Biomarkers & Personalised Healthcare

Chris Harbron

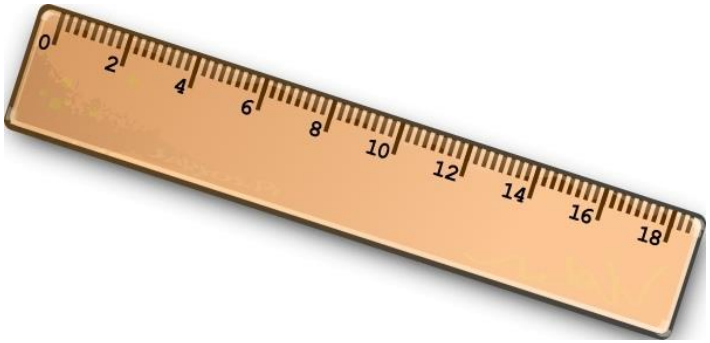
Roche Biostatistics: Methods Collaborations & Outreach (MCO)

ITT5 : 30th January – 3rd February 2017

What Is A Biomarker?

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

the National Institutes of Health Biomarkers Definitions Working Group



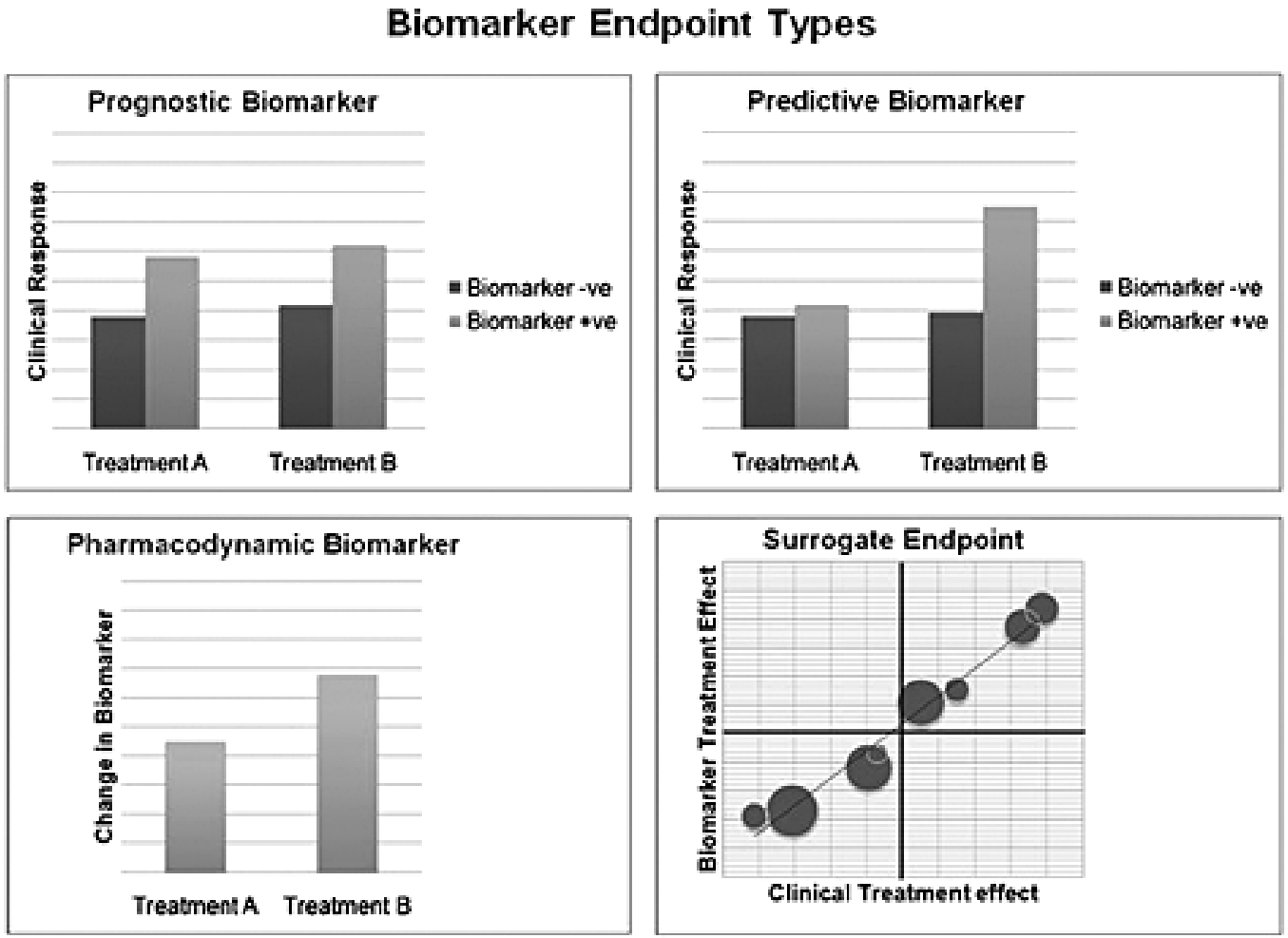
Bio- **-Marker**

What is a Biomarker?

Biomarker applications	Drug Development	Disease management
Stratification markers	Select patients to increase likelihood of clinical trial success	Select the best treatment/drug for each patient
Efficacy biomarkers	Biomarkers as "early killers" or as approved surrogate markers	Improve patient compliance in the absence of early clinical improvement
Differentiation markers	Differentiate efficacy or safety of a drug within the same class	Select the best treatment/drug for each patient
Toxicity biomarkers	Biomarkers as "early killers" or used to exclude certain patient groups from clinical trials	Monitor and avoid potential toxic effects
Screening markers	Patient recruitment for clinical trials	Early disease detection, early treatment
Prognostic markers	Patient recruitment for clinical trials	Predict likely course of disease

Source: Discussion paper, OECD Workshop on "Policy Issues for the Development and Use of Biomarkers in Health" 2008.

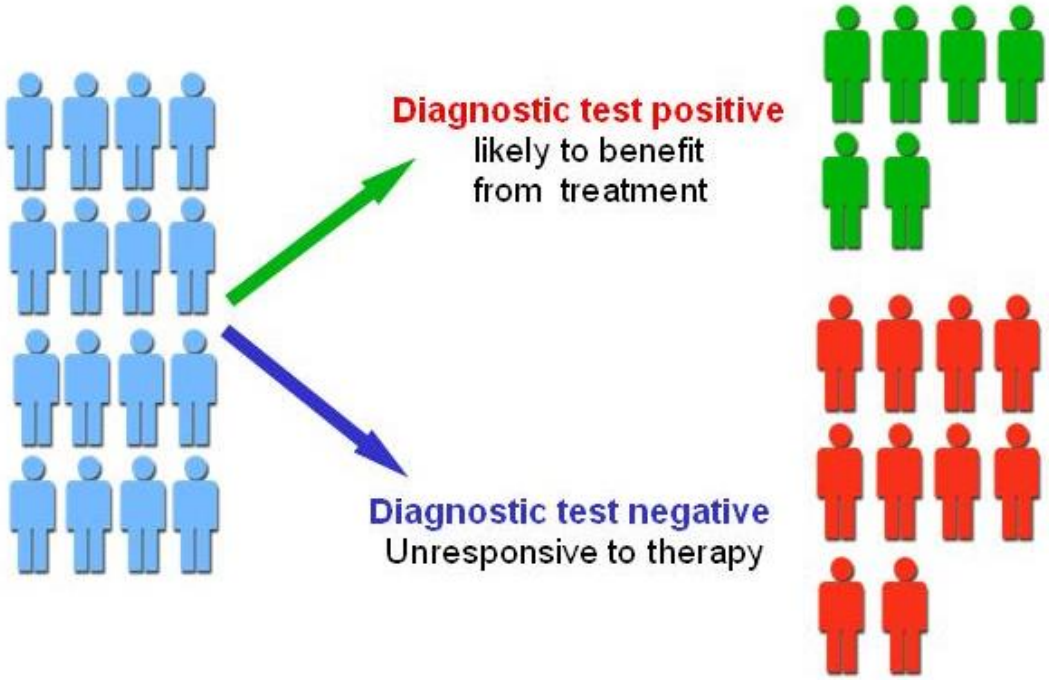
What is a Biomarker?

