Design of Biomarker Studies

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Outline

- Terminology
- Characteristics of biomarkers
- Phases of prognostic and diagnostic biomarker studies
- Study designs for predictive biomarkers

Terminology

- **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.
- **Prognostic biomarker:** A biomarker that predicts the likely course of disease in a defined clinical population under standard treatment conditions.
- **Predictive biomarker:** A biomarker that forecasts the likely response to treatment. Treatment response may be measured either as efficacy or as safety.

Biomarkers Definitions Working Group 2001 Clin Pharmacol Ther 69:89-95
Buyse et al. 2011 Expert Rev Mol Diagn 11:171-82 • Ziegler et al. 2012 Hum Genet 131:1627-38

Terminology

- Predictive biomarker
  Effect in Biomarker+
  No effect in Biomarker–
- Prognostic biomarker
  Consistent effect in Biomarker+ and Biomarker –
- Prognostic-predictive biomarker
  Important in disease response
  Larger effect in Biomarker+ than Biomarker–

Wang et al. 2007 Pharm Stat 6:227-44, Table 1

Terminology

Biomarker	Predictive		Prognostic		Prognostic-predictive	
	Standard	Drug A	Standard	Drug B	Standard	Drug C
Negative –	33%	33%	39%	39%	39%	46%
Positive +	33%	48%	61%	61%	61%	75%

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Statistical Model

- Statistical model

$$y_i = \begin{cases} 1 & \text{cured} \\ 0 & \text{not cured} \end{cases}$$

$$x_{i1}^{\text{Treat}} = \begin{cases} 1 & \text{Treatment A} \\ 0 & \text{Treatment B} \end{cases} \qquad x_{i2}^{\text{Biom}} = \begin{cases} 1 & \text{Biomarker +} \\ 0 & \text{Biomarker –} \end{cases}$$

$$\operatorname{logit} E(y_i \mid \boldsymbol{x}_i) = \beta_0 + \beta_1 x_{i1}^{\text{Treat}} + \beta_2 x_{i2}^{\text{Biom}} + \beta_3 x_{i1}^{\text{Treat}} x_{i2}^{\text{Biom}}$$

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Statistical Model

- Predictive biomarker

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- Prognostic-predictive biomarker

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Examples for Biomarkers in Current Use

Name	Type	Application	Use	Indication	Time
BluePrint	DNA tumor	Predictive	Commercial	Breast ca	Known diagnosis, after surgery
EGFR	DNA tumor	Predictive	Am Soc Clin Oncol	Advanced NSCLC	Known diagnosis, prior to 1-line ther.
IL28b	DNA	Predictive	Non commercial	HepCV-1	Known diagnosis, before treatment
K-RAS	DNA tumor	Prognostic	Am Soc Clin Oncol	Advanced CRC	Known diagnosis, before chemother.
MammaPrint	DNA tumor	Prognostic	Commercial	Breast ca	Known diagnosis, after surgery
OncoTypDX	DNA tumor	Predictive/ prognostic	Commercial	Breast ca, CRC	Known diagnosis, after surgery
RheumaChec	General	Diagnostic	Commercial	RA	Before first symptomatic
CCPointAssay	General	Diagnostic	Commercial	RA	Before first symptomatic
SLCO1B1	DNA	Predictive	Non commercial		Known diagnosis, before treatment

Characteristics of Different Types of Biomarkers

Characteristic	DNA biomarker	Tumor DNA biomarker	General biomarker
Level of measurement	Discrete	Discrete	Continuous
Stability, reproducibility	Yes	Not necessarily: mutations in different parts of the tumor)	Only at one specific time point
Time of measurement	Not to be specified	Specified in advance	Specified in advance
Suitable as surrogate marker	No	No, in general	Yes
Suitable for therapy monitoring	No	Yes	Yes
"Durability" of the final biomarker test	Short- to long-term	Mid-term to long-term	Mid-term to long-term

Prospective vs. Retrospective Biomarker Measurement

- Definition of terms prospective and retrospective not uniform

- Prospective study
  - **All measurements prospectively defined**
  - **All measurements prospectively done**
  - Including patient recruitment
  - Including biomarker measurement
- Retrospective **biomarker** study
  - Biomarker measurement **prospectively or retrospectively** done
  - Patient recruitment **in retrospect**

