

This treatment works
40% of the time on
average!

How about one
that works 100%
of the time on
me?

We are ~~never~~ getting to precision medicine in psychiatry

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Lenze Disclosure of Interest

- Sources of Research Support
 - current: NIH
 - current: McKnight Brain Research Foundation
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- Stock Equity
 - none
- Speaker's Bureau
 - none
- Consulting Relationships
 - none current
 - past: Janssen
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Precision Clinical Trial team

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Eco Perez

Preethi Umashanker

David Plant

Avi Klein

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Bridget Bernstein

Shahadat Aziz

Overview of today's talk

RCTs

Sample population



Group 1

Group 2

Precision Clinical Trials

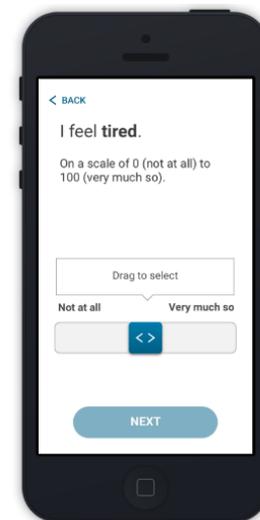


New methods

design flaws in RCTs



biomarkers



This is a day in my life as a psychiatrist

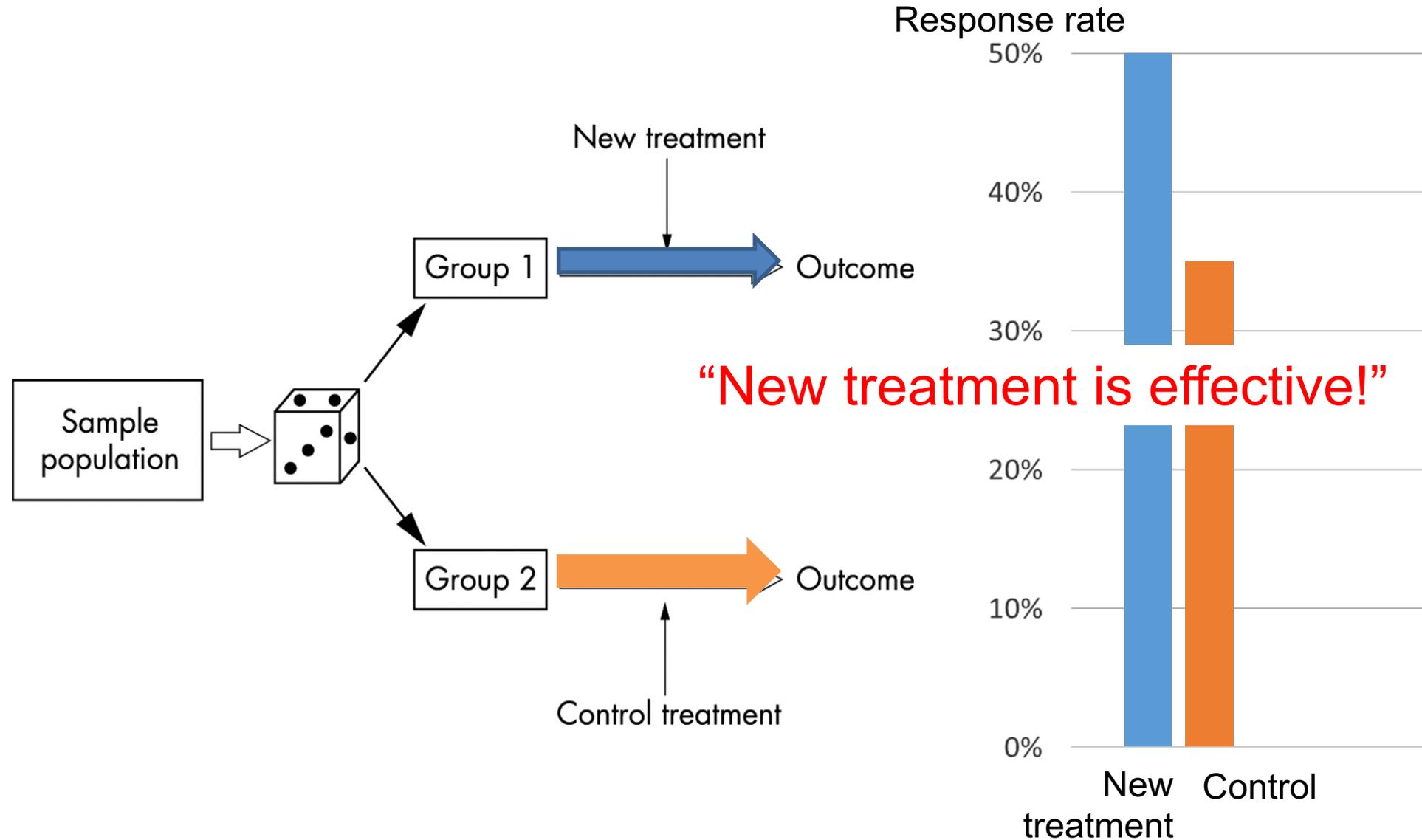
Depression: “I’m on an antidepressant but I still feel depressed. What do I do now?”

Anxiety: “When I get worrying, it is hard to stop.”

Cognitive problems:
“I’m having a lot of trouble with my memory. What can I do about it?”



Randomized controlled trials (RCTs) are a powerful tool for evidence-based medicine



Clinical trials provide answers!

Depression: “I’m on an antidepressant but I still feel depressed. What do I do now?”



Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial

Eric J Lenze, Benoit H Mulsant, Daniel M Blumberger, Jordan F Karp, John W Newcomer, Stewart J Anderson, Mary Amanda Dew, Meryl A Butters, Jacqueline A Stack, Amy E Begley, Charles F Reynolds III

Summary

Lancet 2015; 386: 2404-12

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September 28, 2015
[http://dx.doi.org/10.1016/S0140-6736\(15\)00308-6](http://dx.doi.org/10.1016/S0140-6736(15)00308-6)

Background Treatment-resistant major depression is common and potentially life-threatening in elderly people, in whom little is known about the benefits and risks of augmentation pharmacotherapy. We aimed to assess whether aripiprazole is associated with a higher probability of remission than is placebo.

Methods We did a randomised, double-blind, placebo-controlled trial at three centres in the USA and Canada to



Anxiety: “When I get worrying, it is hard to stop.”

Escitalopram for Older Adults With Generalized Anxiety Disorder

A Randomized Controlled Trial

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Context Generalized anxiety disorder (GAD) is one of the most common psychiatric disorders in older adults; however, few data exist to guide clinicians in efficacious and safe treatment. Selective serotonin reuptake inhibitors (SSRIs) are efficacious for younger adults with GAD, but benefits and risks may be different in older adults.

Objective To examine the efficacy, safety, and tolerability of the SSRI escitalopram in older adults with GAD.

Design, Setting, and Participants A randomized controlled trial in primary care practices and related specialty clinics in Pittsburgh, Pennsylvania, of 177 participants aged 60 years or older with a principal diagnosis of GAD randomized to receive either escitalopram or placebo and conducted between January 2005 and January 2008.

Interventions Twelve weeks of 10 to 20 mg/d of escitalopram (n=85) or matching placebo (n=92).

Main Outcome Measures Cumulative response defined by Clinical Global Impressions-Improvement score of much or very much improved; time to response; and anxiety and role functioning changes measured by the Clinical Global Impressions-Improvement scale, Hamilton Anxiety Rating Scale, Penn State Worry Questionnaire, Late-Life Function and Disability Instrument activity limitations subscale, and the role emotional impairment and

Antidepressant Medication Augmented With Cognitive-Behavioral Therapy for Generalized Anxiety Disorder in Older Adults

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Andrew J. Petkus, M.A.
Kamila S. White, Ph.D.
Hoang Nguyen, M.D.
Sander Kornblith, Ph.D.
Carmen Andreescu, M.D.
Sidney Zisook, M.D.
Eric J. Lenze, M.D.

Objective: Generalized anxiety disorder is common among older adults and leads to diminished health and cognitive functioning. Although antidepressant medications are efficacious, many elderly individuals require augmentation treatment. Furthermore, little is known about maintenance strategies for older people. The authors examined whether sequenced treatment combining pharmacotherapy and cognitive-behavioral therapy (CBT) boosts response and prevents relapse in older adults with generalized anxiety disorder.

Method: Participants were individuals at least 60 years of age with generalized anxiety disorder (N=73) who were recruited from outpatient clinics at three

weeks of maintenance escitalopram; escitalopram alone, followed by maintenance escitalopram; escitalopram plus CBT, followed by pill placebo; and escitalopram alone, followed by placebo.

Results: Escitalopram augmented with CBT increased response rates on the Penn State Worry Questionnaire but not on the Hamilton Anxiety Rating Scale compared with escitalopram alone. Both escitalopram and CBT prevented relapse compared with placebo.

Conclusions: This study demonstrates effective strategies for treatment of generalized anxiety disorder in older adults. The sequence of antidepressant medication augmented with CBT leads to worry



Mindfulness training



Cognitive training



Exercise



Cognitive problems:
“I’m having a lot of trouble with my memory. What can I do about it?”

In spite of evidence-based treatments, mental illness morbidity remains high

Illness category:

Morbidity over time:

Cardiovascular disease



Infectious disease



Cancer



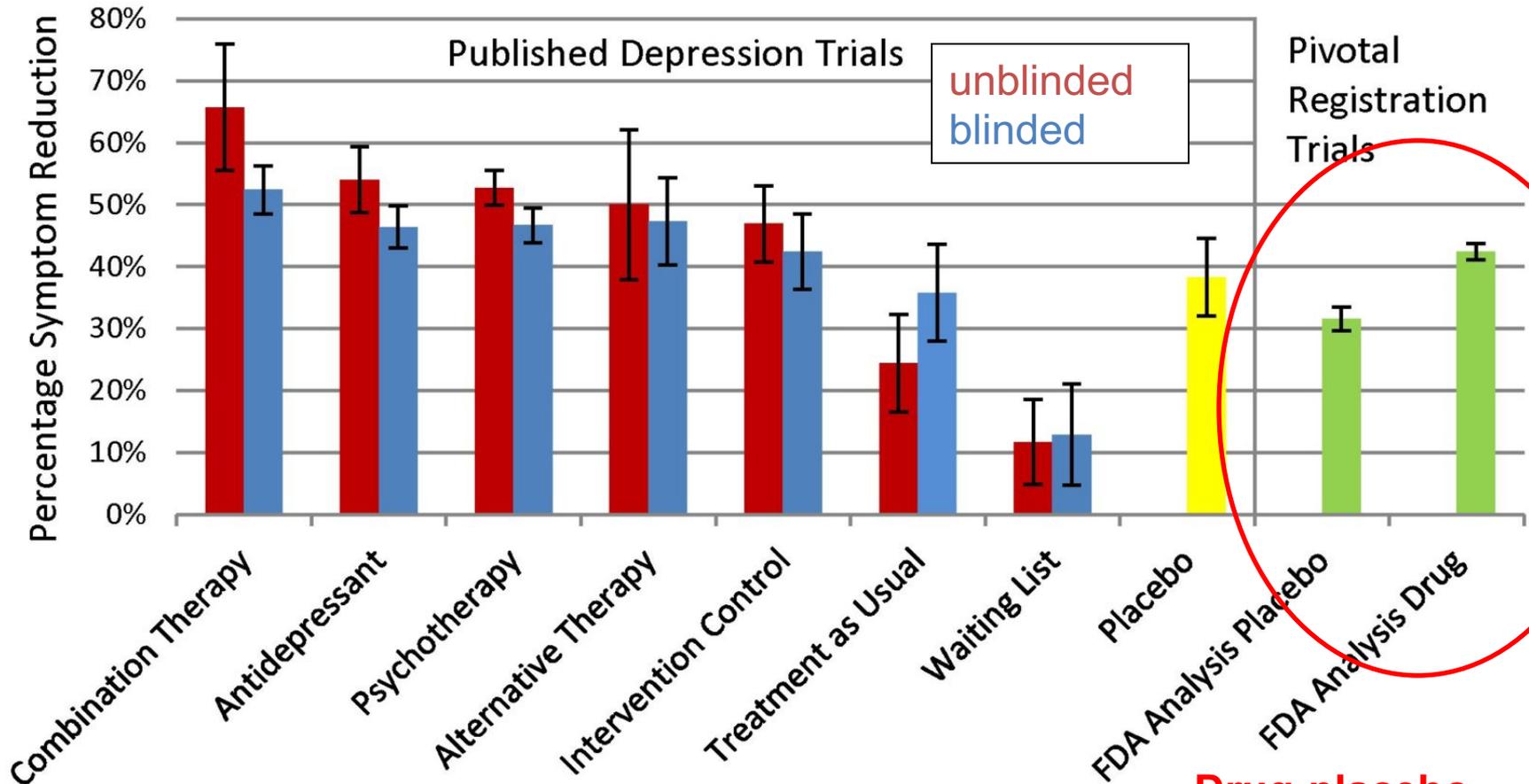
Mental illness



WHY?

