COPD Biomarkers as tools for decision making in early clinical development

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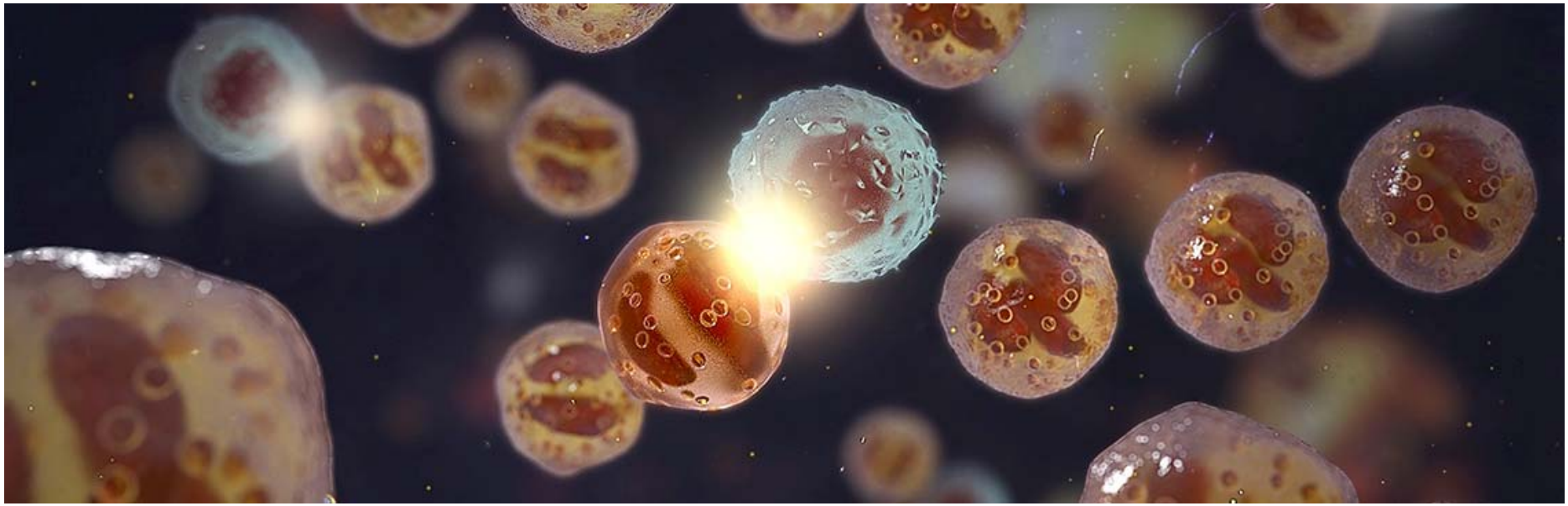


Plan

- COPD Biomarkers
- Examples:

  A. Prognostic: Biomarkers for disease progression
  B. Pharmacodynamic: LPS challenge
  C. Predictive: Eosinophil count
  D. Surrogate: CompEx: Proxy for exacerbation

- Final comments

Chronic Obstructive Pulmonary Disease (COPD)

- COPD, is defined as:

  "a common, preventable and treatable disease (...) characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung".

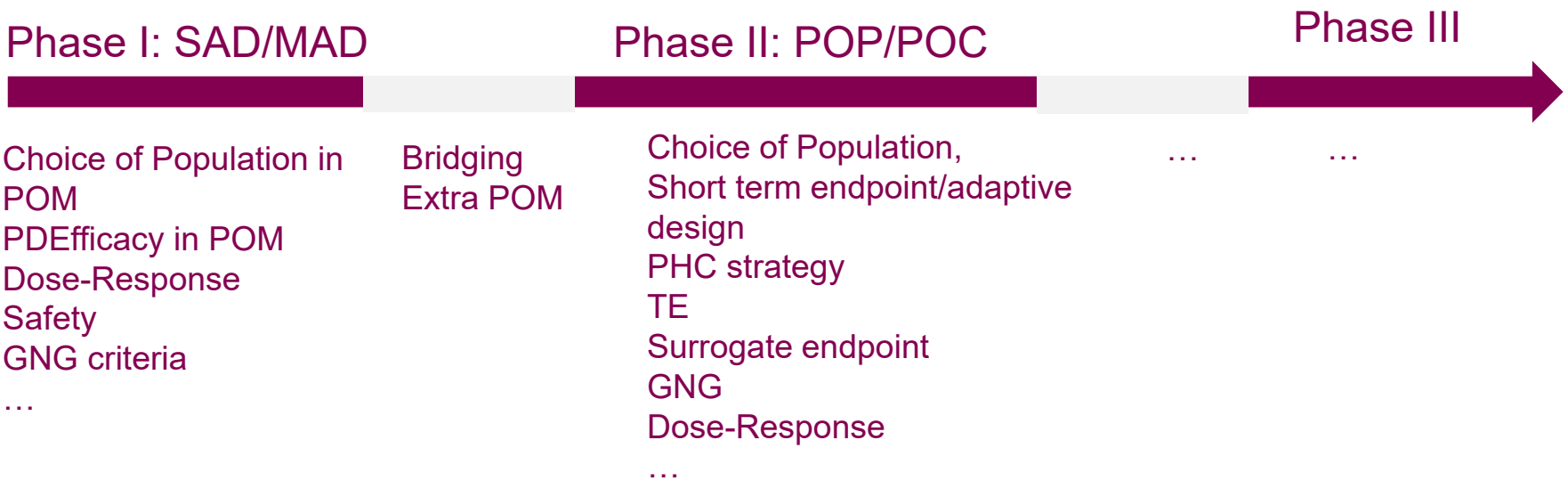
- **Disease progression** is described using Gold stages 0, 1, 2, 3. (at risk, mild, moderate and severe). Usually treatments concern stages 2-3.

- **Endpoints:** Spirometry (FEV1) - Exacerbations – Imaging, QoL. In general, Low correlation between these.

- **Exacerbations** are acute deteriorations triggered by e.g. bacterial and viral pathogens. They accelerate disease progression and have major implications on quality of life, morbidity and mortality. Exacerbations are rare occurrences so trials need to be long and/or large.