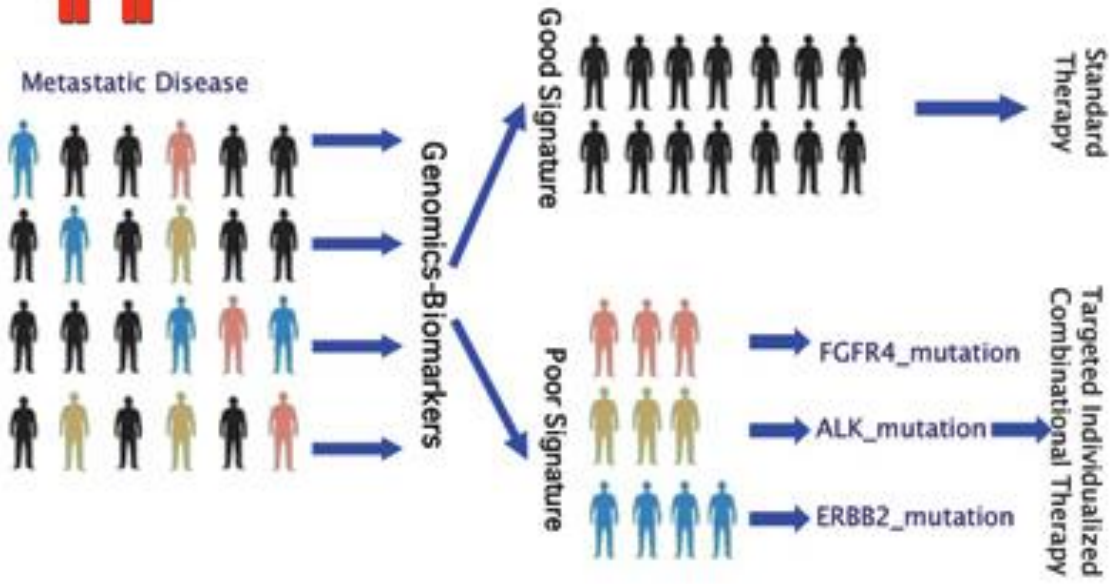


Prognostic Biomarker: Predicts the likely disease prognosis independent of the mode of treatment
Predictive Biomarker: Predicts the likelihood of response to a particular treatment or class of treatments
Pharmacodynamic Biomarker: Responds over time to a treatment intervention
Surrogate Endpoint: Correlates well with an accepted clinical outcome at an individual and group level

A statistician's perspective on biomarkers in drug development **Pharmaceutical Statistics**
Volume 10, Issue 6, pages 494-507, 8 DEC 2011 DOI: 10.1002/pst.532
http://onlinelibrary.wiley.com/doi/10.1002/pst.532/full#pst532-fig-0001

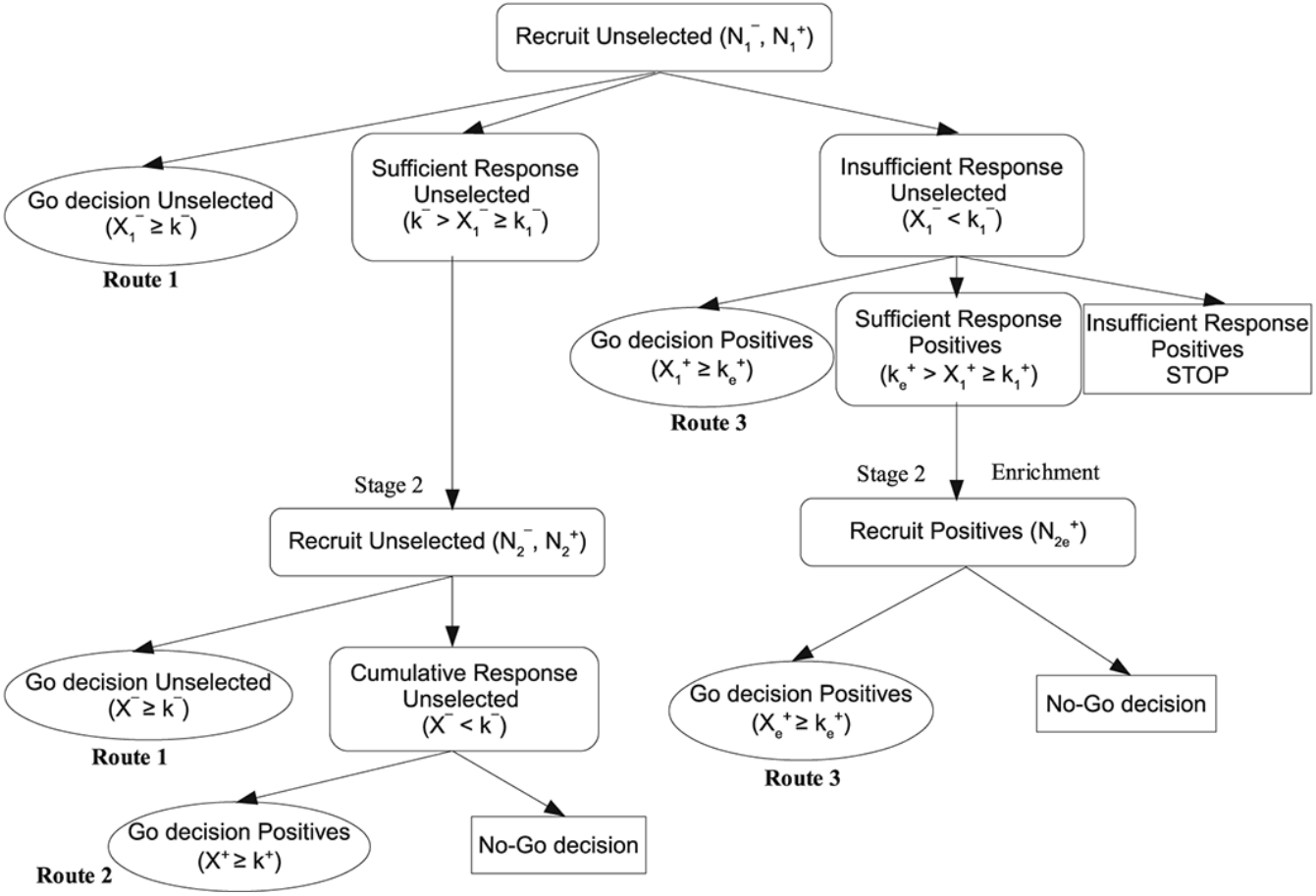
Personalised Medicine





“Simple” Biomarkers -> New Adaptive Designs
Decisions both on stop/continue and patient populations

An optimal stratified Simon two-stage design – Deepak Parashar et al

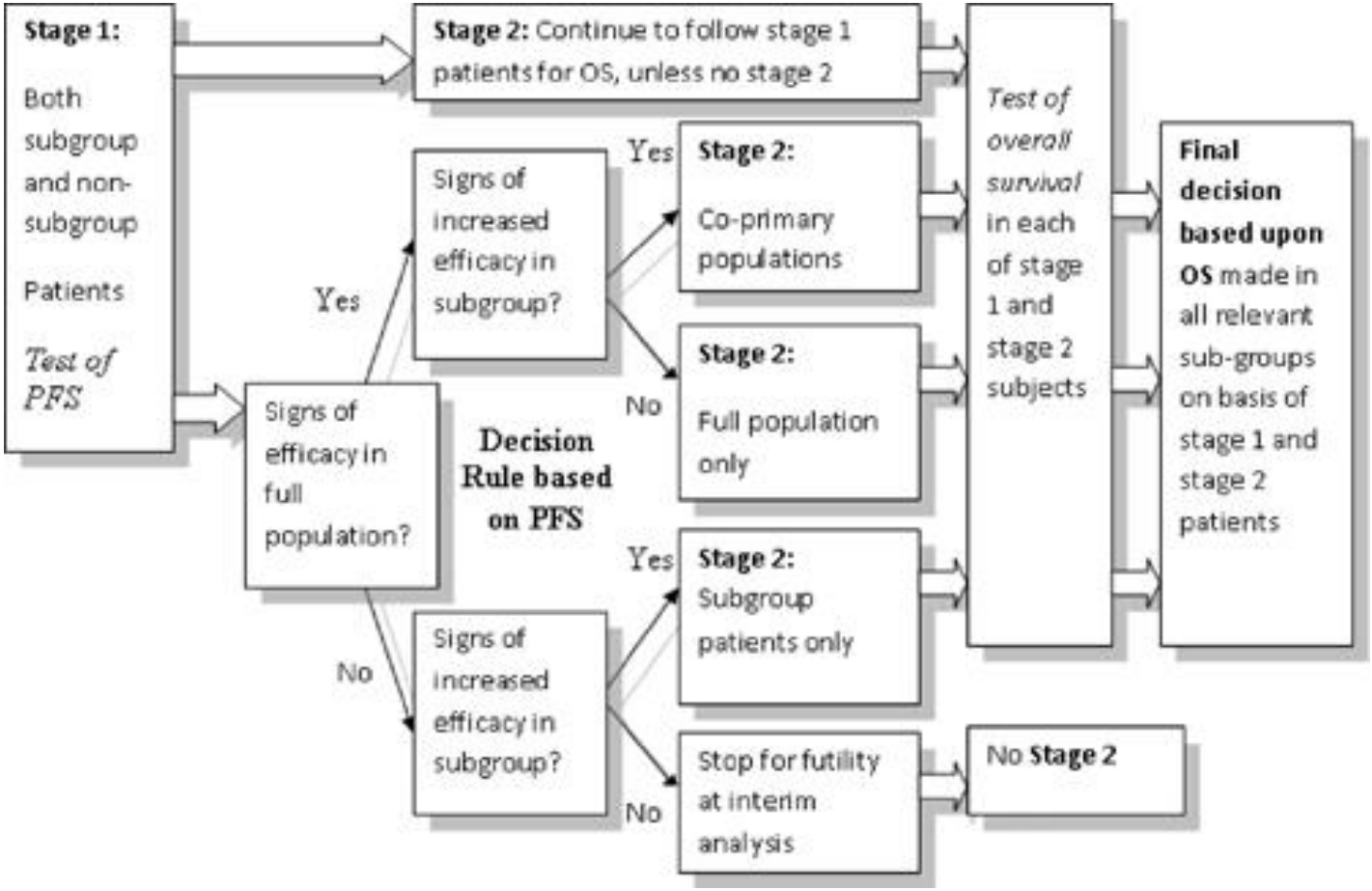


Pharmaceutical Statistics
Volume 15, Issue 4, pages 333-340, 2 MAR 2016 DOI: 10.1002/pst.1742
http://onlinelibrary.wiley.com/doi/10.1002/pst.1742/full#pst1742-fig-0001