Treatments work...

for some



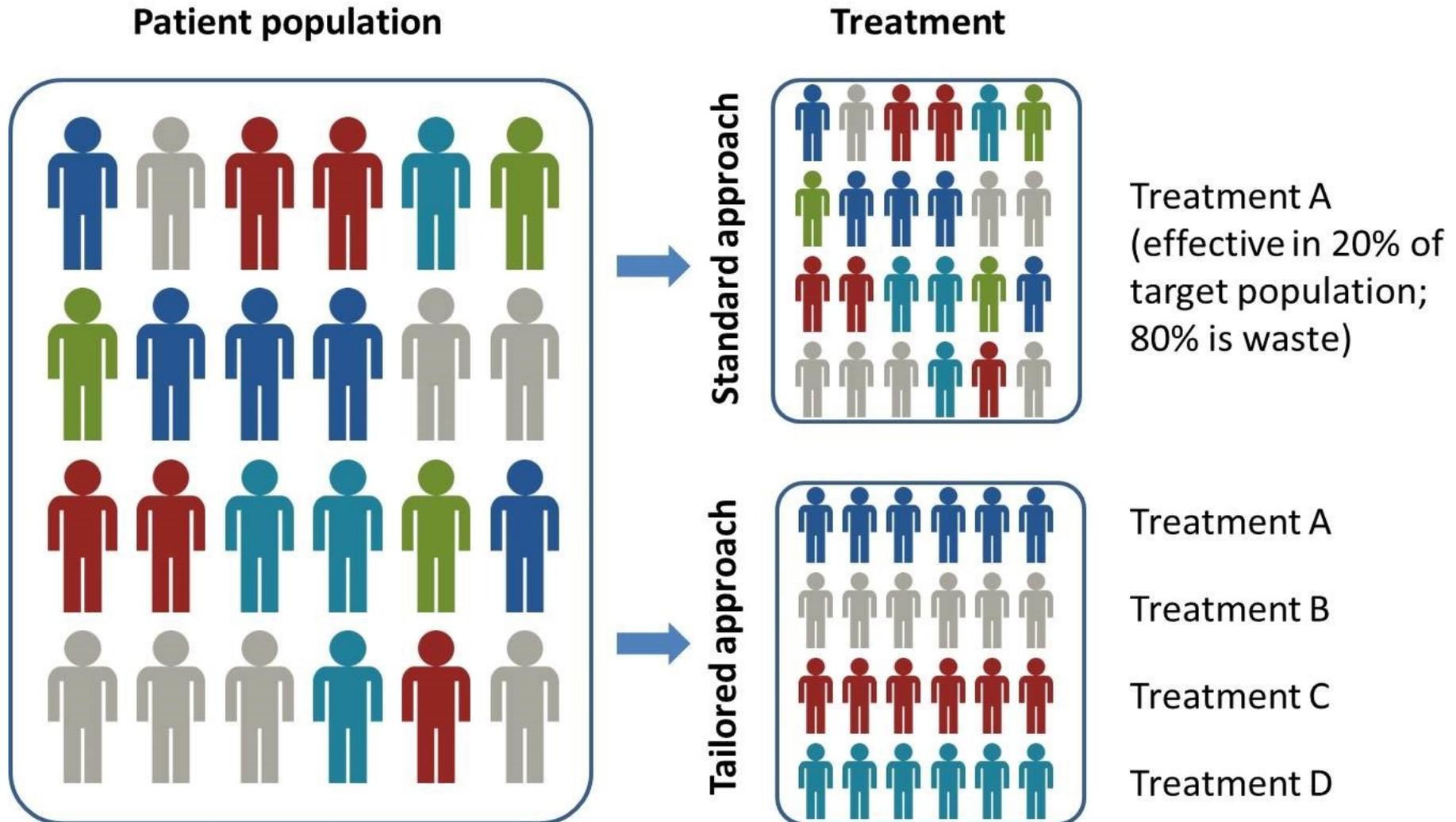
**Drug-placebo
difference is small**

[Arif Khan et al, PLOS One 2012]

Psychiatry is “trial and error” medicine



Precision medicine = individually tailored treatments



Precision medicine in psychiatry means markers as enrichment factors



Genetic variants



Neuroimaging

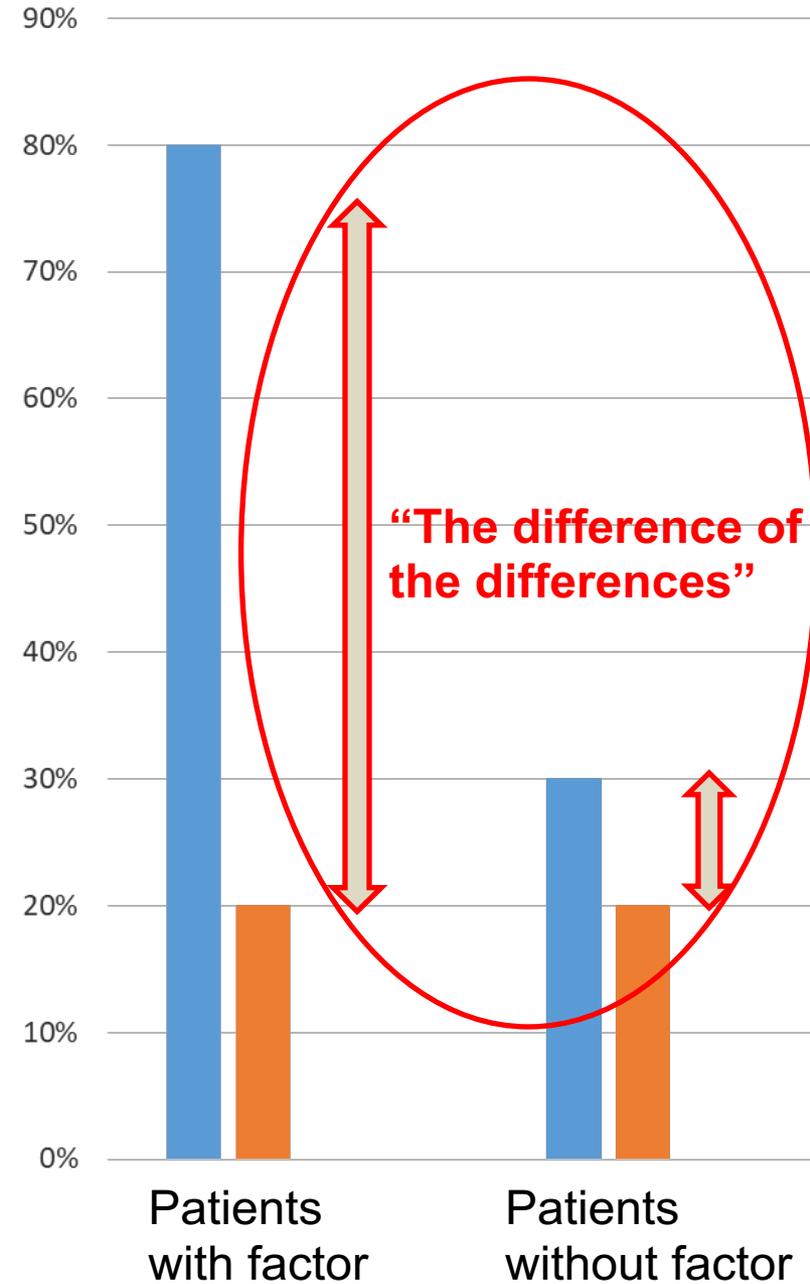
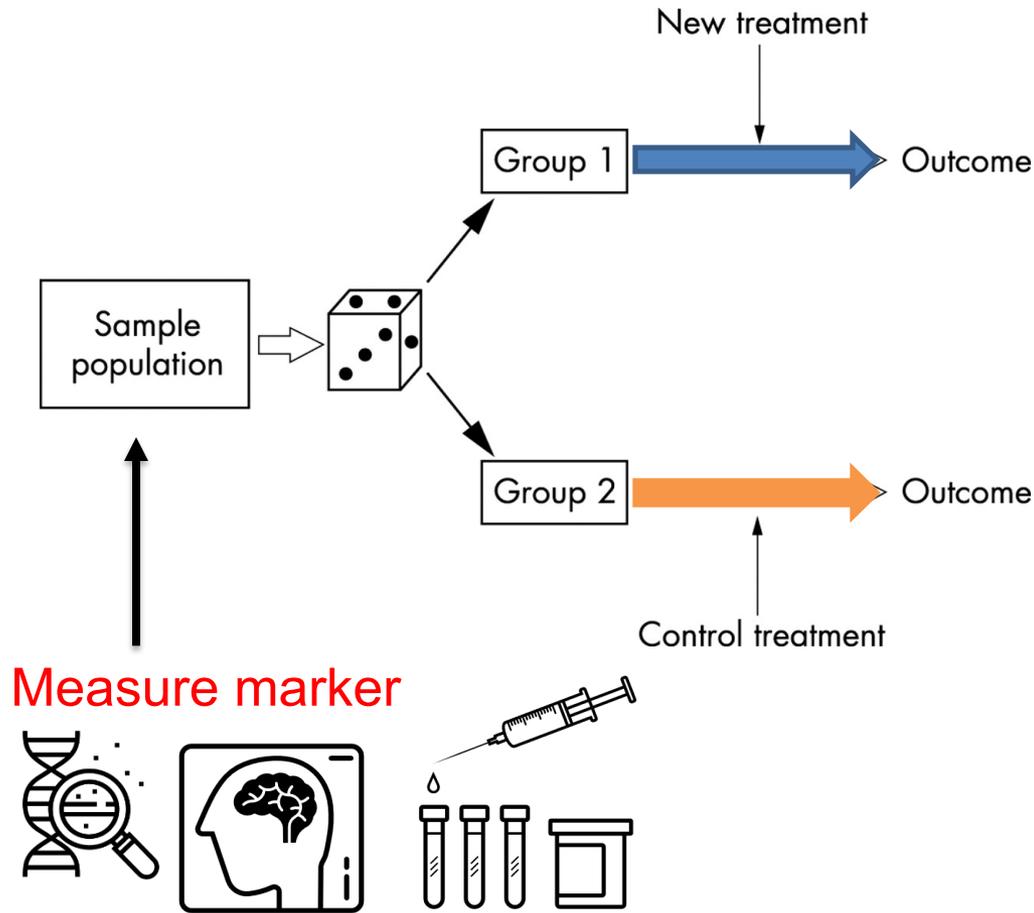


