Centre for Outcomes Research and Effectiveness (CORE)
Research Department of Clinical, Educational and Health Psychology
University College London

# What works for whom under what circumstances? A few examples of 21st Century approaches

Dr Joshua E J Buckman

Clinical Psychologist & Research Fellow

University of College London

Joshua.Buckman@ucl.ac.uk

iCope
Camden and Islington Psychological Therapies Service

Camden and Islington NHS
NHS Foundation Trust

wellcome

# “What works for whom?”

“In all its complexity, the question towards which all outcome research should ultimately be directed is the following: What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?”

- Gordon Paul (1967)

# Where does loneliness come in?

## 3-4, 5-8? Maybe depends on outcome and aims?

3. Does Treatment A work for certain people? (differential prognosis)
4. What indicates whether treatment A will work? (predicting prognosis)
5. Does Treatment B work and is it's effect different to that of treatment A?
6. Do A and B work differently for different people or in different contexts?
7. Can we predict likely differential response for any given person to treatment A and B?
8. Can we use this to help inform treatment choice of A or B

# None of this really tells us what works for whom

Once we know what might be useful to indicate outcomes from treatment we can do more…

Stratifying based on pre-treatment characteristics to tell us a bit more about what treatment might be most effective

# Stratified medicine approach using a Latent Profiling Algorithm, also able to predict several types of outcome

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

## Predicting treatment outcome in psychological treatment services by identifying latent profiles of patients

Rob Saunders *, John Cape, Pasco Fearon, Stephen Pilling

Loneliness here or instead of some other factors?

Took 9 baseline patient factors

1) PHQ-9 score 2) GAD-7 score 3) W&SAS Score 4) Phobias Scales “caseness” 5) Age 6) Ethnicity, 7) Welfare/benefits status 8) Prescribed psychotropic medication, 9) sex.

Performed a Latent-profile analysis in ~16500 discovery sample, tested in ~4500 validation sample.

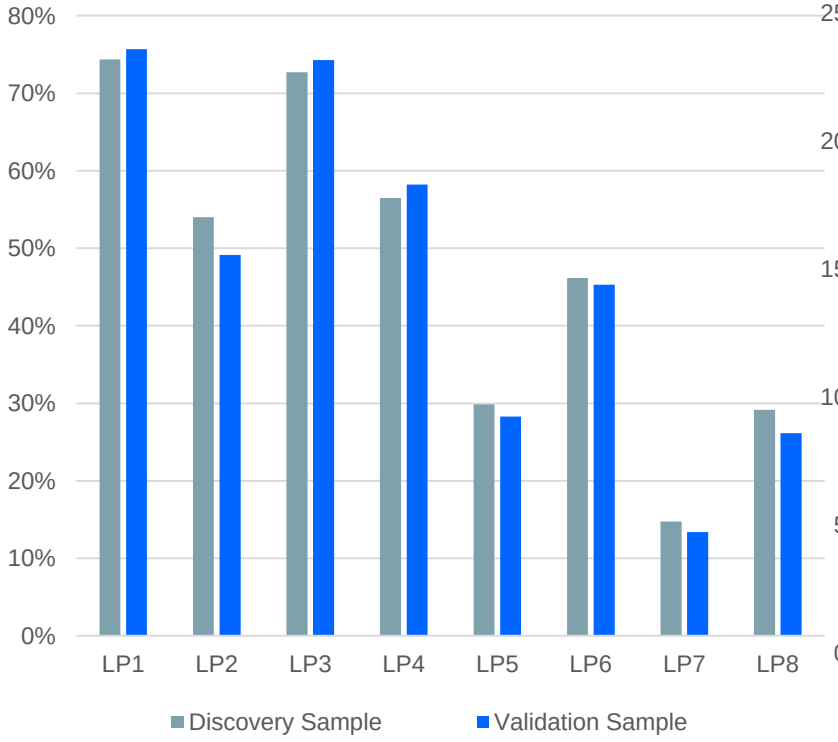
**8 distinct profiles with different outcomes for Recovery, Deterioration & Dropout**

**Led to personalised treatment recommendation via Decision Support Tool**

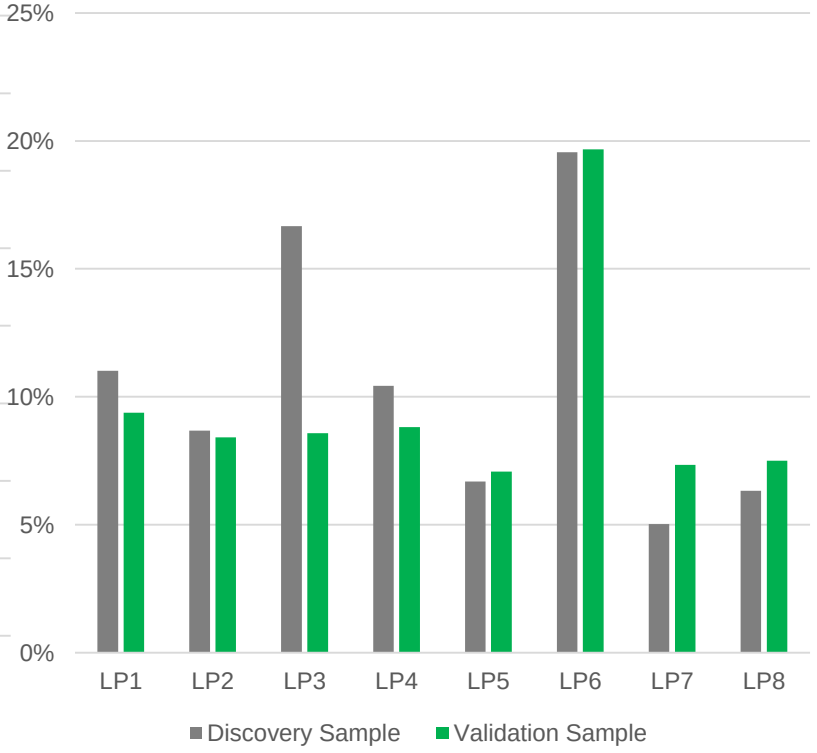
With thanks to Dr Rob Saunders for this slide