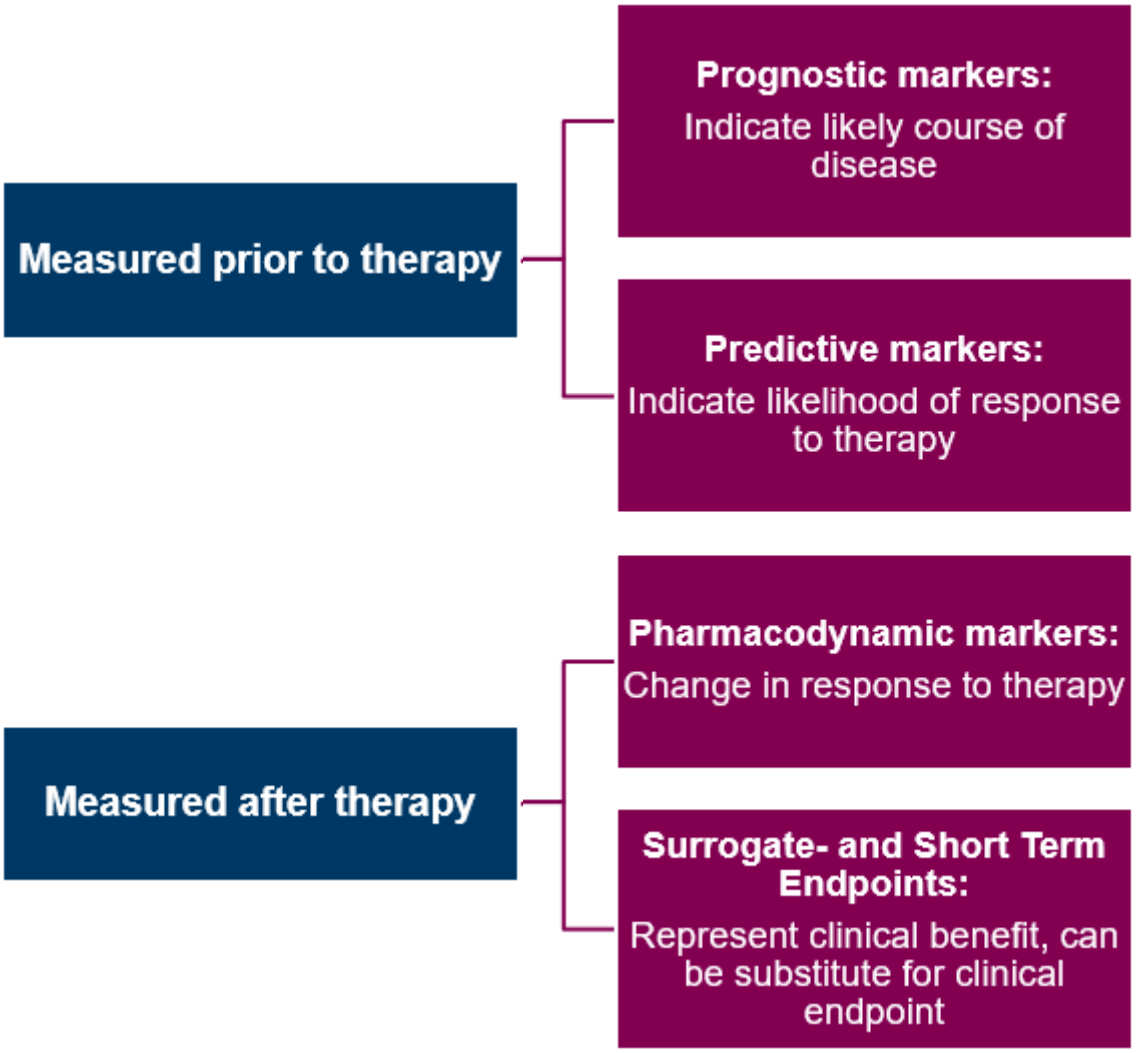
- Unlike Asthma, no advanced therapy exists for COPD and it is believed that **Biomarkers** may allow for better understanding of the disease and the development of new therapies.

Biomarkers as Tools for Decision Making in Early Clinical Development



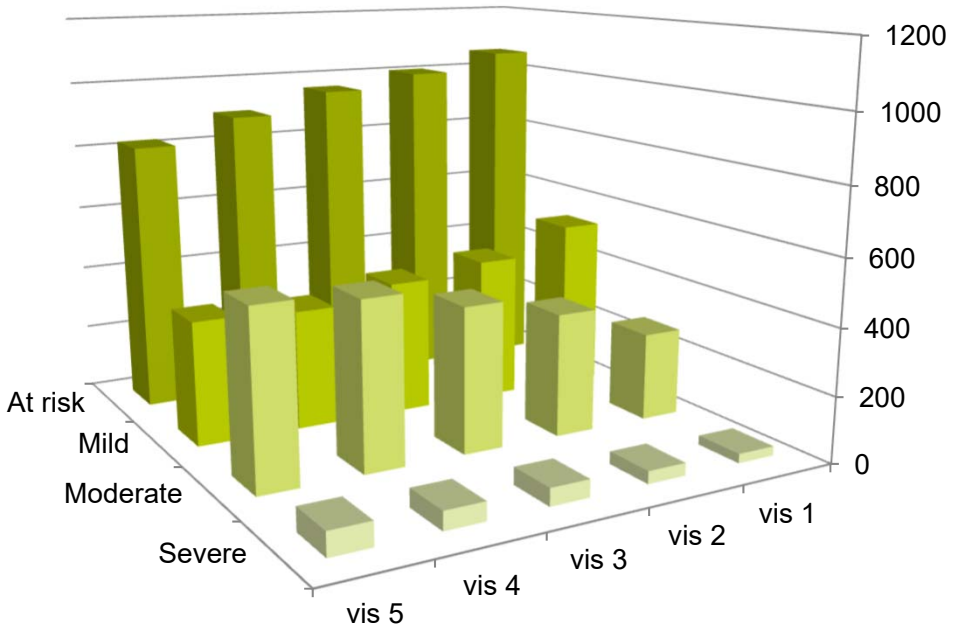
- Biomarkers are used to inform various types of decisions in early clinical development.
- We will present four such examples.

