Bayesian Latent Subgroup Design for Basket Trials

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July 30, 2017

Outline

- Introduction
- Bayesian latent subgroup (BLAST) design
- Simulation Results
- Discussion

Basket Trials

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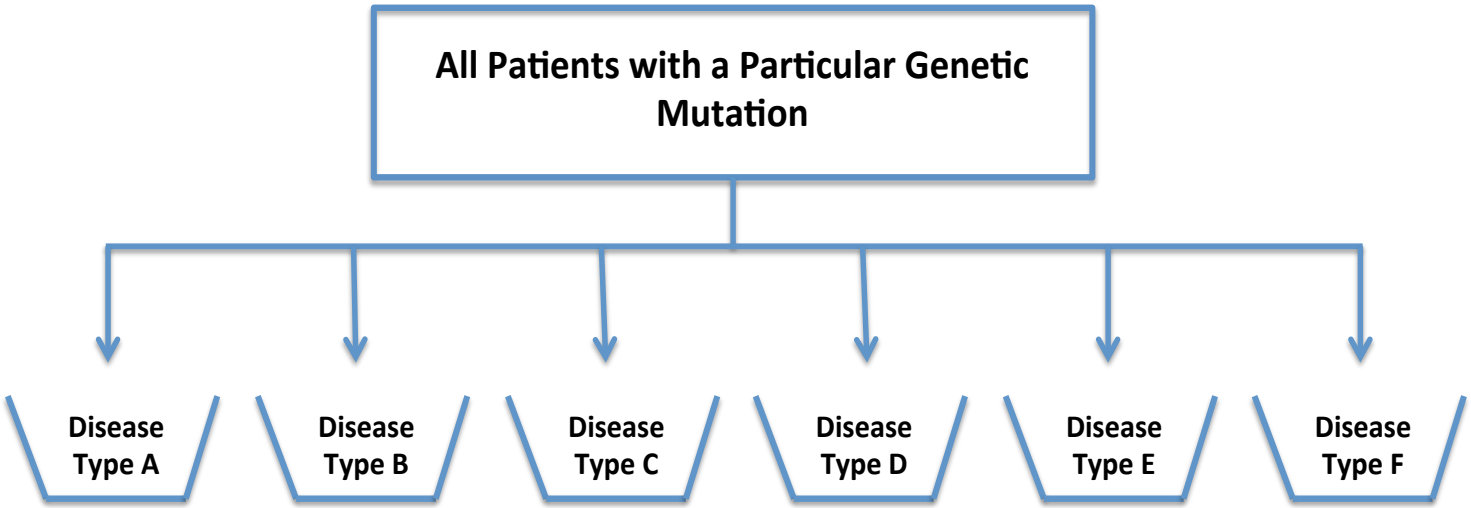
- This is in comparison to the traditional oncology clinical trials, which have been designed to evaluate a single treatment in patients of a particular cancer type.
- The basket trial often requires fewer patients and a shorter duration to identify a favorable response to the targeted therapy.
- It can provide access to molecularly targeted agents for patients across a broad range of tumor types, even for those too rare to study solely within a tumor-specific context (Redig et al., 2015; Renfro et al., 2017).

Basket Trials



Challenges of Basket Trials

- Patients selected into the basket trial may not respond to a drug similarly regardless of the primary tumor sites.
- Tumor type often has profound effects on the treatment effect, and it is not uncommon for a targeted agent to be effective for some tumor types, but not others.

Basket Trials

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- Two approaches have been utilized to assess the therapeutic effectiveness (Freidlin and Korn, 2013): the pooled analysis to simply pool the results across tumor types, or an independent evaluation conducted in each tumor type.
- Bayesian hierarchical model (BHM) has been advocated to evaluate treatment effects in this setting (Berry et al., 2013).

Issues with BHM

- The exchangeable assumption underlying BHM is often violated in practice.
  - BRAF-mutant melanoma and hairy-cell leukemia are sensitive to the BRAF inhibitor PLX4032, whereas BRAF-mutant colon cancer is not (Flaherty et al., 2010).
  - Trastuzumab is effective for HER2-positive breast cancer but not for HER2-positive NSCLC or HER2-positive recurrent endometrial cancer (Fkenubg et al., 2010).

