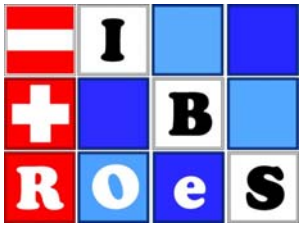
**Wiener Biometrische Sektion (WBS)**
**der Internationalen Biometrischen Gesellschaft**
**Region Österreich – Schweiz (ROeS)**
http://www.meduniwien.ac.at/wbs/



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**WBS Sommer Seminar**

# *Did the genomic data flood overrun the statistical levee?*

## Statistical approaches to analyse genomic data (*without drowning*)

| | |
|---|---|
| **Datum:** | Donnerstag, 4. Juli 2013 |
| **Ort:** | Hörsaal der Universitätszahnklinik der Medizinischen Universität Wien,<br>Sensengasse 2a, 1090 Wien<br>Plan siehe http://www.unizahnklinik-wien.at/de/patientinnen/anreise/ |
| **Beginn:** | 13:00 Uhr (s.t.) |
| **Ende:** | 17:45 Uhr |
| **Vorsitz:** | Georg Heinze (CeMSIIS, Med. Univ. Wien), Stephan Lehr (Baxter Innovations GmbH) |

15.05-15.30 break: there is a bistro in the floor above!!!
18.00-?? informal debriefing, Universitätsbräu (Campus Altes AKH)

# Wiener Biometrische Sektion (WBS)

- Sektion der Region Österreich-Schweiz (ROeS) der Internationalen Biometrischen Gesellschaft (IBS)
- WBS-Mitgliedschaft kostenlos (wünschenswert ROeS-Mitgliedschaft)

**Veranstaltungen**

- **WBS- Biometrisches Kolloquium**
  - einzelne Vorträge zu verschiedensten Themen in der Biometrie
- **NEUE SERIE: WBS-Seminar:**
  - mehrere Vorträge zu einem Thema an einem Tag
- Benachrichtigung per elektronischem Newsletter

- **Vorschläge für Themen, Veranstaltungsorte, Sponsoren.. für kommende Seminare/Kolloquien sind herzlichst willkommen!**
- EMAIL an franz.koenig@meduniwien.ac.at

# Agenda

| | |
|---|---|
| 13 – 13.25 | Stephan Lehr (Baxter Innovations GmbH, Wien): **Some practical aspects in design and analysis of biomarker studies** |
| 13.25 – 13.50 | Andreas Gleiss (CeMSIIS, Med. Univ. Wien): **Test statistics for two-group comparisons of zero-inflated intensity values** |
| 13.50 – 14.15 | Sonja Zehetmayer (CeMSIIS, Med. Univ. Wien): **Stopping rules for sequential trials in high-dimensional data** |
| 14.15 –14.40 | Markus Jaritz (Research Intitute of Molecular Pathology (IMP), Campus Vienna Biocenter): **Next Generation Sequencing Data Analysis: From ChIP-Seq read islands to epigenomics information** |
| 14.40 – 15.05 | Christoph Bock (CeMM, Austrian Academy of Sciences) **The Relevance of Next Generation Sequencing for Personalized Medicine** |
| 15.05 – 15.30 | *Pause (Foyer)* |
| 15.30 – 16.15 | Lara Lusa (University of Ljubljana): **Class-imbalanced class prediction for high-dimensional data** |
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| 17:25 – 17:40 | Georg Heinze (Med. Univ. Wien): **How the levee bears out against the flood: summary and discussion** |

# Some practical aspects in the design and analysis of biomarker studies

**Stephan Lehr**
**Baxter Innovations GmbH**

**July 4, 2013**

# Outline

- Definitions and Guidelines
- Model validation for genomics data
- Design considerations for predictive marker validation

# Definitions

- 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
- Predictive marker
  Forecasts the likely response to a specific treatment
- Prognostic marker
  Forecasts the likely course of disease (irrespective of treatment)
- Surrogate marker
  Measurement providing early and accurate prediction of both a clinical endpoint, and the effects of treatment on this endpoint