Types of biomarkers

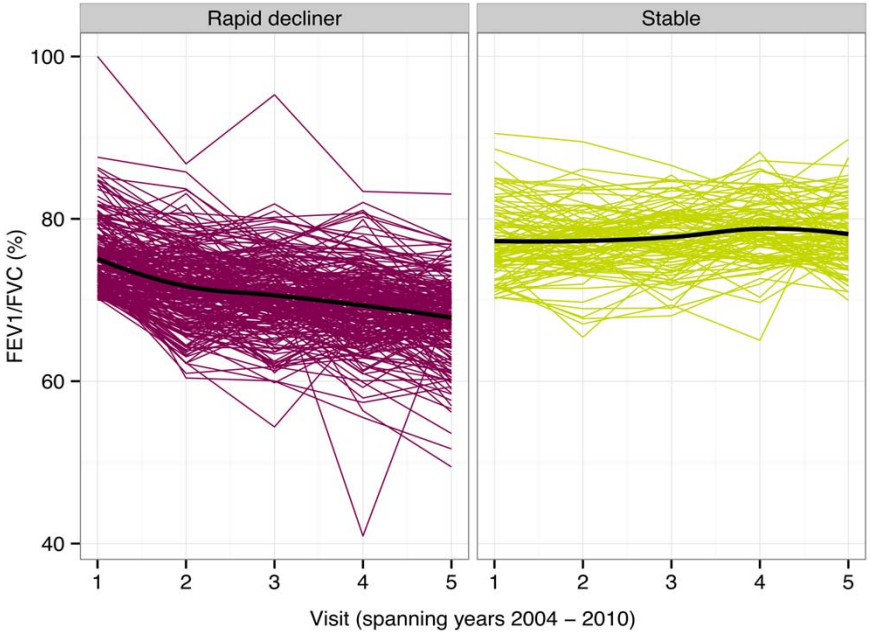


A: Prognostic biomarkers for lung function decline

Disease stages: Lugn function decline



Biomarkers may allow for better understanding of the disease and the development of new therapies already at an early stage of the disease.



Disease stages are described using Gold stages 0, 1, 2, 3.

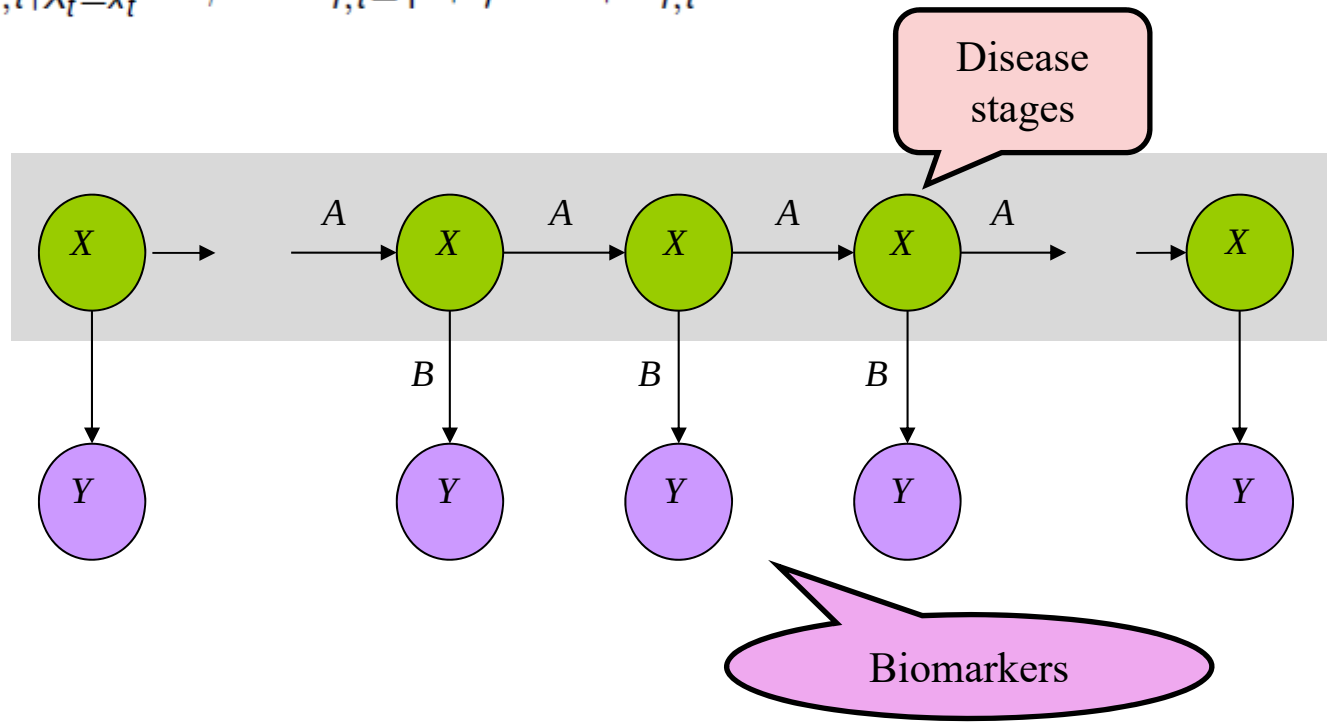
In a longitudinal study conducted in Denmark (CBQ*) with annual visits between 2005 and 2009, lung function decline was followed in a group of healthy smokers and ex-smokers with a history of more than 20 pack years. The overall rational for the study was to determine the risk of smokers to develop cardiovascular disease, lung cancer and/or COPD.

Multivariate (PLS-DA) analysis using the blood biomarker ratio ([ApoD/MMP9]/[E-selectin] identified rapid FEV1 decliners in the GOLD 0 smoker group with at least 80 % accuracy.

Biomarkers for disease progression: a HMM Bayesian approach

- HMM is a stochastic process $\{X_t, Y_t\}_{t=0}^{T}$,
- $\{X_t, Y_t\}_{t=0}^{T}$ is a hidden Markov chain (unobservable)
- $\{Y_t\}_{t=0}^{T}$ is a sequence of observable independent random variables such that Y_t depends only on X_t, $t = 0, 1, ..., T$.

- $Y_{i,t}|_{X_t=x_t} = \beta^{(x_t)} Y_{i,t-1} + \mu^{(x_t)} + \varepsilon_{i,t}$.



Bayesian estimation of Multivariate Autoregressive Hidden Markov Models. H. El Maroufy, H. Hibbah, A. Ziyad and Z. Taib. Bayesian Inference, 2018.