Molecular tests



Behavioral phenotyping

Precision medicine testing in RCTs

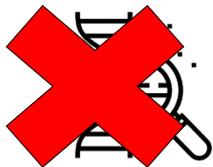


There are 3 treatment-relevant subtypes in depression

Bipolar subtype = Add mood stabilizer

Psychotic subtype = Add antipsychotic

Recurrent subtype = Maintain treatment



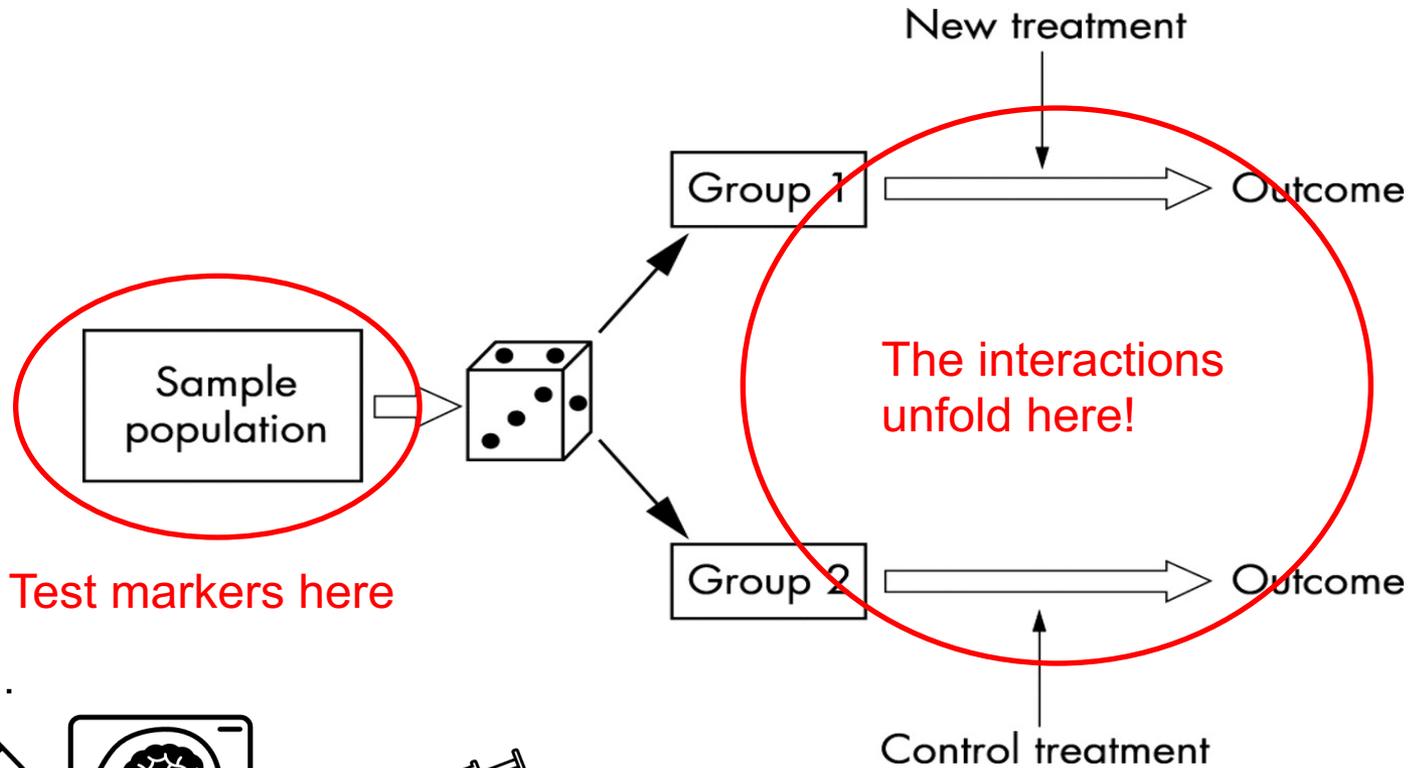
Flawed approach



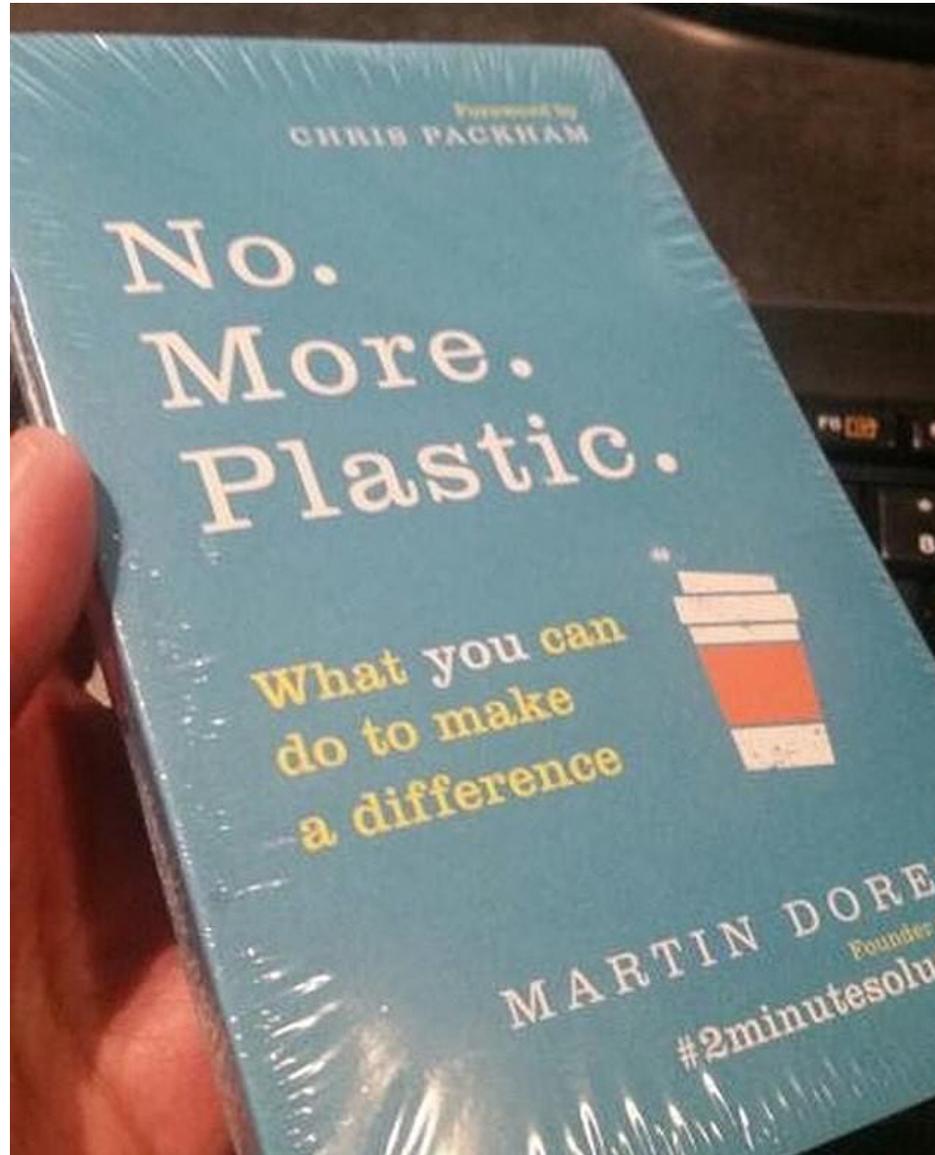
First design flaw



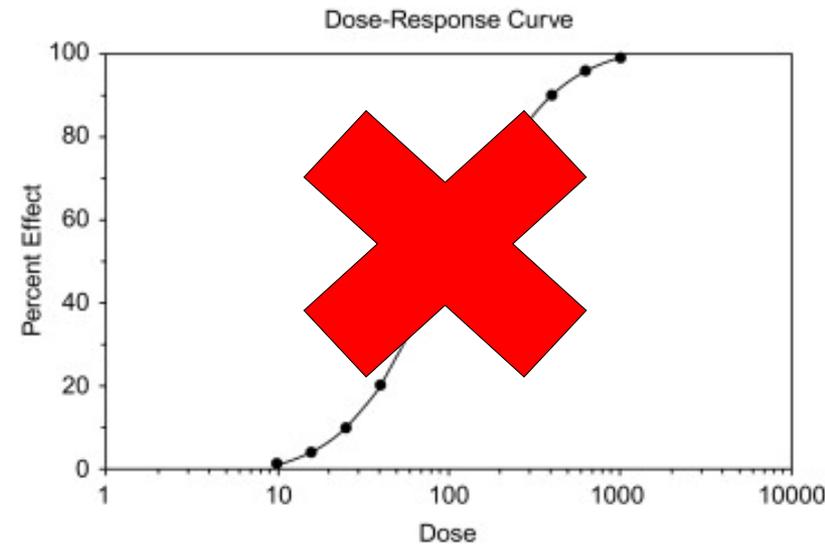
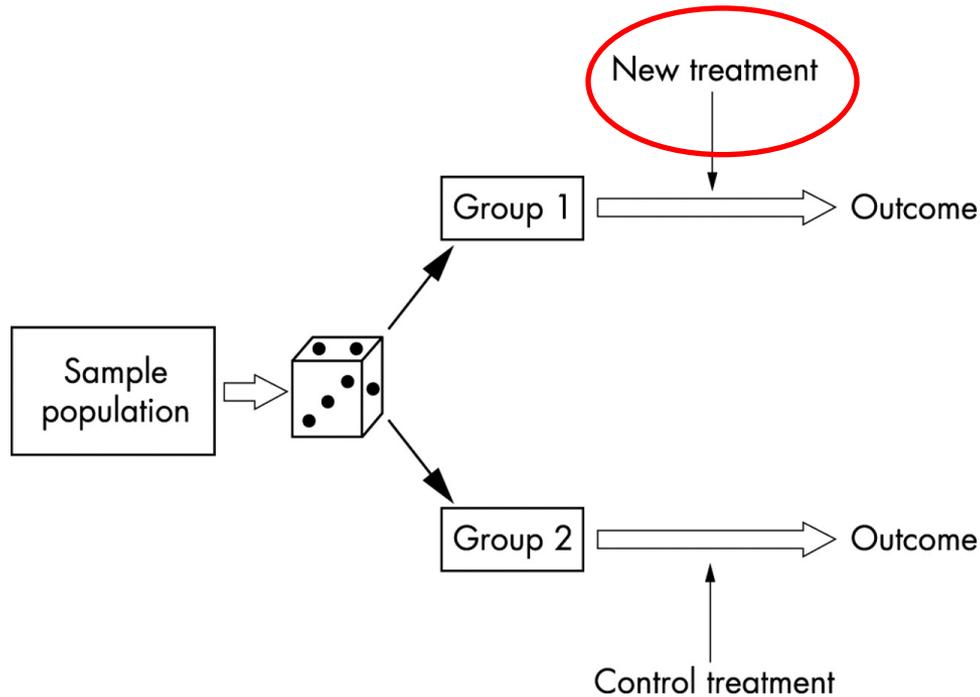
We test biomarkers prior to treatment, not during treatment