# Guidances

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 June 2011
EMA/446337/2011
Committee for Medicinal Products for Human Use (CHMP)

## Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection

Draft

| | |
|---|---|
| **Draft Agreed by Pharmacogenomics Working Party (PGWP)** | **March 2011** |
| Adoption by CHMP for release for consultation | 9 June 2011 |
| End of consultation (deadline for comments) | 25 November 2011 |

Comments should be provided using this template.The completed comments form should be sent to PGWPSecretariat@ema.europa.eu

| | |
|---|---|
| **Keywords** | ***Clinical trial designs, Enriched design, Genomic biomarkers, (GBMS), hybrid design, Predictive markers, Pharmacogenomics, Retrospective data analyses*** |

# Guidance for Industry

## Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

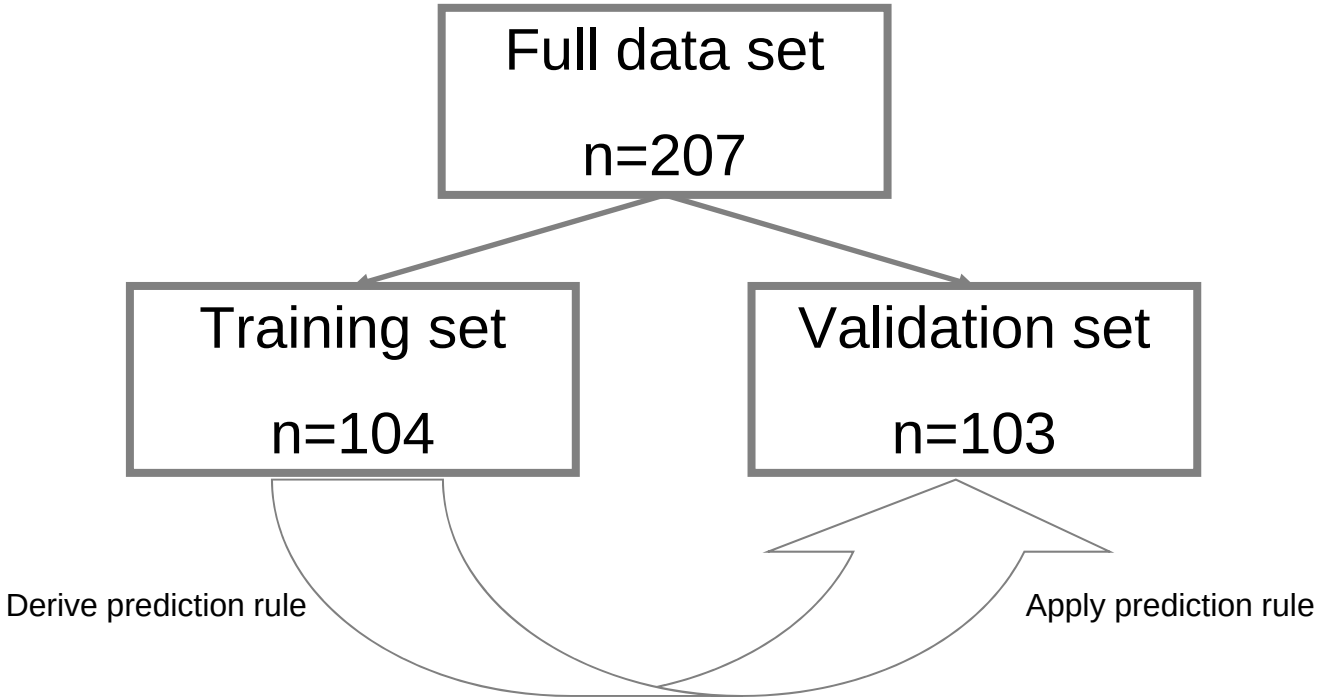
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**Center for Devices and Radiological Health (CDRH)**
**December 2012**
**Clinical Medical**