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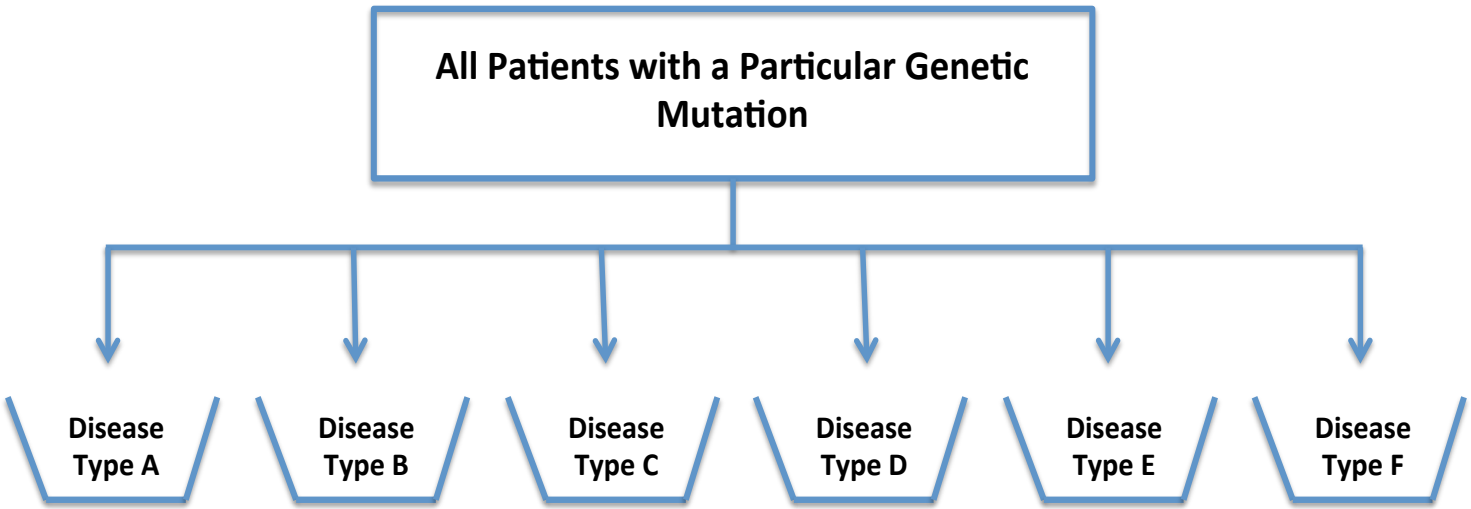
  - Trastuzumab is effective for HER2-positive breast cancer but not for HER2-positive NSCLC or HER2-positive recurrent endometrial cancer (Fkenubg et al., 2010).
- It tends to over-shrink the treatment effect toward the common mean, resulting in inflated type I error rates (Freidlin and Korn, 2013).

Basic Idea of BLAST



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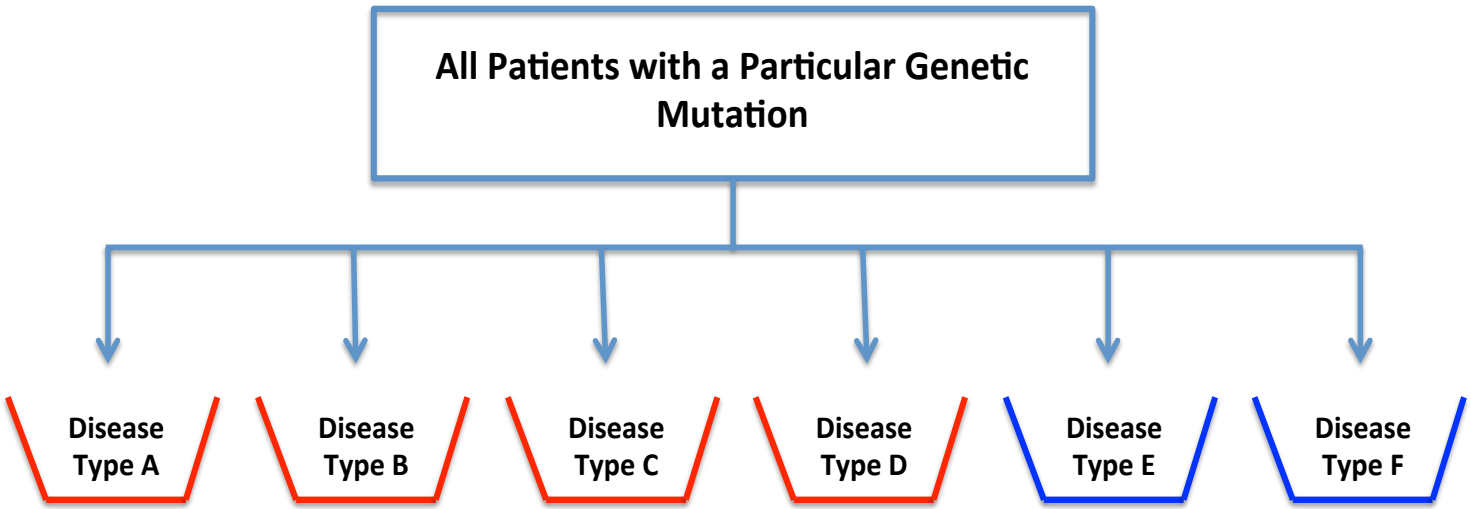