Second design flaw



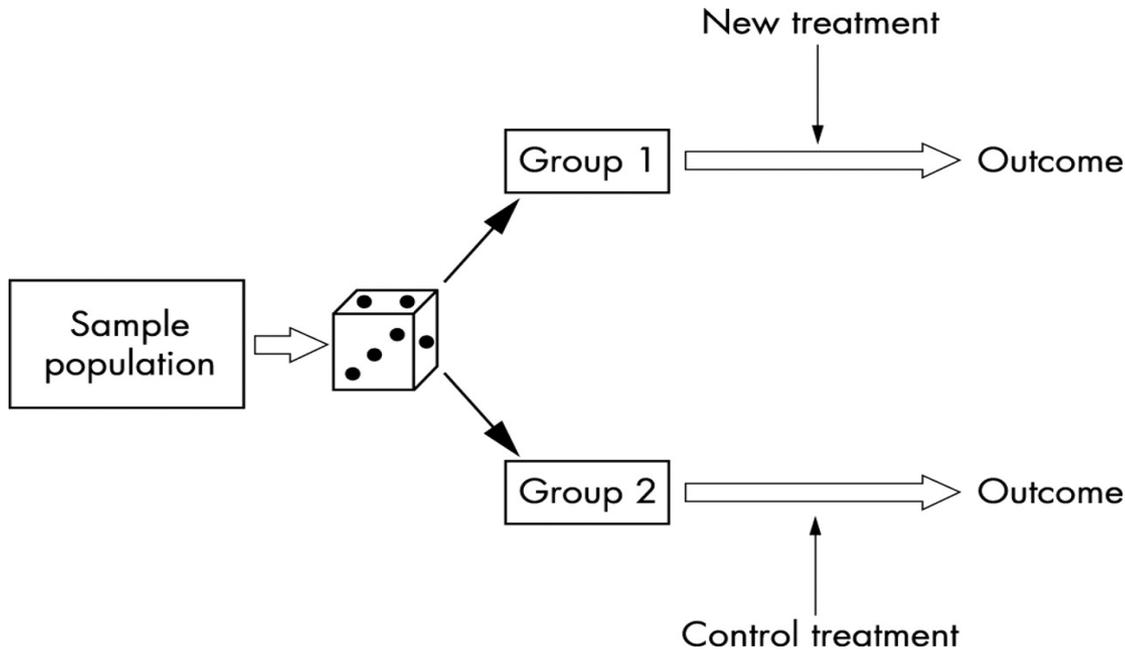
We focus on giving a specified treatment exposure, not achieving a specified goal



Third design flaw



We measure outcomes and predictors imprecisely

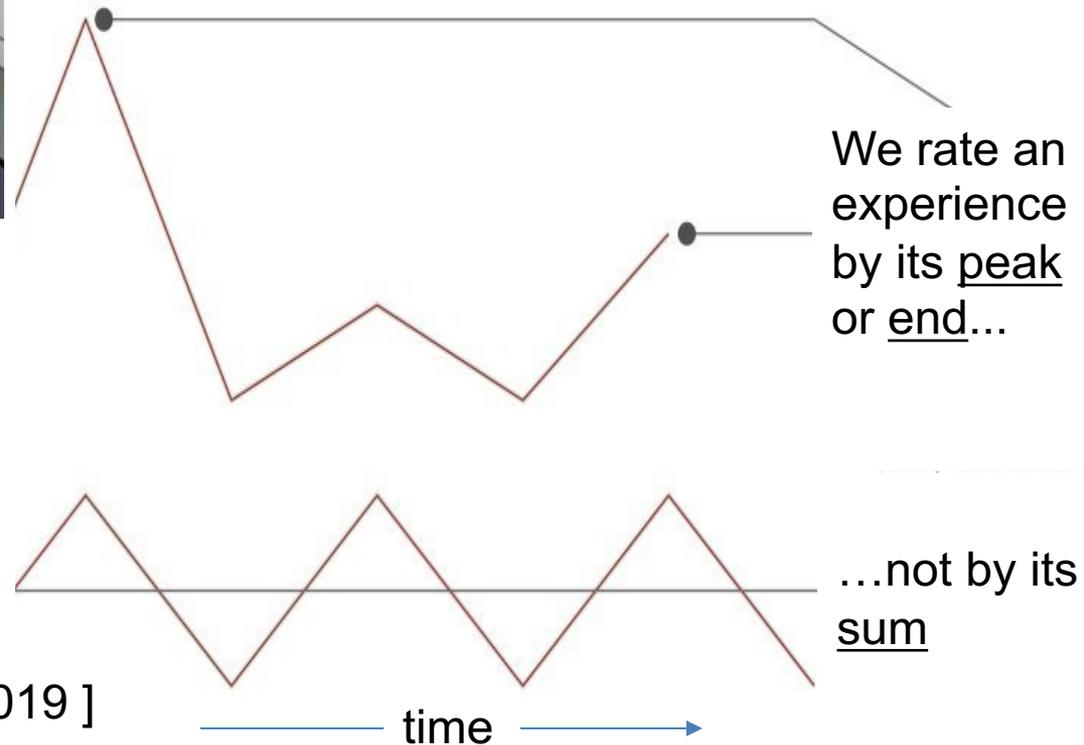


Measure response:
“In the last 7 days,
how has your
mood been?”

Infrequent, retrospective measurement hurts sensitivity



Peak-End rule



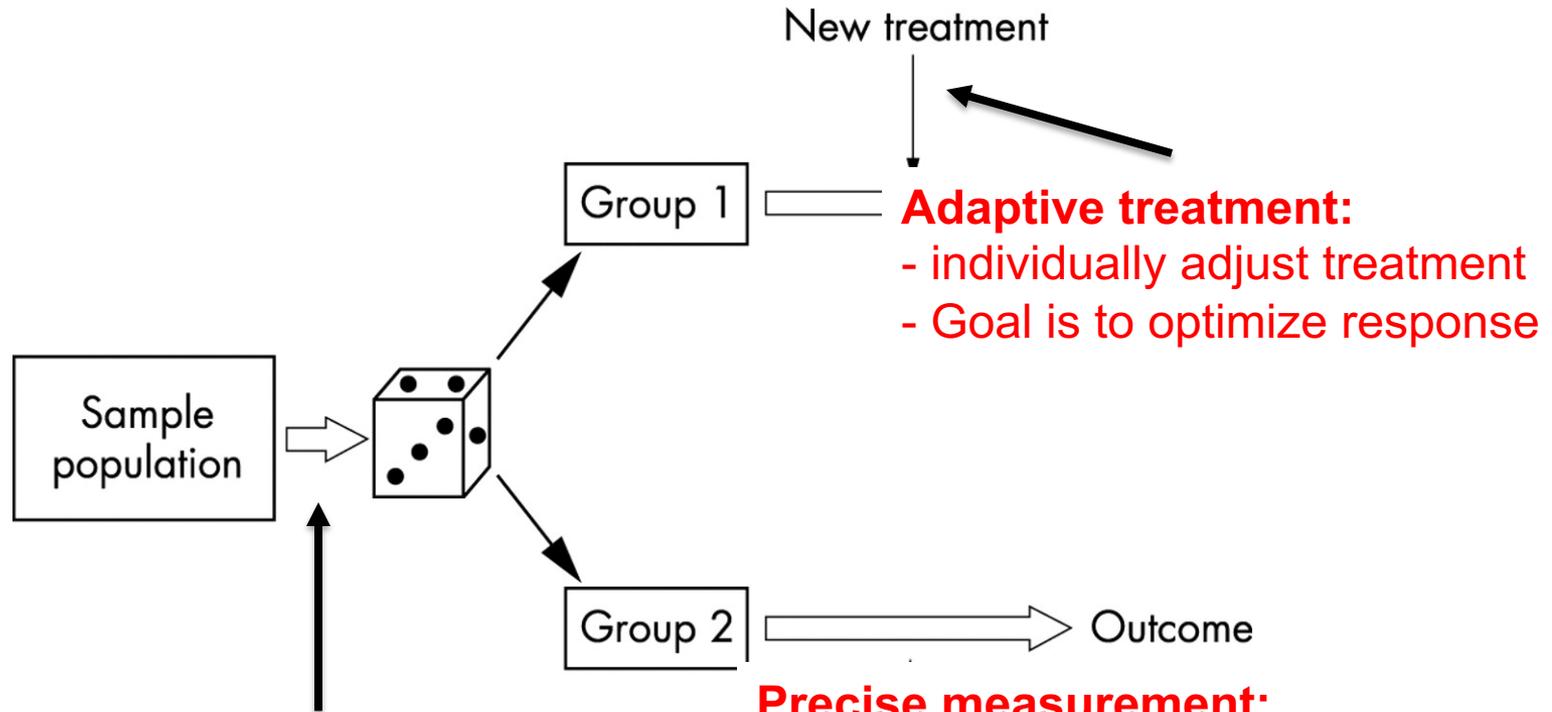
Where's the solution???



Precision Clinical Trials



RCTs should have three features in order to get our field to precision medicine



Adaptive treatment:

- individually adjust treatment
- Goal is to optimize response

Treatment-targeted enrichment:

- give acute bout of treatment
- measure patient's response

Precise measurement:

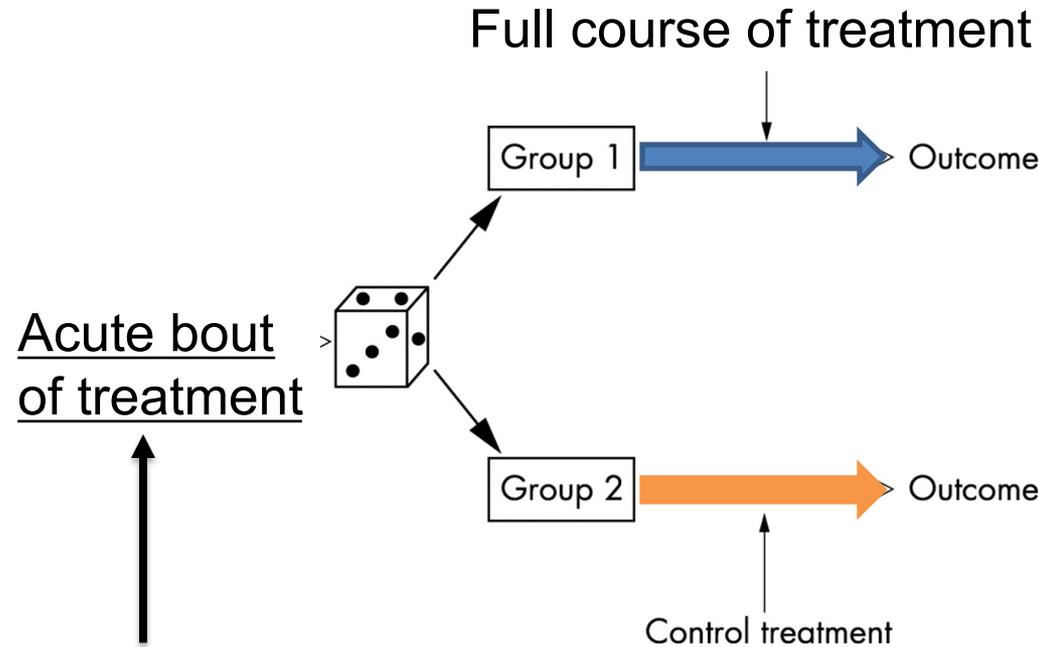
- accurately measure outcomes
- and predictor markers