# Outcomes between profiles

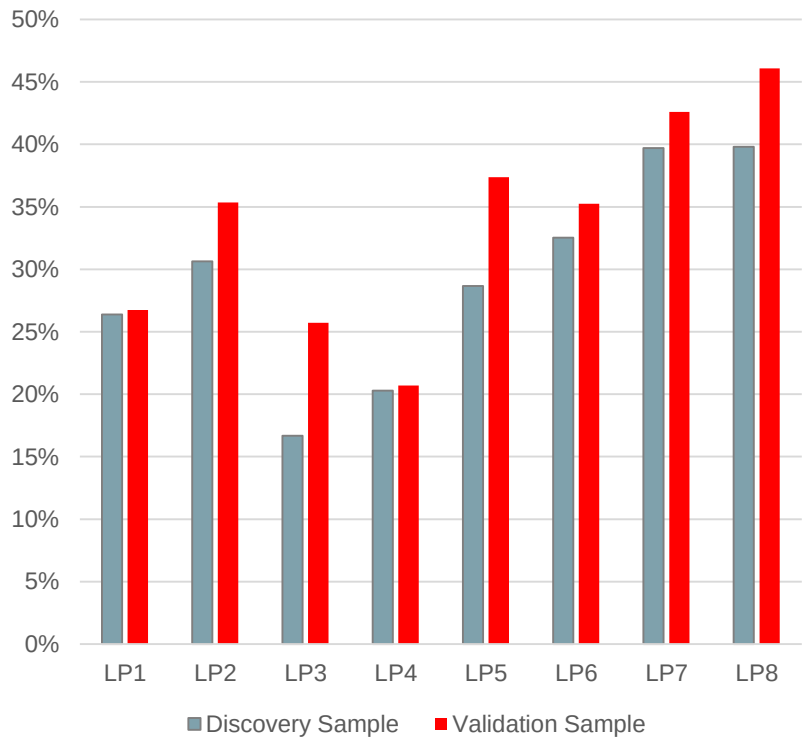
## Recovery




## Clinical deterioration




## Treatment dropout




*Predicting likely profile/group membership pre-treatment can help predict outcome and going further, can be used to recommend different treatments*

With thanks to Dr Rob Saunders for this slide

# Decision support tool embedded within Patient Record System (due to be trialled in RCT soon)

**IAPT Treatment allocation decision support tool.**

| | | |
|---|---|---|
| **Patient ID:** | **Test1** | ***(Please enter Identifier)*** |
| **Age of patient:** | **30** | ***(Please enter value)*** |
| **Gender:** | **Female** | ***(select from drop-down list)*** |
| **Ethnicity group:** | **White British** | ***(select from drop-down list)*** |
| **Benefit status:** | **No** | ***(select from drop-down list)*** |
| **Medication prescribed:** | **No** | ***(select from drop-down list)*** |
| **PHQ-9 total score:** | **10** | ***(Please enter value)*** |
| **GAD-7 total score:** | **5** | ***(Please enter value)*** |
| **W&SAS total score:** | **10** | ***(Please enter value)*** |
| **Caseness on phobia items:** | **No** | ***(select from drop-down list)*** |

**Allocation decision:**

| | | | |
|---|---|---|---|
| **Profile allocation:** | **1** | **Probability profile 1** | **0.903** |
| **Probability:** | **0.903** | **Probability profile 2** | **0.076** |
| | | **Probability profile 3** | **0.000** |
| | | **Probability profile 4** | **0.000** |
| | | **Probability profile 5** | **0.000** |
| | | **Probability profile 6** | **0.021** |
| | | **Probability profile 7** | **0.000** |
| | | **Probability profile 8** | **0.000** |

**Treatment recommendation:**

**Initiate at Step 2, high probability of recovery.**

# None of the above is truly giving personalised predictions of differential benefit of one treatment vs another/others

For this we need prescriptive models and before we can build them we need to know what factors are indicative of a prescriptive effect

Centre for Outcomes Research and Effectiveness (CORE)
Research Department of Clinical, Educational and Health Psychology
University College London

Clinical Psychology Review 64 (2018) 13–38

Contents lists available at ScienceDirect

Clinical Psychology Review

journal homepage: www.elsevier.com/locate/clinpsychrev

Review

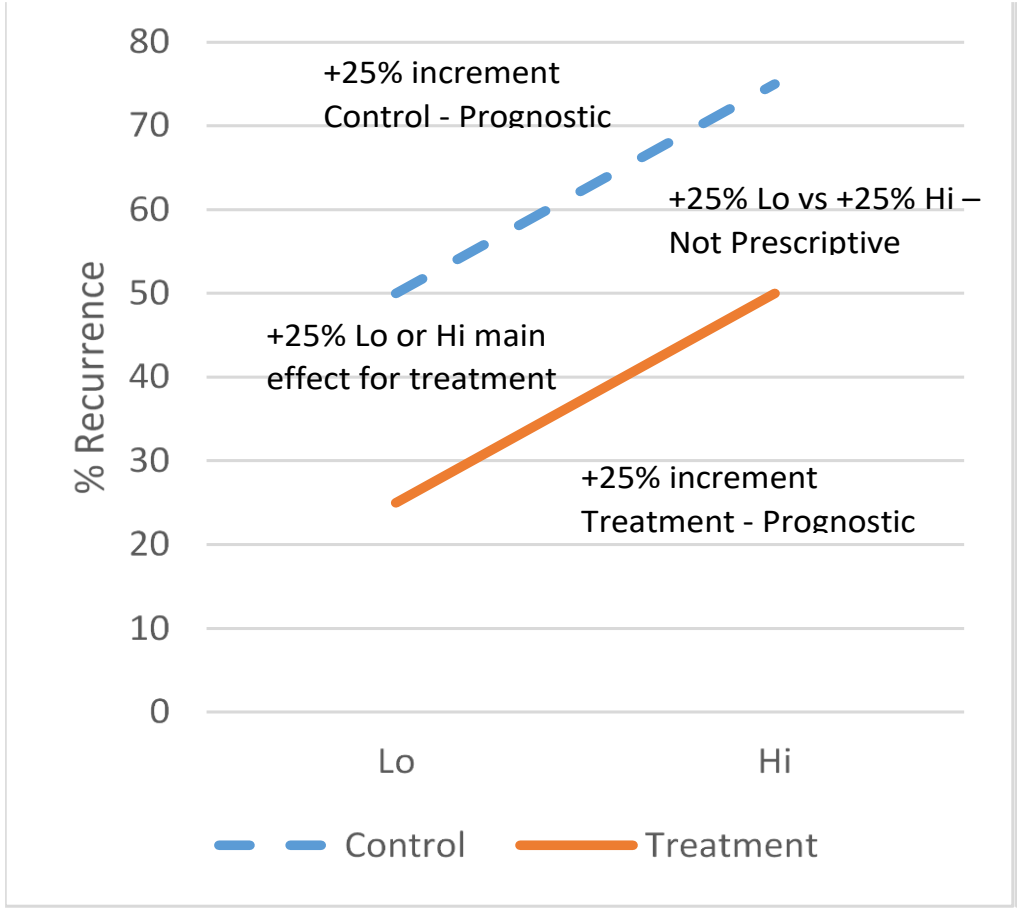
# Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis

