European Statistical Meeting

Recent Developments in Biomarkers and Subgroups in Drug Development

Wednesday March 20, 2019, Gothenburg, Sweden

Biomarkers continue to be present in modern drug development. Ideally, they may help scientists to understand why a patient responds in a particular way to treatment. When biomarkers are used to identify sub-groups of patients who are likely to benefit from new therapies, a whole host of challenges arises, and many of them are of a statistical nature:

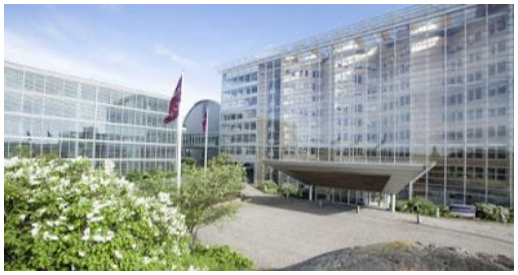
- What do regulators expect to see to support a biomarker-based indication?
- What statistical methods are there to identify biomarkers and subgroups? Some have recently been developed. -
- What are the most recent insights on how to design a study that aims to identify a sub-group of patients with enhanced treatment effect, and what needs to be done to confirm this effect?

In this meeting, experts from industry, academia and regulatory agencies will come together to share recent insights and discuss these challenges, with a focus on practical applications.

9:30 – 10:00	**Registration and Coffee**
10:00 – 10:10	**Welcome**
10:10 – 10:45	**Armin Koch** (Med. Hochschule Hannover) *Setting the Scene*
10:45 – 11:15	**Julien Tanniou** (University Hospital Brest) *Promising subgroup findings*
11:15 – 11:45	**Coffee**
11:45 – 12:15	**Gerd Rosenkranz (**Med. University Vienna) *Precision of the predicted individual treatment effect*
12:15 – 13:15	**Lunch**
13:15 – 13:45	**Mattias Rantalainen (**Karolinska Institutet) *Biomarkers and disease subtyping from an epidemiological perspective*
13:45 – 14:15	**Ziad Taib & Alexandra Jauhiainen** (AZ) *Biomarkers as tools for decision making in early development*
14:15 – 14:45	**David Svensson** (AZ) *Overview of some recent methodologies for Biomarker Subgroup Identification*
14:45 – 15:15	**Coffee**
15:15 – 16:00	**Panel discussion and closure**

Venue

PGN Conference Centre
AstraZeneca
Pepparedsleden 1
431 83 Mölndal,
Sweden



Registration Costs

Fee includes lunch & refreshments

On or before 28th February
Industry rate: €170.00
Academic rate: €110.00

After 28th February
Industry rate: €200.00
Academic rate: €130.00

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Armin Koch - Med. Hochschule Hannover

Setting the Scene

Traditionally phase III clinical trials are planned for a broad and unrestricted patient population under the assumption of a consistent treatment effect that applies to the whole target population. Obviously, this is an assumption which needs to be checked after the trial has been completed, even though it is plausible after careful discussion of appropriate criteria for inclusion and exclusion and of the setting in which the trial is supposed to be conducted. Assessment of subgroups of phase III clinical trials is an important part of risk-benefit assessment and reflects the way how physicians decide, who should be treated with the medication under investigation.

The tension that repeated tests of the same data may lead to findings that pretend to be interesting, but are just a chance finding, will always remain. In line with this subgroup analyses that seem to identify patients with no benefit from being treated may lead to thrilling discussions and often a smaller than average treatment effect in a well-defined subgroup may raise questions about whether the risk-benefit for patients in the subgroup is still positive. Because of their mandate, regulators are more willing to assume that subgroup findings in a properly conducted trial have value and will undertake efforts to better understand this signal. As an introduction to the discussion, positions and proposals of the guideline are briefly summarized and the specific problems of biomarker based subgroup definitions are explained. Examples are presented, where subgroup findings have been plausible, credible and have substantially improved our understanding of who should be treated and who should not be treated.