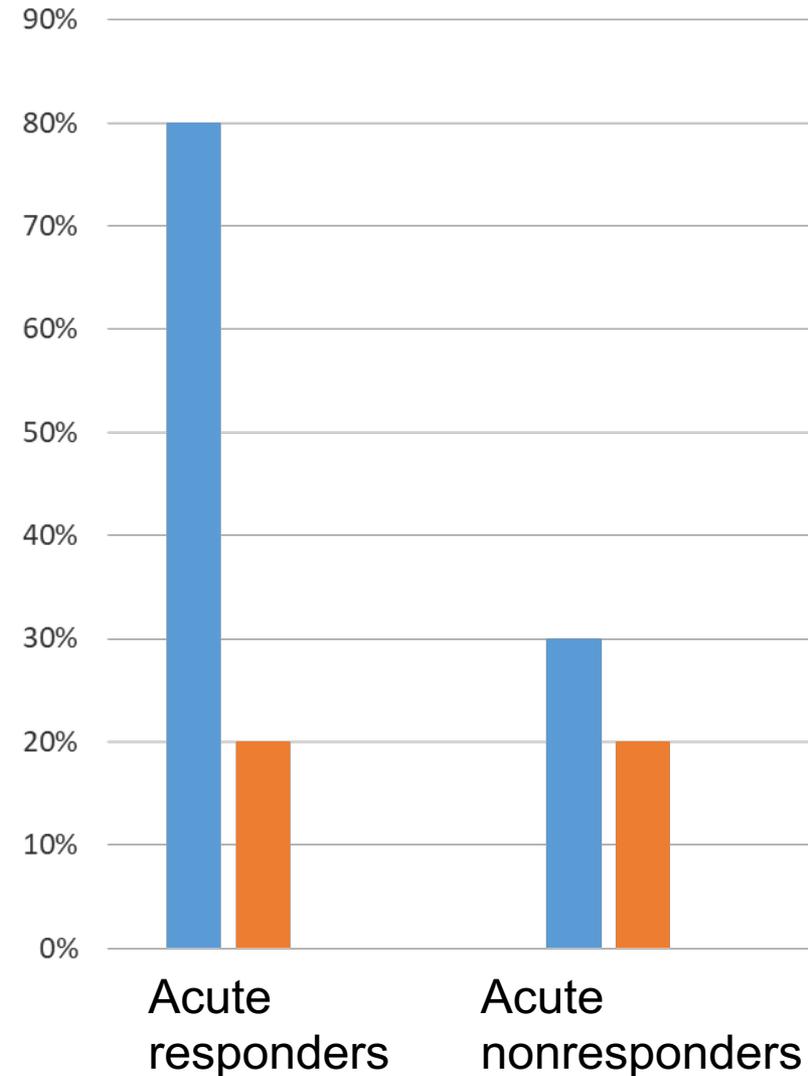
Precision clinical trials: the easy part



Treatment targeted enrichment uses an acute phase of treatment to determine ultimate response



- Measure response
- Symptoms or mechanism



Time out for a
Clinical Pearl

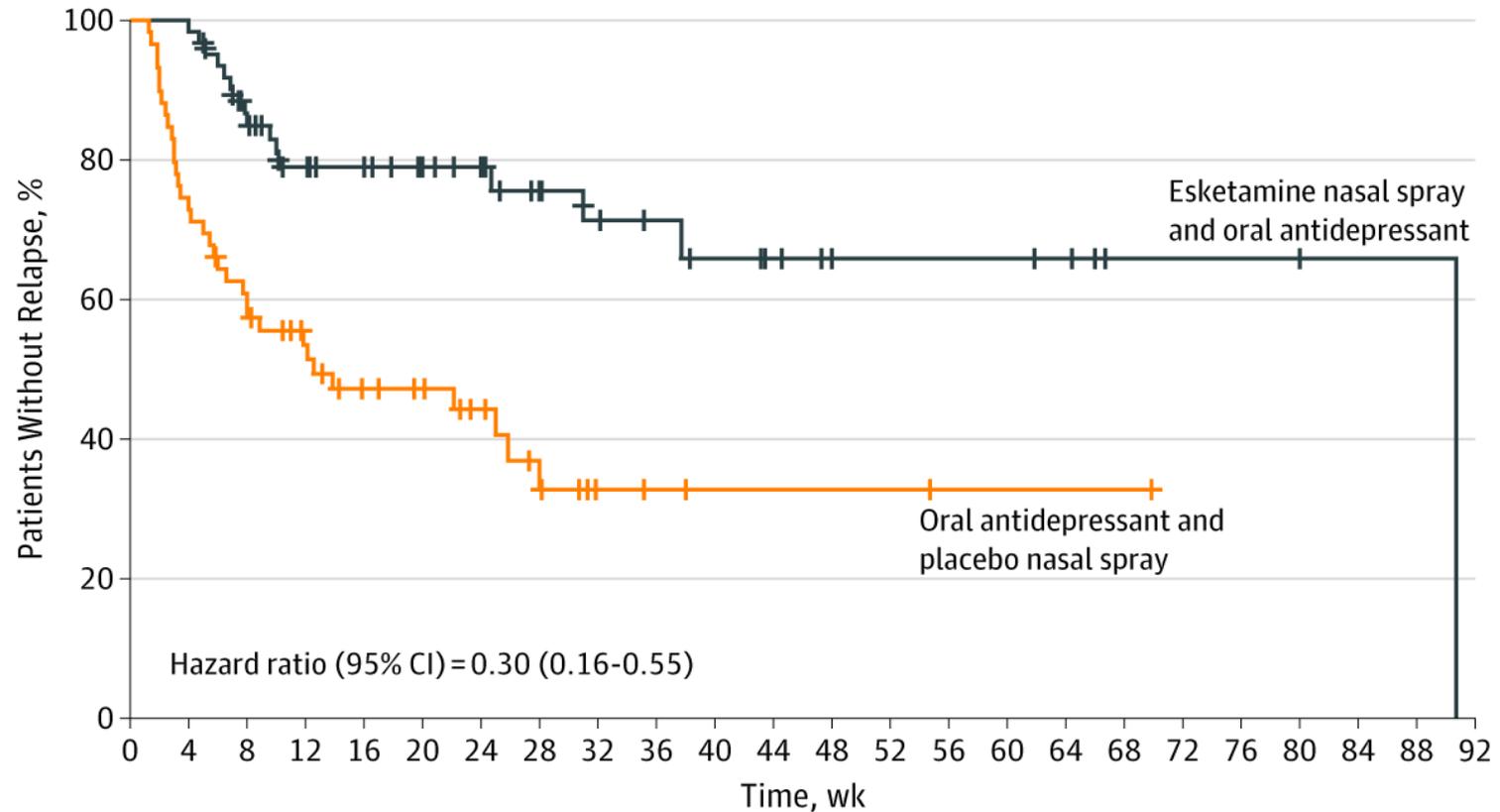


You took paroxetine before; how did that work for you?

Really well!

Let's try paroxetine!

Acute treatment response predicts long-term outcome



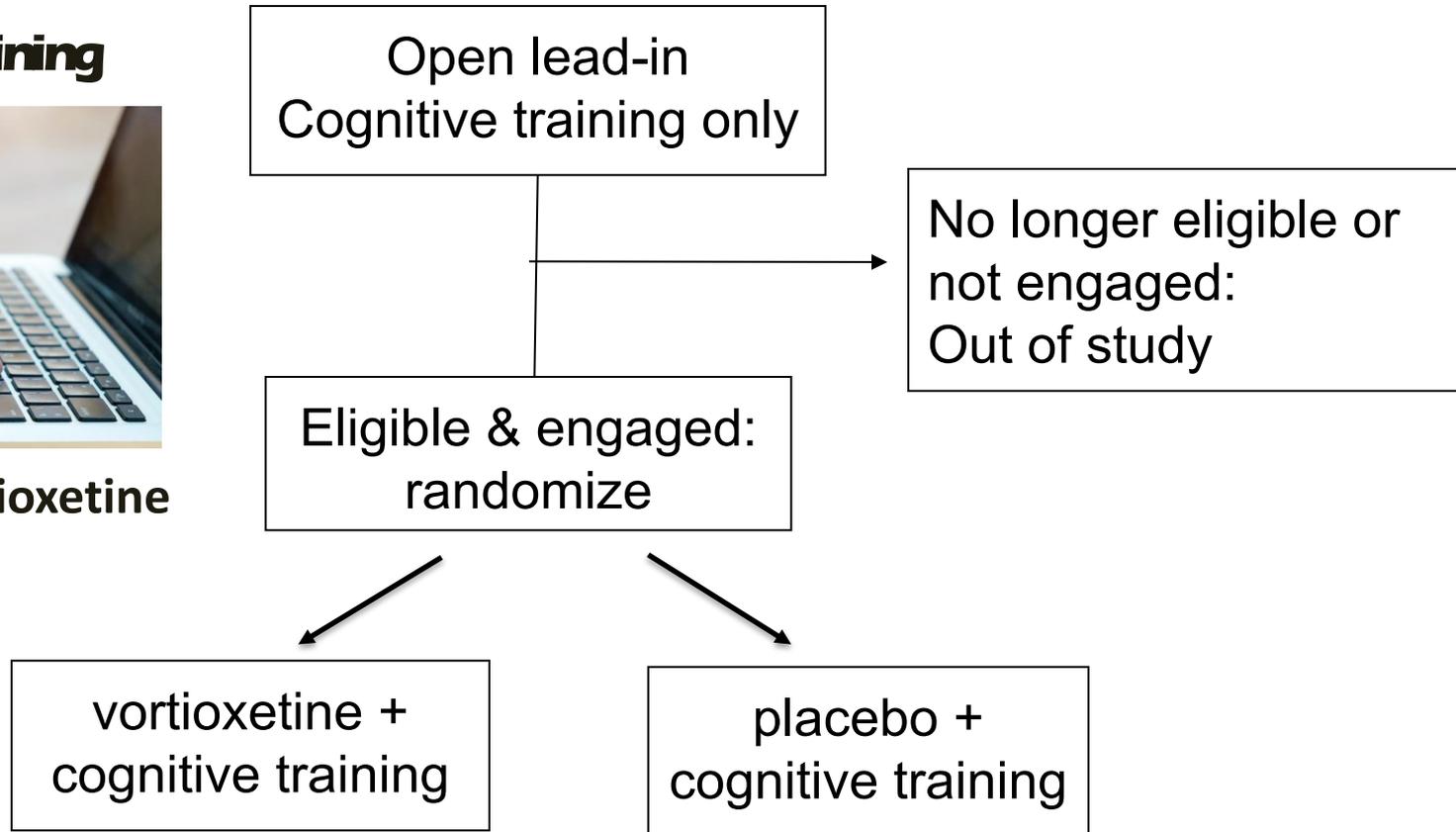
Responders to open-label esketamine had better long-term outcome with maintenance esketamine compared to placebo

A lead-in phase enriches the sample

Cognitive training



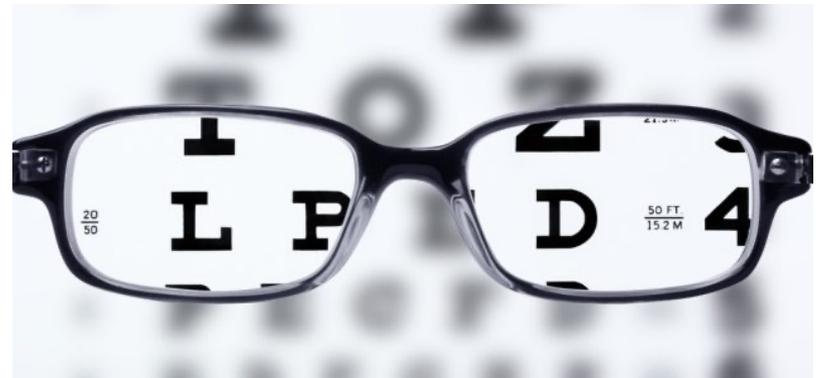
Does adding vortioxetine help?