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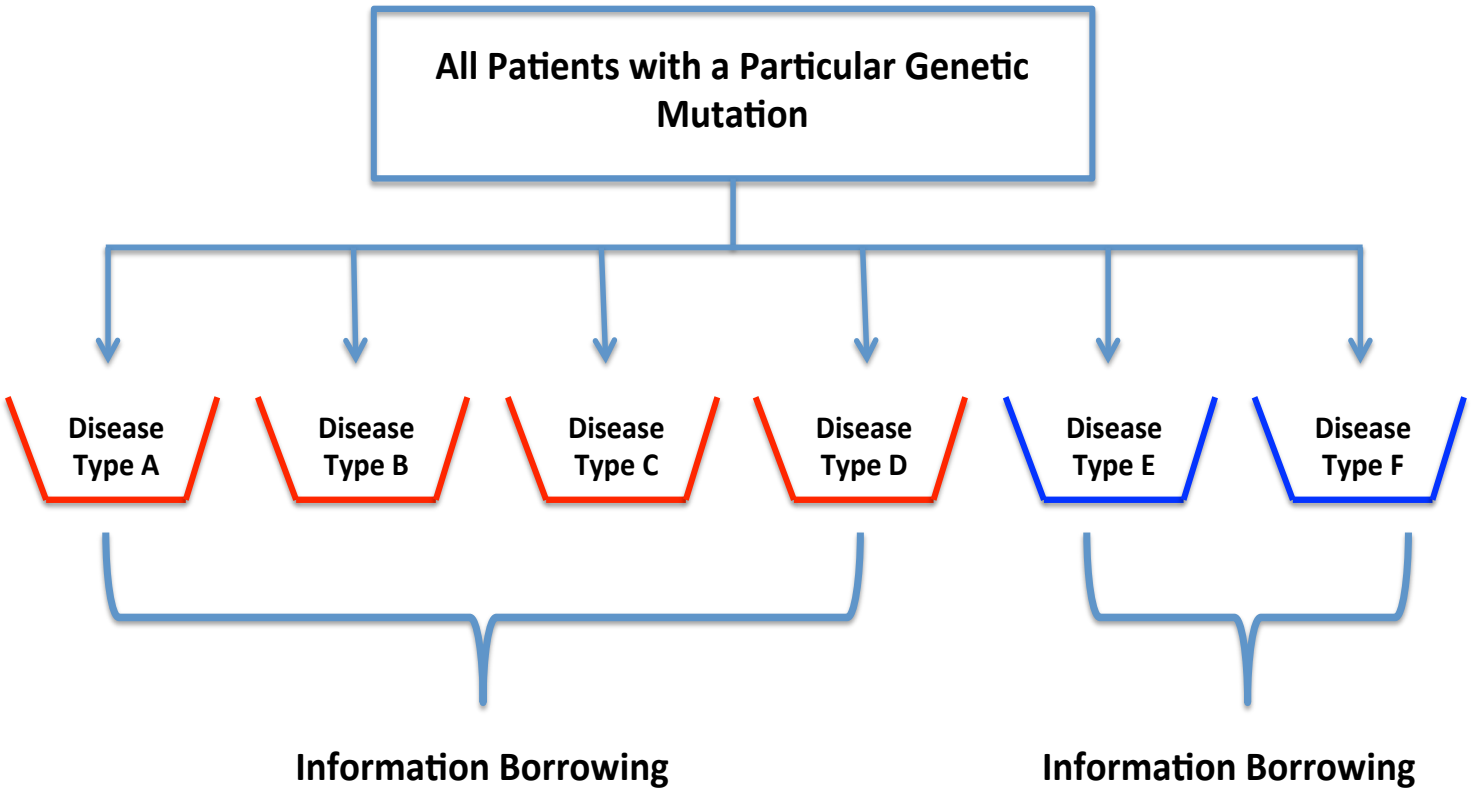

Basic Idea of BLAST

- Leverage longitudinal biomarker measurements that are routinely taken in clinical trials to improve the efficiency of the basket trial.
  - Biomarker: the type of biomarkers that measure the biological activity of targeted agent, e.g., the number of CD8+ T-cells and the biological activity of immune checkpoint inhibitors.
- A semi-parametric model is used to jointly model the longitudinal biomarker measurements with the binary clinical outcome.