Prospective vs. Retrospective Biomarker Measurement

PRO retrospective studies

- Maximize number of measurements by pooling over all completed studies
- Biomarker definition a posteriori
- Exploration and refinement of genomic biomarker with large patient database compared to small randomized trials
- Evaluation of treatment effect in biomarker positive and biomarker negative groups
- Treating physician bias possible in prospective studies if unblinded

CON retrospective studies

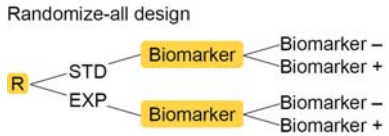
- Informed consent difficult ⇒ convenience samples
- Sample collection, handling, and storage difficult
- Time impacts sample quality
- Missing data more likely
- Relevant tissue might not be available
- Only inappropriate time point for biomarker measurement might be available
- Generally higher bias (60% overestimation)

Phases of Diagnostic or Prognostic Biomarker Studies

Phase	Description	Aim of study
Ia	Discovery	Identification of promising biomarkers
Ib	Assay development, assay validation	Define and optimize analytical process into robust, reproducible, and valid device
Ic	Retrospective validation	Clinical assay detects disease; development of first algorithm for combination test
II	Retrospective refinement	Validation of early detection properties of biomarker (set); development and/or refinement of algorithm(s) for combination tests
III	Prospective investigation	Determination of diagnostic accuracy (sensitivity, specificity) in the situation of clinical routine
IVa	Randomized controlled trial	Quantification of effect of making the biomarker information available to the doctor to reduce disease burden
IVb	Health economics study	Quantification of cost-effectiveness

Study Designs for Predictive Biomarkers Randomize-All Design

- Randomize-all
  - Biomarker not balanced
  - Time of biomarker measurement hard to define
  - Biomarker measurements not for all
- Example
  - p53 EORTC study 10994
  - Advanced breast cancer
  - Randomization to standard anthtrcycline regimen or taxane-based regimen
  - Primary endpoint progression free survival according to TP53 status

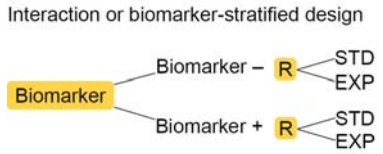


Study Designs for Predictive Biomarkers
Randomize-All Design

- When there is **no biological plausibility** or no established known drug target, there is generally less confidence to exclude patients on the basis of a genomic biomarker; thus, the study of all randomized patients is preferred
- First, a composite objective, H_0: $\Delta = 0$ and $\Delta_+ = 0$ vs. H_1: $\Delta > 0$ or $\Delta_+ > 0$; that new treatment is effective in all randomized patients or in the biomarker positive subset can be tested in a fixed design or an adaptive design setting

- When there is a **reasonable body of biological evidences** to support a specific hypothesis that a therapeutic agent inhibits a specific molecular target, an enrichment design may be pursued to address the targeted biomarker positive hypothesis, H_0: $\Delta_+ = 0$ vs. H_1: $\Delta_+ > 0$.
- Enrichment design requires **an available diagnostic assay**. To ensure generation of meaningful data, it is imperative that the **analytical validation of the diagnostic assay be established before initiating an enriched design approach**

Study Designs for Predictive Biomarkers
Biomarker-Stratified Randomization



- Biomarker-stratified
  - Biomarker to be known in advance
  - No balancing of multiple markers
  - Biomarker measurements may fail
- Example
  - NCCTG 0723 trial
  - Marker Validation for Erlotinib in Lung Cancer (MARVEL)
  - Second-line advanced non-small cell lung cancer (NSCLC)
  - Randomization to Erlotinib (EGFR tyrosine kinase inhibitor) or Pemetrexed (multitargeted antifolate)
  - Randomization by EGFR status, measured by FISH

Study Designs for Predictive Biomarkers
Biomarker-Stratified Randomization

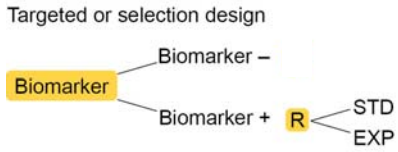
- A design stratified by the genomic biomarker status that tests H_0: $\Delta_+ = 0$ vs. H_1: $\Delta_+ \neq 0$ and H_0: $\Delta_- = 0$ vs. H_1: $\Delta_- \neq 0$ separately, essentially undertakes two independent clinical trials, which may not be useful if the clinical utility of the biomarker is predictive, i.e. $\Delta_+ > 0$ and $\Delta_- = 0$ in truth …
- The **sample size** for the null effect in the biomarker negative subset **will be very troublesome** in placebo-controlled trials and will likely be very large if a non-inferiority objective is required to show that the effect with the new treatment is essentially no different from the comparator with a tight non-inferiority margin in active-controlled trials.