International Journal of COPD

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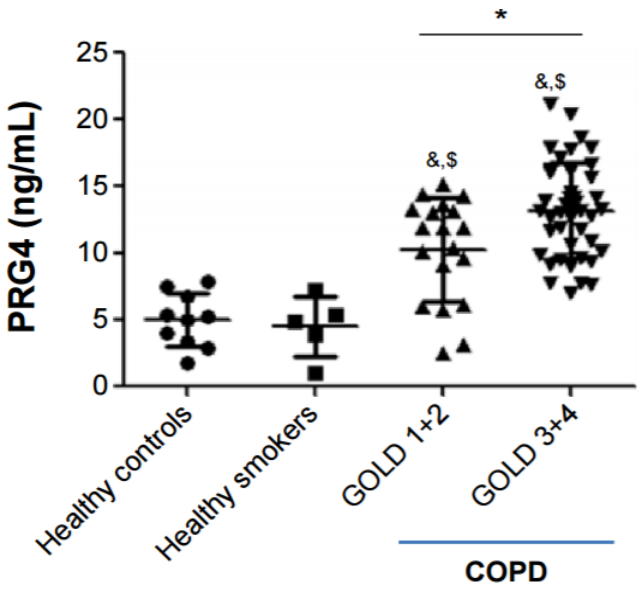
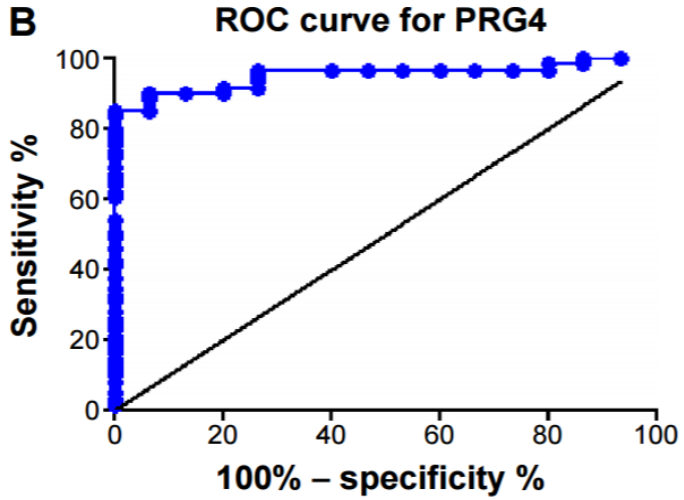
Proteoglycan 4 is a diagnostic biomarker for COPD

Kang-Yun Lee[1,2]
Hsiao-Chi Chuang[1,3]
Tzu-Tao Chen[1]
Wen-Te Liu[1,3]
Chien-Ling Su[1,3]
Po-Hao Feng[1,2]
Ling-Ling Chiang[1,3]
Mauo-Ying Bien[3,4]
Shu-Chuan Ho[3]





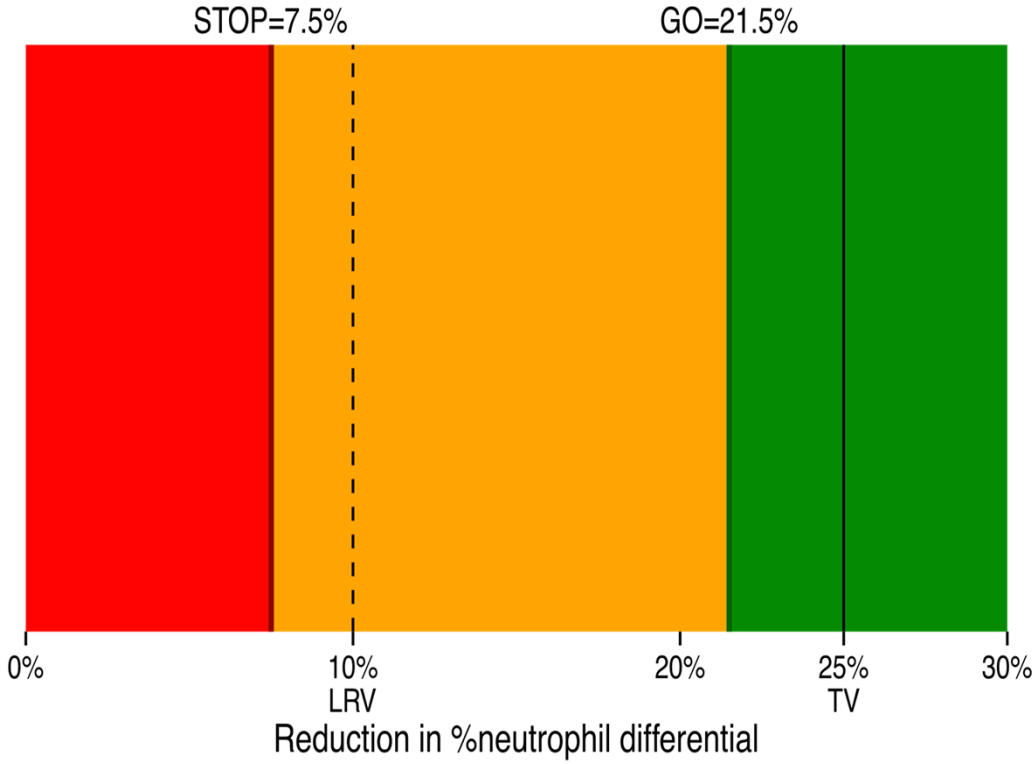
Serum PRG4 is an important biomarker for supporting the COPD diagnosis and relates to the decline in lung function in patients with COPD

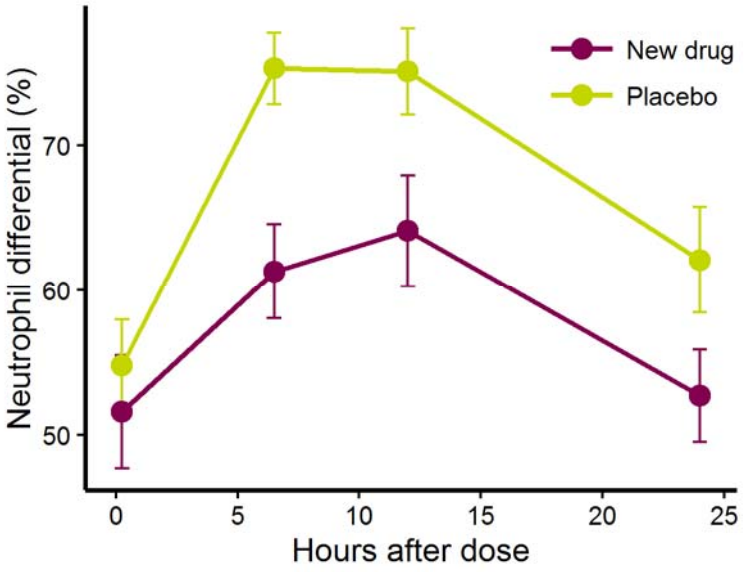
B: Pharmacodynamics markers in COPD

Illustration of Go/No Go in Phase POM Trial

- Can a new compound prevent acute exacerbations of COPD?
- The effect of a novel drug on lung inflammation is believed to correlate with effects on systemic biomarkers of inflammation. These markers are associated with risk of COPD exacerbations.
- LPS challenges have been proposed as models for testing the mechanism of action of drugs that aim to reduce the frequency of exacerbations in COPD.
- A Phase 1b proof of mechanism trial based on an LPS challenge, i.e. inhalation of an endotoxin lipopolysaccharide (LPS) that induces a neutrophilic airway inflammation.
- Data from a competitor suggested that their (similar) compound achieved 25% reduction in Neutrophil differential under similar conditions.
  - We use this effect (25% reduction) as our Target Value (TV).
  - We also fix the Lower Reference Value to LRV to 10% reduction (TPP).