"Simple" Biomarkers -> New Adaptive Designs

Decisions both on stop/continue and patient populations

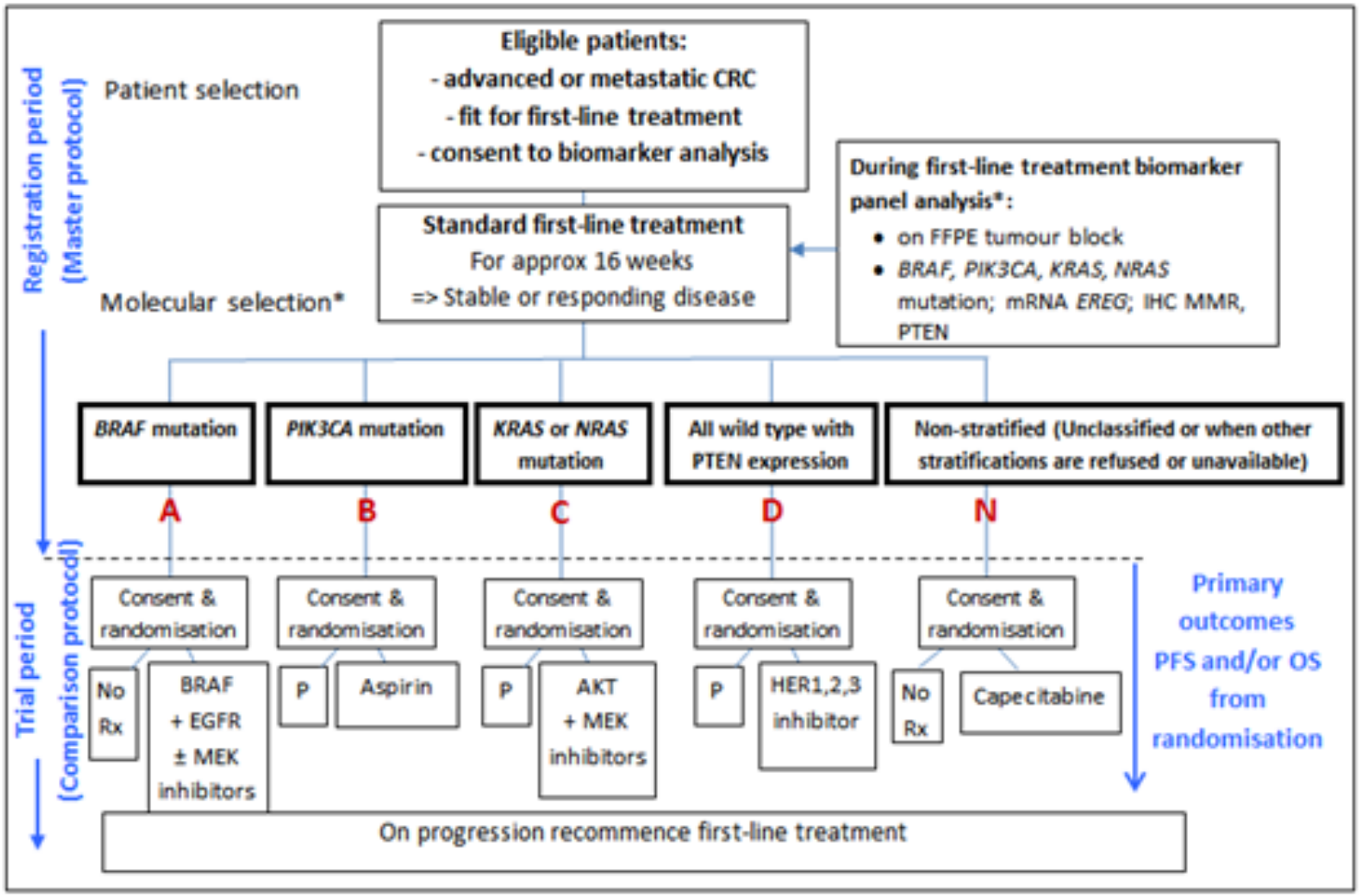
An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints – Jenkins, Stone & Jennison



Pharmaceutical Statistics
Volume 10, Issue 4, pages 347-356, 8 DEC 2010 DOI: 10.1002/pst.472
http://onlinelibrary.wiley.com/doi/10.1002/pst.472/full#fig1

“Simple” Biomarkers -> New Designs

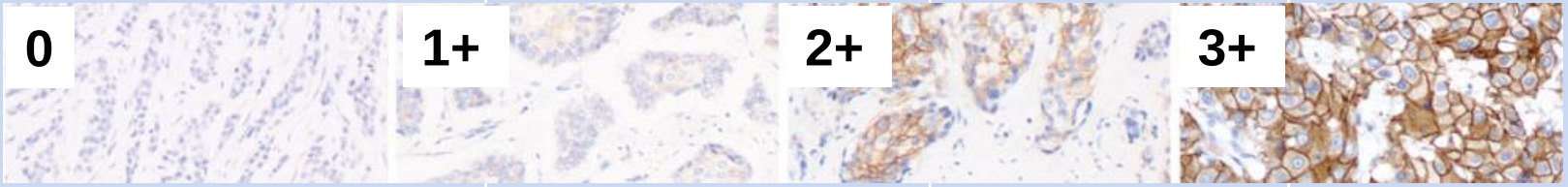
FOCUS 4

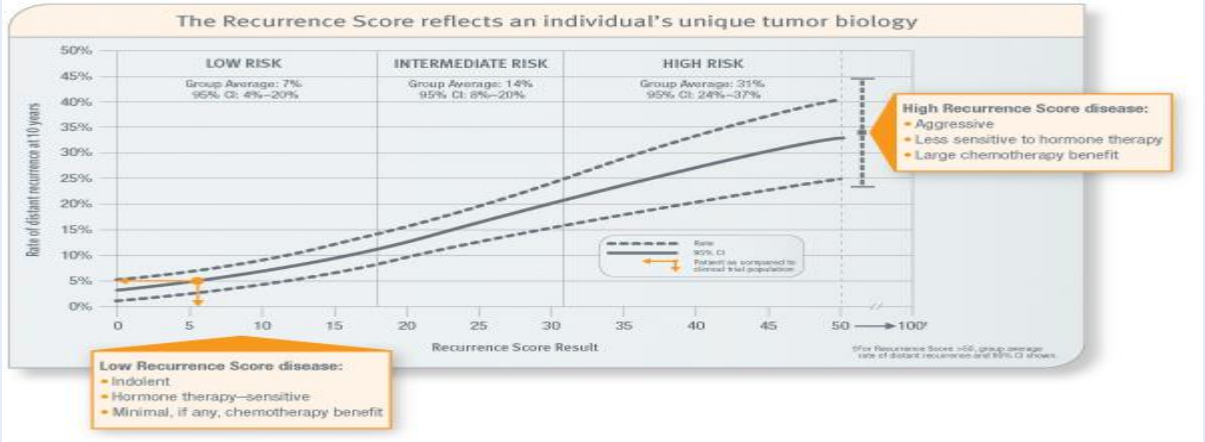


** The molecular cohorts are arranged in a hierarchy from left to right. For example a patient with both a PIK3CA mutation and a KRAS mutation will be classified into the PIK3CA mutation cohort.*

Continuous Biomarkers

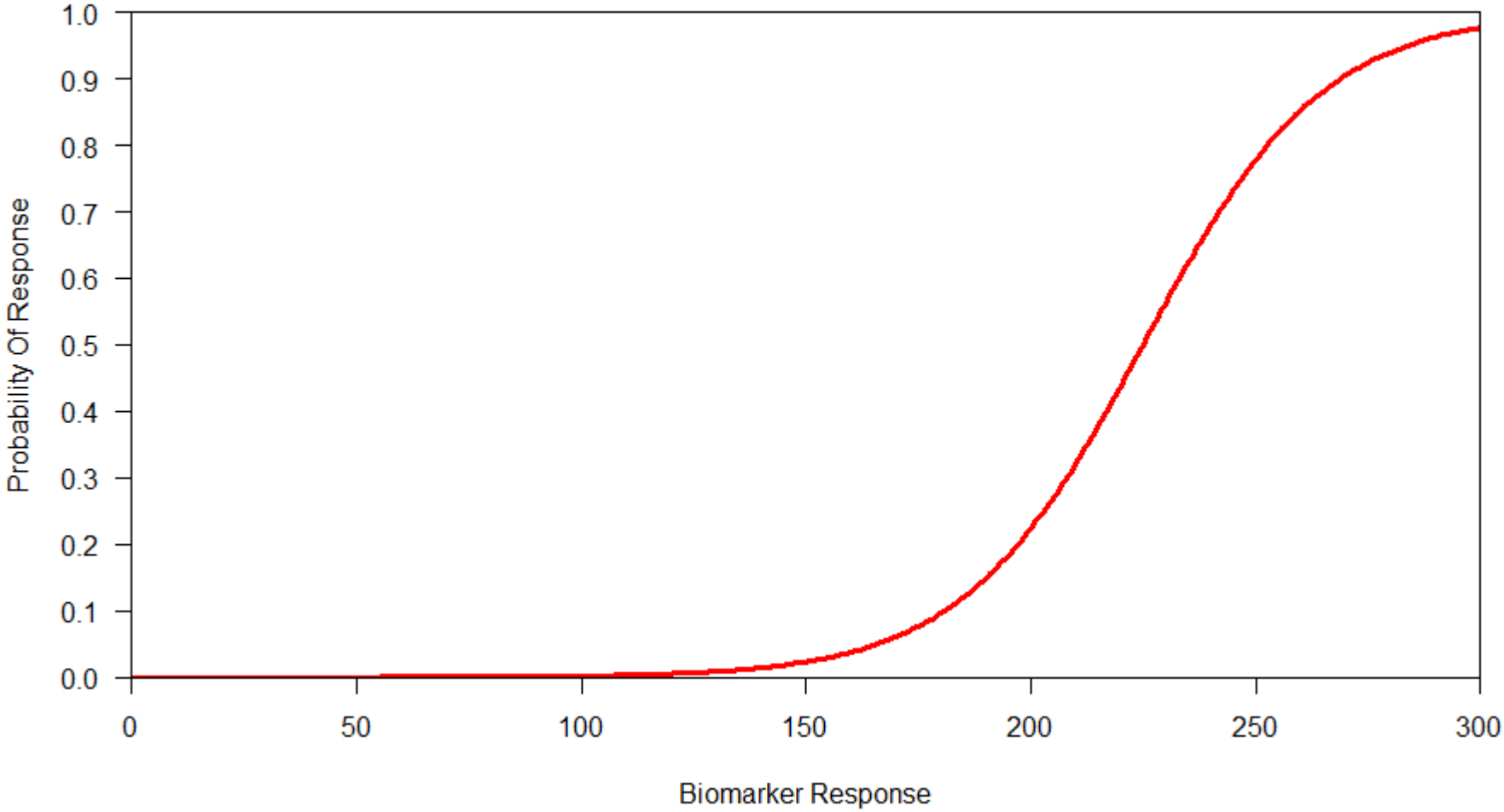
Biomarker Type	Example	Measurement	Treated As
Host genetic polymorphism	CYP inhibitors	Binary	Binary
Tumour genetics	BRCA mutations	Continuous (% of tumour with mutation)	Binary (detected or not)
IHC	Her2	Continuous	Categorical
Gene / protein expression	OncoType Dx	Continuous	Continuous