Notations

- The objective of the trial is to test whether the drug is effective in the disease types:

$$H_0 : p_i \leq q_0 \qquad \text{vs.} \qquad H_a : p_i \geq q_1 \qquad \text{for} \quad i = 1, \cdots, I,$$

- We assume that I cancer types can be classified into K latent subgroups, $1 \leq K \leq I$.
- C_i: the latent subgroup membership indicator, with $C_i = k$ denoting that the ith cancer type belongs to the kth subgroup, $k = 1, \cdots, K$.
- Y_{ij}: a binary variable for the treatment response of the jth patient in the ith cancer type.
- Z_{ijl}: the biomarker measurement for the jth patient in the ith cancer type at the time t_l, for $l = 1, \cdots, L$.

BLAST Model Formulation

- We assume that C_i follows a multinomial distribution

$$C_i \sim \text{Multinomial}(\pi_1, \cdots, \pi_K),$$

where $\pi_k = \Pr(C_i = k), k = 1, \cdots, K$.

- The treatment response Y_{ij} follows a latent-subgroup hierarchical model

$$\begin{aligned} Y_{ij}|p_i &\sim Ber(p_i) \\ \theta_i &= \log\left(\frac{p_i}{1-p_i}\right) \\ \theta_i|C_i = k &\sim N(\theta_{(k)}, \tau^2_{(k)}), \end{aligned}$$

BLAST Model Formulation

- We model Z_{ijl} using a semiparametric mixed model as follows,

$$Z_{ijl}|(Y_{ij}, C_i = k) = \mu_{(k)}(t_l) + v_i + w_{ij} + \beta Y_{ij} + \epsilon_{ijl}$$
$$v_i \sim N(0, \sigma_v^2)$$
$$w_{ij} \sim N(0, \sigma_w^2).$$

$\mu_{(k)}(t_l)$: mean trajectory of the biomarker for the kth subgroup;
v_i: cancer-type-specific random effect;
w_{ij}: subject-specific random effect;
β: captures the relationship between Z and Y.

- $\mu_{(k)}(t_l)$ is modeled using the penalized spline (Eilers and Marx, 1996; and Ruppert et al., 2003),

$$\mu_{(k)}(t_l) = \gamma_{0(k)} + \gamma_{1(k)} t_l + \gamma_{2(k)} t_l^2 + \cdots + \gamma_{d(k)} t_l^d + \sum_{s=1}^{S} a_{s(k)} (t_l - \kappa_s)_+^d,$$

$$a_{s(k)} \sim N(0, \sigma_{a(k)}^2).$$

the Number of Latent Subgroups

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- We choose the value of K such that the corresponding model has the best goodness-of-fit according to the deviance information criterion (DIC). In practice, it is often adequate to restrict the search space of K to $\{1, 2\}$.
- The value of K will be updated in the light of accumulating data. As a result, it may differ from one interim evaluation to another, depending on the observed data.

Simulations

- We considered six cancer types and up to two latent subgroups (i.e., effective and ineffective subgroup) with null $q_0 = 0.2$ and alternative $q_1 = 0.3$.
- The maximum sample size for each cancer type was 25, with three interim analyses conducted when the sample size in each cancer type reached 10, 15 and 20.
- We constructed 10 different scenarios by varying the true response rate and trajectory shape for the cancer type.