Go/No Go criteria for neutrophil differential



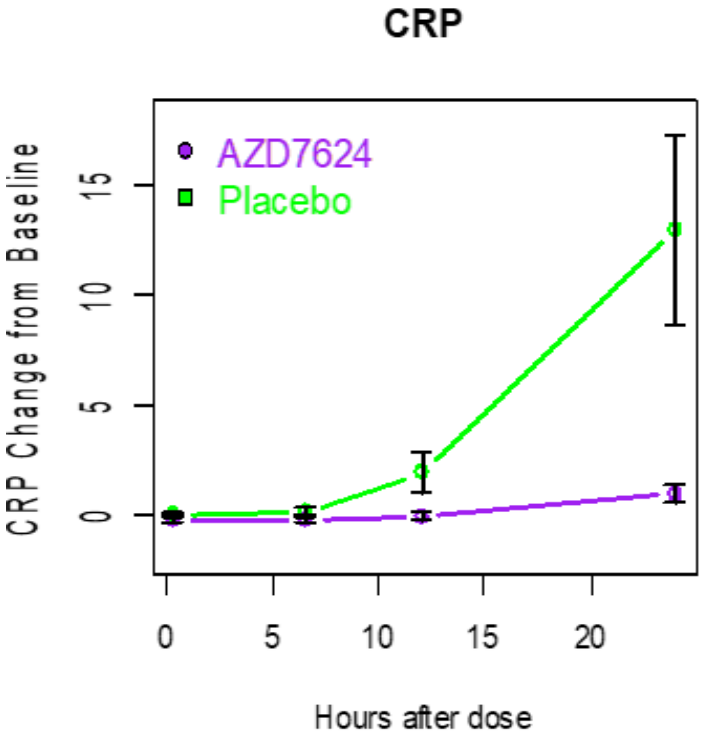


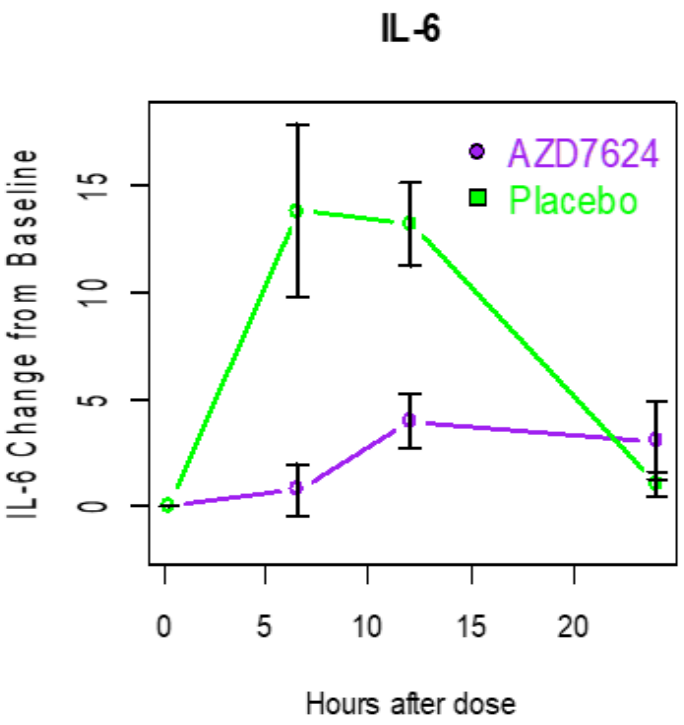
Reduction in Neutrophil differential after a challenge with LPS in healthy volunteers.

Δ = True effect
GO: >80% confidence that Δ >LRV
STOP: <10% confidence that Δ > TV
Think: either of the above (other biomarkers)

The observed level of reduction turned out to be 56% indicates a clear GO.

AZD7624, an inhaled p38 inhibitor for COPD, attenuates lung and systemic inflammation after LPS Challenge in humans
Naimish Patel, et al
European Respiratory Journal 2015 46: OA483; DOI: 10.1183/13993003.congress-2015.OA483





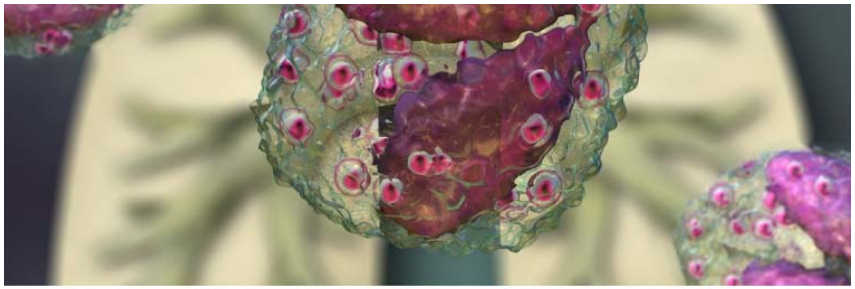
- What if we are in the ”Think” zone? Additional biomakers could be used.
- How extend to multivariate case? MCDA.
- Sample size can be chosen as to get good decision criteria rather than statistical power.