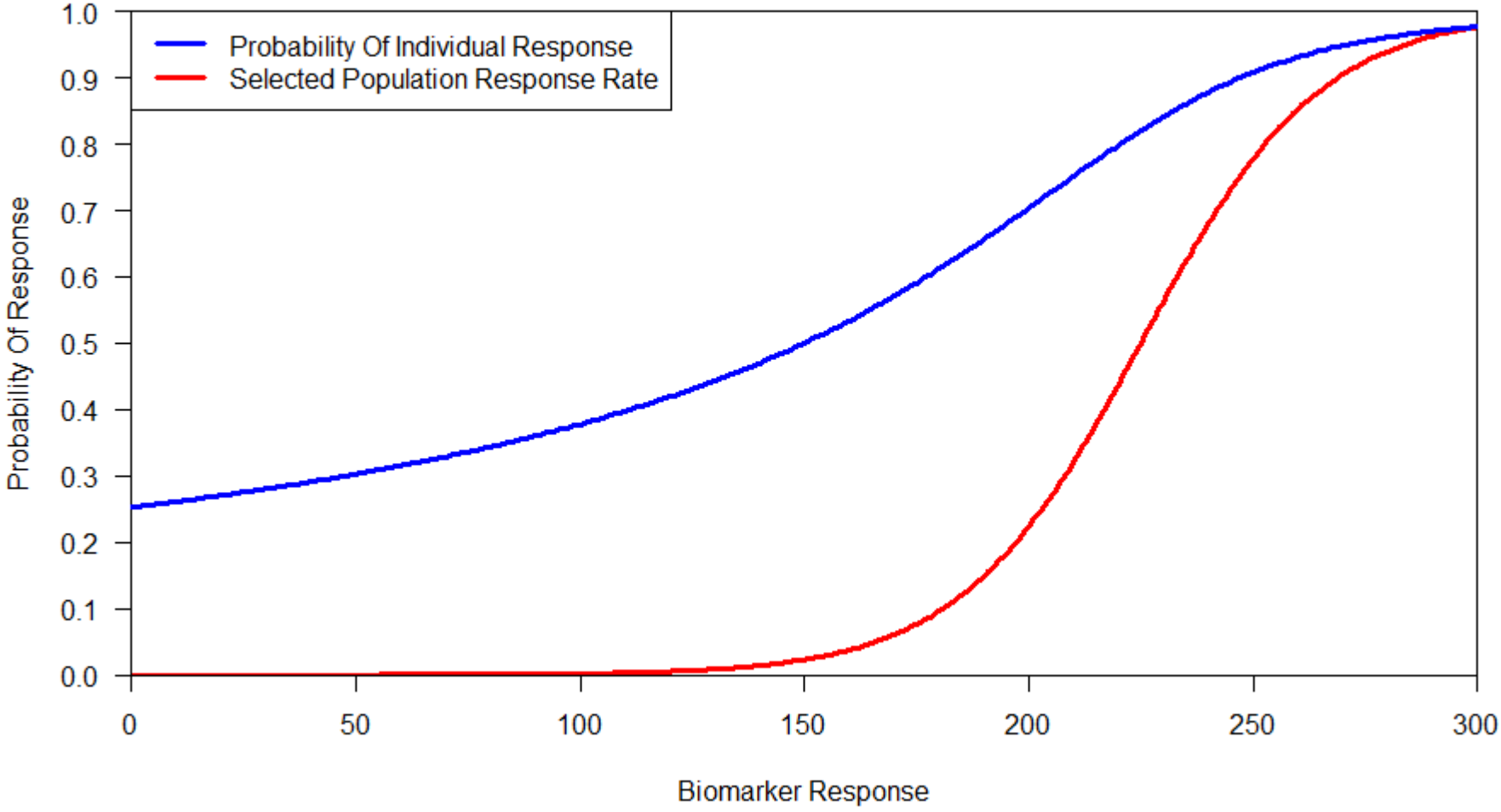


Continuous Biomarkers

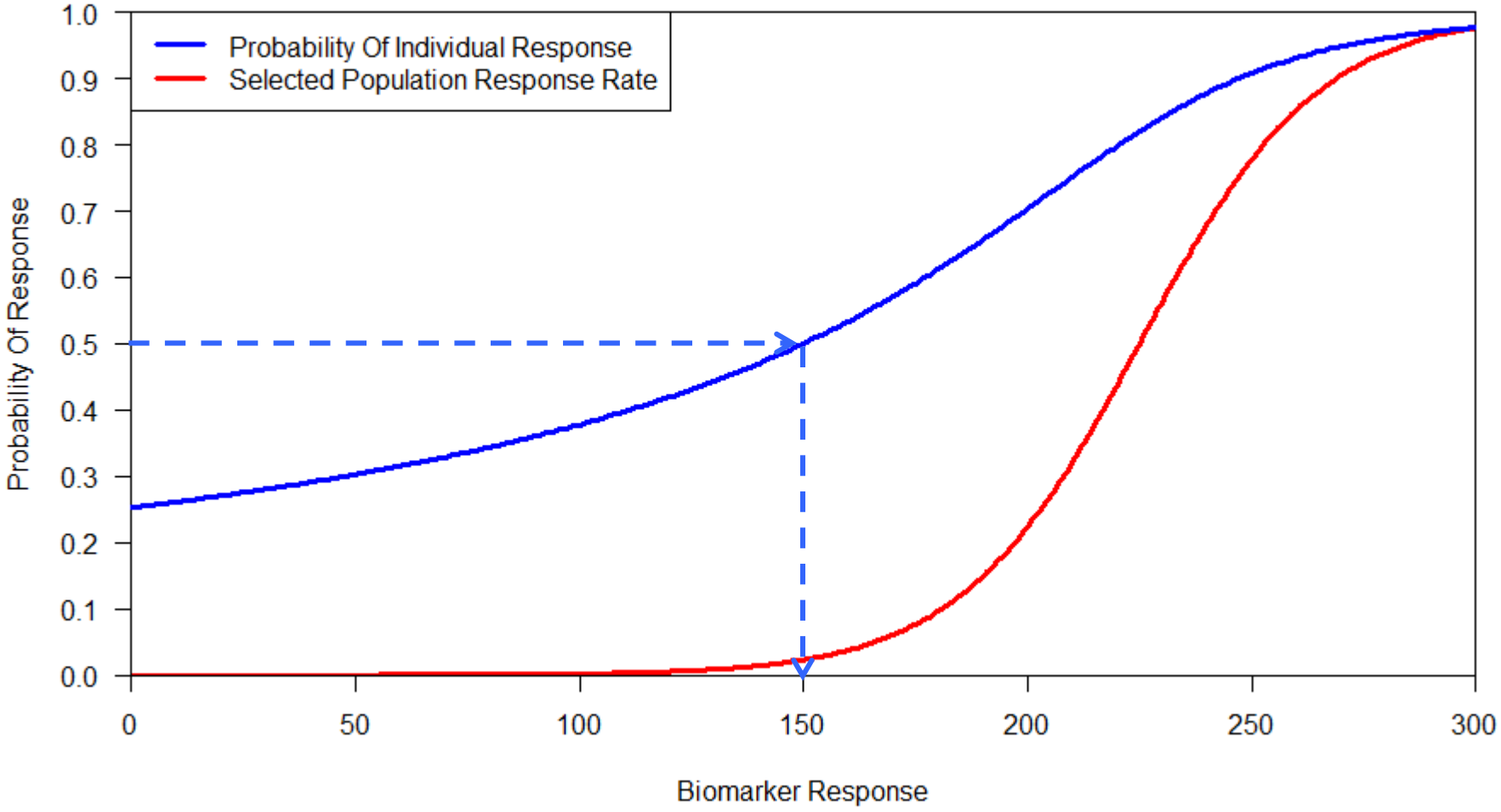
How To Define The Biomarker Positive Patients?



