Jessica Riley, *Shells*
Artwork from Reflections Art in Health

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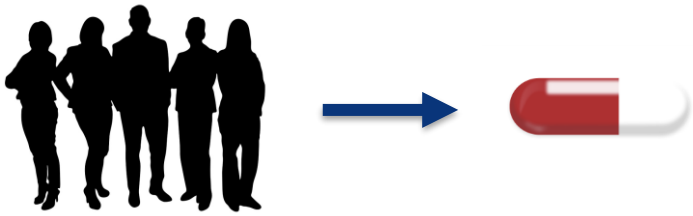
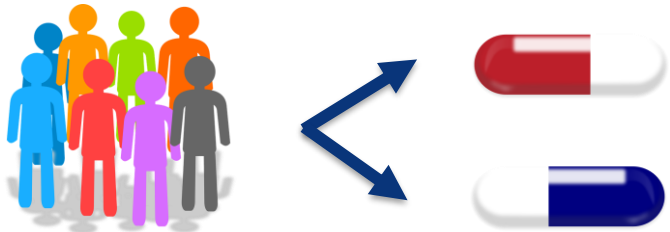
Focus on personalized medicine:

- **Traditional medical paradigm**: one-size fits all treatment



- **Personalized medicine**: treatment is tailored to an individual patient



Q: how can we predict which treatment is optimal for a given patient?
=> New statistical method to evaluate **predictive biomarkers**

Setting the scene:

- Design: data from a **randomized** clinical trial with **two parallel treatment arms**
- **Candidate-predictors of treatment success** (predictive biomarkers): $\boldsymbol{S} = (S_1, S_2, \ldots S_p)'$
- True endpoint ***T***: outcome to **evaluate which treatment is best**

S: candidate-predictors of treatment success (= candidate-predictive biomarkers):

S_1: basal EGF concentration

S_2: proportion of CD4 T−cells

…

S_9: monocyte count

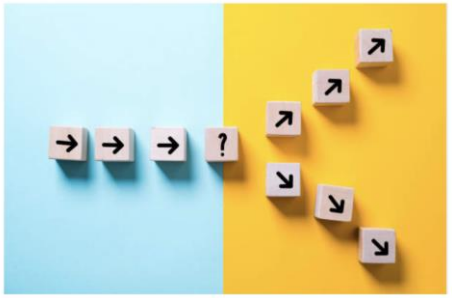
S_{10}: white blood cell count

T = outcome to evaluate which treatment is best, e.g., survival time

Q: based on ***S***, can we predict which treatment is optimal/best for this particular patient?

Rubin's causal-inference framework:

- Central concept: **potential outcomes** (or **counterfactuals**)



T_0: true endpoint if the patient receives the control treatment

T_1: true endpoint if the patient receives the experimental treatment

- **Individual causal treatment effect**: $\Delta T = T_1 - T_0$
  - E.g., survival time for a patient with treatment A = 5 years and with treatment B = 3 years, then ΔT = 2 years.
  - This is the individual causal treatment effect for this particular patient

The Predictive Causal Information (PCI; R^2_ψ):

- How well can we predict $\boldsymbol{\Delta T}$ based on the candidate predictive biomarkers $\boldsymbol{S}$?
- PCI quantifies the mutual information between $\boldsymbol{S}$ and $\boldsymbol{\Delta T}$
  - How much uncertainty in $\boldsymbol{\Delta T}$ is removed when we know $\boldsymbol{S}$ for a patient?

$$R^2_\psi = \frac{\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} \boldsymbol{\Sigma}_{SS}^{-1} \boldsymbol{\Sigma}_{ST} \boldsymbol{a}_1'}{\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TT} \boldsymbol{a}_1'}$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma}_{TT} & \boldsymbol{\Sigma}_{TS} \\ \boldsymbol{\Sigma}_{ST} & \boldsymbol{\Sigma}_{SS} \end{pmatrix}$$

$$\boldsymbol{\Sigma}_{TT} = \begin{pmatrix} \sigma_{T0T0} & \sigma_{T0T1} \\ \sigma_{T0T1} & \sigma_{T1T1} \end{pmatrix}, \quad \boldsymbol{\Sigma}_{TS} = \begin{pmatrix} \sigma_{T0Sr} \\ \sigma_{T1Sr} \end{pmatrix}$$

$$\boldsymbol{\Sigma}_{SS} = (\sigma_{SrSn}),$$

R^2_ψ (PCI) is the squared correlation between $\boldsymbol{\Delta T}$ and a linear combination of $\boldsymbol{S}$ (~coefficient of determination)