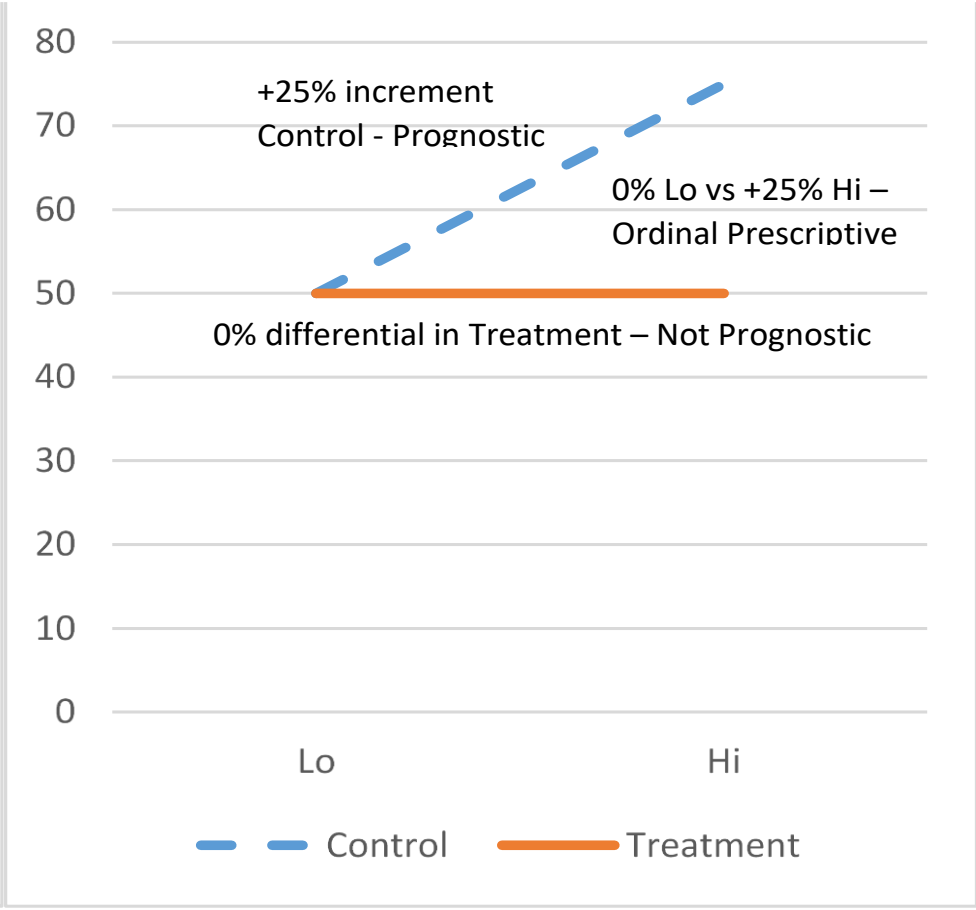
Buckman J.E.J.[a,*], Underwood A.[a], Clarke K.[a], Saunders R.[a], Hollon S.D.[b], Fearon P.[a], Pilling S.[a]

[a] Research Department of Clinical, Educational and Health Psychology, University College London, London, UK
[b] Department of Psychology, Vanderbilt University, Nashville, TN, USA

Centre for Outcomes Research and Effectiveness (CORE)
Research Department of Clinical, Educational and Health Psychology
University College London

## Risk indices can be prognostic or prescriptive: Prognostic indices are best studied in longitudinal designs with minimal treatment. Prescriptive effects require treatment interventions.



## Prognostic factors

- Residual symptoms
- History of childhood maltreatment
- Any prior episodes
- Comorbid Anxiety Disorder
- Rumination

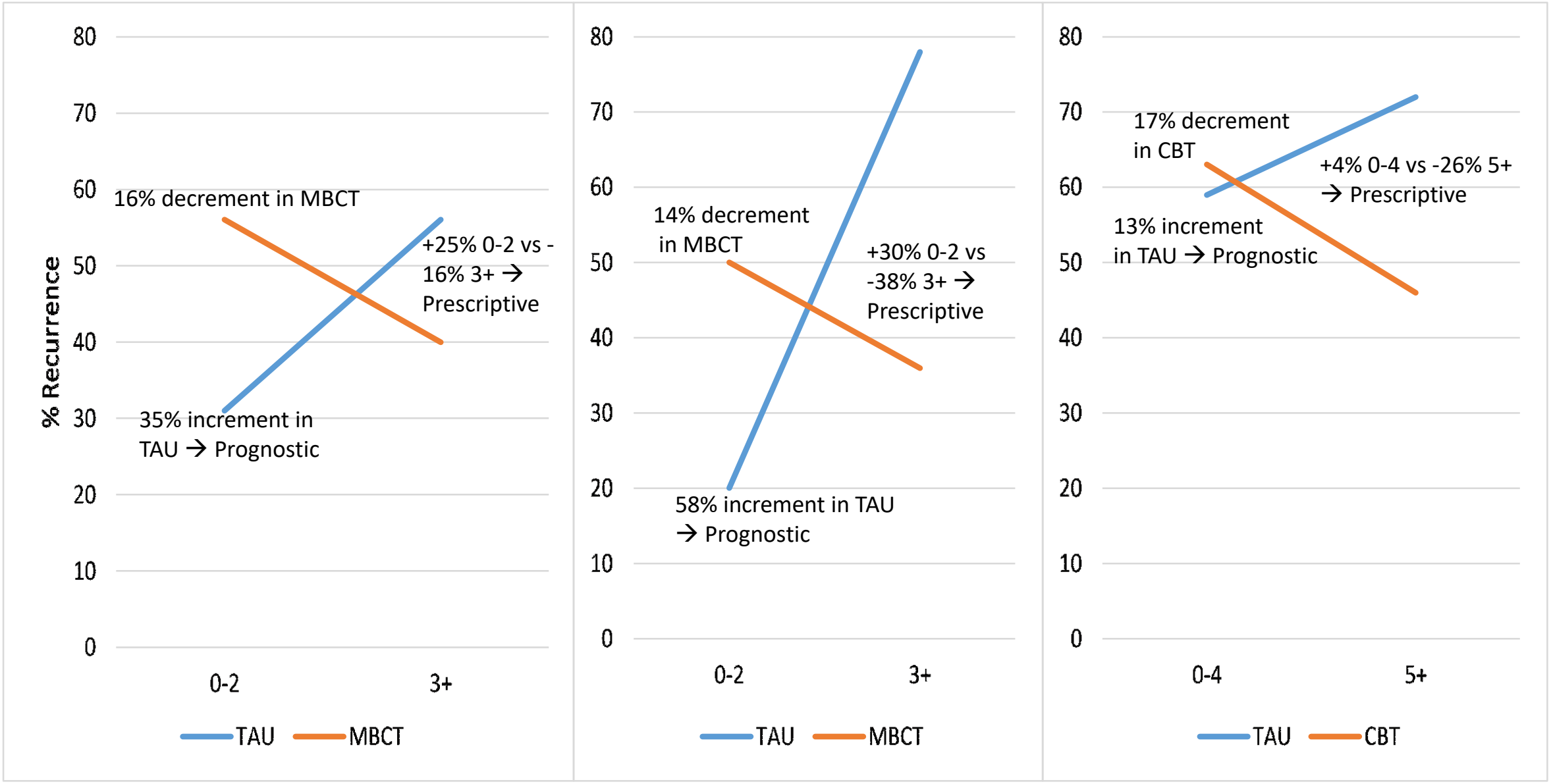
**INCREASED RISK OF RELAPSE or RECURRENCE**