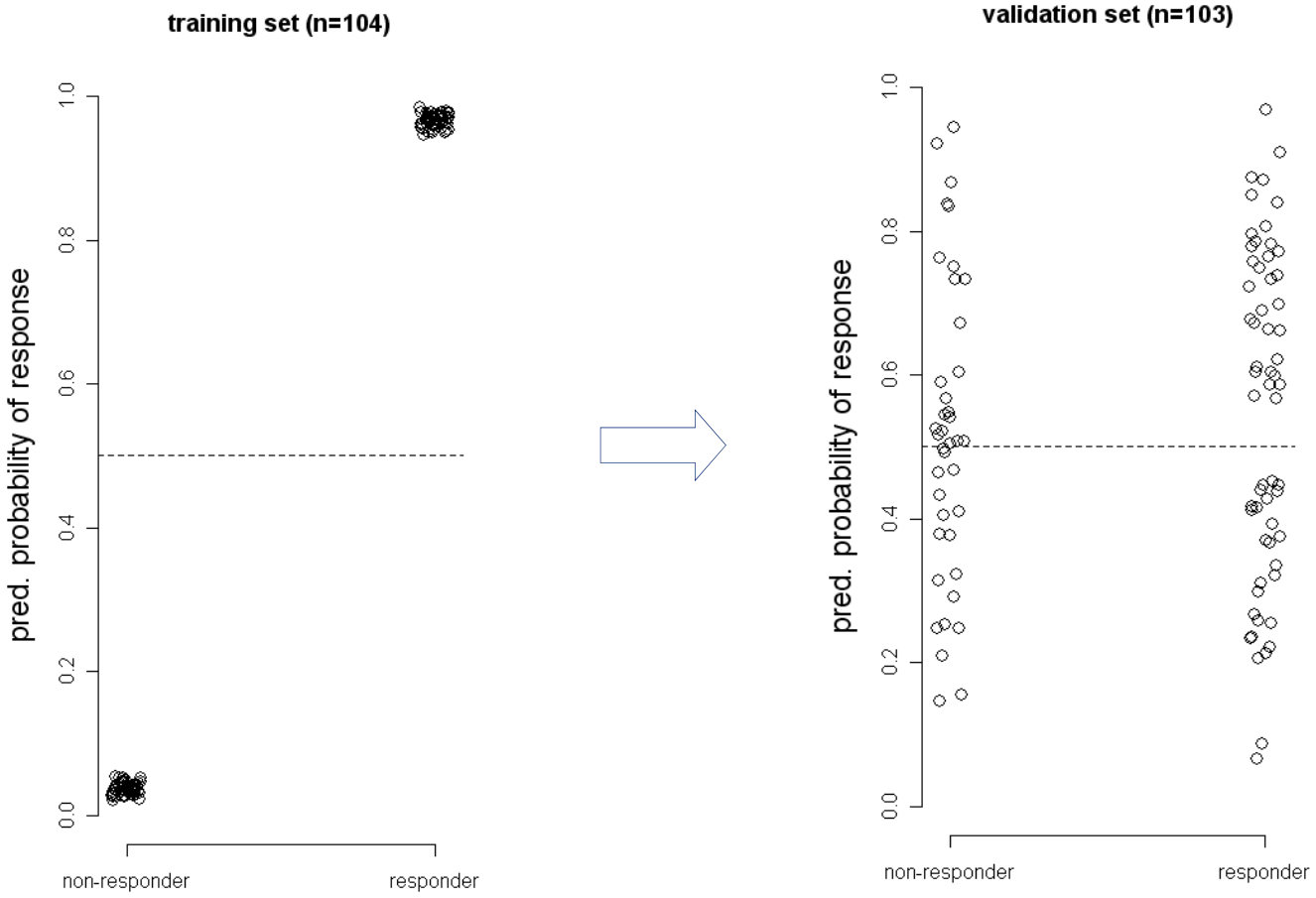
# Statistical model validation
## – A gene expression example

Data set of size n=207 patients (oncology study)
k=10.068 genes (mRNA gene expression – continuous explanatory variables)
2 outcome classes (response / non-response) of approx. equal size