The fundamental problem of causal inference (Holland, 1986):

- Idea of **potential outcomes** (or **counterfactuals**)
  - T_0: true endpoint if the patient receives the control treatment
  - T_1: true endpoint if the patient receives the experimental treatment

- PCI: how well can we predict $\Delta T (= T_1 - T_0)$ based on ***S***?

$$\boldsymbol{\Sigma}_{TT} = \begin{pmatrix} \sigma_{T0T0} & \sigma_{T0T1} \\ \sigma_{T0T1} & \sigma_{T1T1} \end{pmatrix}$$

- Setting here: parallel treatment arms
  - σ_{T0T1} is **unidentifiable** -> PCI is **unidentifiable…**

Dealing with unidentifiability:

- Sensitivity analysis

$$R^2_{\psi} = \frac{\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} \boldsymbol{\Sigma}_{SS}^{-1} \boldsymbol{\Sigma}_{ST} \boldsymbol{a}_1'}{\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TT} \boldsymbol{a}_1'}$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma}_{TT} & \boldsymbol{\Sigma}_{TS} \\ \boldsymbol{\Sigma}_{ST} & \boldsymbol{\Sigma}_{SS} \end{pmatrix}$$

$$\boldsymbol{\Sigma}_{TT} = \begin{pmatrix} \sigma_{T0T0} & \sigma_{T0T1} \\ \sigma_{T0T1} & \sigma_{T1T1} \end{pmatrix}, \quad \boldsymbol{\Sigma}_{TS} = \begin{pmatrix} \sigma_{T0Sr} \\ \sigma_{T1Sr} \end{pmatrix}$$

$$\boldsymbol{\Sigma}_{SS} = (\sigma_{SrSn}),$$

Approach:

- Fix **identifiable parameters** at their estimated values
- Define a grid for the **unidentifiable correlation** ρ_{T0T1}; ***G*** = {-1, -0.99, … 1}
- Consider each value of ***G*** in $\boldsymbol{\Sigma}$ and retain the PD $\boldsymbol{\Sigma}$
- Compute PCI for the retained $\boldsymbol{\Sigma}$

=> We will get estimates of the PCI **across all "plausible realities"**, i.e., in all scenarios where the unidentifiable ρ_{T0T1} is compatible with the observed data

A case study in oncology:

- **CIMAvax-EGF**: therapeutic anti-cancer vaccine in lung cancer (Lorenzo-Luaces *et al.*, 2022)
- Evidence of **heterogeneity in treatment response** (T = survival time): why do some patients respond well to the treatment, and others not?
- **Q**: are there predictive biomarkers?

TABLE 3 Summary statistics for R^2_ψ using the combinations of S_1 = Basal EGF concentration, S_2 = proportion of CD4+ T cell, S_3 = CD8+CD28- T cells , S_4 = CD4/CD8 ratio, S_5 = CD19 B cell, S_6 = absolute lymphocyte count, S_7 =neutrophil-to-lymphocyte ratio , S_8 =absolute eosinophil count, S_9 = absolute monocyte count,S_{10} = white blood cell count as pretreament predictors and T = The elapsed time since trial inclusion to death in the control (T_0) and CIMAvaxEGF treatment (T_1) groups