# Answering Questions 5 and 6 from previous slide

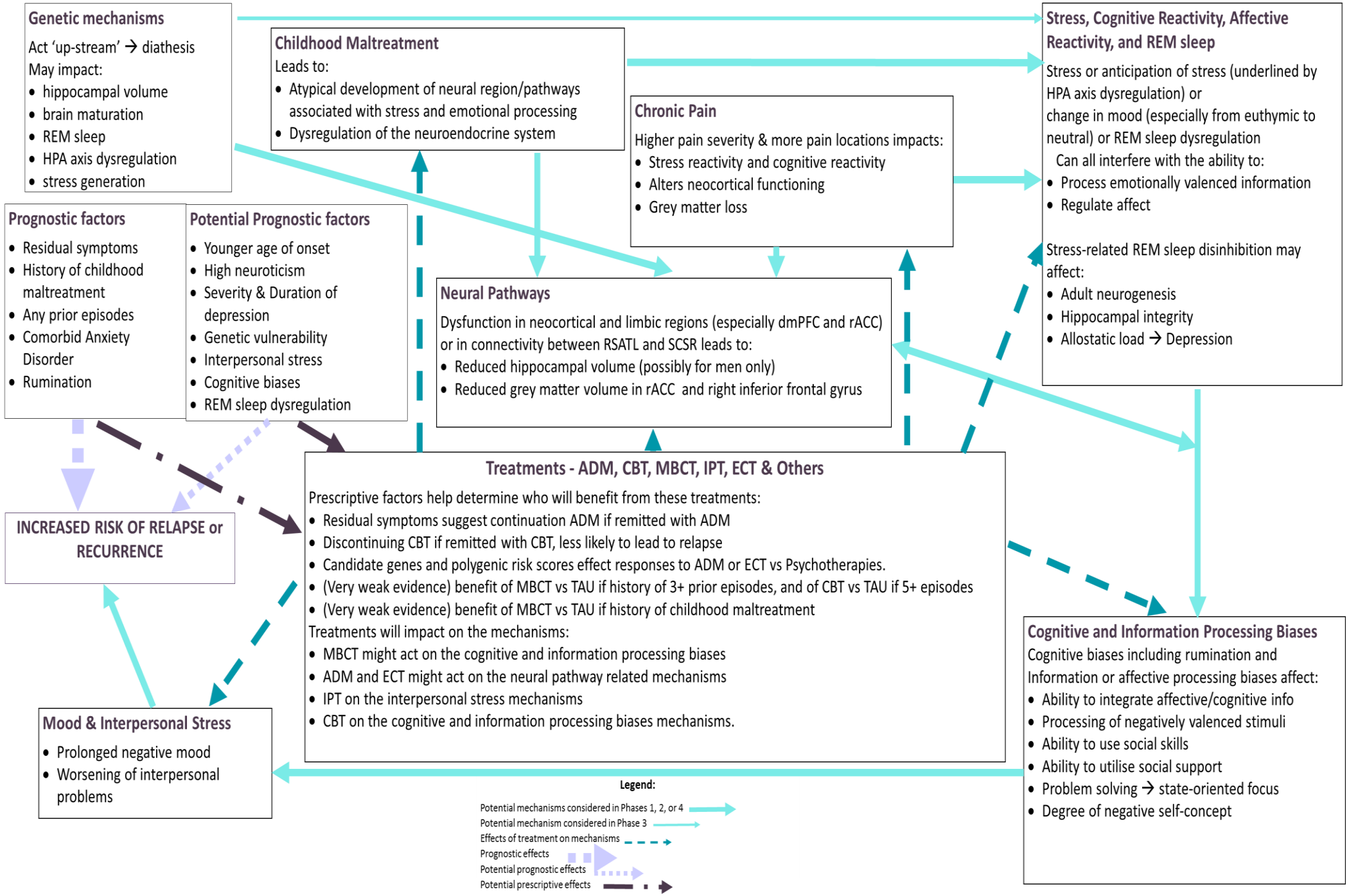
- **Treatments - ADM, CBT, MBCT, IPT, ECT & Others**

- Residual symptoms suggest continuation ADM if remitted with ADM
- Discontinuing CBT if remitted with CBT, less likely to lead to relapse
- Candidate genes and polygenic risk scores effect responses to ADM or ECT vs Psychotherapies.
- (Very weak evidence) benefit of MBCT vs TAU if history of 3+ prior episodes, and of CBT vs TAU if 5+ episodes
- (Very weak evidence) benefit of MBCT vs TAU if history of childhood maltreatment

Percentage recurrence by treatment group in three RCTs, showing that number of prior episodes is both prognostic (in TAU) and prescriptive (in both MBCT and CBT)




Source: Left panel – Teasdale et al. (2000); Middle Panel – Ma & Teasdale (2004); Right Panel – Bockting et al. (2005).