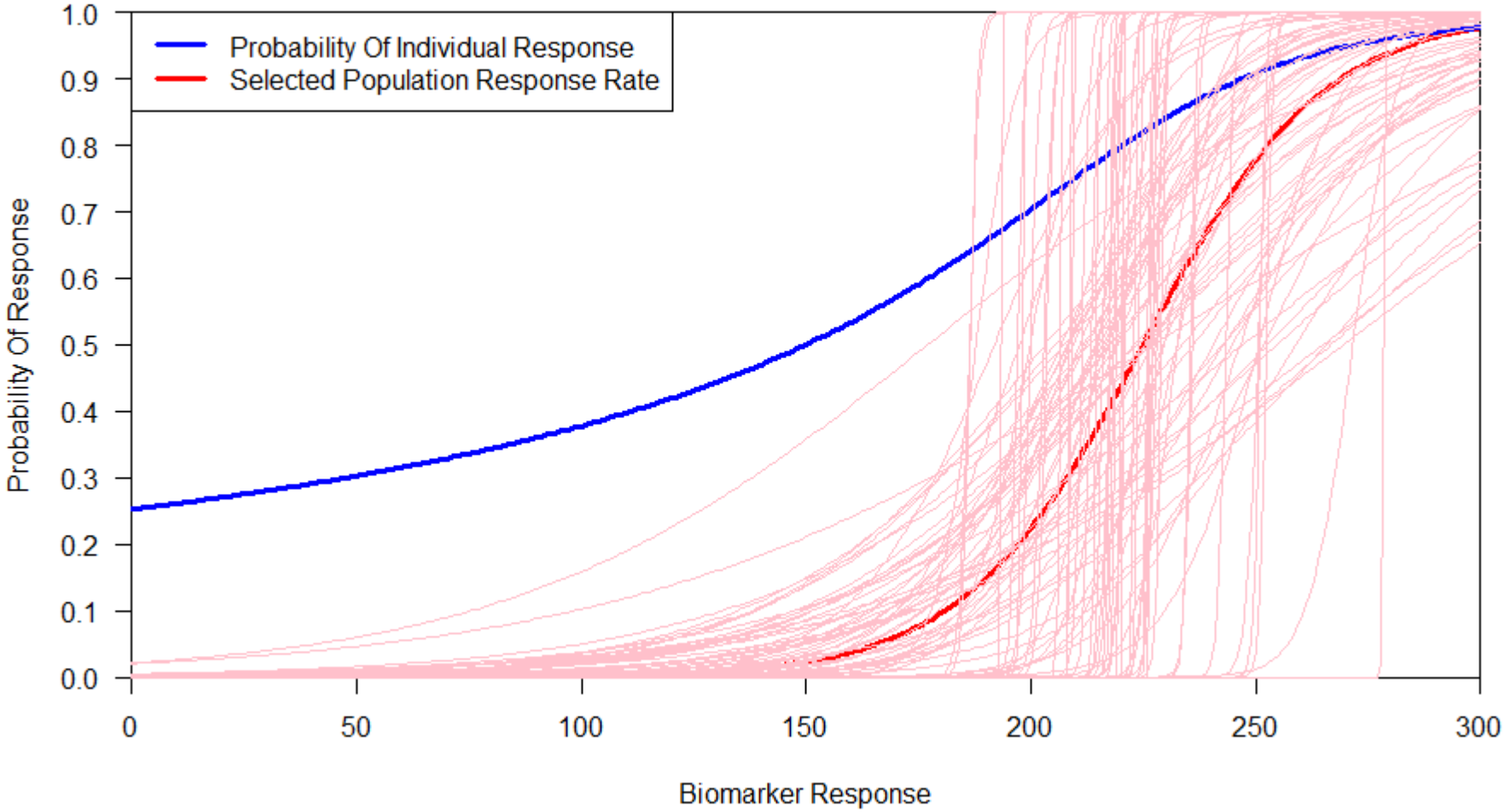
Continuous Biomarkers
How To Define The Biomarker Positive



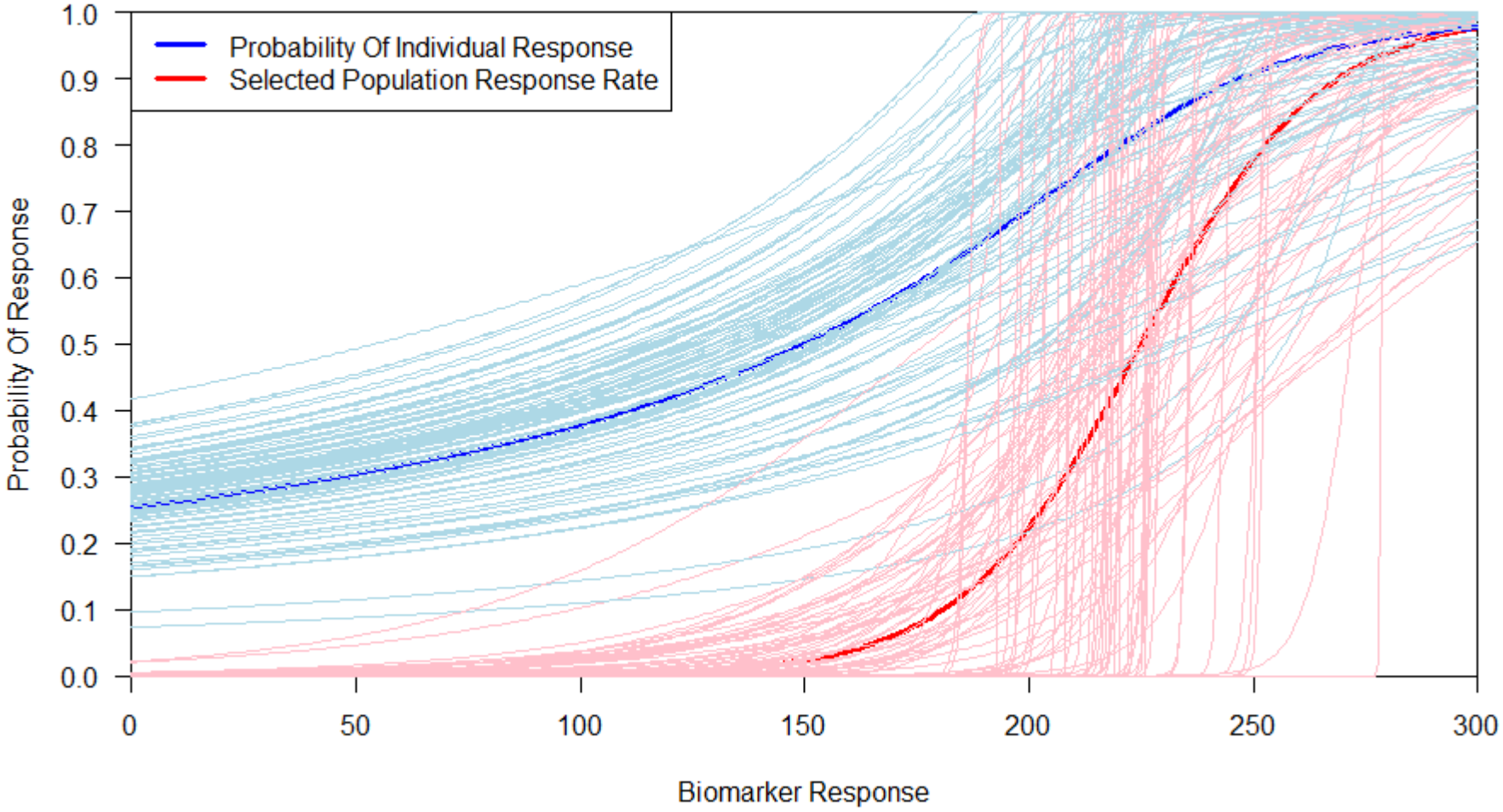
Continuous Biomarkers
How To Define The Biomarker Positive



