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Performance of subgroup selection rules for a targeted therapy in oncology

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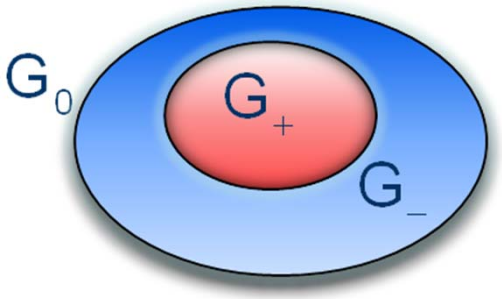
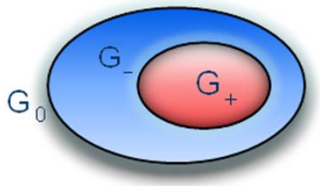
Background

- Total patient population G_0
- Prospectively defined subgroup G_+
  - Potentially increased benefit
  - Identified by biomarker
- Complementary subgroup $G_- := G_0 \setminus G_+$
- Selection of the target population based on data
  - (Pilot / phase II) study A $\rightarrow$ (pivotal / phase III) study B
  - First stage $\rightarrow$ second stage of adaptive enrichment design (e.g. Wang et al. 2007, Jenkins et al. 2011)

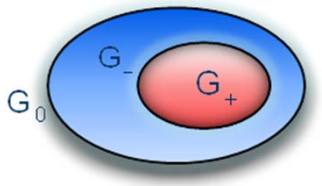




Assumptions and notations

- Assumptions:
  - Binary outcome
  - Two groups: T='treatment', C='control'
- Notations:
  - p_{T+} / p_{T-} : Event probability for patients from subgroup G_+ / G_- assigned to the treatment group
  - p_{C+} / p_{C-} : Event probability for patients from subgroup G_+ / G_- assigned to the control group
  - π : Prevalence of subgroup G_+
  - n : Sample size per group

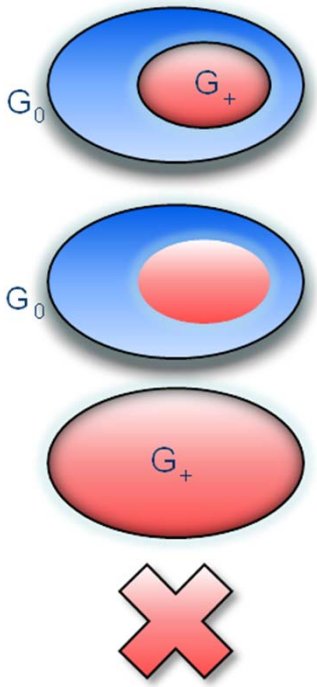
Basics



- Effect estimators $\hat{\Delta}_0$ / $\hat{\Delta}_+$ for total population / subgroup:
  - Approximately normally distributed for sufficiently large n
  - $E(\hat{\Delta}_0) = \pi(p_{T+} - p_{C+}) + (1-\pi)(p_{T-} - p_{C-}) =: \Delta_0$
  - $E(\hat{\Delta}_+) = p_{T+} - p_{C+} =: \Delta_+$
  - $Var(\hat{\Delta}_0) = [\pi(p_{T+}(1-p_{T+}) + p_{C+}(1-p_{C+})) + (1-\pi)(p_{T-}(1-p_{T-}) + p_{C-}(1-p_{C-}))] / n$
  - $Var(\hat{\Delta}_+) = (p_{T+}(1-p_{T+}) + p_{C+}(1-p_{C+})) / (\pi n)$
  - $Cov(\hat{\Delta}_0, \hat{\Delta}_+) = (p_{T+}(1-p_{T+}) + p_{C+}(1-p_{C+})) / n$

Example for a decision rule

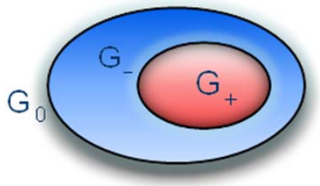
- Rule proposed by Jenkins et al. 2011:
  - $\hat{\Delta}_0 > c_0,\ \hat{\Delta}_+ > c_+$: continue with G_0 and G_+
  - $\hat{\Delta}_0 > c_0,\ \hat{\Delta}_+ \leq c_+$: continue with G_0 only
  - $\hat{\Delta}_0 \leq c_0,\ \hat{\Delta}_+ > c_+$: continue with G_+ only
  - $\hat{\Delta}_0 \leq c_0,\ \hat{\Delta}_+ \leq c_+$: stop for futility



How to choose $(c_0,\ c_+)$ in case of uncertain p_{T+} / p_{C+} / p_{T-} / p_{C-}?