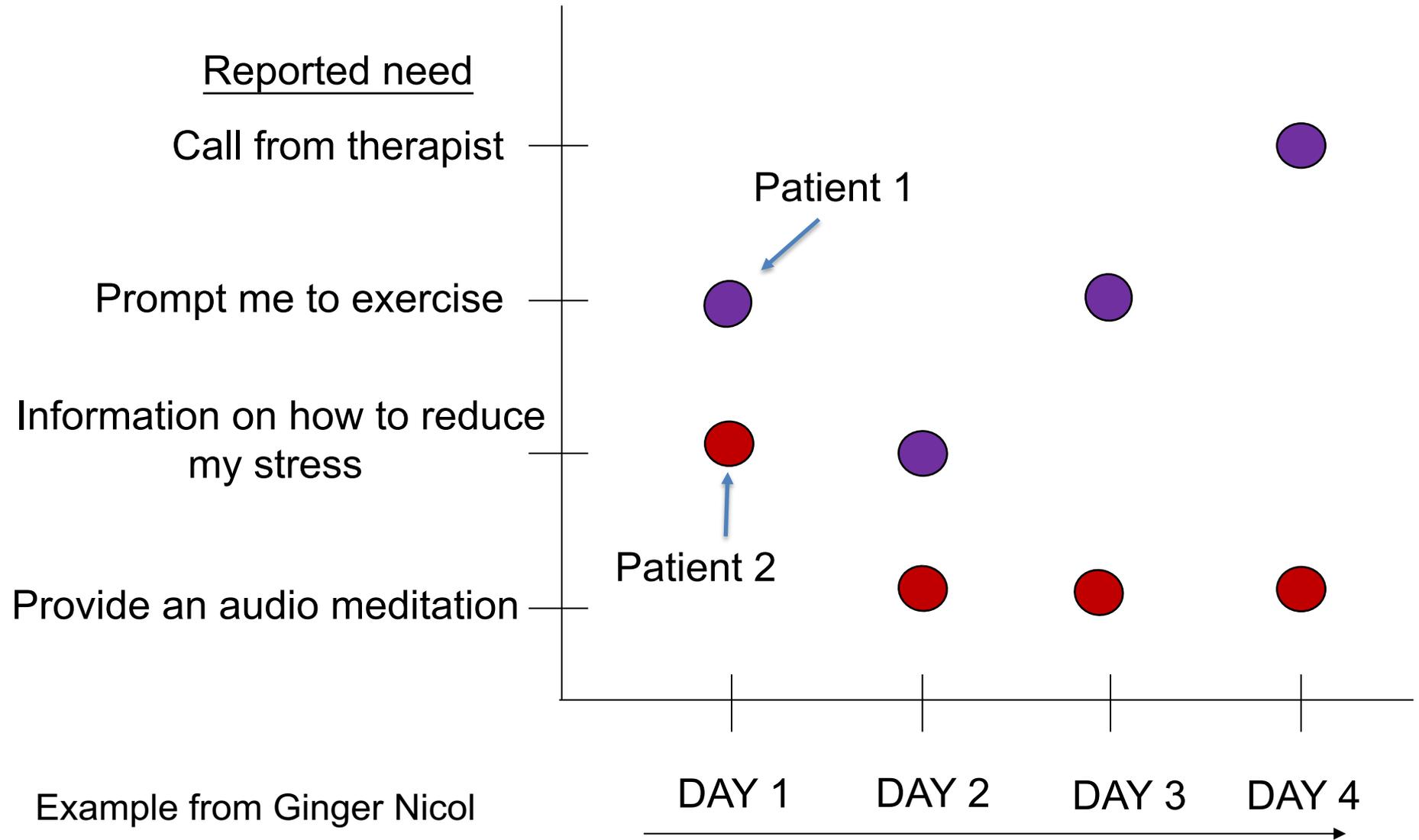
Adaptive Treatment



Which is better, A or B?



Treatment should adapt to patient needs and preferences



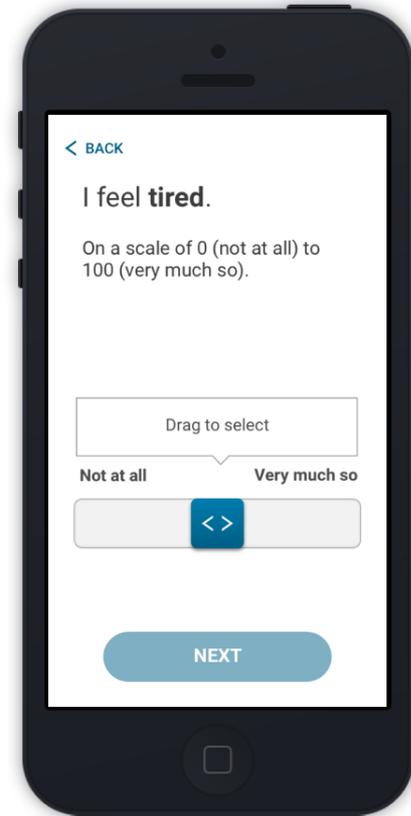
Example from Ginger Nicol

Precise measurement

Which is better?

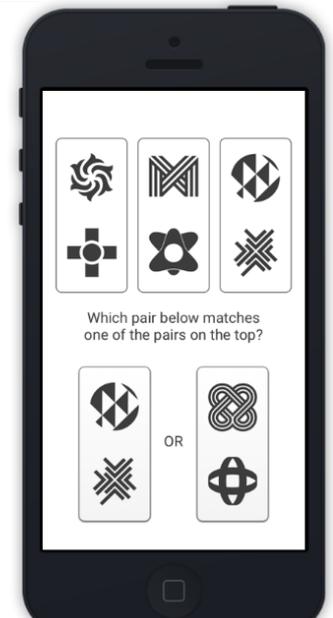
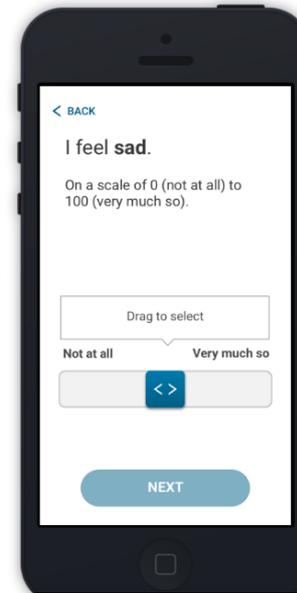
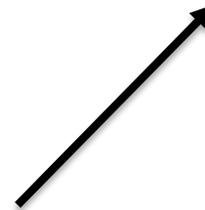
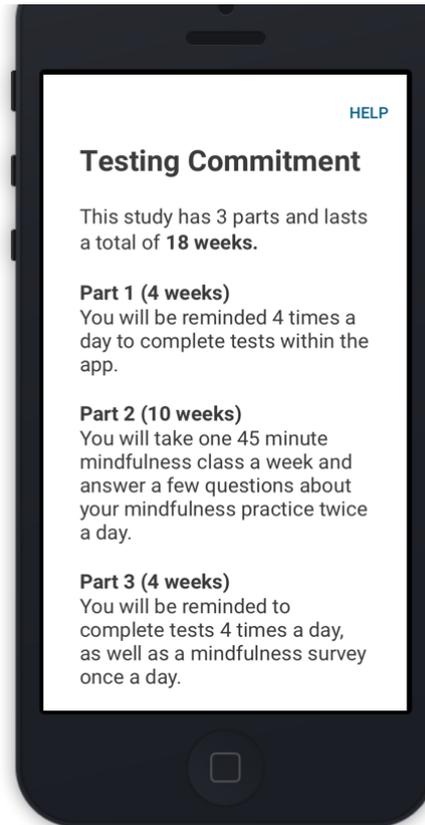


Or...



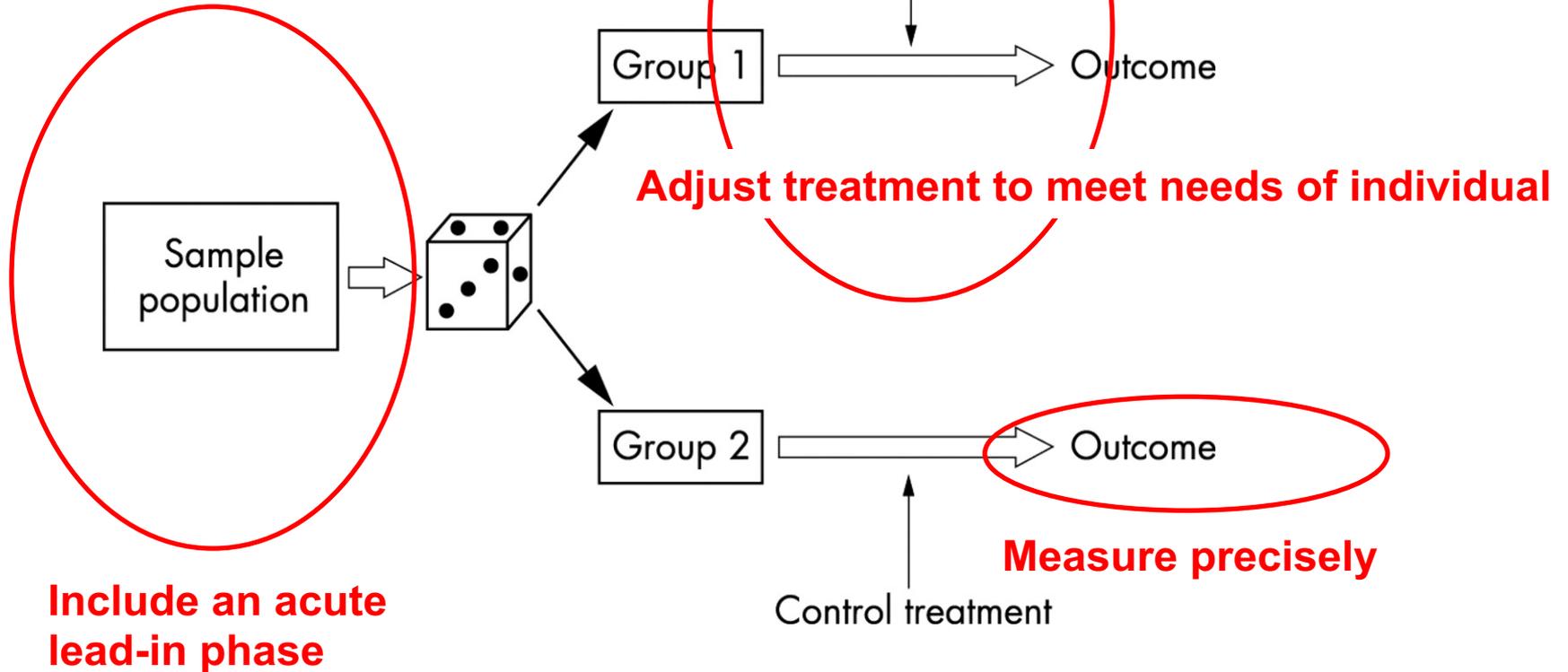
High-frequency smartphone assessments can measure outcomes with high precision