C: Predictive biomarkers in COPD

Blood eosinophils

- Eosinophils:
  - A type of white blood cell
  - In some COPD patients, eosinophils contribute to inflammation that promotes airway obstruction
  - easy and reproducible to measure

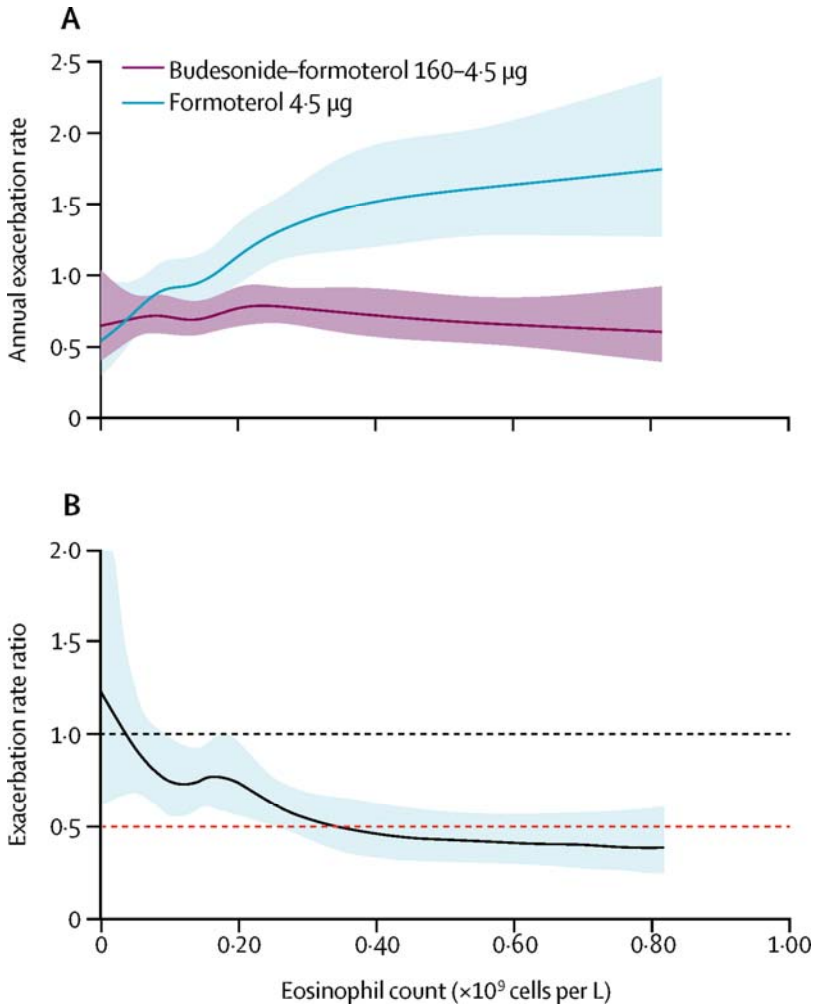
- The level of eosinophils in blood can be predictive of the response to treatment with inhaled corticosteroids (ICS) to prevent exacerbations



Are blood eosinophil counts helpful in predicting patient responses to **inhaled corticosteroids in COPD?**

Best Practice Journal – Issue 74

Blood eosinophils, example 1



Data from 3 AZ RCTs in patients with COPD with a history of exacerbations.

In patients treated with formoterol, blood eosinophil count predicts exacerbation risk and the clinical response to ICS.

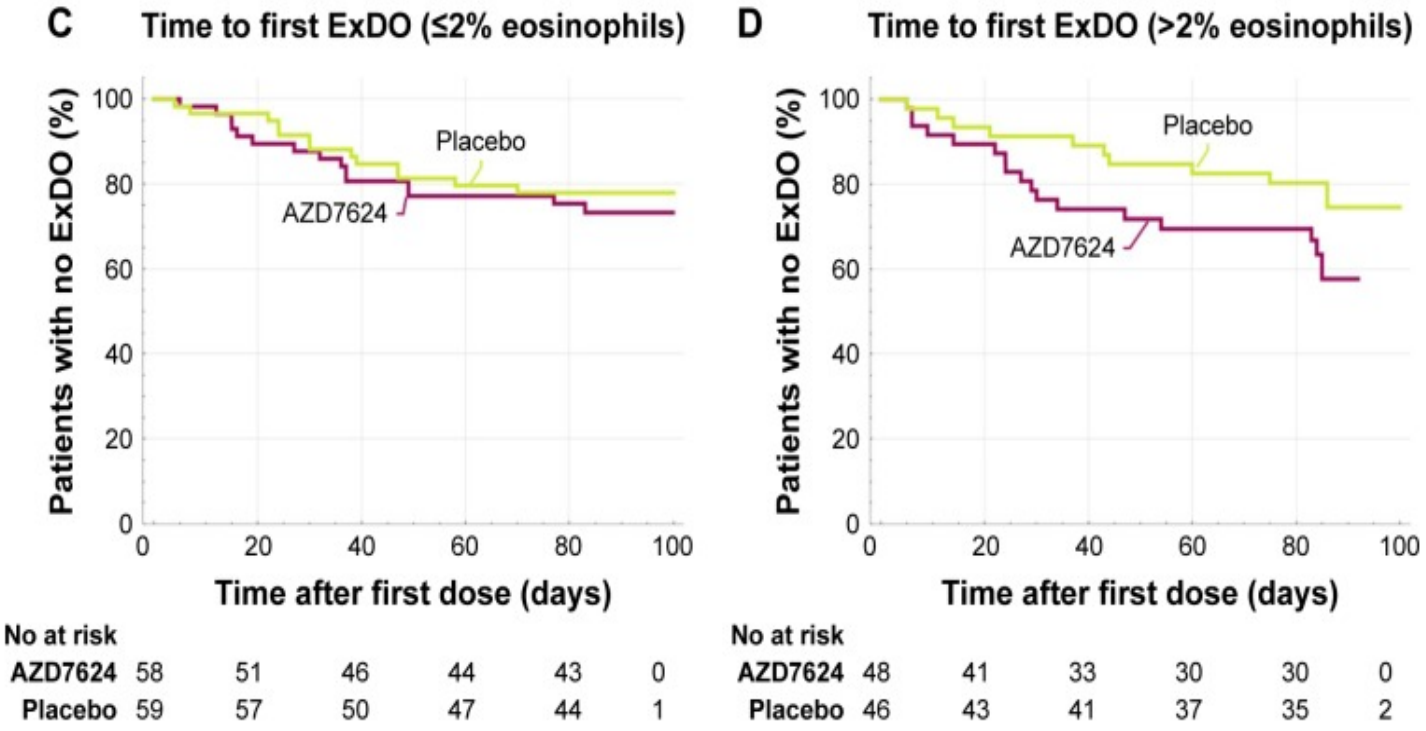
In 79% of the population studied, there is benefit of ICS+LABA to reduce the risk of future exacerbations.

Patients with low levels constitute a group with an unmet need for better treatment.

Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fagerås M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med. 2018 Feb;6(2):117-126.

Blood eosinophils, example 2

Proof of Principle study with AZD7624 in patients with COPD on at least ICS+LABA.