Jenkins M, Stone A, Jennison C (2011). An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints. *Pharmaceutical Statistics* **10**: 347-356.

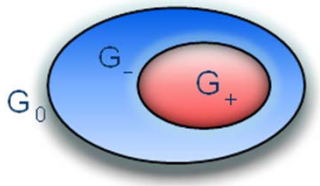
Optimal decision rules



- Assumptions:
  - Selection of G_0 desired if $\Delta_0 > \tau_0$
  - Selection of G_+ desired if $\Delta_+ > \tau_+$
  - *A priori* distributions for p_{T+} / p_{C+} / p_{T-} / p_{C-}
  - Quadratic loss function for wrong decision

    → Optimal decision rule minimizes expected loss (“risk”)
- Optimal decision thresholds (c_0^*, c_+^*) can be computed using numerical integration assuming, e.g., continuous uniform priors.

Optimal decision rules (2)

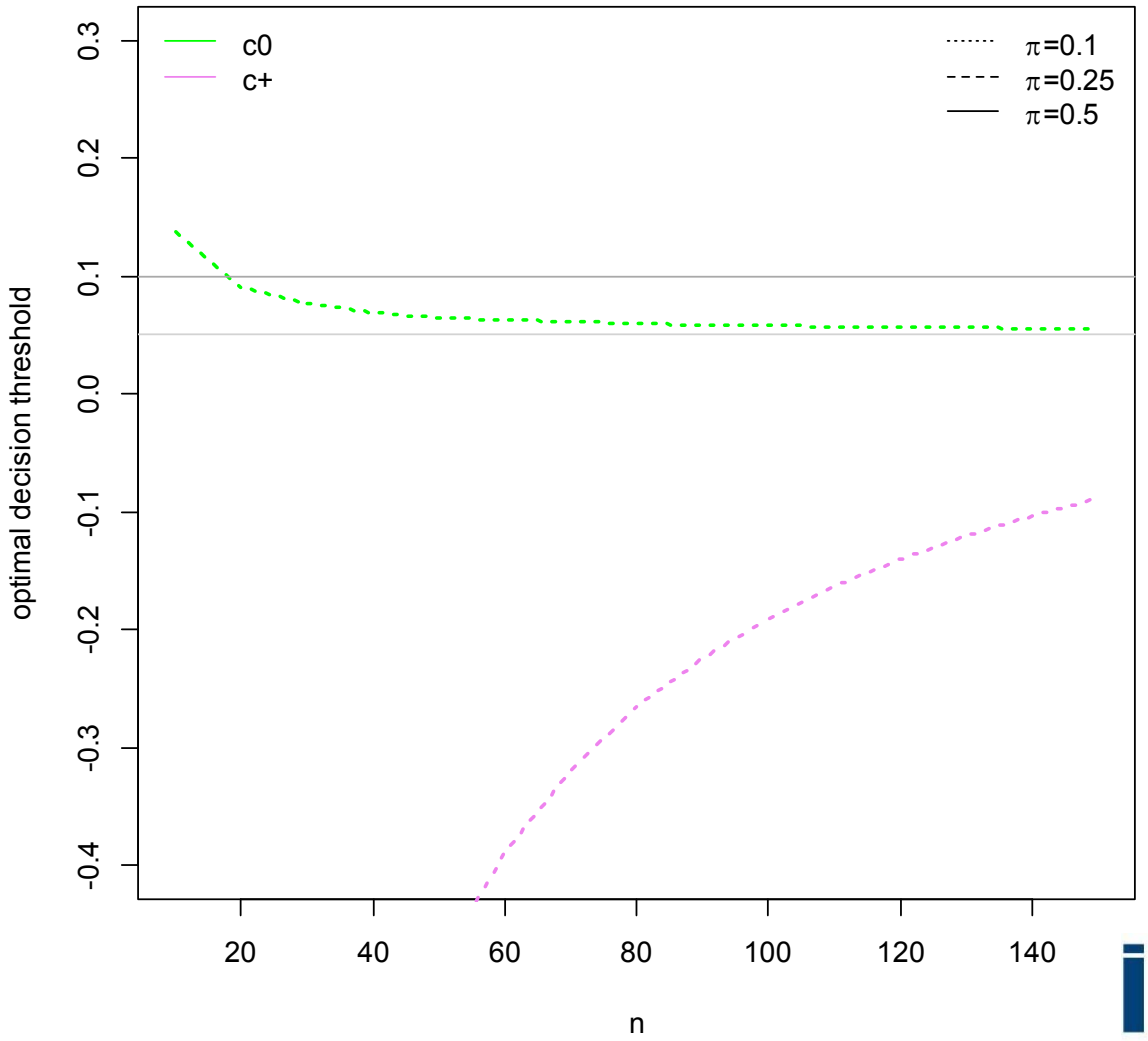


- In the following, we will consider
  - Relevance thresholds $\tau_0 = 0.05, \quad \tau_+ = 0.1$
  - Prevalences $\pi = 0.1,\ 0.25,\ 0.5$
  - Biomarker assumed to be predictive, i.e.

$$p_{T+} \sim U_{[0.3,\ 0.6]},\ p_{T-}, p_{C+}, p_{C-} \sim U_{[0.1,\ 0.4]}$$

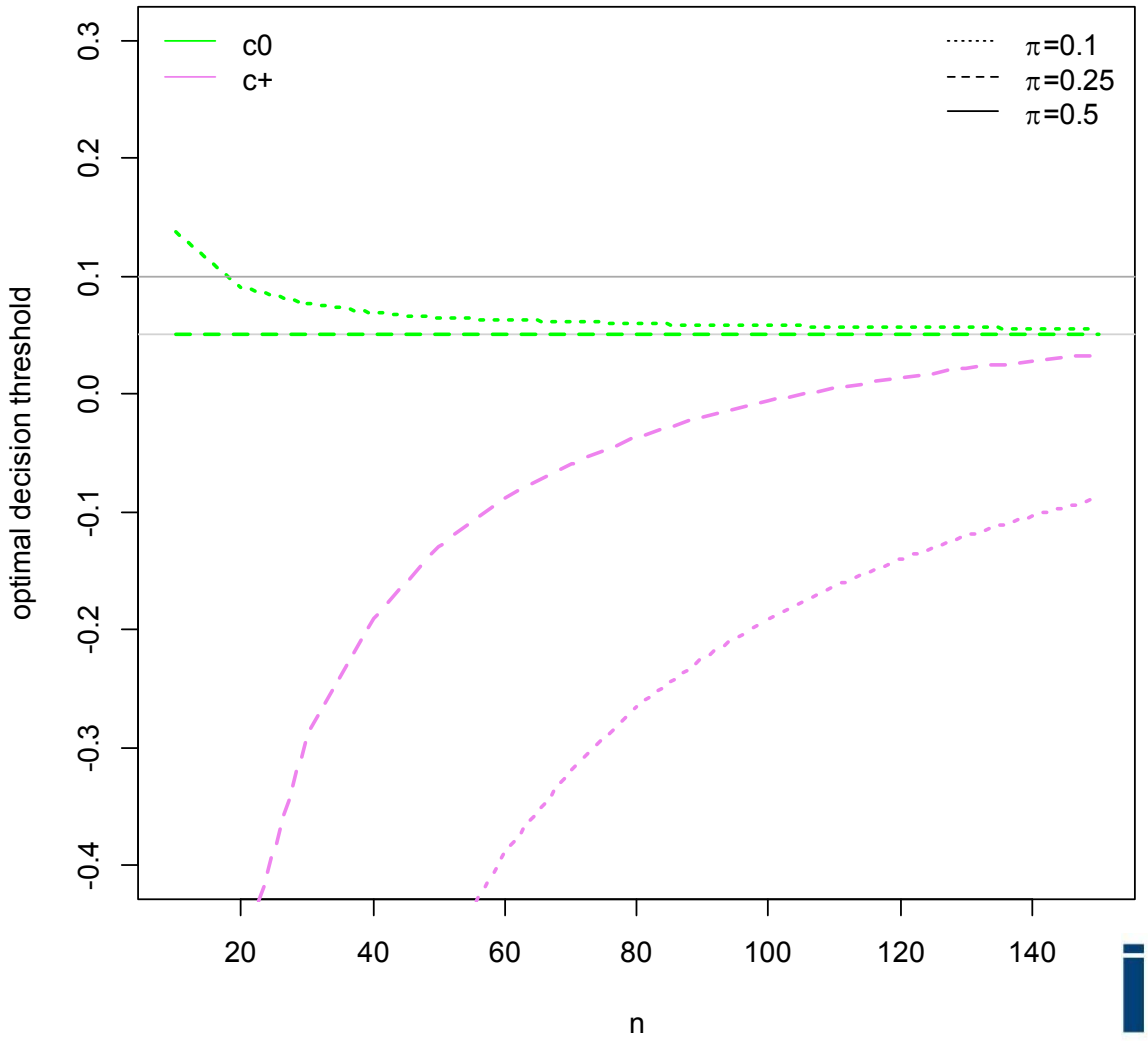
Optimal decision rules (3)