Mindful MyWay study



App created by happyMedium | healthyMedium;
Burst Cognitive Sampling created by Jason Hassenstab

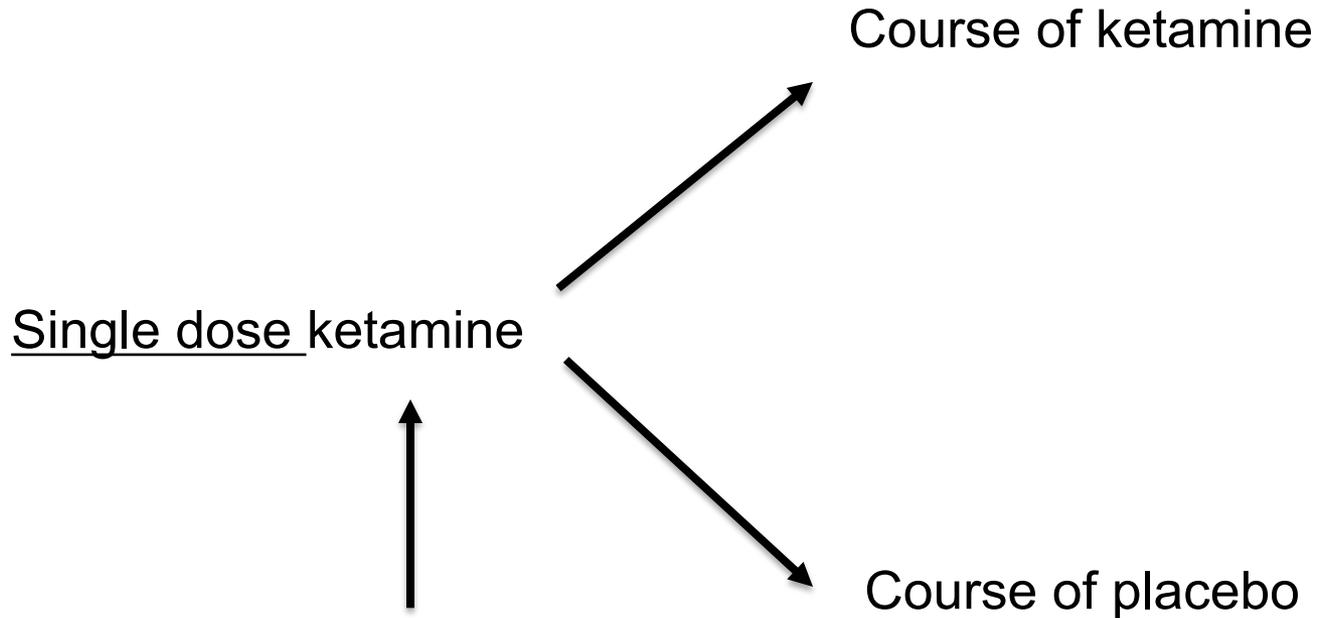
Getting to precision medicine: the easy part



Precision clinical trials: new methods and tools



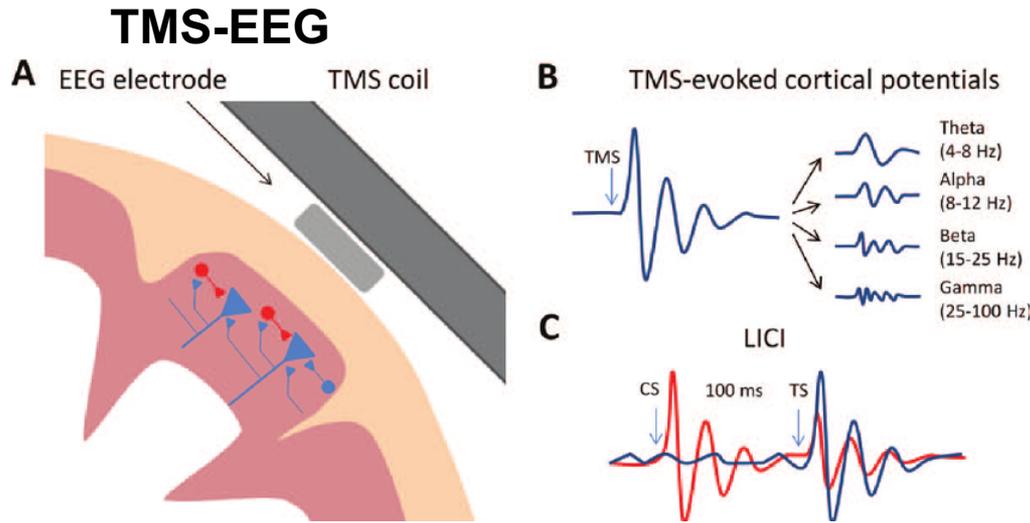
How brief can an acute lead-in phase be?



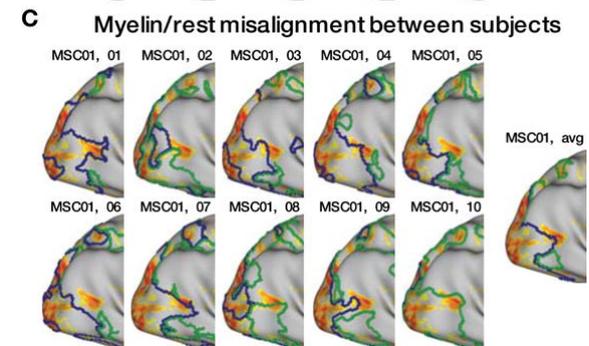
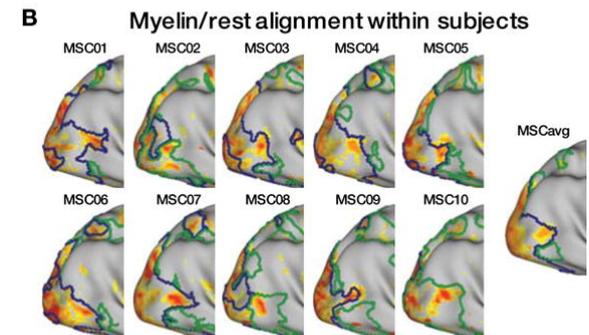
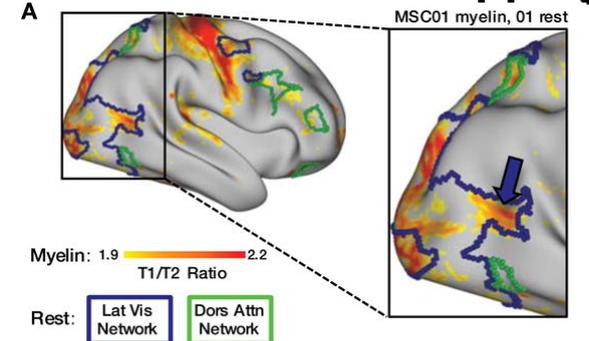
- Measure response
- Symptoms or mechanism



New tools will help us determine response to a brief bout of treatment – even a single dose