S	R^2_ψ Mean	Min	Median	Max
(S_2)	0.486	0.354	0.469	0.694
(S_2, S_9)	0.563	0.423	0.546	0.772
(S_2, S_7, S_9)	0.658	0.521	0.645	0.847
(S_2, S_4, S_7, S_9)	0.721	0.603	0.713	0.873
$(S_1, S_2, S_4, S_7, S_9)$	0.795	0.689	0.789	0.923
$(S_1, S_2, S_4, S_5, S_7, S_9)$	0.814	0.727	0.810	0.915
$(S_1, S_2, S_4, S_5, S_6, S_7, S_9)$	0.836	0.751	0.832	0.933
$(S_1, S_2, S_4, S_5, S_6, S_7, S_9, S_{10})$	0.847	0.796	0.846	0.902
$(S_1, S_2, S_4, S_5, S_6, S_7, S_8, S_9, S_{10})$	0.851	0.815	0.851	0.889
$(S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8, S_9, S_{10})$	0.855	0.825	0.854	0.886

Observe:

- When **only 1 S is considered**, PCI is low and the uncertainty attributable due to non-identifiability is large (many ρ_{T0T1} are compatible with the observed data)
- When more S are considerded, PCI increases and uncertainty reduces

A case study in oncology:

- Based on the model, we can also predict ΔT based on ***S*** for an individual patient