# Statistical model validation
## – A gene expression example

1. Model building using all genes (k=10.068)
2. Model validation by data splitting approach

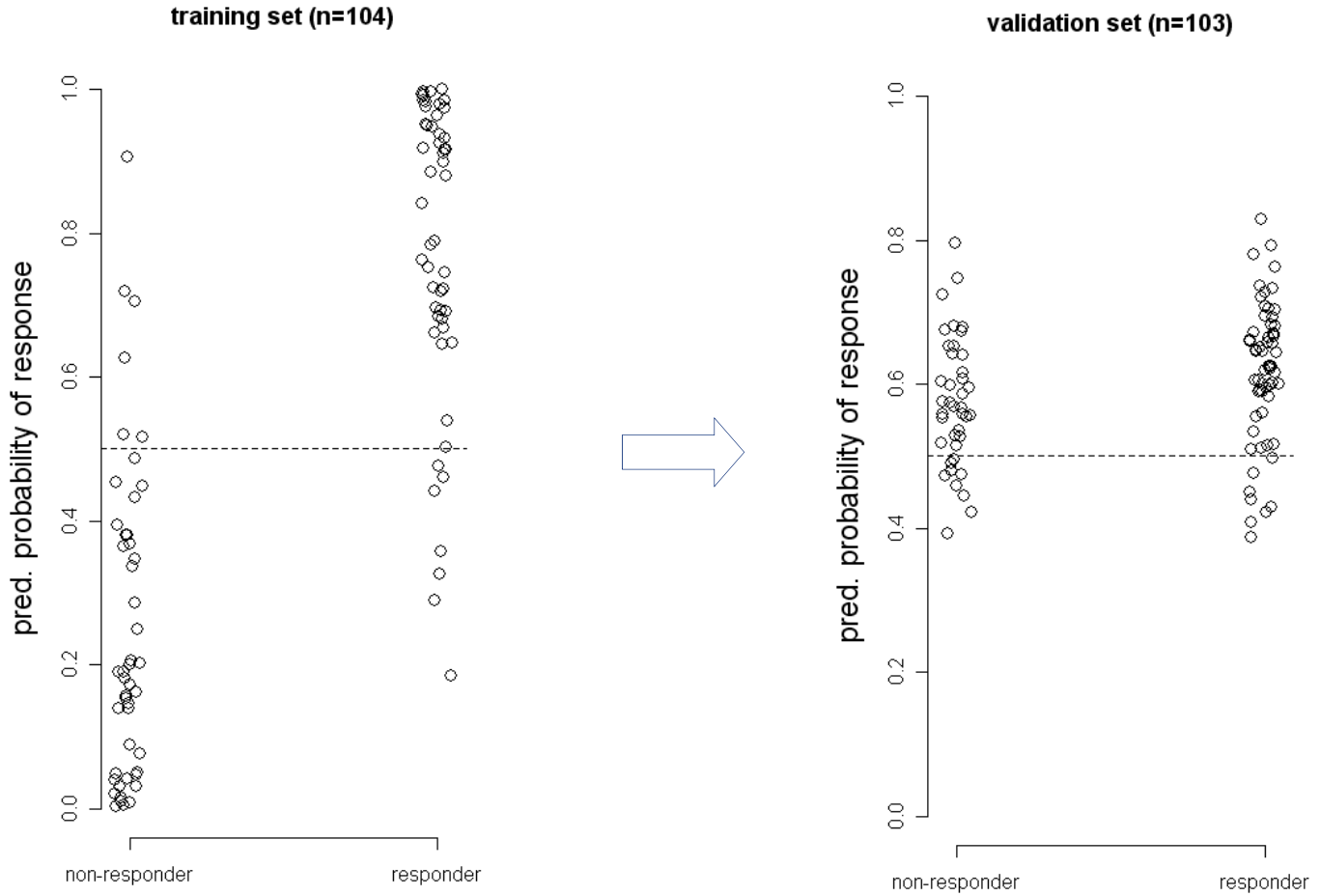



misclassification rate = 0 %

misclassification rate ≈ 50 %

# Statistical model validation
## – A gene expression example

1. Variable selection: k=10 “best” genes
2. Model validation by cross-validation and data splitting




misclassification rate (“re-substitution”) = 14 %

misclassification rate (cross validation) = 21 %

misclassification rate ≈ 50 %