Continuous Biomarkers
How To Define The Biomarker Positive

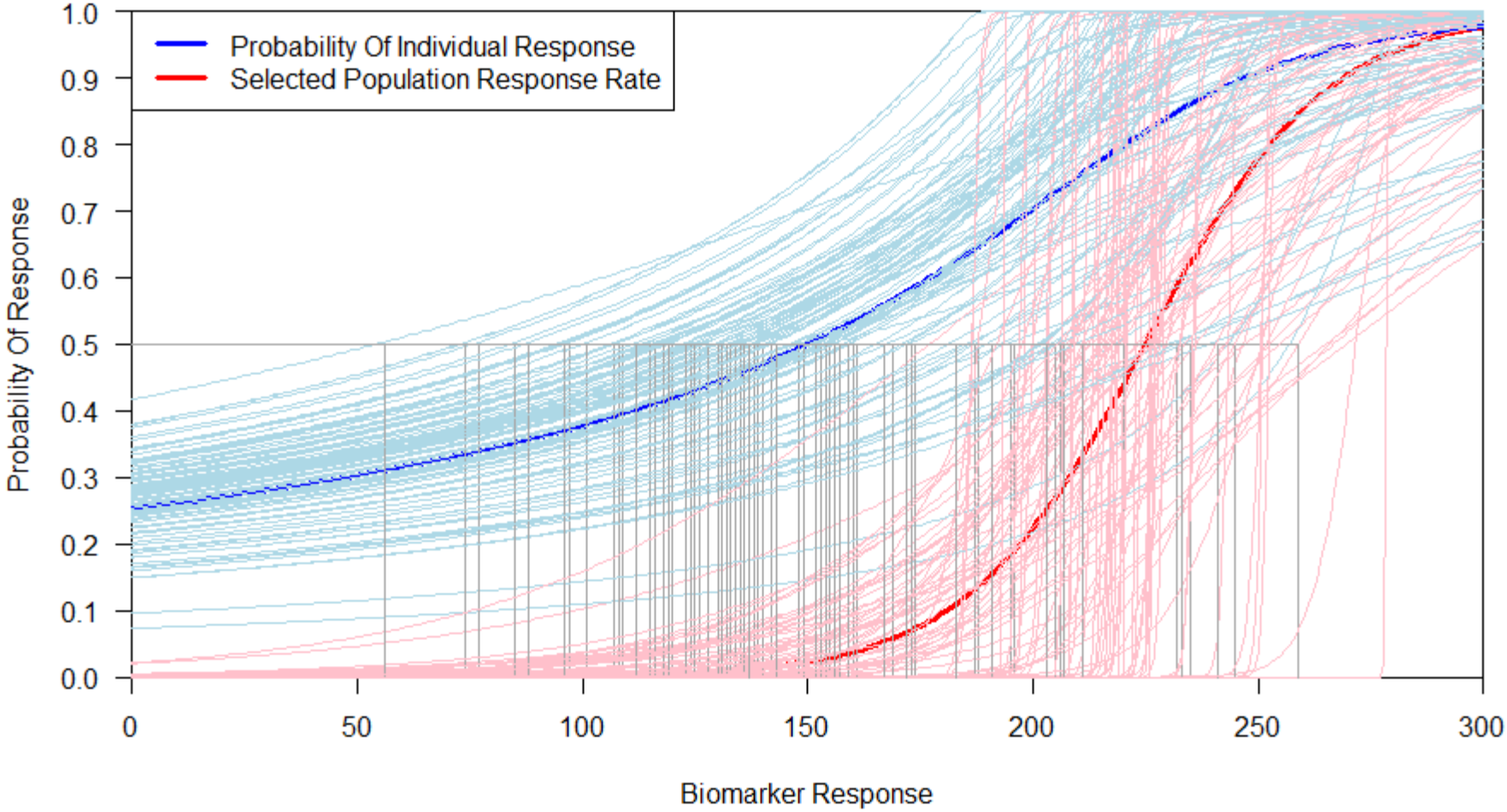


Continuous Biomarkers
How To Define The Biomarker Positive

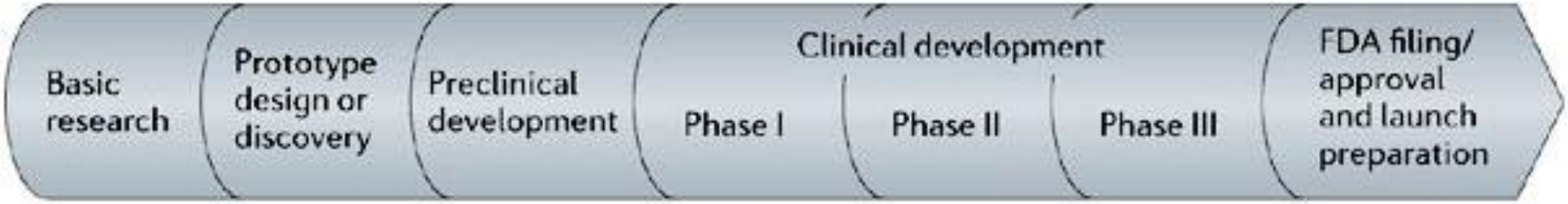


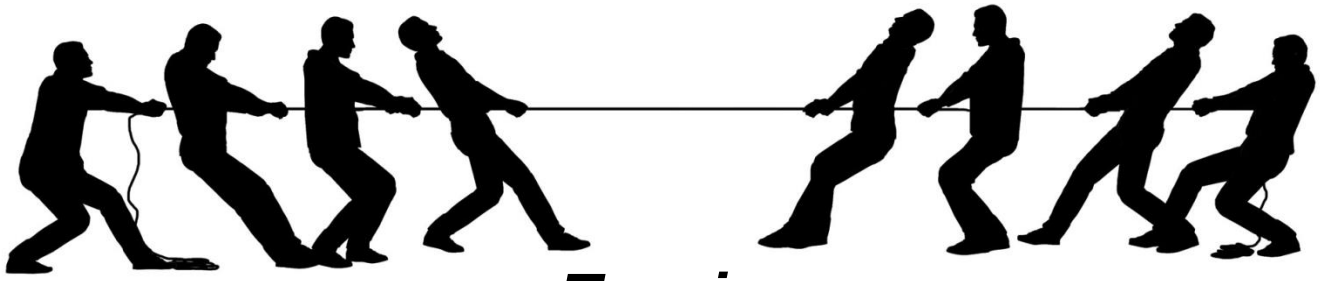
Continuous Biomarkers

How To Define The Biomarker Positive Patients?



Continuous Biomarkers





Tension

Drug development wants a pre-specified biomarker as early as possible

Specifying a cutoff on more data will be more accurate

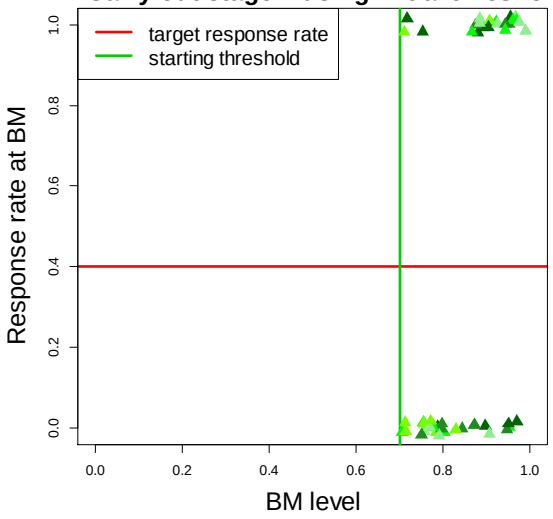
Biomarker Adaptive Designs

An adaptive design for updating the threshold value of a continuous biomarker

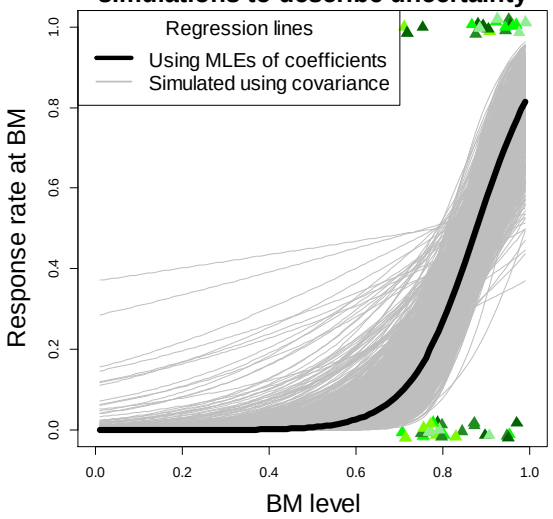
Statistics in Medicine

Amy V. Spencer
Chris Harbron
Adrian Mander
James Wason
Ian Peers

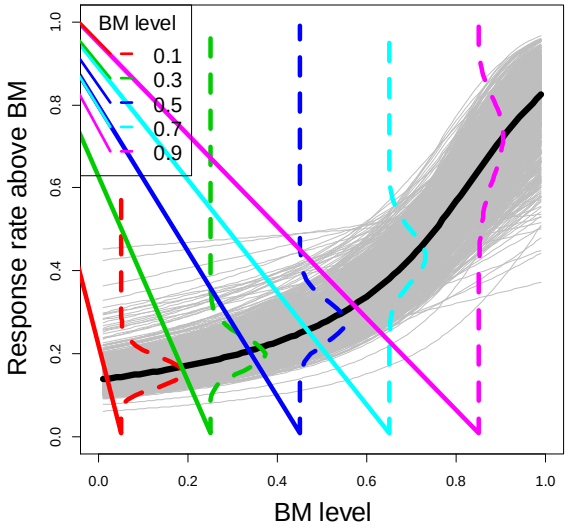
1. Set sample size and target response rate
2. Carry out stage 1 using initial threshold



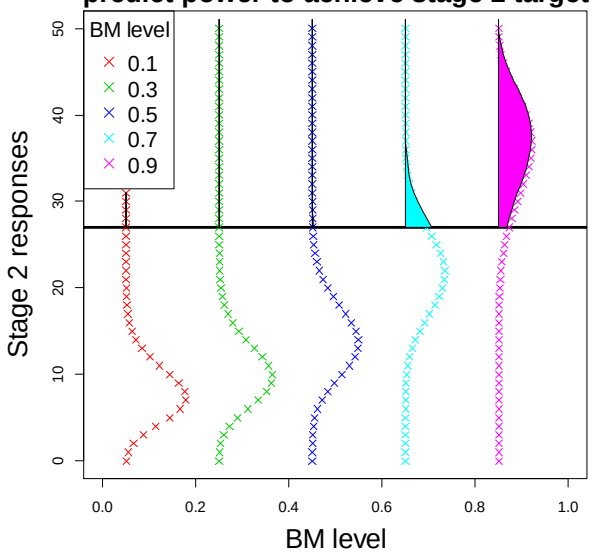
3. Fit logistic model and use simulations to describe uncertainty