- Example: Optimal decision thresholds for „predictive“ prior



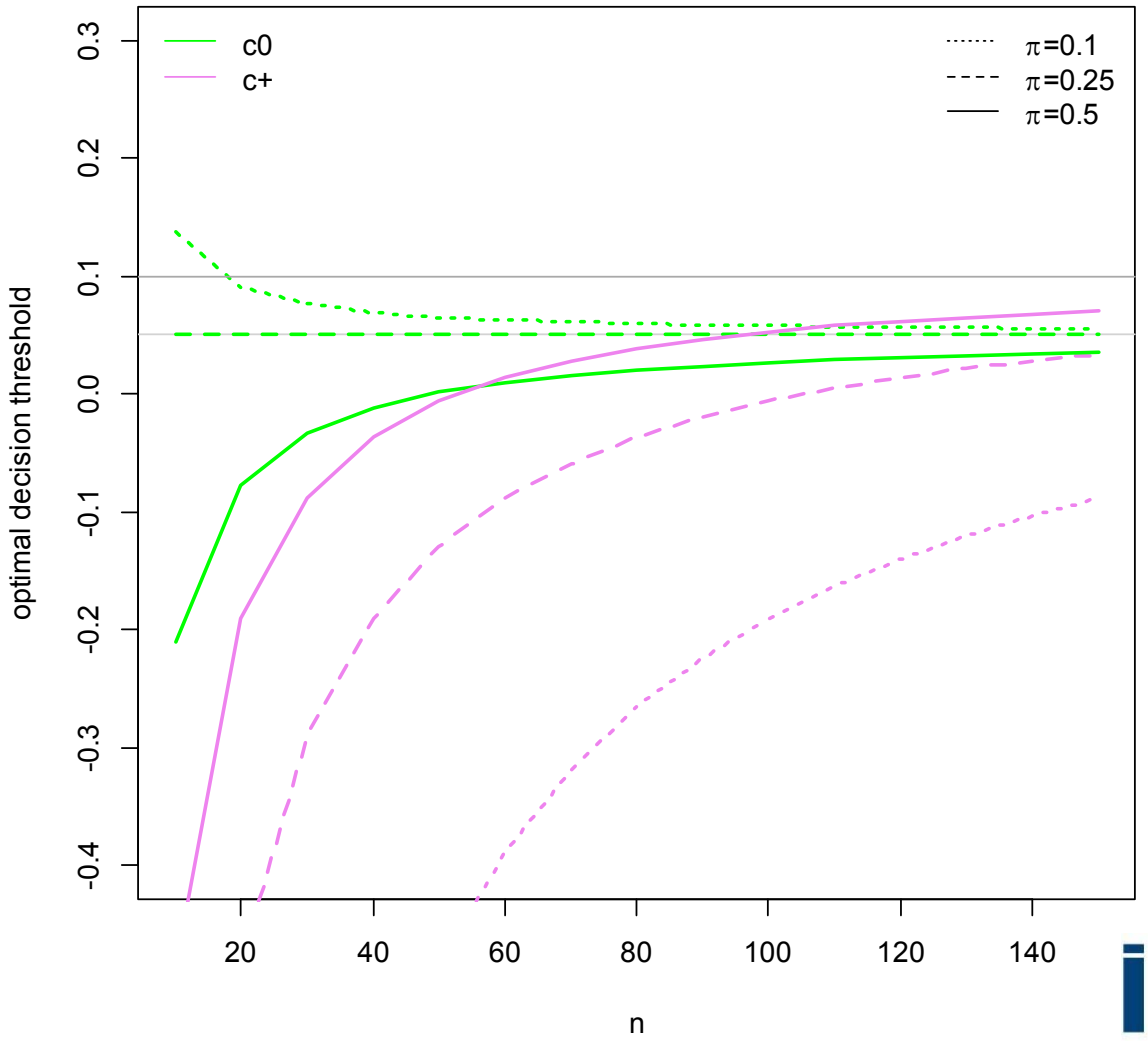
Optimal decision rules (3)