**Data from the example are completely random !**

# Statistical model validation – Lessons learned

## Overfitting disaster

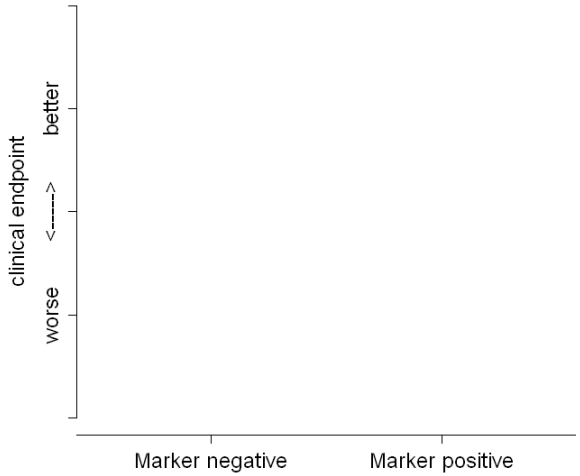
Finding a separating statistical model when the number of genes by far exceeds the number of patients (“k >> n”) might mean nothing

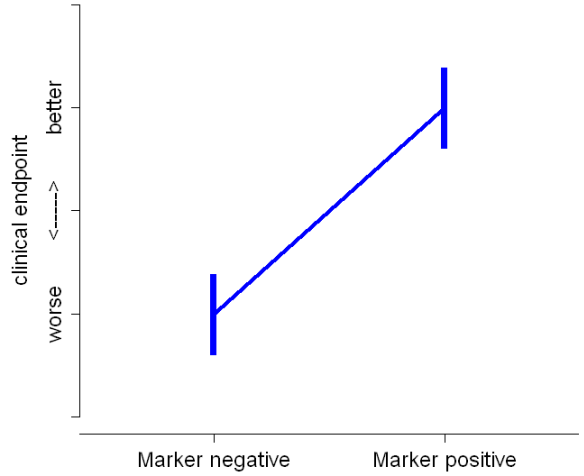
## Selection Bias

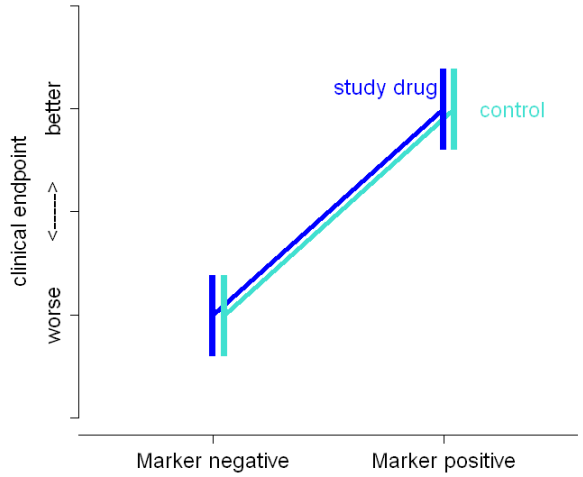
Gene selection is part of the training and must not be separated from it

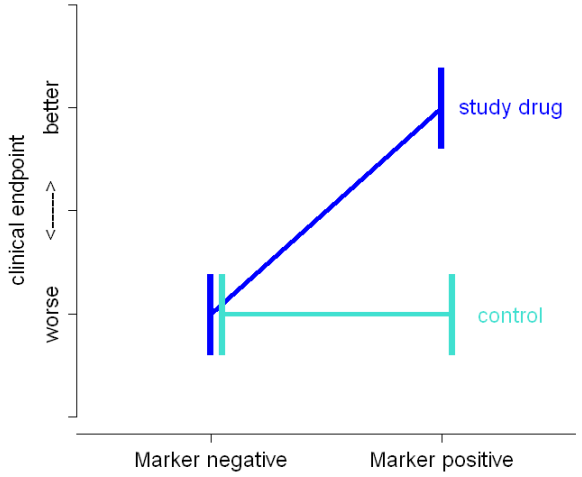
⇒ consequences of inappropriate cross validation , refer e.g. to Simon et al (2003)
⇒ computational details to obtain unbiased error rate estimates, refer e.g. to Ruschhaupt et al (2004)