Study Designs for Predictive Biomarkers
Biomarker-Stratified Randomization

- Often, the composite hypothesis is addressed indirectly when one **starts with the interaction test**. …
  - Interaction test not significant, test treatment effect in all patients
  - Interaction test significant, separate tests in biomarker positive and biomarker negative subsets
- It is not clear what significance level the interaction test should be with the branch testing scheme described above so as to maintain the control of the overall type I error rate.
- In addition, the interaction test generally requires much larger sample size as compared with a study sized for an overall effect.
- For this reason, when the composite objective is of primary focus, the interaction objective may not be preferred …

Study Designs for Predictive Biomarkers
Targeted Design

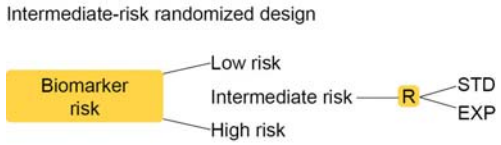
- Targeted design
  - Does not show predictiveness of biomarker
  - Superiority in subgroup
  - Used in special applications only
  - Low power if prevalence of biomarker low
- Example
  - ToGA trial (Trastuzumab for Gastric Cancer)
  - Gastric or gastro-oesophageal junction cancer
  - Only patients with overexpression of HER2 protein (immunohistochemistry or FISH)
  - Randomization to chemotherapy regimen or chemotherapy in combination with intravenous trastuzumab



Mallal et al. 2008 N Engl J Med 358:568-79 • Ziegler et al. 2012 Hum Genet 131:1627-38
Bang et al. 2010 Lancet 376:687-97

Study Designs for Predictive Biomarkers
Biomarker-Guided Design No Control

- Biomarker-guided design without control
- Example
  - TAILORx trial (Trial Assigning IndividuaLized Options for Treatment (Rx))
  - ER+ and/or PR+, node negative BRCA patients
  - Onco*type* DX mRNA 21 gene expression array (FFPE)
  - Intermediate risk score 11 – 25
  - STD: chemotherapy plus hormonal therapy
  - EXP: hormonal therapy alone
    Primary hypothesis in patients at intermediate risk



Sparano 2006 Commun Oncol 3:494-6

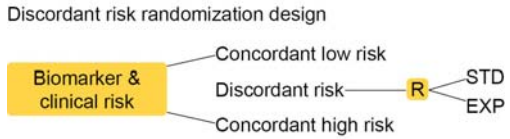
Study Designs for Predictive Biomarkers
Biomarker-Guided Design No Control

- Rationale TAILORx trial

Sparano 2006 Commun Oncol 3:494-6

Study Designs for Predictive Biomarkers
Biomarker-Guided Design No Control

- Biomarker-guided design without control
- Example
  - MINDACT trial (Microarray In Node negative Disease may Avoid ChemoTherapy)
  - Node negative BRCA patients with discordant clinical / genomic risk
  - Diagnostic test: MammaPrint mRNA 70 gene expression array (FFPE)
  - STD: clinical decision
    - High clinical risk (low genomic risk): Chemotherapy
    - Low clinical risk (high genomic risk): no chemotherapy
  - EXP: genomic tool
    - High genomic risk (low clinical risk): Chemotherapy
    - Low genomic risk (high clinical risk): no chemotherapy

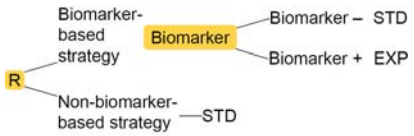


Bogaerts et al. 2006 Nat Clin Pract Oncol 3:540-51 • Cardoso et al. 2007 Mol Oncol 1:246-51
Rutgers et al. 2011 Eur J Oncol 47:2742-9

Study Designs for Predictive Biomarkers
Biomarker-Guided Design

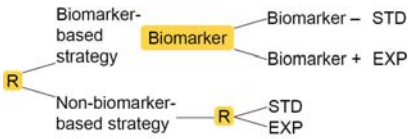
- Biomarker with standard control
  - Does not show predictiveness of biomarker
  - Shows superiority of strategy
  - Used in special applications only
  - Low power if prevalence of biomarker low
- Example
  - ERCC1 trial
  - Advanced NSCLC patients
  - ERCC1 mRNA expression
  - Control group: docetaxel plus cisplatin
  - Biomarker group
    - Low ERCC1 levels: docetaxel plus cisplatin
    - High ERCC1 levels: docetaxel plus gemcitabine

