covariates for decision points.

- What if we are interested in an objective that is censored?
  - Zhiguo Li is working on incorporating survival analysis techniques.
<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dan Lizotte</td>
<td><a href="mailto:danjl@umich.edu">danjl@umich.edu</a></td>
</tr>
<tr>
<td>Zhiguo Li</td>
<td><a href="mailto:zhiguo@umich.edu">zhiguo@umich.edu</a></td>
</tr>
<tr>
<td>Peng Zhang</td>
<td><a href="mailto:pczhang@umich.edu">pczhang@umich.edu</a></td>
</tr>
<tr>
<td>Susan Murphy</td>
<td><a href="mailto:samurphy@umich.edu">samurphy@umich.edu</a></td>
</tr>
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