Trajectory Shapes

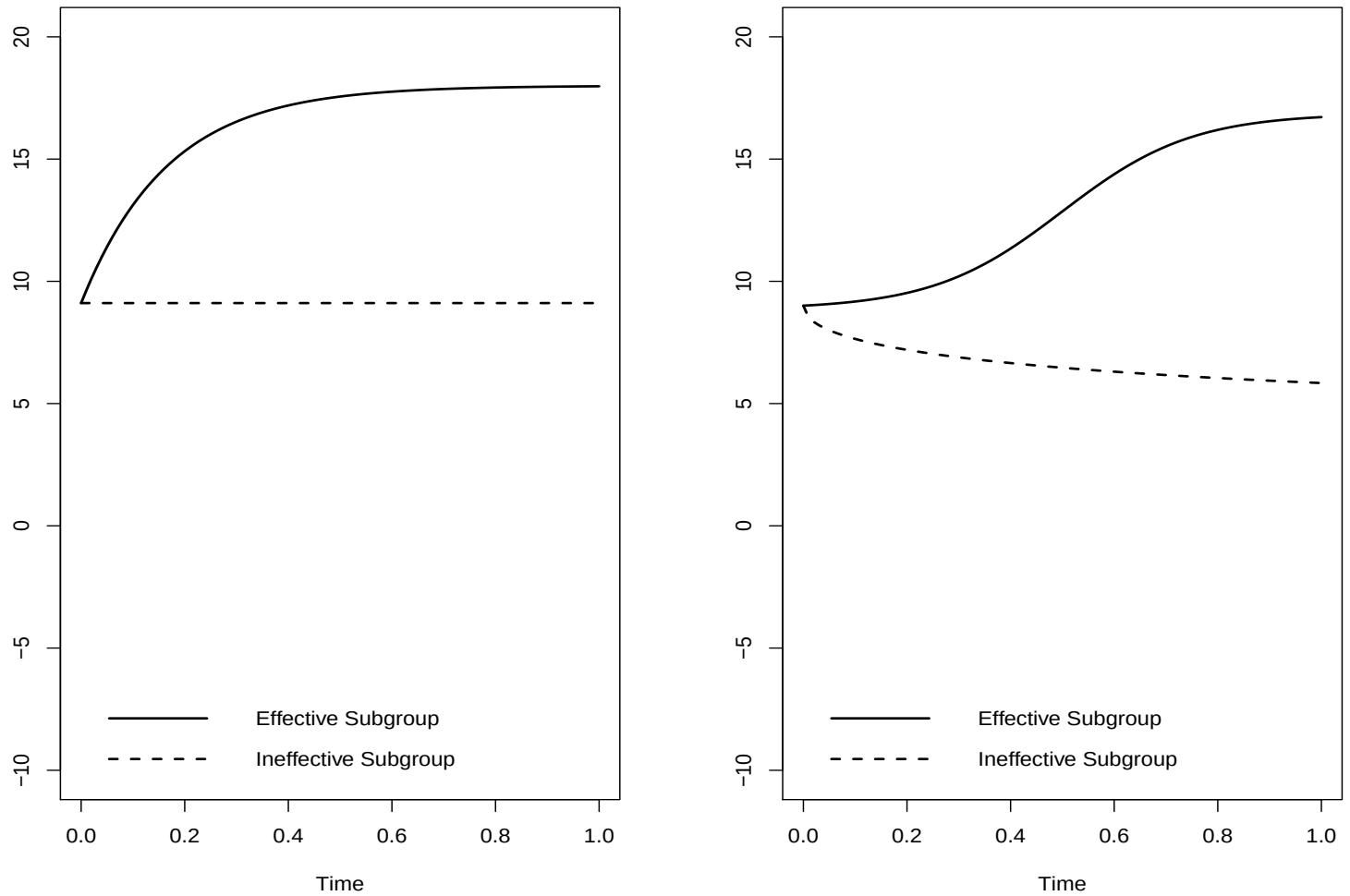


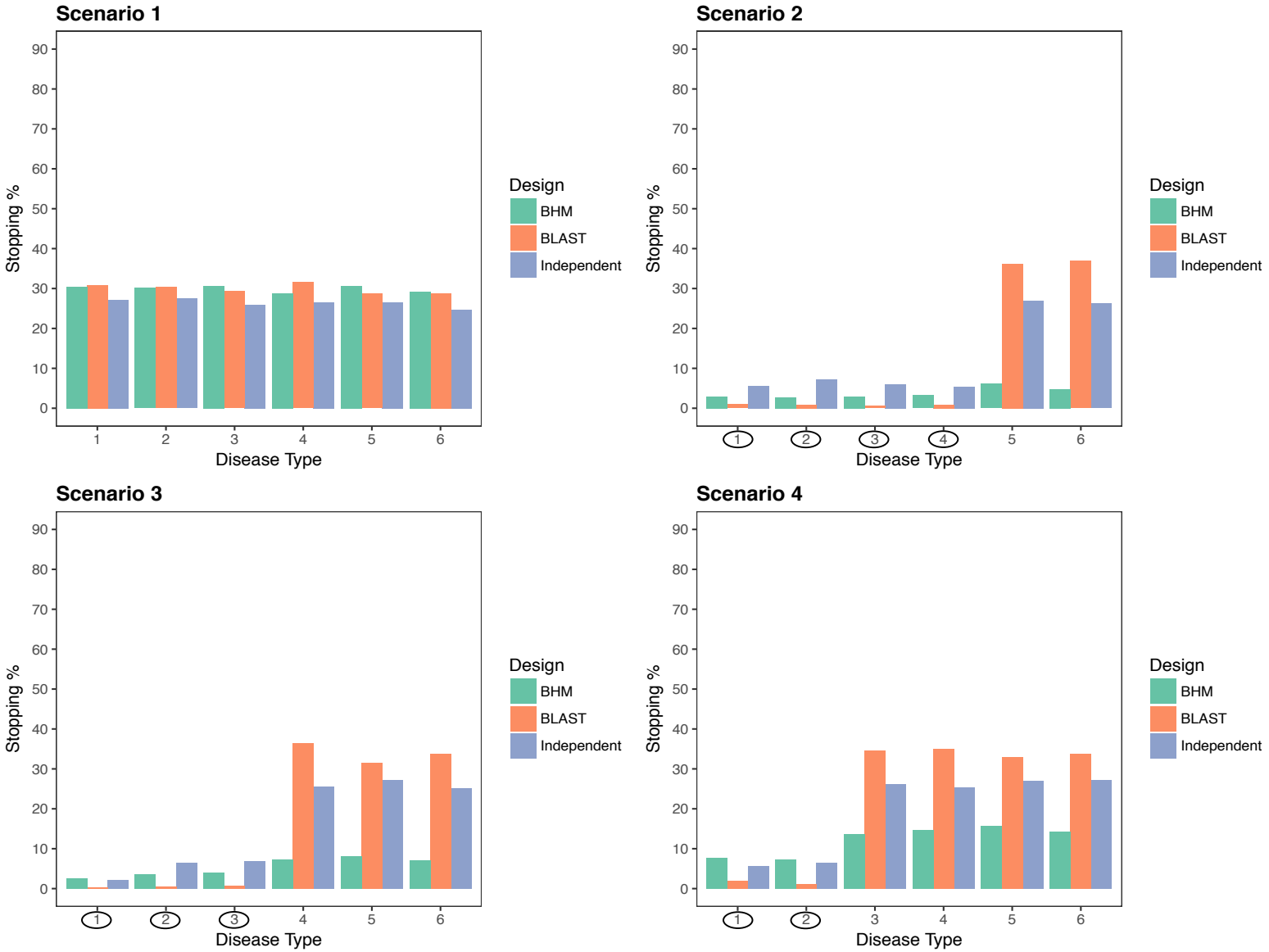
Figure: The trajectory shapes considered in the simulation study.