- Example: predict ΔT for a patient with **high level of basal EGF concentration** (S_1) and **CD4 T-cells** (S_2), and average values for the other S

```
Predict.Treat.Multivar.ContCont(Sigma_TT = Sigma_TT, Sigma_TS = Sigma_TS,
    Sigma_SS = Sigma_SS, Beta = Beta, S = S_high, mu_S = mu_S,
    T0T1 = seq(-1, 1, by = 0.01))


# Predicted (Mean) Delta_T_j | S_j
#~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

67.8753


# Variances and 95% support intervals of Delta_T_j | S_j for different values of rho_T0T1
#~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

                 rho_T0T1   Var Delta_T_j | S_j   95% supp. int. around Delta_T_j | S_j

 (min. value)     0.150           114.184          [46.93174; 88.81886]
 (max. value)     0.290           69.357          [51.5526; 84.198]
 (median value)   0.220           91.770          [49.09948; 86.65113]
 (mean value)     0.220           91.770          [49.09948; 86.65113]


# Proportion of 95% support intervals for Delta_T_j | S_j
that include 0, are < 0, and are > 0
#~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

0 included in support interval:  0
Entire support interval below 0:  0
Entire support interval above 0: 1     (obtained for rho_T0T1 values in range [0.15; 0.29])
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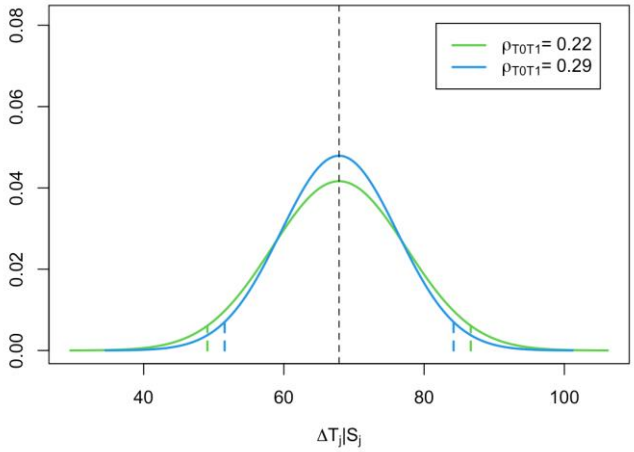

A case study in oncology:

- Easy to implement in user-friendly software like MS Excel:

Predicting treatment success based on immunologic markers in advanced lung cancer
(experimental treatment: CIMAvaxEGF; control treatment = best supportive care)

Pretreatment predictors:		
EGF	1500	
Proportion of CD4+	45	
CD8+CD28-T cells	21	
CD4/CD8 ratio	1,5	
Proportion of CD19+ B cells	5	
Absolute lymphocyte count	34	
Neutrophil-to-lymphocyte ratio	2,5	
Absolute eosinophil count	2	
Absolute monocyte count	5	
White blood cell count	50	
Assumed correlation $r(T_0, T_1)$:	0,22	*(range [0,15, 0,29])*

Results:

Expected individual causal treatment effect ($\Delta T \mid \mathbf{S}$):	**67,8753**
95% support interval:	**[49,0995; 86,6511]**

Conclusion:
The expected individual causal treatment effect is above 0, which indicates that the experimental treatment is more beneficial to the patient
The difference is significant (the 95% support interval does not contain zero)

Figure 2: Excel sheet for user-friendly prediction of $\Delta T \mid \mathbf{S}$ and its 95% support interval.

A case study in oncology:

- Good responder (probability >50% of positive response) versus bad responders (probability <50%)

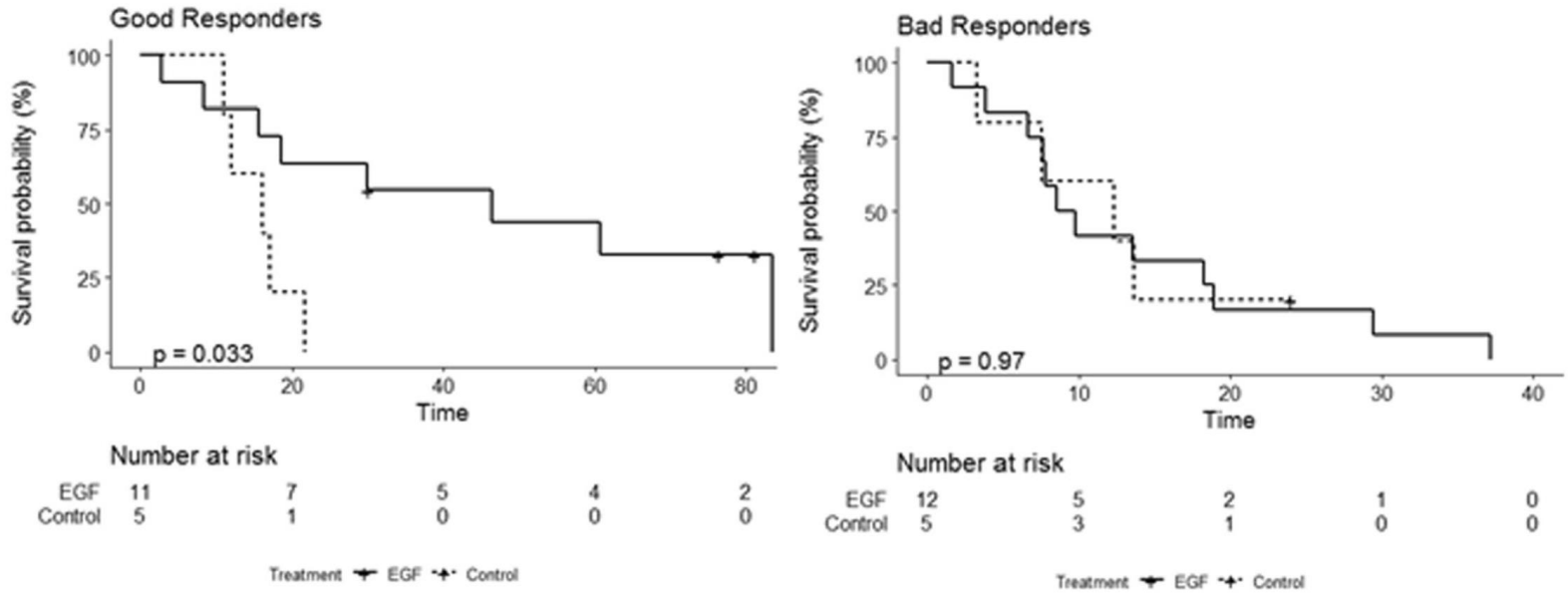

Fig. 3 Kaplan Meier survival curves for patient treated with CIMAvax-EGF and control for a) good responders, b) bad responders

Summary:

- Causal-inference based approach to predict treatment success
  - PCI: how well can we predict ΔT based on S
  - Unidentifiability: sensitivity analysis

- Focus was here on predictive biomarkers, but similar methodology can be used for multivariate **surrogate endpoints** (Van der Elst *et al.*, 2019)

- Methodology is implemented in the R package *EffectTreat*
  https://cran.r-project.org/web/packages/EffectTreat/index.html

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