Genetic mechanisms
Act 'up-stream' → diathesis
May impact:
• hippocampal volume
• brain maturation
• REM sleep
• HPA axis dysregulation
• stress generation
Childhood Maltreatment
Leads to:
• Atypical development of neural region/pathways associated with stress and emotional processing
• Dysregulation of the neuroendocrine system
Chronic Pain
Higher pain severity & more pain locations impacts:
• Stress reactivity and cognitive reactivity
• Alters neocortical functioning
• Grey matter loss
Stress, Cognitive Reactivity, Affective Reactivity, and REM sleep
Stress or anticipation of stress (underlined by HPA axis dysregulation) or
change in mood (especially from euthymic to neutral) or REM sleep dysregulation
Can all interfere with the ability to:
• Process emotionally valenced information
• Regulate affect
Stress-related REM sleep disinhibition may affect:
• Adult neurogenesis
• Hippocampal integrity
• Allostatic load → Depression
Prognostic factors
• Residual symptoms
• History of childhood maltreatment
• Any prior episodes
• Comorbid Anxiety Disorder
• Rumination
Potential Prognostic factors
• Younger age of onset
• High neuroticism
• Severity & Duration of depression
• Genetic vulnerability
• Interpersonal stress
• Cognitive biases
• REM sleep dysregulation
Neural Pathways
Dysfunction in neocortical and limbic regions (especially dmPFC and rACC) or in connectivity between RSATL and SCSR leads to:
• Reduced hippocampal volume (possibly for men only)
• Reduced grey matter volume in rACC and right inferior frontal gyrus
INCREASED RISK OF RELAPSE or RECURRENCE
Treatments - ADM, CBT, MBCT, IPT, ECT & Others
Prescriptive factors help determine who will benefit from these treatments:
• Residual symptoms suggest continuation ADM if remitted with ADM
• Discontinuing CBT if remitted with CBT, less likely to lead to relapse
• Candidate genes and polygenic risk scores effect responses to ADM or ECT vs Psychotherapies.
• (Very weak evidence) benefit of MBCT vs TAU if history of 3+ prior episodes, and of CBT vs TAU if 5+ episodes
• (Very weak evidence) benefit of MBCT vs TAU if history of childhood maltreatment
Treatments will impact on the mechanisms:
• MBCT might act on the cognitive and information processing biases
• ADM and ECT might act on the neural pathway related mechanisms
• IPT on the interpersonal stress mechanisms
• CBT on the cognitive and information processing biases mechanisms.
Cognitive and Information Processing Biases
Cognitive biases including rumination and
Information or affective processing biases affect:
• Ability to integrate affective/cognitive info
• Processing of negatively valenced stimuli
• Ability to use social skills
• Ability to utilise social support
• Problem solving → state-oriented focus
• Degree of negative self-concept
Mood & Interpersonal Stress
• Prolonged negative mood
• Worsening of interpersonal problems
Legend:
Potential mechanisms considered in Phases 1, 2, or 4
Potential mechanism considered in Phase 3
Effects of treatment on mechanisms
Prognostic effects
Potential prognostic effects
Potential prescriptive effects

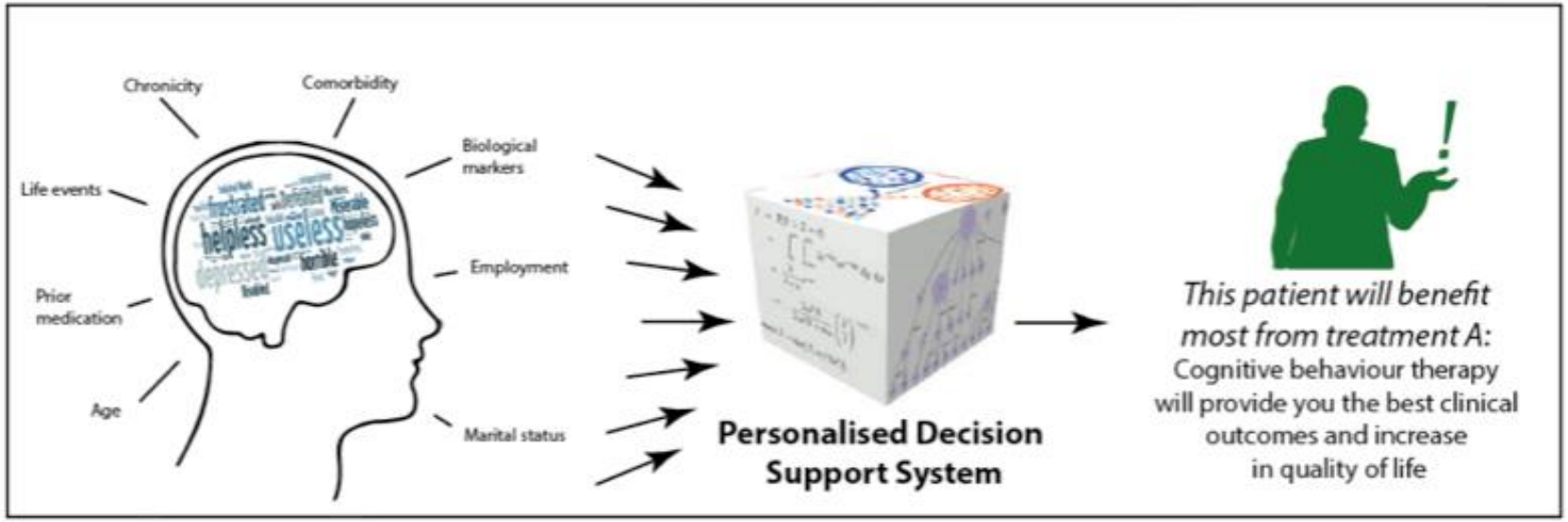
# Now we can get into treatment selection

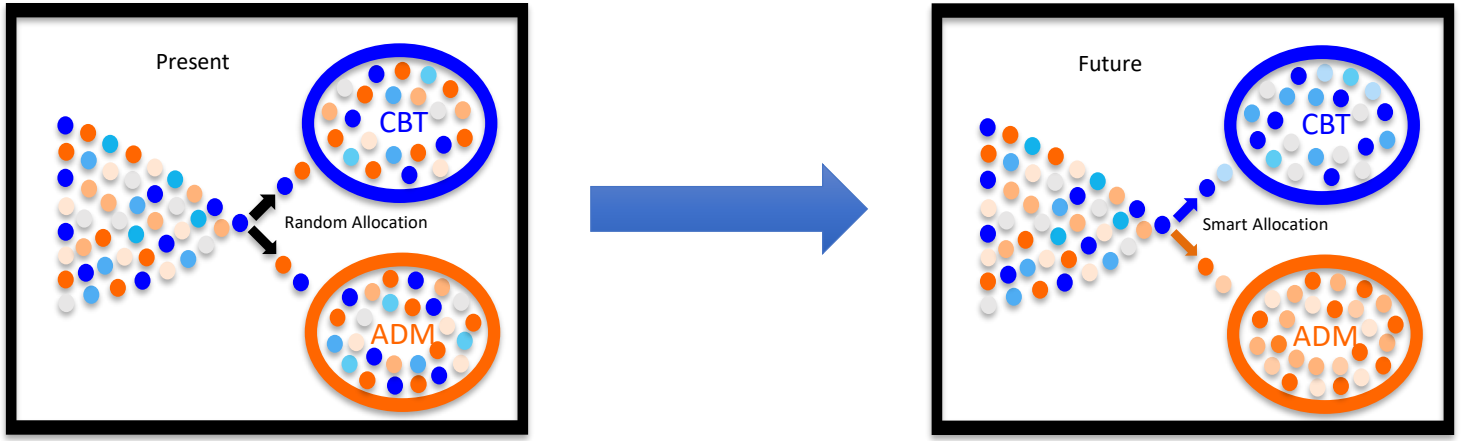
Using this kind of knowledge to develop personalised predictions

The PAI approach

With thanks to Dr Zach Cohen for this slide and those that follow on PAI and SMART