Results - Rejection Percentage

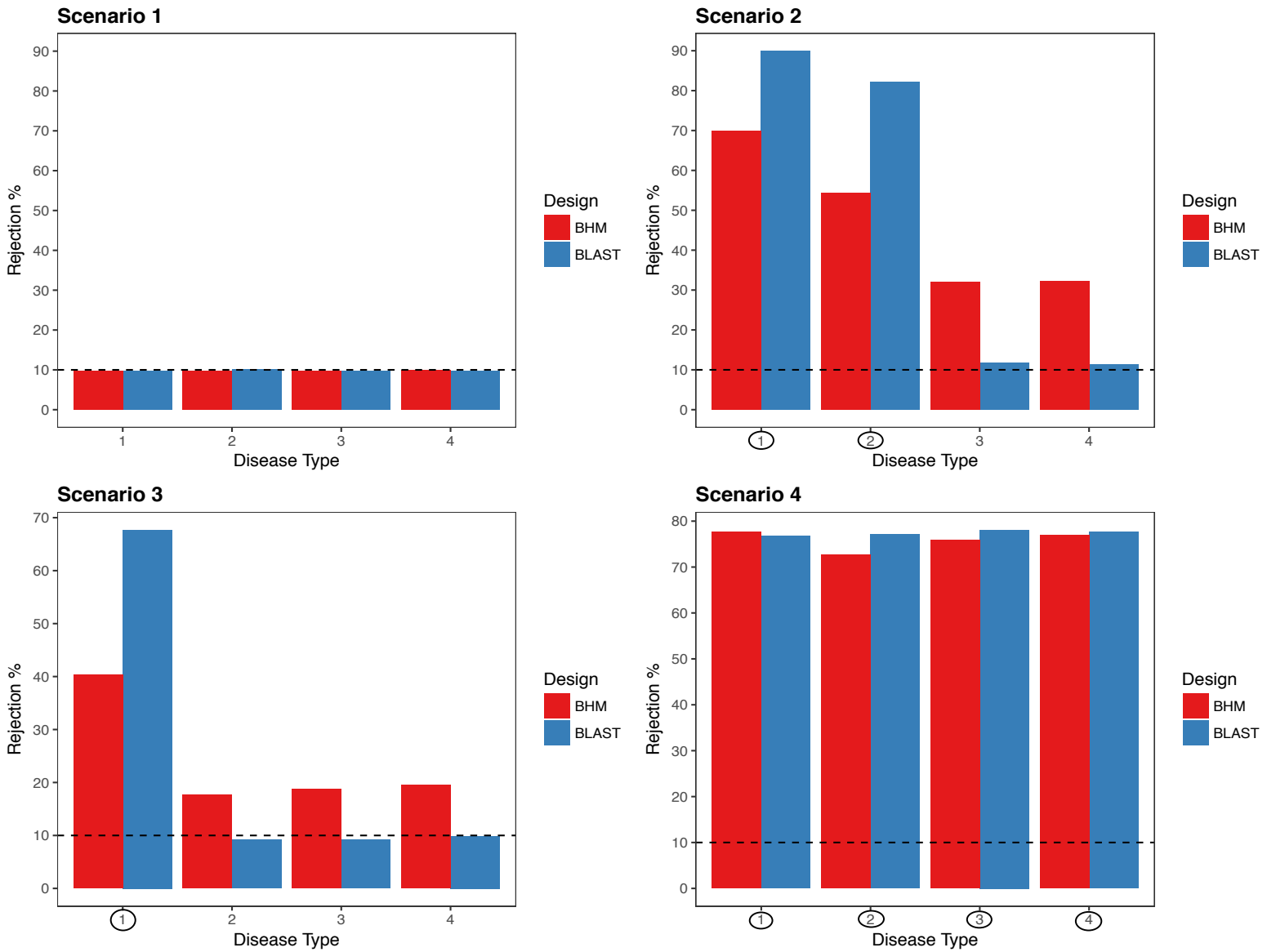
Table 1: Simulation results of the independent, Bayesian hierarchical model (BHM) and BLAST designs under biomarker trajectory setting A.

Scenario	Design		Cancer type 1	2	3	4	5	6	Sample size
A1		Resp. rate	0.2	0.2	0.2	0.2	0.2	0.2	
	Independent	% reject	9.9	10.1	10	10.1	10	9.9	132.9
	BHM	% reject	9.8	10.2	9.9	9.9	9.8	9.8	129.1
	BLAST	% reject	9.8	10.1	9.8	9.9	10.1	9.8	129.6
A2		Resp. rate	0.3	0.3	0.3	0.3	0.2	0.2	
	Independent	% reject	46.5	45.4	45.9	41.4	9.2	11.6	141.5
	BHM	% reject	69.6	68.6	72.2	70.8	45.8	42.3	147.2
	BLAST	% reject	90.4	91.3	91.8	91.2	11.8	12	140.5
A3		Resp. rate	0.35	0.3	0.3	0.2	0.2	0.2	
	Independent	% reject	69	44.5	46.6	9.7	9.9	10.5	139.8
	BHM	% reject	74.9	62.8	66.6	39	36.4	36.4	146.0
	BLAST	% reject	94.7	89.2	91.3	8.6	9.9	7.8	137.6
A4		Resp. rate	0.3	0.3	0.2	0.2	0.2	0.2	
	Independent	% reject	45.4	43.4	10	9.4	10.6	10.2	137.3
	BHM	% reject	46.5	47.4	26.3	26.5	25.2	23.9	141.3
	BLAST	% reject	82.1	85.7	10	9.3	8.2	9	133.4
A5		Resp. rate	0.3	0.2	0.2	0.2	0.2	0.2	
	Independent	% reject	45	11.4	7.8	8.6	10.4	9.4	135.2
	BHM	% reject	35.8	15.9	18.7	17.8	15.7	16.2	135.9
	BLAST	% reject	71.3	11.3	10.1	11.1	10.7	10.9	129.9