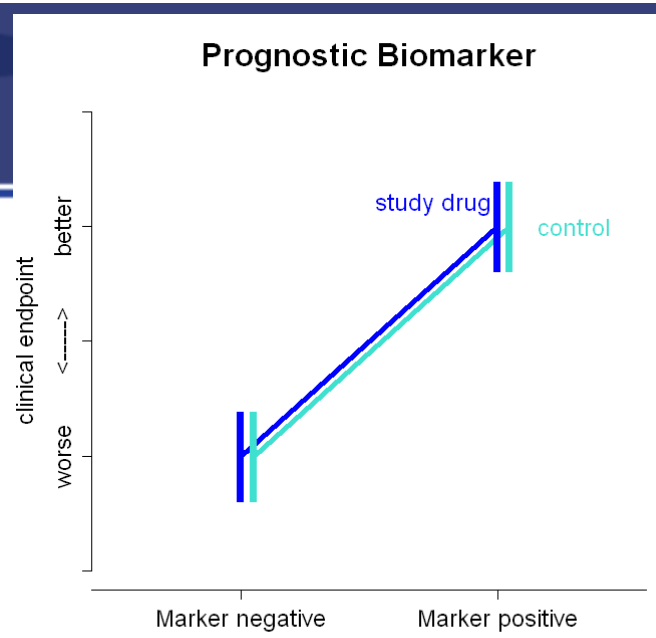
# Identification of markers for patient selection

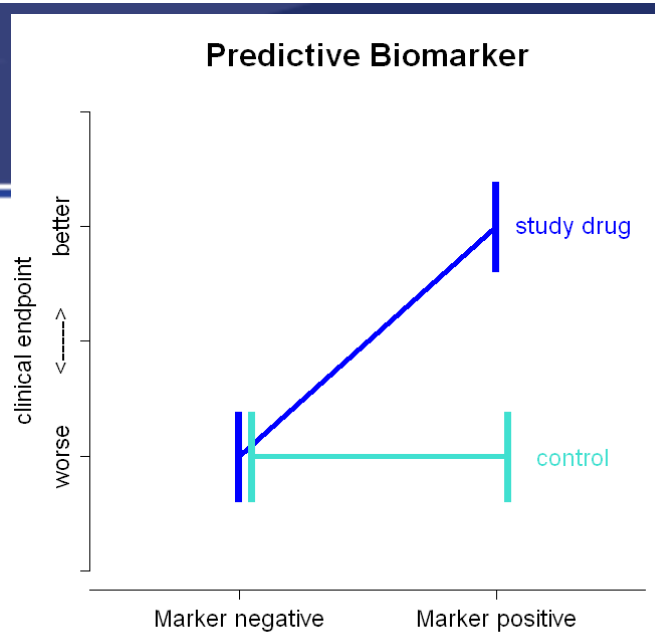





- Not useful in identifying subpopulation with better response to study drug than to control
- Possible disease aggressiveness marker
- Balance randomization by prognostic factor
- Adjust analysis for prognostic marker covariate