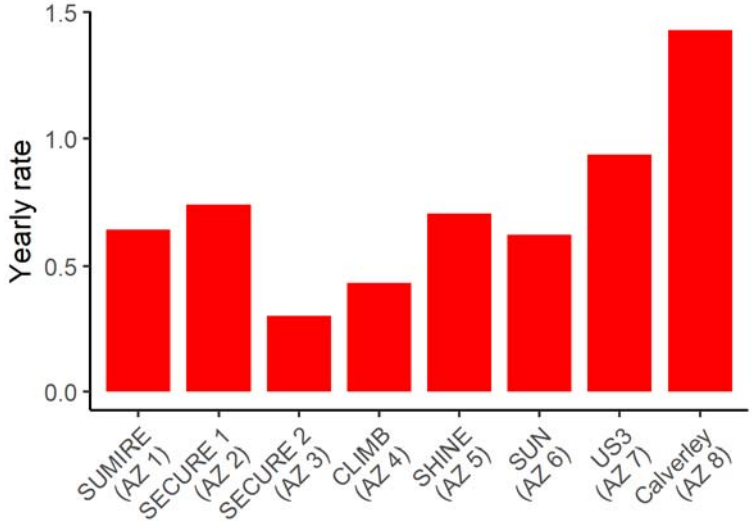


Patel NR, Cunoosamy DM, Fagerås M, Taib Z, Asimus S, Hegelund-Myrbäck T, Lundin S, Pardali K, Kurian N, Ersdal E, Kristensson C, Korsback K, Palmér R, Brown MN, Greenaway S, Siew L, Clarke GW, Rennard SI, Make BJ, Wise RA, Jansson P. The development of AZD7624 for prevention of exacerbations in COPD: a randomized controlled trial. Int J Chron Obstruct Pulmon Dis. 2018 Mar 27;13:1009-1019.

D: Surrogate Biomarkers for COPD

Symptom-based surrogate endpoints

- Clinical trials in COPD with moderate/severe exacerbations as the main endpoint
  - Large and lengthy
  - Troublesome in early clinical development
- Establish a composite endpoint, adding events defined by mixed diary variables
  - Capture clinically relevant disease deteriorations
  - Surrogate for exacerbations, predictive of effect in Ph3 trials



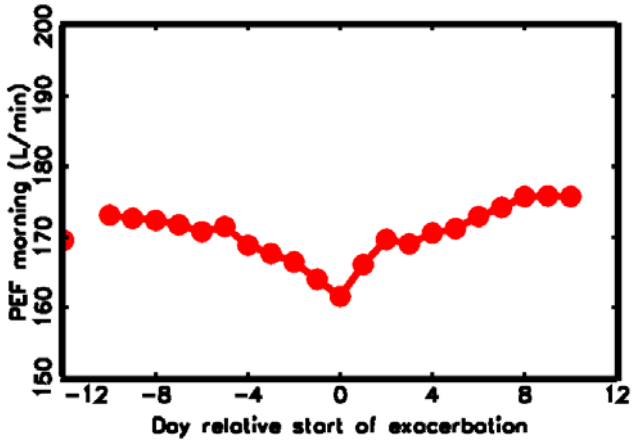
COPDCompEx: A Novel Composite Endpoint to Accelerate Early Clinical Development of New Agents for Treatment of COPD

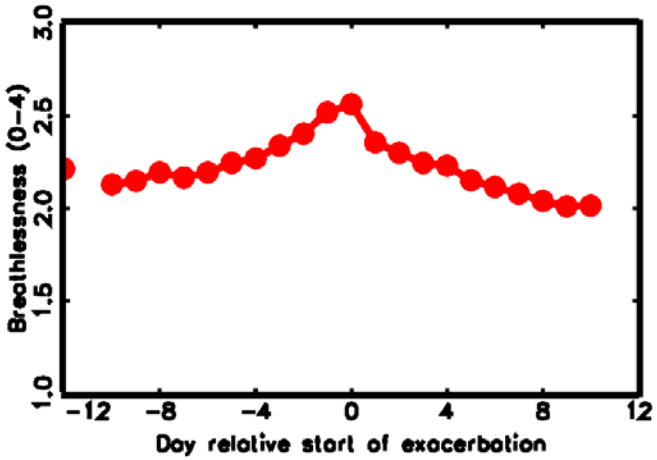
- The algorithm defining diary events using
  - morning PEF
  - evening PEF
  - total reliever medication use
  - COPD symptoms

  reflected the treatment effect on exacerbation with the best statistical power.

- A decreased sample size by at least 50% on average (range 35%-88%, except for one trial).

- Enables shorter (3m) and smaller trials.