Julien Tanniou - University Hospital Brest

Promising subgroup findings

In case no statistically significant overall treatment effect is found in a clinical trial, this does not necessarily indicate that no patients will benefit from treatment. Subgroup analyses could be conducted to investigate whether a treatment might still be beneficial for particular subgroups of patients. However, claiming efficacy of a drug based on an apparent positive subgroup finding in an overall non-significant trial and without replication is usually considered as a no-go decision by regulatory authorities. Nevertheless, assessment of the level of evidence associated with such subgroup findings is primordial as it may form the basis for performing a new clinical trial or, in exceptional circumstances, drawing the conclusion that a specific patient group could benefit from a new therapy. This work is mainly about how to deal with observed data post-hoc, with a focus on the case when a covariate of interest is represented by ordered subgroups, e.g. biomarkers, as this "trend" may reflect an underlying mechanism. Based on simulation studies, the paper assesses the credibility of such "trend" findings in overall non-significant trials and provides practical recommendations for evaluating the strength of evidence of subgroup findings in these setting.

Gerd K. Rosenkranz Statistical Consultant / Medical University of Vienna

Precision of the predicted individual treatment effect

The predicted individual treatment effect (PITE) quantifies the potential benefit of a test treatment over a control in a patient with a specific set of biomarkers. Formally, the PITE is defined by

$$PITE(X) = E[Y(X,T=1) - Y(X,T=0)].$$

Here Y is an outcome of interest, X the vector of biomarkers at baseline and T=0, 1 refers to control and test treatment, respectively.

Patients with a PITE exceeding a given threshold form a subgroup that benefits most from test treatment while the complementary subgroup has little benefit or may be even harmed by test. In a way, the PITE can support a physician in selecting the optimal treatment out of two treatment options based on the patient's biomarker status.

Since in reality a patient may only receive test or control but not both, an estimation of the prediction error is not possible (apart from an upper bound) without some restrictions on the predictor. We present an estimator of the prediction error of the PITE for continuous outcomes and for a predictor φ of Y which is linear in treatment and a function of the biomarkers, namely,

$$\varphi(X,T) = \beta' W(X) + T\, \gamma' W(X)$$

for parameters β and γ. This predictor is still more general then one which is linear in the covariates. The prediction error can also help in selecting important biomarkers. The results are illustrated with an Alzheimer dataset.

Mattias Rantalainen - Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Biomarkers and disease subtyping from an epidemiological perspective

Many diseases are heterogeneous in respect to clinical manifestation, molecular mechanisms and outcomes. Precision medicine aims to take individual phenotypic variability into account in clinical decision-making, including the choice of treatment strategy. Molecular phenotyping and subtyping are core components of precision medicine. However, the process of identifying and validating biomarkers and disease subtypes remains challenging in practice, and there are many factors that can influence the validity and robustness of subtypes, including the choice of study design, statistical methodology and validation strategy.

I will provide an overview of some strategies and statistical methodologies commonly applied for biomarker discovery and subtyping in high-dimensional molecular profiling data generated from DNA- and RNA-sequencing, or other –omics platforms. I will also introduce how epidemiological approaches can be utilised in the context of biomarker discovery and validation. Finally, I will highlight some common challenges encountered in biomarker and subtype discovery, using examples from cancer precision medicine.

Ziad Taib & Alexandra Jauhiainen - AstraZeneca

Biomarkers as tools for decision making in early development

Over the last decades, substantial investments were made in identifying biomarkers that are associated to various disease states, with the hope that such biomarkers will be useful in decision making in early clinical drug development (Phase I and II). We illustrate, from a statistician's perspective, how and when biomarkers associated with Chronic Obstructive Pulmonary Disease (COPD) can be useful in in early clinical drug development. Accordingly, we consider uses of biomarkers to target patients in early- versus advanced stage of the disease, Go/No-Go decisions, establishing proof of mechanism in Phase I trials and how surrogate biomarkers can be used as short term endpoints leading to shorter and more efficient proof-of-principle and dose-finding trials.

David Svensson - AstraZeneca

Overview of some recent methodologies for Biomarker Subgroup Identification

A number of statistical methods for personalized/precision medicine emerged in recent literature borrowing from such diverse fields as machine learning, causal inference and multiple comparisons. Two large groups of methods can be distinguished: one looking into identifying subgroups of patients with enhanced treatment effect and the other optimizing treatment assignments rules for a given patients population. In this presentation, we focus on methods of the former type and consider their key features as well as relative strengths and weaknesses. One of important and often neglected challenge is accounting properly for prognostic effects when identifying predictive biomarkers and associated cut-offs.