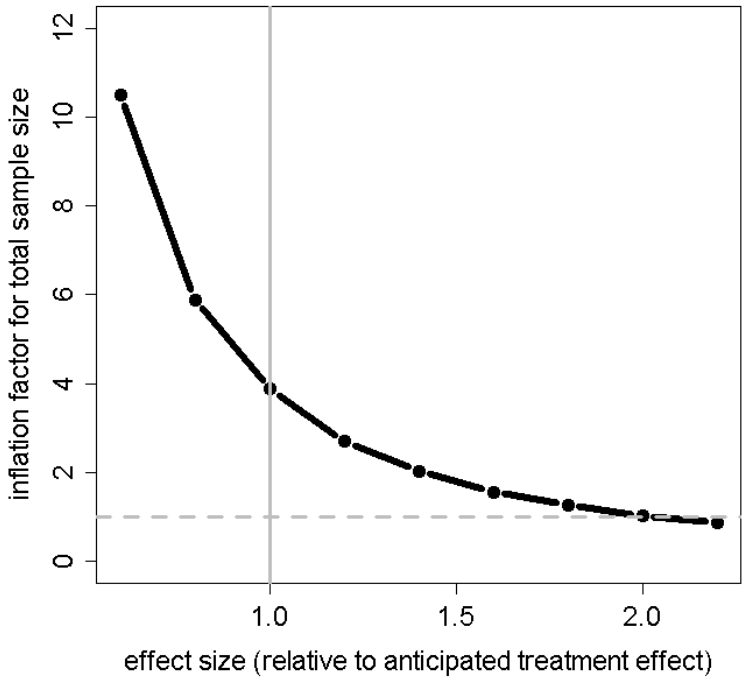
- Useful in identifying subpopulation with substantially better response to study drug than to control
- Efficacy marker for study drug
- Test for marker-by-treatment interaction
- Likely to be underpowered

# Consider a clinical trial to show superiority of study drug over control with a power of 80%

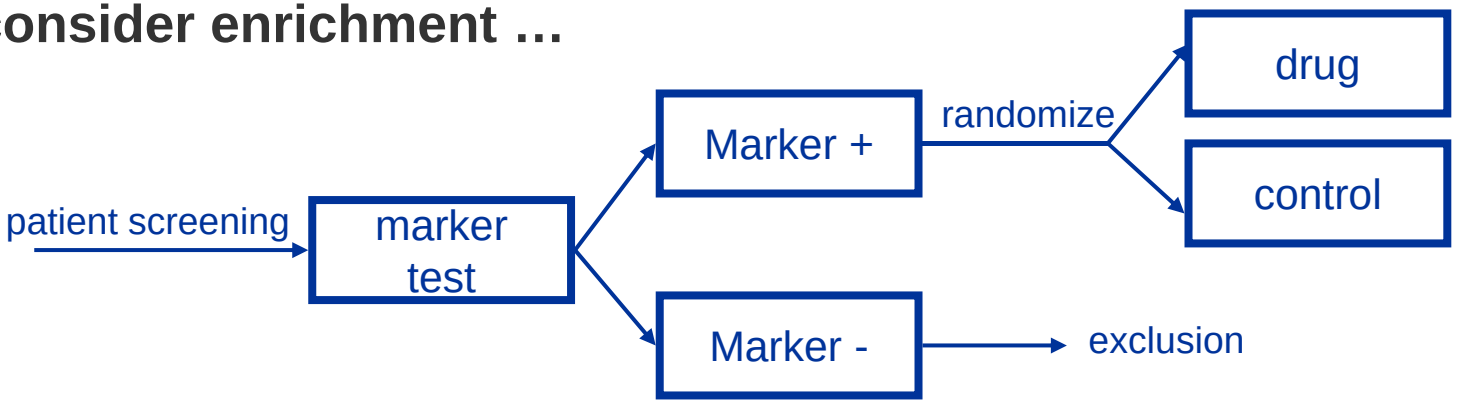
Example:

- Drug is only effective in „marker+“
- 50% of patients are „marker+“

=> the power to detect interaction effect of same magnitude is 28%!



## Let‘s consider enrichment …

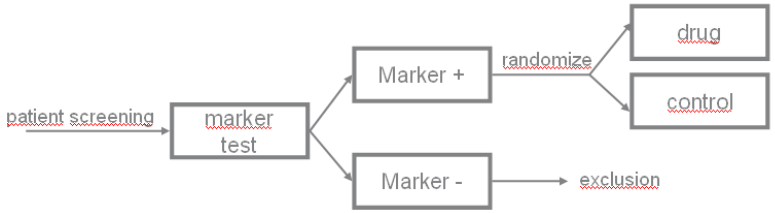



Example:

- Drug is only effective in „marker+“
- 50% of patients are „marker+“

=> less than one third (=29%) of patients have to be randomized in enrichment design compared to unselected (non-enrichment) design to achieve the same power!