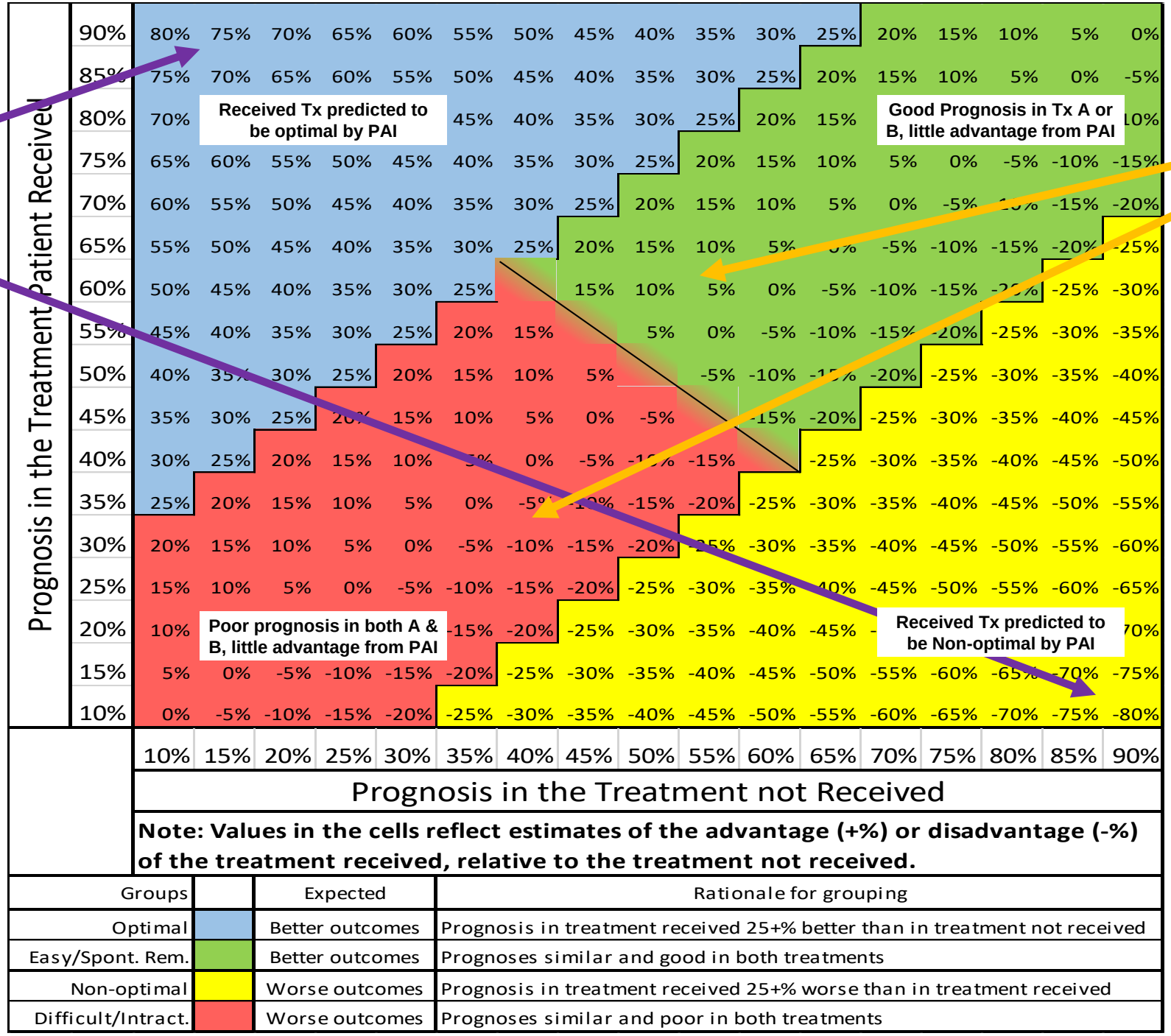
# Personalized Advantage Index



# the Personalized Advantage Index approach

- Identify moderators
- Build a statistical model with moderators that can generate predicted outcomes in TxA and TxB
- Generate predictions for new individuals in each available treatment
- The treatment predicted to have the best outcome is their indicated treatment
- An individual's PAI is: $\hat{Y}_{TxA} - \hat{Y}_{TxB}$
  - Sign indicates which Tx
  - Magnitude indicates strength of predicted advantage




Tx A would definitely be better

Availability, side-effects, ease for pt, cost…other considerations → choice of A vs B

**Note: Values in the cells reflect estimates of the advantage (+%) or disadvantage (-%) of the treatment received, relative to the treatment not received.**

| Groups | | Expected | Rationale for grouping |
|---|---|---|---|
| Optimal | | Better outcomes | Prognosis in treatment received 25+% better than in treatment not received |
| Easy/Spont. Rem. | | Better outcomes | Prognoses similar and good in both treatments |
| Non-optimal | | Worse outcomes | Prognosis in treatment received 25+% worse than in treatment received |
| Difficult/Intract. | | Worse outcomes | Prognoses similar and poor in both treatments |