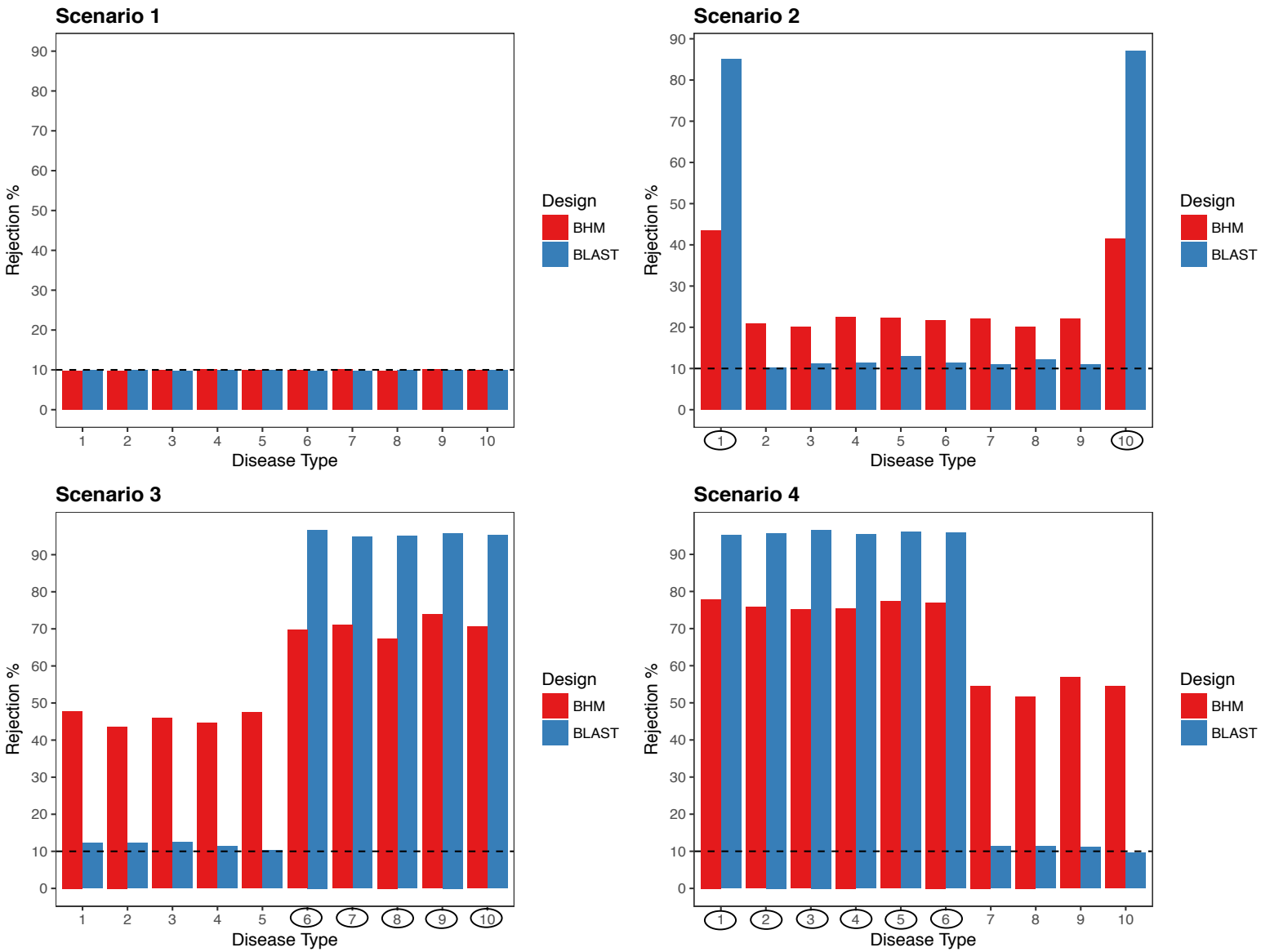
Results - Stopping Percentage



Sensitivity Analysis - 4 cancer types



Sensitivity Analysis - 10 cancer types



Discussion

- By jointly modeling the longitudinal biomarker measurements and treatment responses, the BLAST design simultaneously groups cancer types into different subgroups and makes Bayesian inference and go/no-go interim treatment decisions for each cancer type.
- It yields high power to detect the treatment effect for sensitive cancer types that are responsive to the treatment, and maintains a reasonable type I error rate for insensitive cancer types that are not responsive to the treatment.

Discussion

- The proposed BLAST design can be easily extended to the case where more than one targeted therapies are considered.
- We treat K as fixed and use DIC to select the optimal number of latent subgroups. Alternatively, we can treat K as an unknown parameter, and estimate it together with the other parameters.

Thank you!

Simulation Settings