Improving guided treatment decisions for patients

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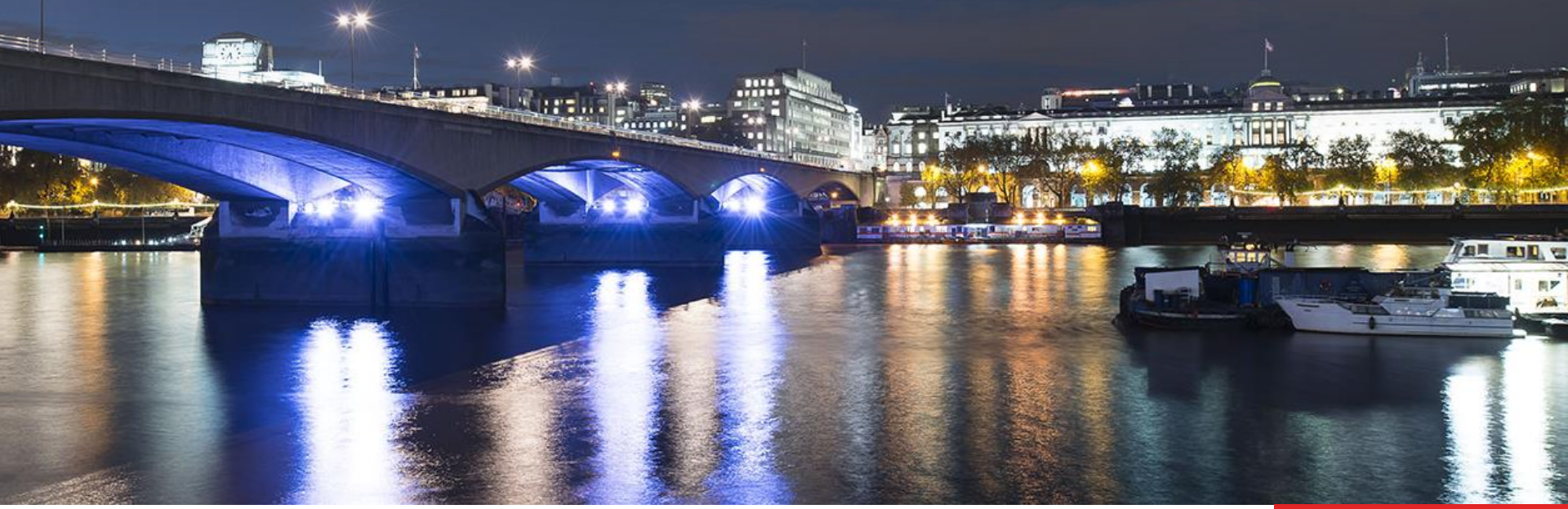

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Rationale: stratified medicine

- Motivating question: what is the optimal treatment to give to this patient right now, given their current and previous characteristics?
- Moving beyond 'one size fits all' approach to medicine
- "Right treatment at right dose to right person at right time"
- Also known as:
  - Personalised/targeted/precision medicine
- We want to identify '**predictive biomarkers**'
  - a measurement made before treatment to identify which patient is likely or unlikely to benefit from a particular treatment

Treatment response

- Consider an RCT comparing treated and control subjects, where the aim is to find whether biomarker values can predict treatment response

- For any subject the treatment response is an unobserved quantity – unlike disease status or disease outcome

- After follow-up a continuous outcome for control subjects:

$$Outcome_C = Baseline + Prognostic$$

Where *Baseline* is the level of outcome at beginning of study
And *prognostic* is the (treatment free) change over follow-up

- For treated subjects:

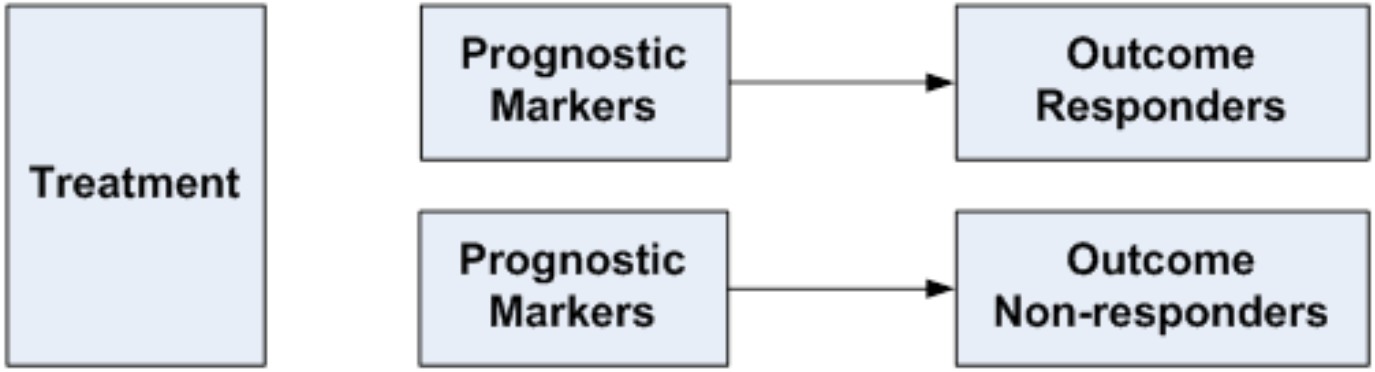
$$Outcome_T = Baseline + Prognostic + Treatment\ response$$

Prognostic markers in a treated cohort

- For treated subjects:

$$Outcome_T = Baseline + Prognostic + Treatment\ response$$

- Searching for prognostic markers of response in a treated only cohort is akin to a (nested) case-control study:



Predicting response

- When are we interested in predicting response?
  - For the individual patient who is responding
  - But why they are responding?

- For non-responders, it doesn't give enough information to decide on an alternative treatment:
  - treatment with a different mechanism (IL-6 vs. TNF-α)
  - more likely to comply with treatment (oral vs. injection)

- So this can't tell us about stratified medicine…

- Stratified medicine assists in treatment decision making for next cohort of patients, not for current cohort…

Multiple markers

- How likely is it to be a single predictive marker?
  - Cancer e.g. genotype of tumour
  - Other disciplines…unlikely?
- For many diseases, combination of markers multi-modal markers
  - E.g. imaging, genotype, clinical
- Question: how do we combine multiple markers into a rule for treating patients?

Personalised treatment recommendations (PTR)

- Consider a randomised trial with randomisation variable $A_i \in \{0,1\}$
- A subject's observed outcome following treatment is the value under the control condition (Y_{0i}), plus the change attributable to treatment ($Y_{1i} - Y_{0i}$), if the subject was treated ($A_i = 1$):

$$Y_i = Y_{0i} + A_i(Y_{1i} - Y_{0i})$$

- Formally, a PTR is an algorithm that maps baseline biomarkers X to a treatment decision:

$$PTR(x) : X \rightarrow A\{0,1\}$$

- An outcome following an personalised treatment recommendation based on X is given by:

$$Y_i = Y_{0i} + \mathrm{PTR}(X_i)(Y_{1i} - Y_{0i})$$

Personalised treatment recommendations (PTR)

- The PTR might be a single biomarker (treat if aged at least 60):

$$PTR(x) = I(age \geq 60)$$

Or multiple biomarkers:

$$PTR(x) = I(age \geq 60 \ \& \ blood\ pressure > 140/90mmHg)$$

where I is the indicator function.

- There are numerous conflicting PTR's for any set of biomarkers, e.g. $I(age \geq 40), I(age \geq 41)$ etc.