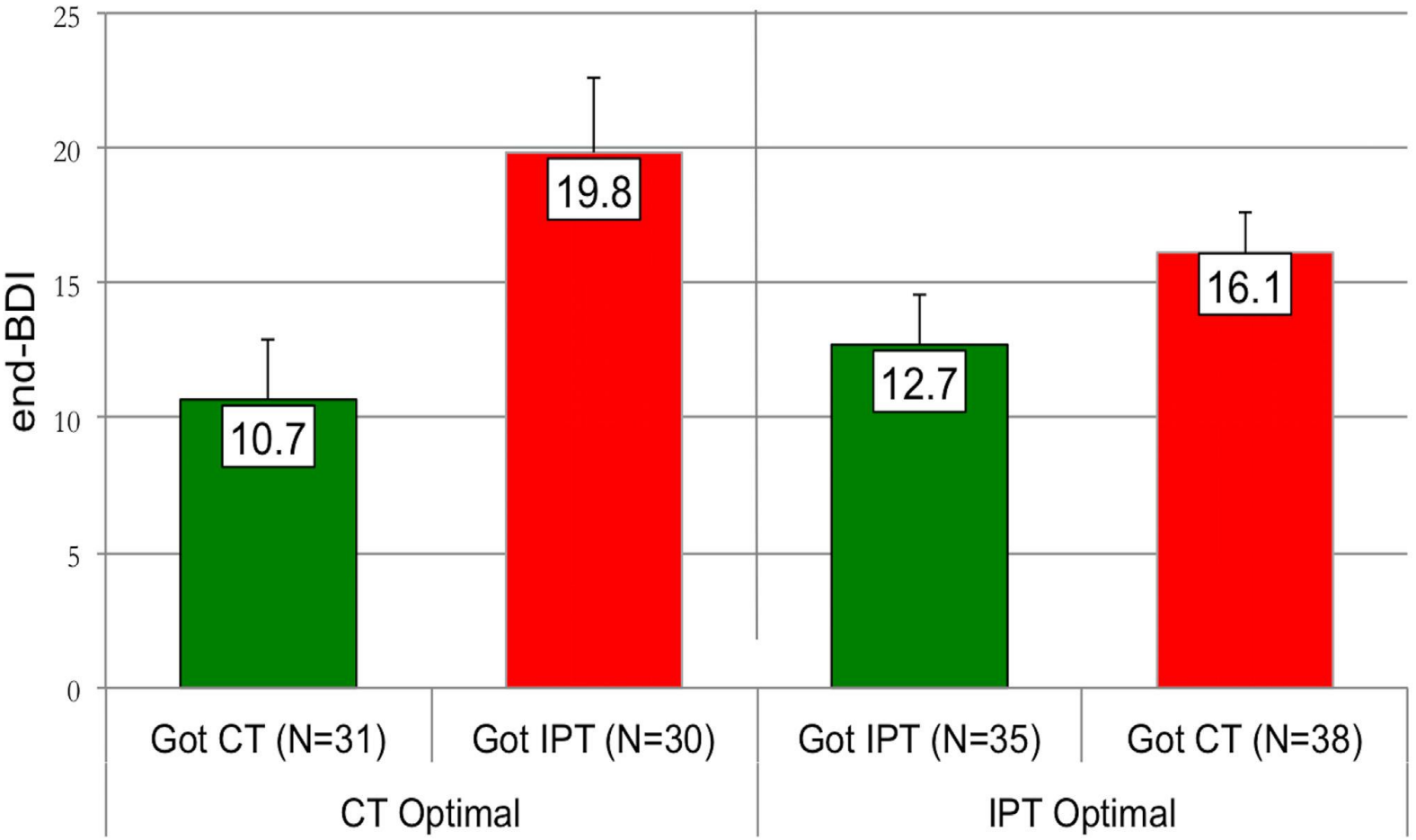


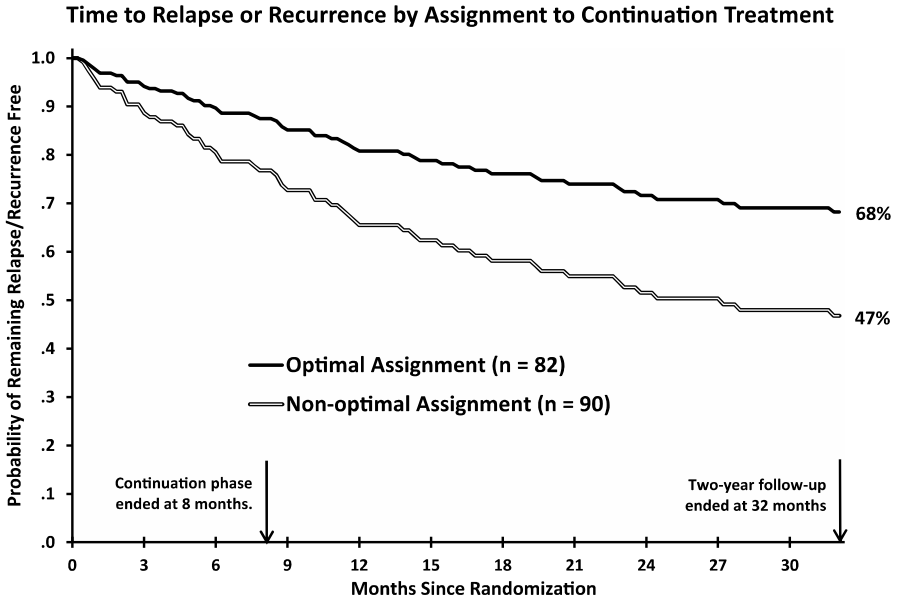

**Fig 3. Comparison of observed mean end-BDI scores for patients randomly assigned to their Optimal treatment versus those assigned to their Non-Optimal treatment, by psychotherapy type.**

doi:10.1371/journal.pone.0140771.g003

CT v IPT

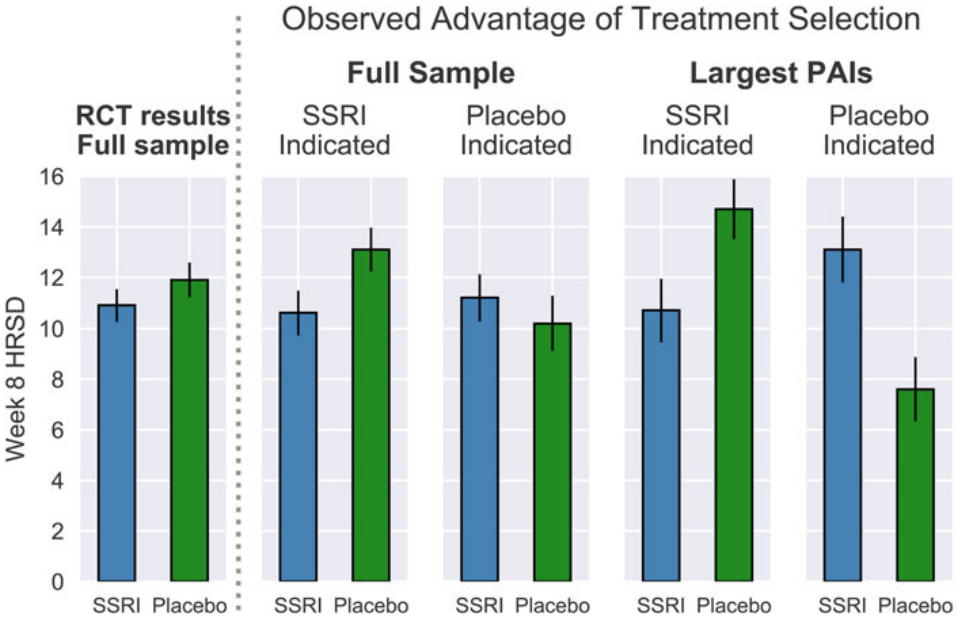
Huibers, Cohen, et al., 2015. Plos One

C-CT v ADM




Vittengl, et al., 2017. Psychiatry Research

ADM v Placebo




Webb, Trivedi, Cohen, et al., 2018. Psychological Medicine

**TABLE 5** Testing the Utility of the PAI Approach with Regard to Observed Scores and Reliable Change

| | | Optimal *n* (%) | Suboptimal *n* (%) |
|---|---|---|---|
| Reliable change | Yes | 78 (62.90) | 34 (33.66) |
| | No | 46 (37.10) | 67 (66.34) |

PAI, personalized advantage index; Reliable change index ≥ 6 for the PHQ-9 (Richards & Borglin, 2011); optimal, treatment condition with a predicted benefit for the individual patient; suboptimal, treatment condition that is predicted as being less effective for the individual patient.