# Enrichment design




Example:

- Clinical trial, drug vs control, power = 80%
- 50% of patients are marker+

  ⇒29% patients randomized as compared to classical design

- **70% of patients are marker+**

  => 55% patients randomized as c ed to unselected design

- **...AND test sensitivity = test specificity = 8**

  => 67% patients randomized as compared to ted design

- **... AND treatment effect in marker- half that of marker+**

  => 82% of patients randomized (compared to unselecte

  => 132% of patients need to be screened (compared to nts randomized in the unselected design)

Marker prevalence

Diagnostic Test characteristic

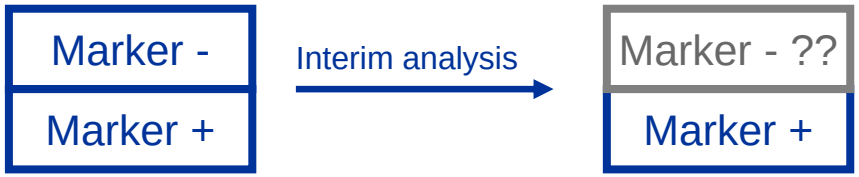
Treatment effect

# Is an enrichment design appropriate?

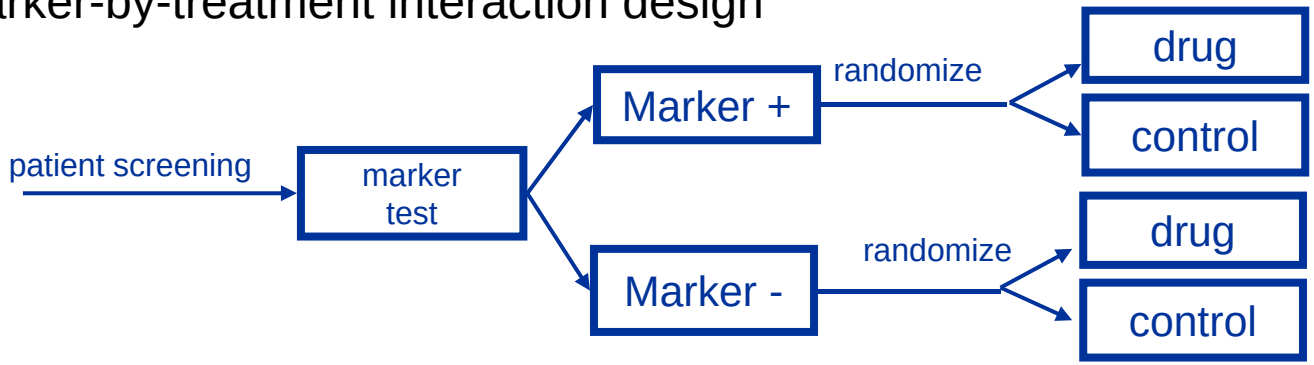
- Is there compelling preliminary evidence to suggest that marker- patients do not benefit from the new treatment?
- Is the assay reproducibility and accuracy well established?
- Is the threshold to define marker+/marker- clearly defined?
- How well can the expected marker prevalence be estimated?

# Alternative predictive biomarker designs

- Sequential/adaptive design




- Biomarker adaptive threshold (statistical analysis) design
  - Test for overall treatment effect ⇔ establish and validate cut-point for marker
- Retrospective Analysis
- Marker-by-treatment interaction design




- Further marker-based designs (see e.g. EMA guidance)

# References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- Simon R et al (2003): „Pitfalls in the Use of DNA Microarray Data for Diagnostic and Prognostic Classification“, *J Natl Cancer Inst* 95(1): 14-18

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# ROeS

- http://www.meduniwien.ac.at/roes/
- ROeS-Seminar findet alle zwei Jahre statt
  - Abwechselnd in der Schweiz und Österreich
  - 2013: ROeS-Seminar in Dornbirn (9-12 September)