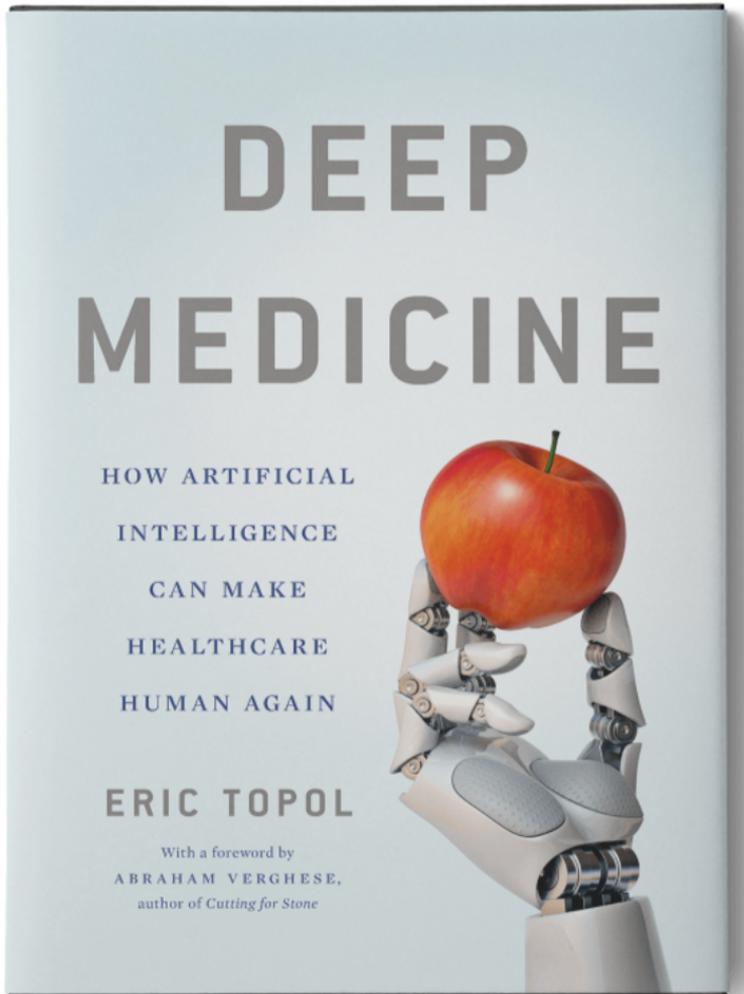
Precision brain-mapping



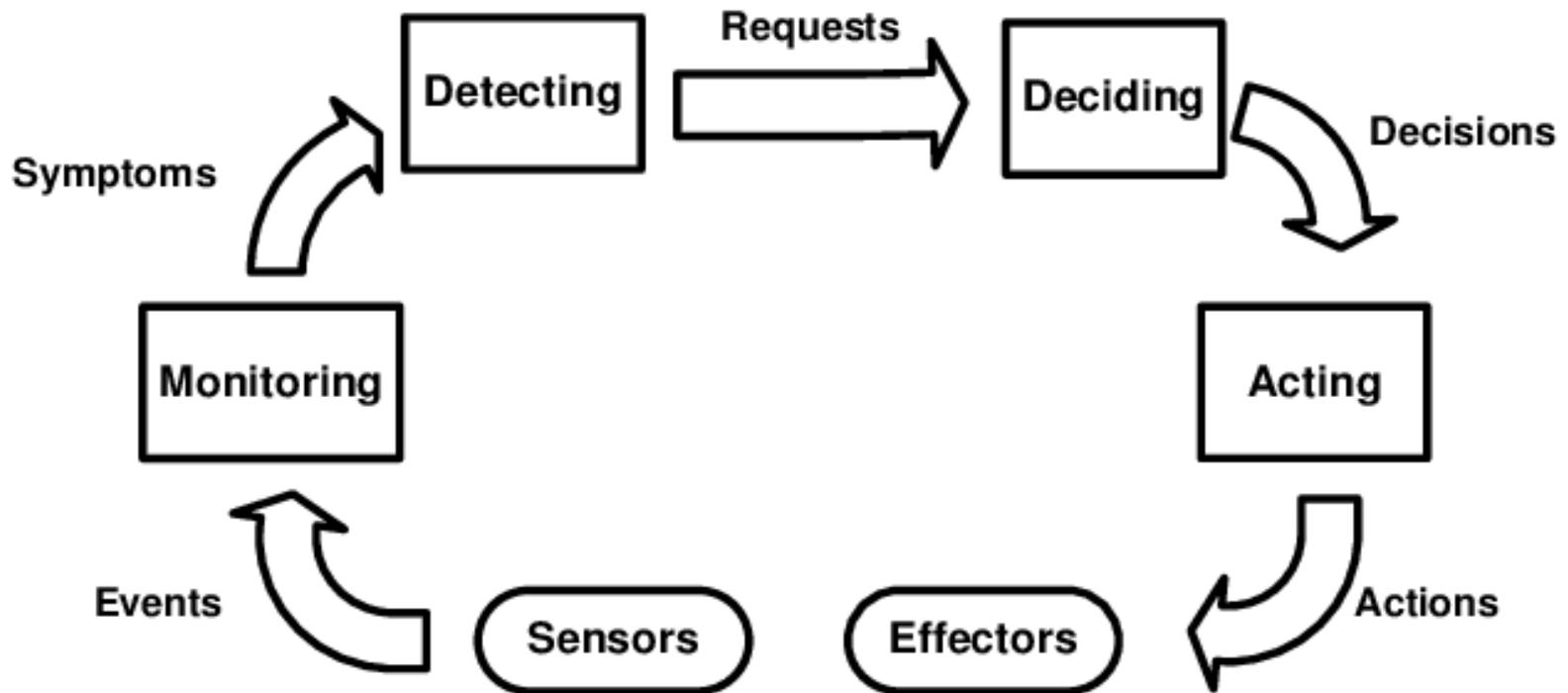
Precision TMS:

Research rounds by Rita Haddad MD
Wednesday Feb 5, 11:30-12:45
Clopton Auditorium

mHealth interventions will combine smartphones and machine learning

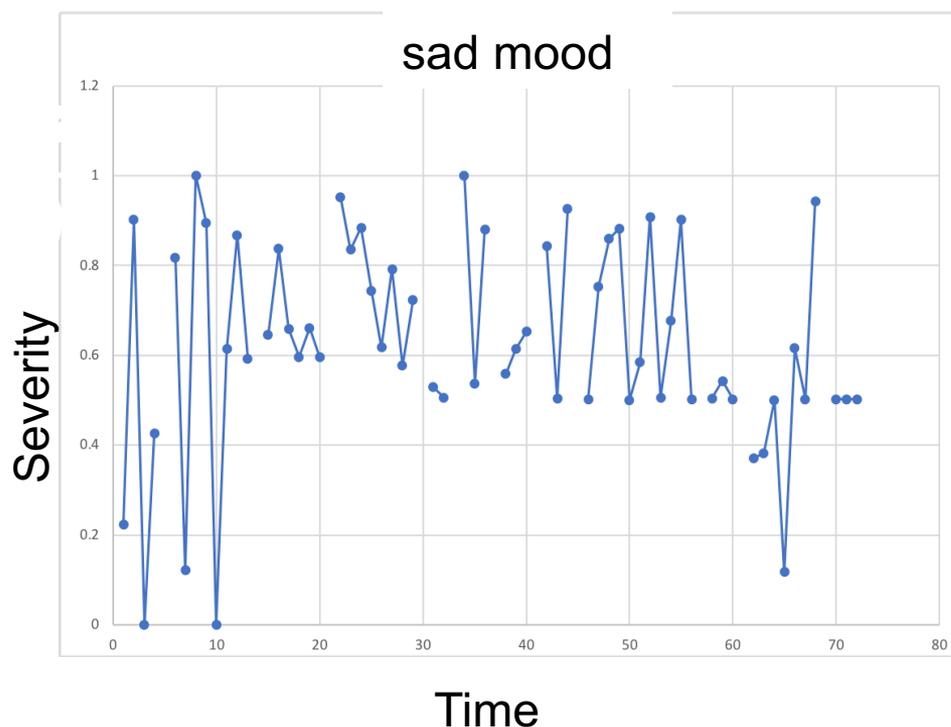


A treatment could continuously *self*-adapt to the individual patient



New statistical methods can capture individual-level temporal dynamics

4 weeks' data from an older adult with MDD



The mHealth Research Core is a new service for researchers

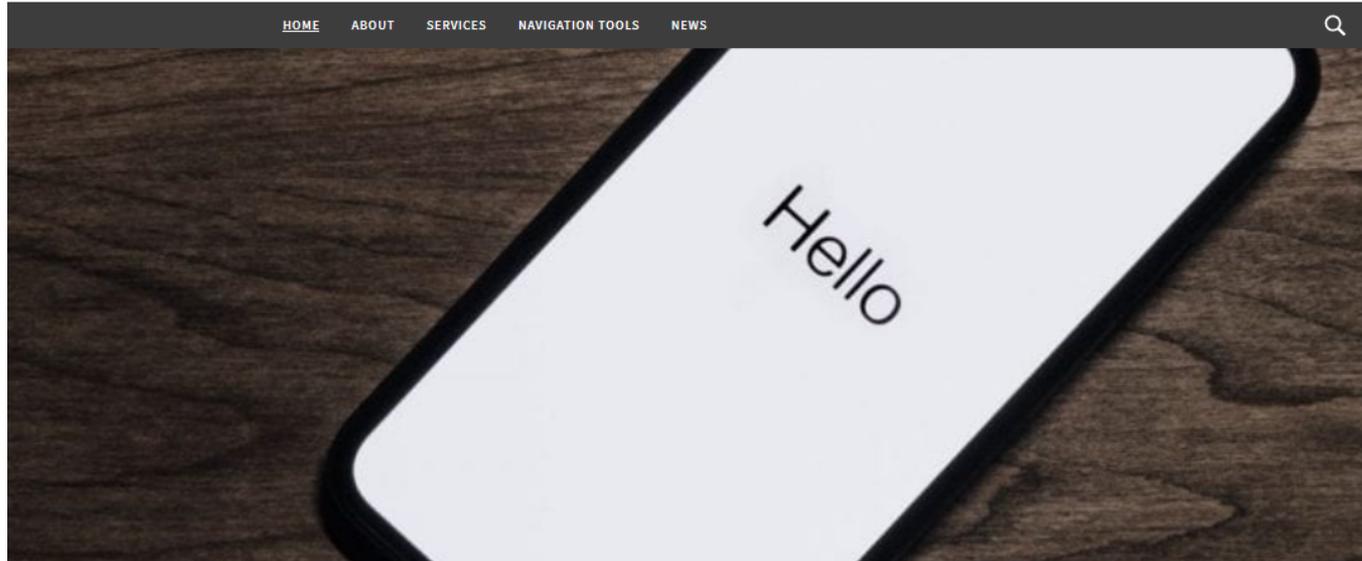
<https://mhealth.wustl.edu/>

 Washington University School of Medicine in St. Louis

INSTITUTE OF CLINICAL AND TRANSLATIONAL SCIENCES

mHealth Research Core

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Overview

Mobile Health (mHealth) research is focused on the use of social media, smartphone devices, tablets, web sites, sensors, wearables and/or other remote technology to measure and improve health research and outcomes.

mHealth is widespread and understudied relative to its importance and potential.

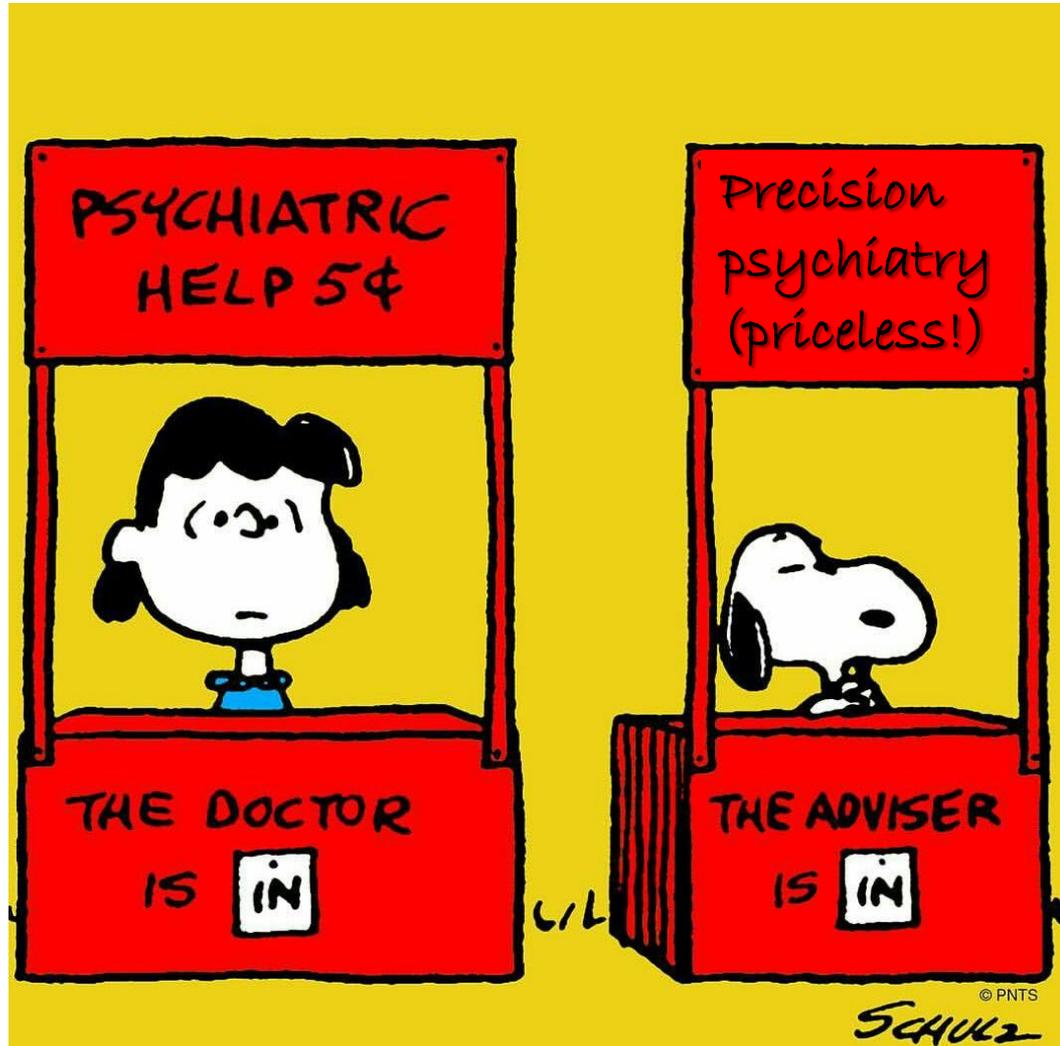
To foster collaboration at WUSTL, the Institute for Clinical and Translational Sciences (ICTS) recently established the mHealth Research Core, in partnership with the Institute for Informatics (I2), the HealthCare Innovation Lab and the Healthy Mind Lab.

Next meeting Wednesday March 11 10-11:30am, Schwarz auditorium

Changing the culture will be the hardest part.



What will psychiatric treatment be like if we succeed?



QUESTIONS?