An optimal PTR

- Define the treatment contrast as the difference in mean outcome between treated and control subjects with the same biomarker value(s):

$$\Delta(X) = \mu(A = 1, X) - \mu(A = 0, X)$$

- Assuming higher values of outcome are better, an optimal PTR is one that recommends treatment if the contrast is positive:

$$PTR^{opt}(X) = I[\Delta(X) > 0]$$

- Note that zero is chosen by convention as the minimum change in outcome required to recommend it over control.
  - This can be substituted for any value, for example a minimum threshold for improvement necessary to counter costs/side-effects

Estimating a PTR: regression approach

- The regression approach specifies a linear model, with predictive biomarkers included as treatment interaction terms

$$\mu(A,X) = \alpha_0 + \alpha X^{prog} + A\left(\beta_0 + \beta X^{pred}\right)$$

- The PTR under this model is:

$$PTR^{reg}(X) = I\left\{\left(\beta_0 + \beta X^{pred}\right) > 0\right\}$$

i.e. treat if the estimated effect of treatment plus the predictive-marker effects is greater than zero

- Fails to estimate the optimal treatment contrast when the regression model is misspecified:
  - for example uses the wrong link-function, or fails to include interactions or higher order terms

Evaluating a PTR: does it improve on an alternative policy?

- A natural parameter to use to evaluate a PTR is the extent that it improves on an outcome compared to an alternative policy:

- Compared with treating everybody:

$$\theta_T = \mu\{PTR(X)\} - \mu\{A = 1\}$$

  - $\mu\{A = 1\}$ is the mean outcome in the treated

- Compared with not-treating everybody:

$$\theta_C = \mu\{PTR(X)\} - \mu\{A = 0\}$$

- Positive θ indicates a better outcome under treatment rule

- Choice between θ_T and θ_C should be based on what the default policy would be

`ptr.ado` Stata command

- This programme estimates a PTR using (potentially multiple) biomarker input(s) using the regression method.
- It also evaluates the PTR, comparing a biomarker based strategy to one where everybody is either treated or in control group.
- Inference for theta using bootstrap procedures

`ptr.ado` Stata command

```
ptr command: constructing and evaluating personalised treatment recommendations
Weights for each modifier variable: inference from regression
```

Variable	Weight	Std. Err.	p	[95% Conf.	Interval]
A	2.200728	.4523488	0.000	1.314142	3.087313
X1	1.433679	.4828866	0.004	.487241	2.380118
X2	-1.399476	.443991	0.002	-2.26968	-.5292711
X3	-.0316271	.4764358	0.947	-.9654223	.9021681

```
ptr was generated using:
      I(  2.20073 + 1.43368*X1 + -1.39948*X2 + -0.03163*X3 > 0)

Evaluating PTR: inference from 2 bootstrap samples
```

	Estimate	Std. Err.	p	[95% Conf.	Interval]	
mu ptr	1.549422	.2304552	0.000	1.097738	2.001105	(N)
mu contrast	1.389529	.1898098	0.000	1.017509	1.761549	(N)
theta	.1598927	.420265	0.352	-.6638116	.983597	(N)

```
 (N)    normal confidence interval

.
end of do-file
```

Our outputs

- Pierce M, Dunn G, Emsley RA. (2018). Combining moderators for personalised treatment recommendations: a comparison of approaches (under review).
- Pierce M, Emsley RA. (2018). Ptr: Estimating and evaluating personalised treatment recommendations from randomised trials (in submission).
- Marsden A, Emsley RA, Dixon W, Dunn G. (2018). Evaluating treatment effect modification on the additive scale: methods to investigate predictors of differential treatment response (under review).
- Dunn G, Emsley RA, Liu H & Landau S. (2013). Integrating biomarker information within trials to evaluate treatment mechanisms and efficacy for personalised medicine. *Clinical Trials*, 10(5):709-19.

Acknowledgments and funding

- Joint work with **Dr Matthias Pierce**, Prof Graham Dunn, Dr Antonia Marsden

- Support from MRC Methodology Research Programme/HTMR grants:

  - Estimation of causal effects of complex interventions in longitudinal studies with intermediate variables (2009-2012)
  - Designs and analysis for the evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health (2010-12)
  - Developing methods for understanding mechanism in complex interventions (2013-15)
  - Theme 4, North West Hub for Trials Methodology Research (2013-18)

MRC Medical Research Council