- Example: Optimal decision thresholds for „predictive“ prior



Optimal decision rules (3)

- Example: Optimal decision thresholds for „predictive“ prior



Performance of optimal decision rules – clinical trial example

- Can the incorporation of an optimal decision rule lead to an increase in the probability of the selection of the correct target population?
- Demonstration by clinical trial example:
  - The monoclonal antibody trastuzumab has been shown to be effective as an add-on-therapy exclusively for breast cancer patients which overexpress HER2, which is the case for ~ 20-30% of all patients.
  - However, there is some evidence that trastuzumab might also be effective for HER2-negative patients, which is currently investigated within a large RCT (ClinicalTrials.gov Identifier: NCT01548677).

Assumptions for clinical trial example

- Assume that it is planned to investigate the efficacy of trastuzumab within an enrichment design with subgroup selection at interim with
  - Primary endpoint “event-free survival at five years” (an event is either disease recurrence, progression, or death)
  - $n = 400,\ \pi = 0.2,\ \tau_0 = 0.08,\ \tau_+ = 0.1$
  - Actual event rates
    - $p_{T-} = 0.65$ (Scenario A), $p_{T-} = 0.7$ (Scenario B)
    - $p_{T+} = 0.6$
    - $p_{C-} = 0.6$
    - $p_{C+} = 0.45$

Clinical trial example - a*d hoc* decision rule (a)

- Relevant treatment effect in the subgroup ($\Delta_+ = 0.15 > 0.1 = \tau_+$)
- For Scenario A, i.e. $p_{T-} = 0.65$,
  - $\Delta_0 = 0.07 \leq 0.08 = \tau_0$
  - Selection of G_+ only is desirable
- For Scenario B, i.e. $p_{T-} = 0.7$,
  - $\Delta_0 = 0.11 > 0.08 = \tau_0$
  - Selection of both G_0 and G_+ is desirable
- One could, e.g., simply choose an *ad hoc* decision rule

$$(c_0, c_+) = (\tau_0, \tau_+) = (0.08, 0.1) \rightarrow \textbf{Decision rule (a)}$$

Clinical trial example – optimal decision rule based on a "predictive" prior (b)

- However, consider the situation of prior knowledge about event rates from a previously conducted trial.
  - Reported 95%-confidence intervals can be used to derive an optimal decision threshold by modelling uniform prior distributions from them.
  - Example (based on results from Gianni et al., 2014):
    - $p_{T+} \sim U_{[0.48,\ 0.66]}$, $p_{C+} \sim U_{[0.34,\ 0.52]}$
    - $p_{T-} \sim U_{[0.5,\ 0.7]}$, $p_{C-} \sim U_{[0.5,\ 0.7]}$
- Incorporating this prior knowledge yields optimal decision thresholds $(c_0^*, c_+^*) = (0.0822, 0.0601)$ → **Decision rule (b)**

Gianni L et al. (2014). Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet Oncology* **15**: 640-647.