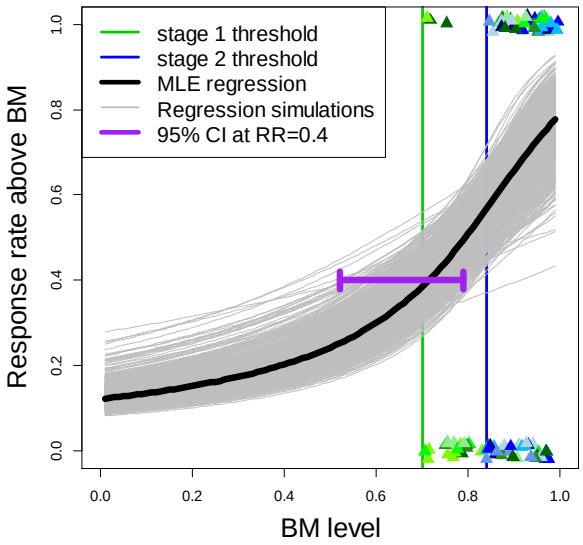
4. Transform to more relevant response rate and fit beta distributions



5. Fit beta-binomial distributions and predict power to achieve stage 2 target



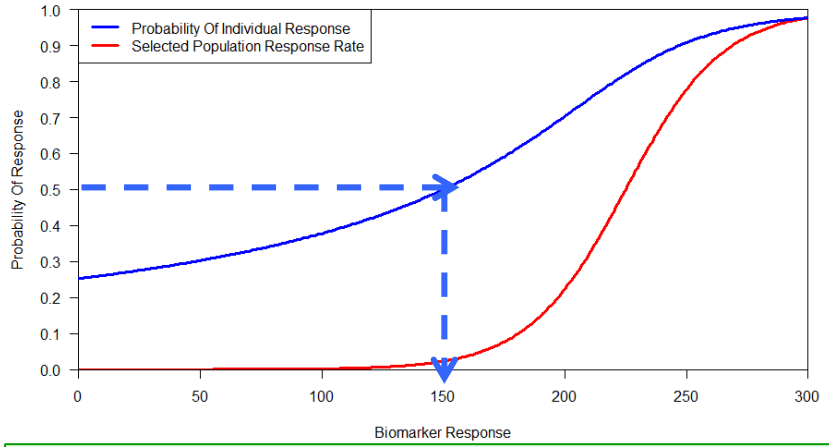
6. Carry out stage 2 using chosen threshold
8. Estimate true threshold and uncertainty

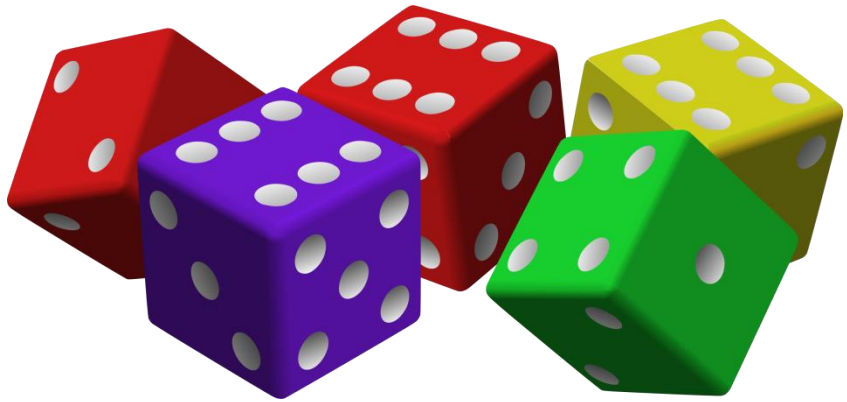


Setting Thresholds Within Confirmatory Trials Based Upon A Target Efficacy

Simultaneously use Phase 3 Data to both :

- Demonstrate efficacy within a patient population and
- Identify what that population is





Make the estimation of the cut-off with less variability from a larger sample size

Maintain rigour in confirmatory evidence that the agent is working by addressing multiplicity issues from looking at multiple populations