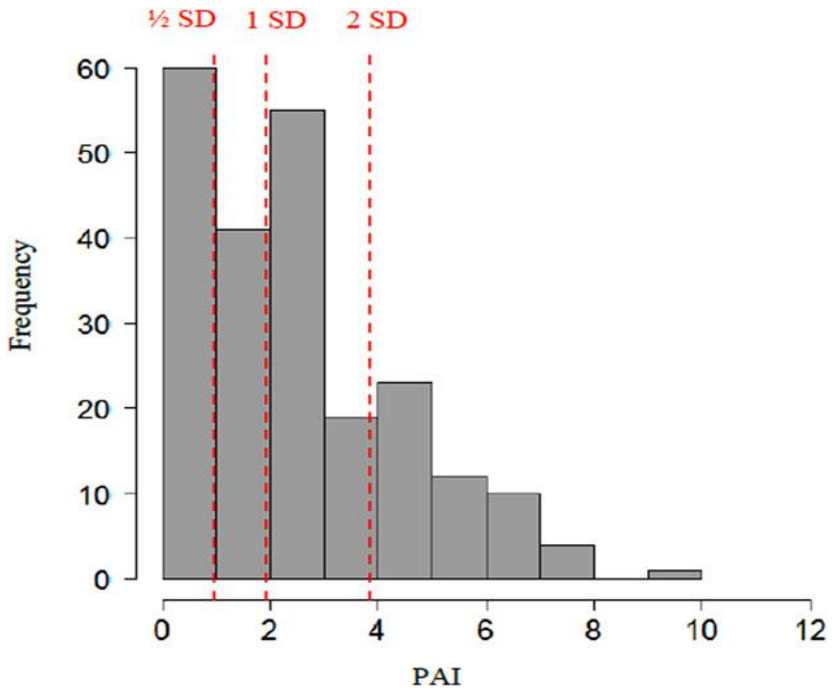



**FIGURE 3** Distribution of PAI scores. PAI, personalized advantage index (magnitude of the predicted difference between optimal and sub-optimal treatment); ½ SD, 0.96; 1 SD, 1.92; 2 SD, 3.85

Deisenhofer et al., 2018. Depression & Anxiety

TF-CBT vs EMDR

With thanks to Dr Zach Cohen for this slide

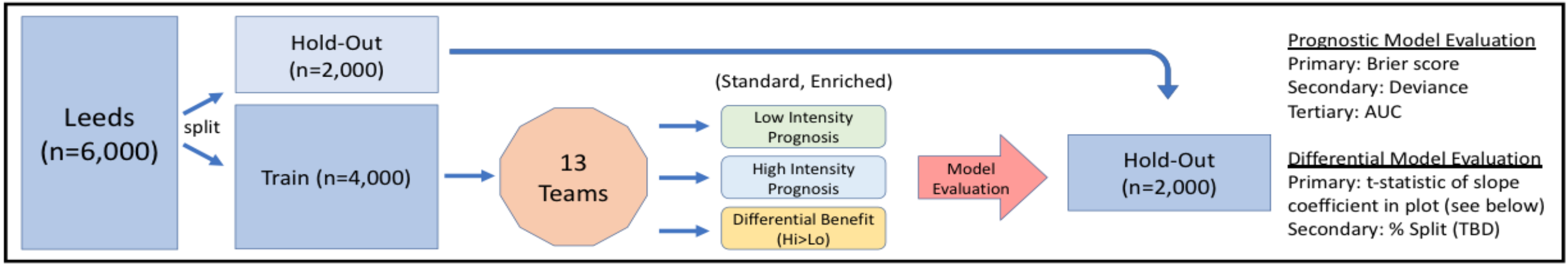
# Are we overfitting? Will the models generalize?

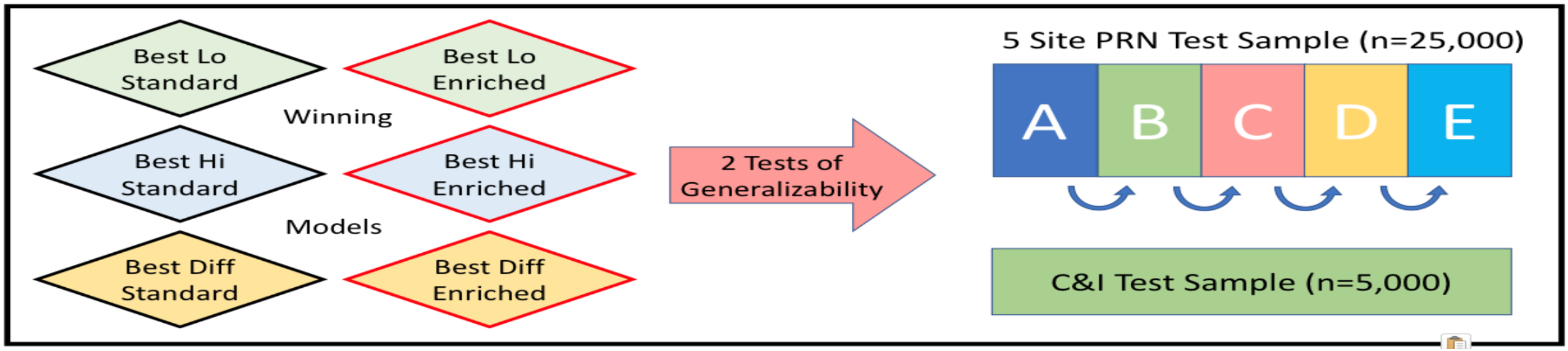
# Stratified Medicine Approaches foR Treatment Selection (SMART) Mental Health Prediction Tournament

SMART Mental Health Prediction Tournament
Hosted on the Open Science Framework
OSF.IO

https://osf.io/wxgzu/

- 13 teams comparing different approaches to treatment selection in the same data (training sample, held-out test sample)



We can predict response in held-out real-world data!

We compared different methodological approaches (results differed)

# How could these models be used in IAPT? (example)

# Acknowledgements & Thanks

**Funder: Wellcome Trust**
**Sponsors: Steve Pilling & Glyn Lewis**
**Fellowship Collaborators: Steve Hollon, Rob DeRubeis, Ed Watkins, Tony Kendrick, Simon Gilbody & Gareth Ambler**
**IPD collaborators: Dave Richards, Nicola Wiles, Deborah Sharp, David Kessler, Judy Chatwin, Melanie Chalder, Laura Thomas, Liz Littlewood**
**Day-to-day lifesavers & collaborators: Rob Saunders, Ciaran O'Driscoll, Zach Cohen, Eiko Fried, John Cape, Rebecca Minton & Judy Leibowitz**
**Clinical employer: Camden & Islington NHS Foundation Trust, iCope – Camden & Islington Psychological Therapies Services**