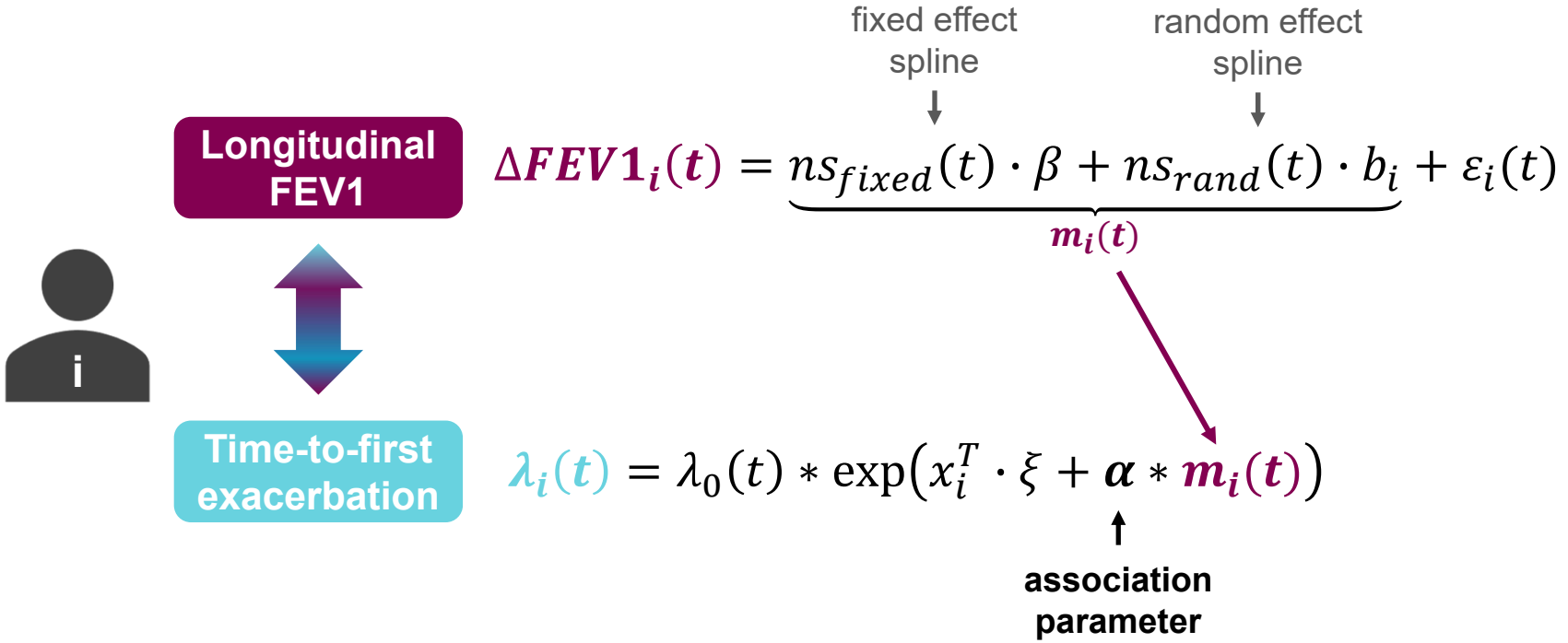




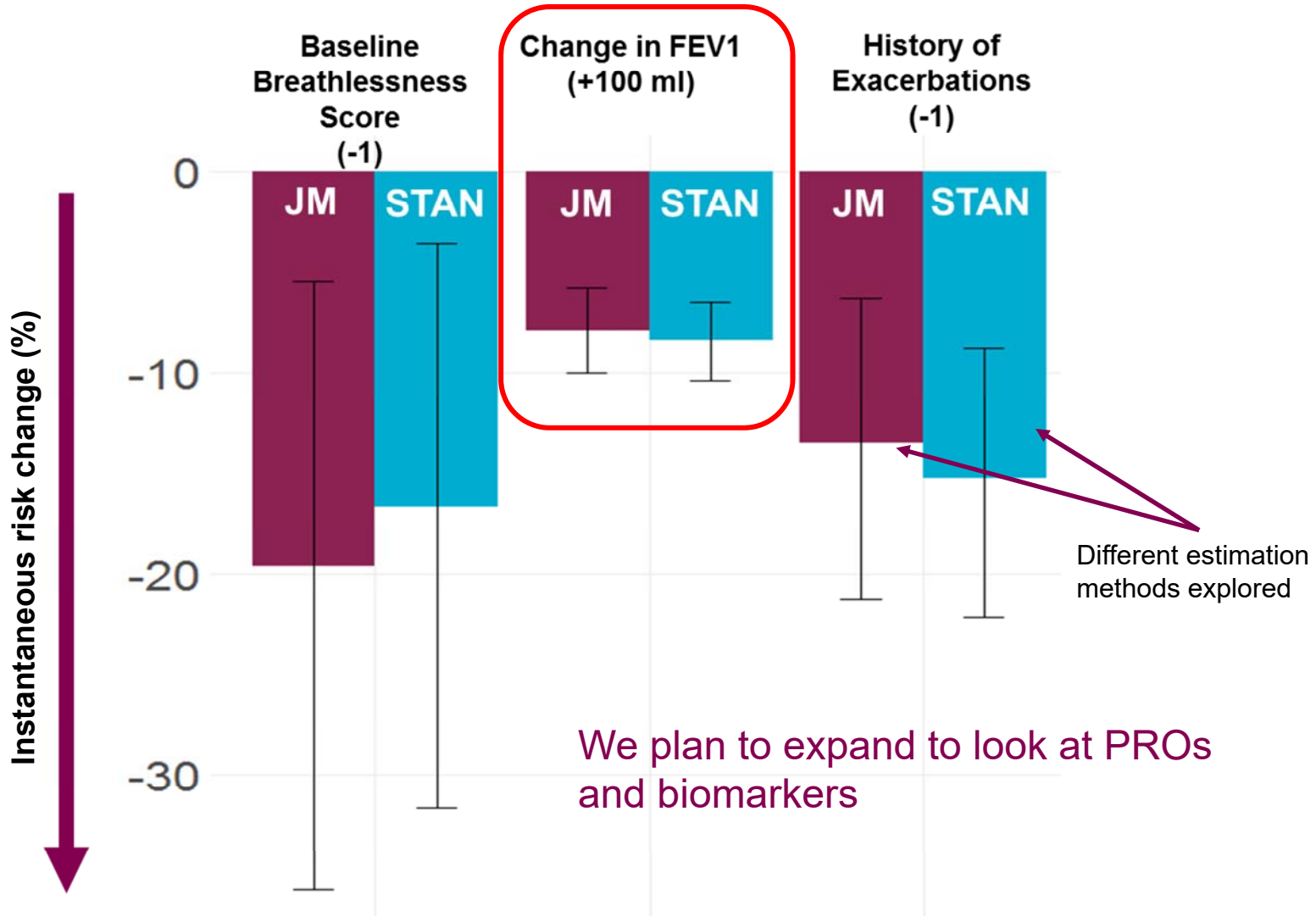
C.A. Da Silva, T. Bengtsson, S. Peterson, N. Karlsson, M. Fageras, and A. Jauhiainen
D101. MECHANISTIC AND TRANSLATIONAL STUDIES IN COPD. May 1, 2018, A7428-A7428

How can we make sure that an effect on early phase endpoints reflects a treatment effect in Phase 3?

- We have explored joint models of different endpoints in COPD
  - Joint modelling example: linking FEV1 and exacerbations



How can we make sure that an effect on early phase endpoints reflects a treatment effect in Phase 3?



Quantification of lung function and risk of COPD exacerbation association to predict long-term effects for new treatment arms using a drug-differentiated joint model. Kirill Zhudenkov, Oleg Stepanov, Ulf Eriksson, Robert Palmér, Alexandra Jauhiainen, Kirill Peskov, Gabriel Helmlinger, Ulrika Wählby Hamrén. Poster, ACoP conference 2018.

Final comments

We have seen examples demonstrating existing and potential use of Biomarkers and surrogate endpoints in early drug development possibly leading to

- New treatment paradigm: treating rapid decliner patients at an early stage.
- Better understanding of treatment effect in terms of disease progression.
- Better decision making in early clinical drug development by using proof of mechanism biomarkers to trigger further clinical activities.
- Tailor treatment to fit patient needs by e.g. taking eosinophil levels into account
- New surrogate endpoints could potentially lead to shorter, smaller and yet more conclusive clinical trials.
- Use of short term endpoints can be used to achieve adaptive designs

But more validation is needed and rigorous use of Statistical methods is necessary!