Clinical trial example – optimal decision rule based on a non-informative prior (c)

- Alternatively, one could consider non-informative priors to derive optimal decision thresholds, i.e. $p_{T+}, p_{T-}, p_{C+}, p_{C-} \sim U_{[0,\ 1]}$.
- In this case, the optimal decision rule is

$$(c_0^*, c_+^*) = (0.0807, 0.1029) \rightarrow \textbf{Decision rule (c)}$$

➢ We evaluated the performance of decision rules **(a)**, **(b)**, **(c)** in terms of selection probabilities by Monte-Carlo simulation (1,000,000 simulated studies per scenario)

Selection probabilities for scenario A ($p_{T-} = 0.65$)

decision rule / probability	**(a)** $(c_0, c_+) =$ $(0.08, 0.1)$	**(b)** $(c_0^*, c_+^*) =$ $(0.0822, 0.0601)$	**(c)** $(c_0^*, c_+^*) =$ $(0.0807, 0.1029)$
select G_0 and G_+	0.3226		
select G_0 only	0.0493		
select G_+ only	0.3919		
stop for futility	0.2361		

Selection probabilities for scenario A ($p_{T-} = 0.65$)

decision rule / probability	**(a)** $(c_0, c_+) =$ (0.08, 0.1)	**(b)** $(c_0^*, c_+^*) =$ (0.0822, 0.0601)	**(c)** $(c_0^*, c_+^*) =$ (0.0807, 0.1029)
select G_0 and G_+	0.3226	0.3587	
select G_0 only	0.0493	0.0132	
select G_+ only	0.3919	0.5262	
stop for futility	0.2361	0.1077	

Selection probabilities for scenario A ($p_{T-} = 0.65$)

decision rule / probability	**(a)** $(c_0, c_+) = (0.08, 0.1)$	**(b)** $(c_0^*, c_+^*) = (0.0822, 0.0601)$	**(c)** $(c_0^*, c_+^*) = (0.0807, 0.1029)$
select G_0 and G_+	0.3226	0.3587	0.3226
select G_0 only	0.0493	0.0132	0.0493
select G_+ only	0.3919	0.5262	0.3919
stop for futility	0.2361	0.1077	0.2361

- Decision rules (a) and (c) perform identically.
- Relatively high probability for a futility stop for rules (a) and (c).
- Decision rule (b) shows the highest probability for a correct selection.

Selection probabilities for scenario B ($p_{T-} = 0.7$)

decision rule / probability	**(a)** $(c_0, c_+) = (0.08, 0.1)$	**(b)** $(c_0^*, c_+^*) = (0.0822, 0.0601)$	**(c)** $(c_0^*, c_+^*) = (0.0807, 0.1029)$
select G_0 and G_+	0.6232		
select G_0 only	0.1796		
select G_+ only	0.0914		
stop for futility	0.1059		

Selection probabilities for scenario B ($p_{T-} = 0.7$)

decision rule / probability	**(a)** $(c_0, c_+) =$ $(0.08, 0.1)$	**(b)** $(c_0^*, c_+^*) =$ $(0.0822, 0.0601)$	**(c)** $(c_0^*, c_+^*) =$ $(0.0807, 0.1029)$
select G_0 and G_+	0.6232	0.7419	
select G_0 only	0.1796	0.0609	
select G_+ only	0.0914	0.1431	
stop for futility	0.1059	0.0542	

Selection probabilities for scenario B ($p_{T-} = 0.7$)

decision rule / probability	(a) $(c_0, c_+) =$ (0.08,0.1)	(b) $(c_0^*, c_+^*) =$ (0.0822,0.0601)	(c) $(c_0^*, c_+^*) =$ (0.0807,0.1029)
select G_0 and G_+	0.6232	0.7419	0.6232
select G_0 only	0.1796	0.0609	0.1796
select G_+ only	0.0914	0.1431	0.0914
stop for futility	0.1059	0.0542	0.1059

- Again, decision rules (a) and (c) perform identically.
- As before, decision rule (b) shows the highest probability for a correct selection.

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Conclusions

- Optimal decision rules incorporate various aspects of the design of a clinical trial with subgroup selection.
- Under the situation of no prior knowledege on treatment effects, optimal decision rules can also be derived and show a performance comparable to *ad hoc* rules in terms of correct selection probability.
- If there is prior knowledge on treatment effects, optimal decision rules may lead to an increased probability for a correct selection of the target population, which also yields an increased statistical power (Krisam & Kieser, 2015b).

Krisam J, Kieser M (2015b). Optimal decision rules for biomarker-based subgroup selection for a targeted therapy in oncology. *International Journal of Molecular Sciences* **16**(5), 10354-10375.

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