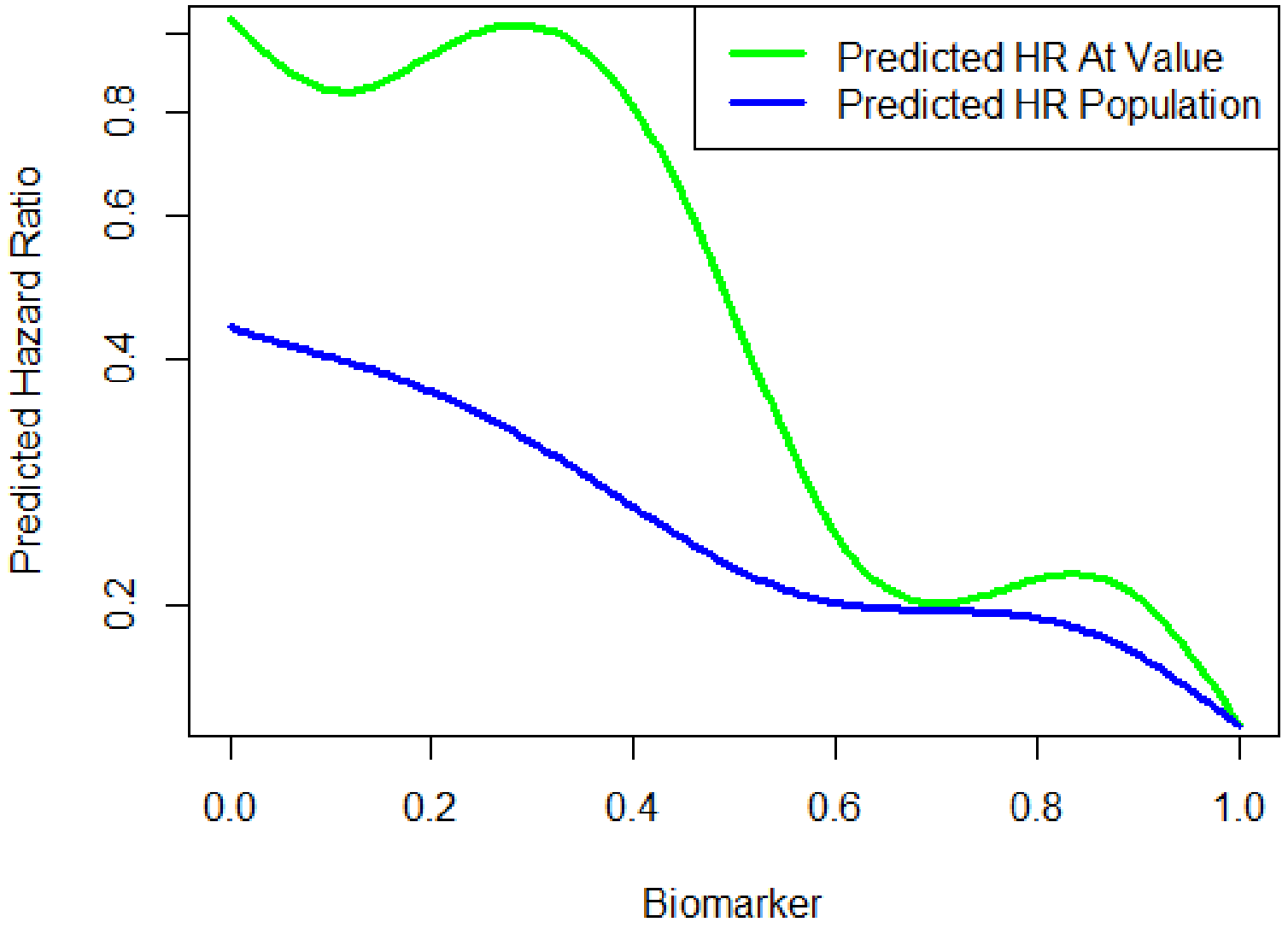
Idea : Combination of

Model with Spines

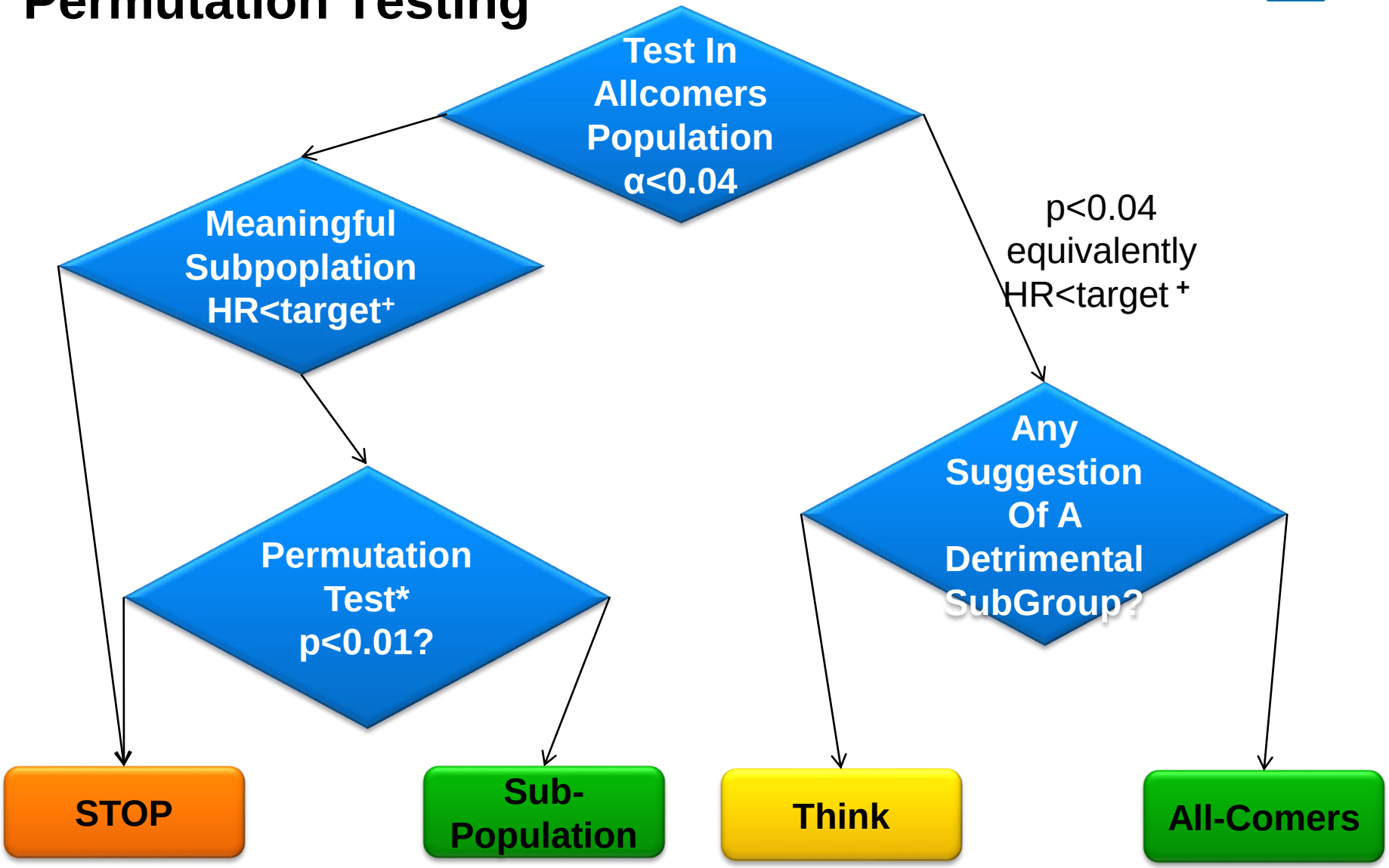
Permutation Testing

Spline Modelling

$$\ln HR_{POP}(BM) = \int_{BM}^{1} \ln HR(BM) \Big/ (1 - BM)$$



Permutation Testing



* Through permutation of treatment labels (and appropriate recalculation of interaction term), maintaining any prognostic relationship

+ Subpopulation target may be less than allcomers target

Issues To Consider

- Optimising spline fits
- Selection of smoothness of spline models
- Modelling prognostic and predictive effects
- Bias and variability of threshold estimation and its impact on patients and the selected population
- Powering
- Understanding of operating characteristics
  - under which scenarios does the method gives an advantage?

Doing now what patients need next

Setting Thresholds Within Confirmatory Trials Based Upon A Target Efficacy

- Simultaneously use Phase 3 Data to both demonstrate efficacy of the agent within a patient population and identify what that population is

- Cox Proportional Hazard Modelling incorporating Splines to model biomarker effect
  - Spline models for both prognostic & predictive effects
  - Smoothness / Degrees Of Freedom determined by monotonicity over a target range
- Permutation testing with a split alpha to maintain Type 1 error

Spline Modelling

Fit model :

Log(HR) = Treatment + Spline(Biomarker) + Spline(Interaction)

Prognostic Effect

Predictive Effect

= Biomarker : Treatment=Novel Agent

= mean(Biomarker for treated patients) : Treatment = Placebo

$$\ln \hat{HR}(BM) = Treatment + \text{Predictive Spline} - \text{Predictive Spline At Mean}$$

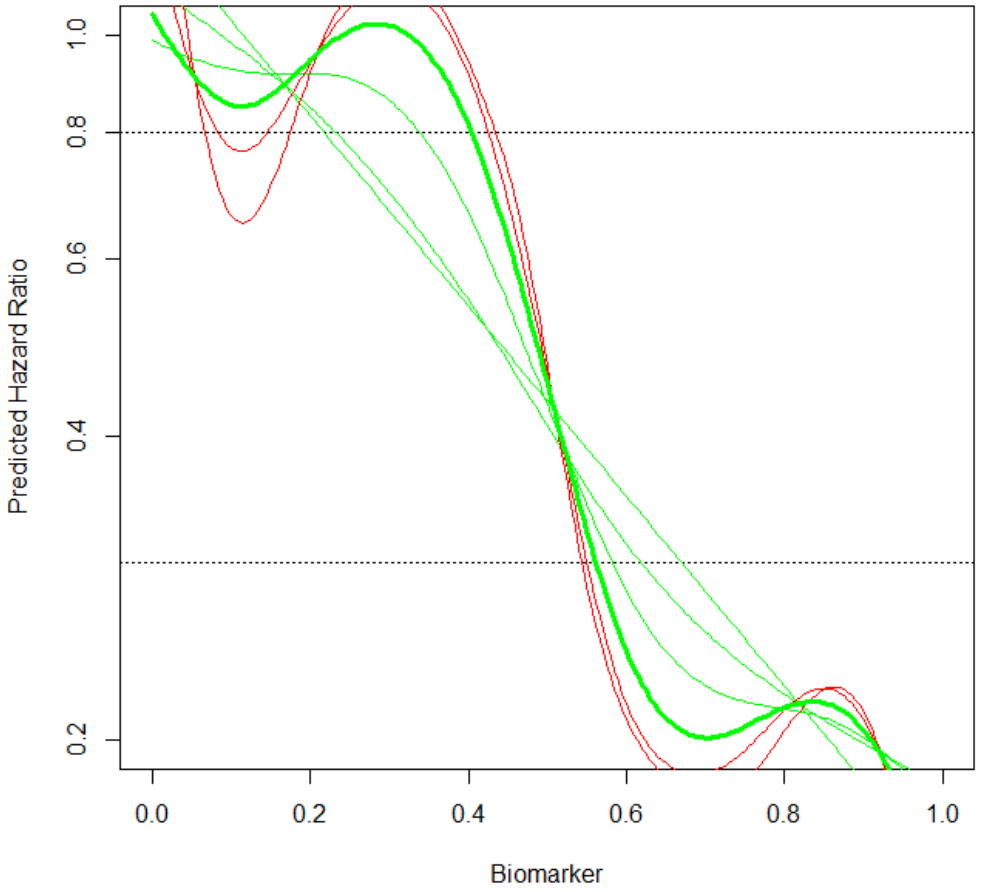
Ref : Therneau , Eilers et al

Spline Modelling
Selecting Smoothness Parameters (Degrees Of Freedom)

Default methodology in R based upon Akaike Information Criterion (AIC) tends to overfit

- Start with DF=1 (linear relationship)
- Fit model
- If relationship monotonic within a target range of predicted HRs, increase DF by 1 (up to a maximum of 6) and repeat, otherwise stop
- Select model with the minimum AIC from the monotonic models

Actually doing this for two splines, prognostic and predictive, simultaneously



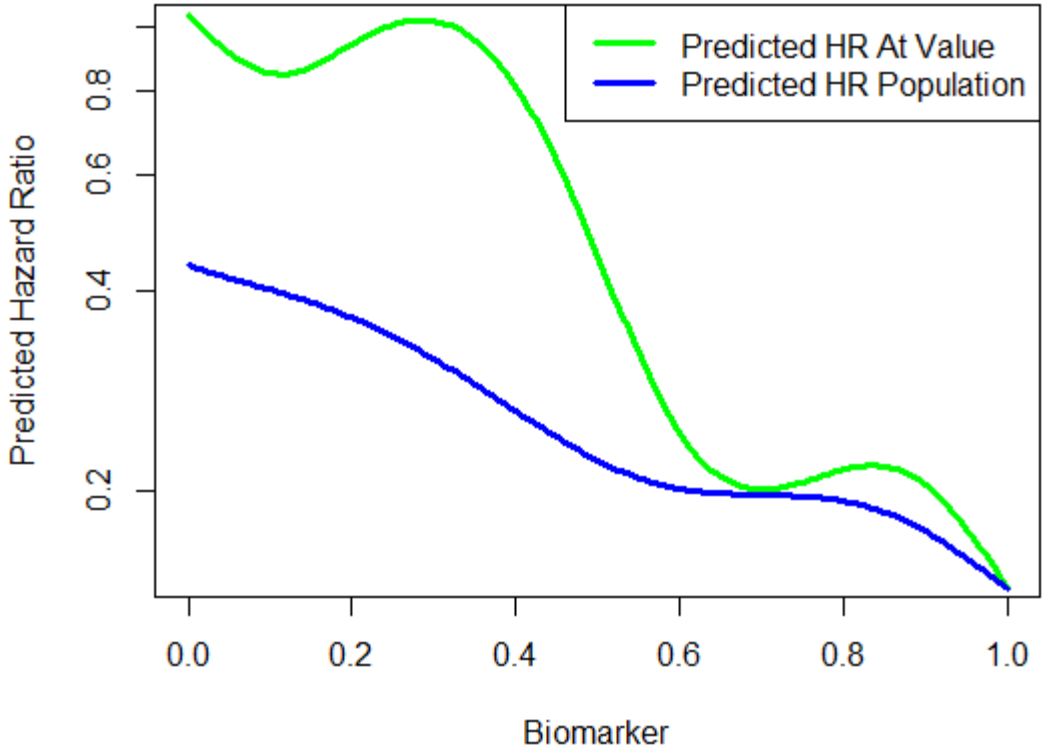
Spline Modelling

Integration

We model the hazard ratio at a specific value of the biomarker HR(BM)

We are interested in the hazard ratio within the population defined as greater than the biomarker . This can be calculated by numerical integration:

$$\ln HR_{POP}(BM) = \int_{BM}^{1} \ln HR(BM) \Big/ (1 - BM)$$



Doing now what patients need next