Biomarker-strategy design with standard control

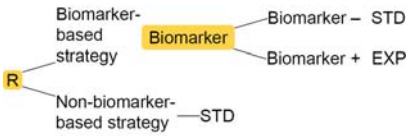


Study Designs for Predictive Biomarkers
Biomarker-Guided Design

Biomarker-strategy design with randomized control

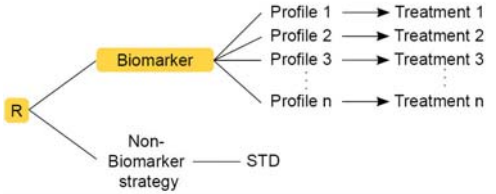


Biomarker-strategy design with standard control

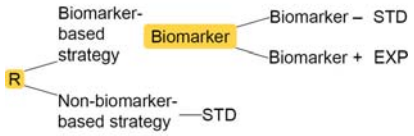


Study Designs for Predictive Biomarkers
Biomarker-Guided Design

Individual profile design



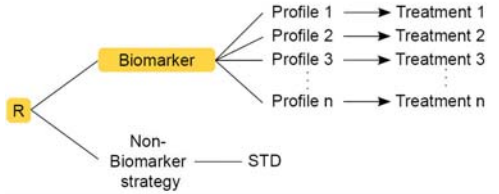
Biomarker-strategy design with standard control



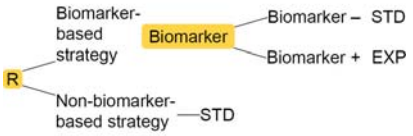
- Identical in interpretation
- Subgroup analysis problematic

Study Designs for Predictive Biomarkers
Biomarker-Guided Design

Individual profile design

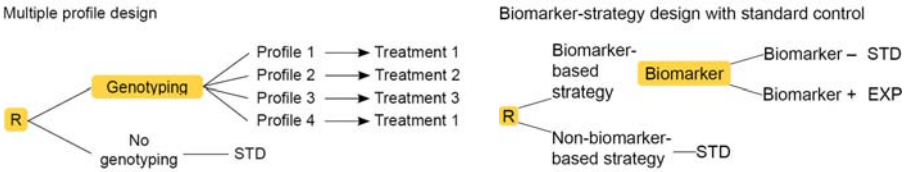


Biomarker-strategy design with standard control



- Example
  - Inflammatory diseases (Crohn, psoriasis, rheumatoid arthritis)
  - ① anti TNFα, ② anti IL-6, ③ anti IL-1ß, ④ anti IL-17, ⑤ anti IL-12/23 p40, ⑥ anti IL-23, ⑦ anti a4b7-integrin, ⑧ JAK3/1 Anti-IgE

Study Designs for Predictive Biomarkers
Biomarker-Guided Design



- Applied for funding
  - Psoriasis with indication for biological
  - STD: anti-TNFα
  - EXP: Three biologicals

Study Designs for Predictive Biomarkers
Biomarker-Guided Design

- Different biomarker-guided designs

G1	G2	G3	Add-on	Conditional
+	+	+	T1 + T2 + T3	T1
+	+	–	T1 + T2	T1
+	–	+	T1 + + T3	T1
+	–	–	T1	T1
–	+	+	T2 + T3	T2
–	+	–	T2	T2
–	–	+	T3	T3
–	–	–	None	T1

Study Designs for Predictive Biomarkers
Biomarker-Guided Design

- Different biomarker-guided designs

G1	G2	G3	Add-on	Conditional
+	+	+	T1 + T2 + T3	T1
+	+	–	T1 + T2	T1
+	–	+	T1 + + T3	T1
+	–	–	T1	T2
–	+	+	T2 + T3	T2
–	+	–	T2	T2
–	–	+	T3	T3
–	–	–	None	T1

Quantitative biomarker: maximum design

Discussion

- Novel efficient clinical trial designs required
- Practicalities of biomarker measurement important
  - Time point
  - Missing measurements
  - Coefficient of variation
- When is clinical utility of biomarker proven? …
  - Biomarker+ superiority
  - Biomarker- inferiority or equivalence or …
  - Subgroup analysis