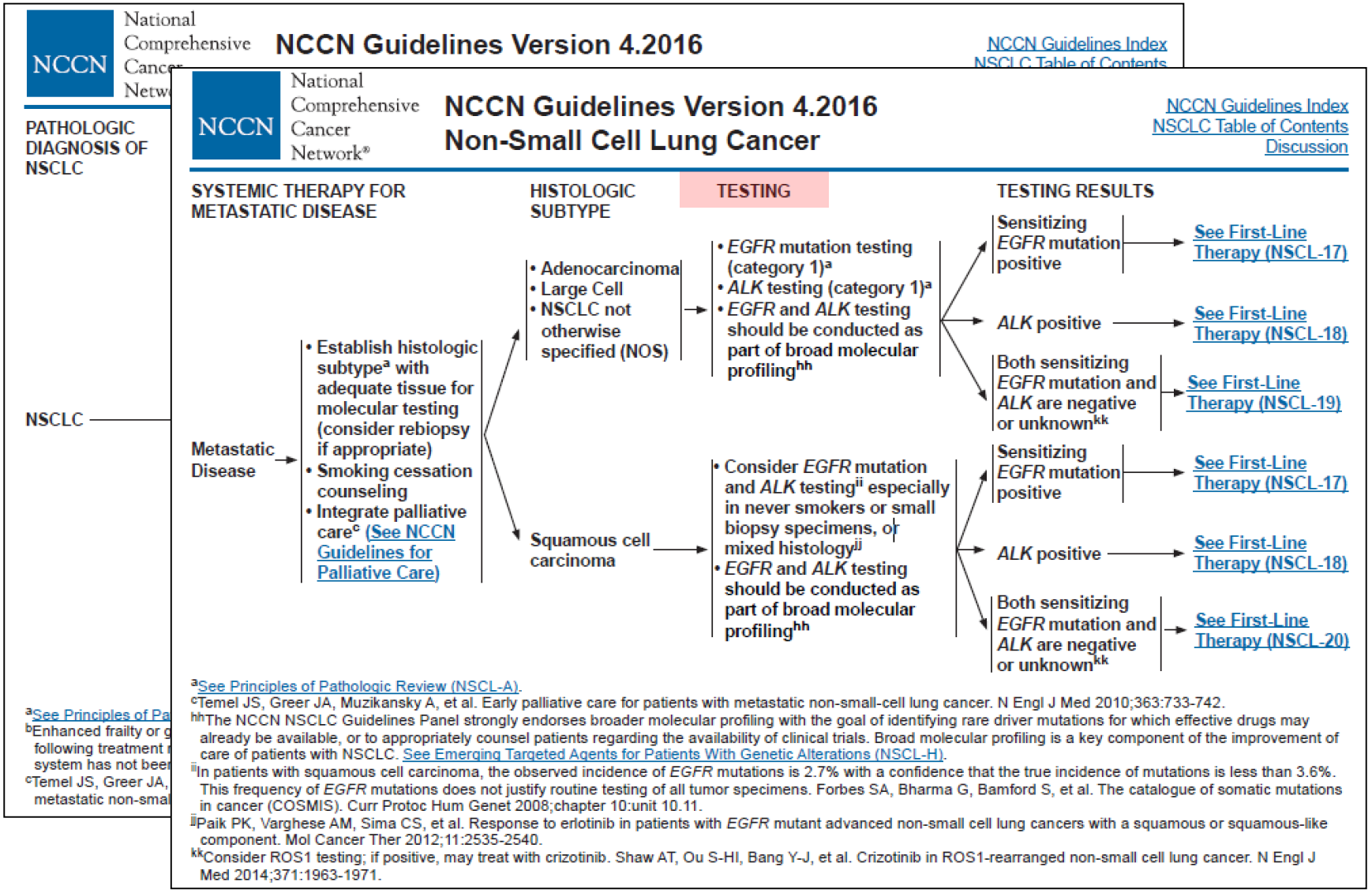
Biomarkers in COPD

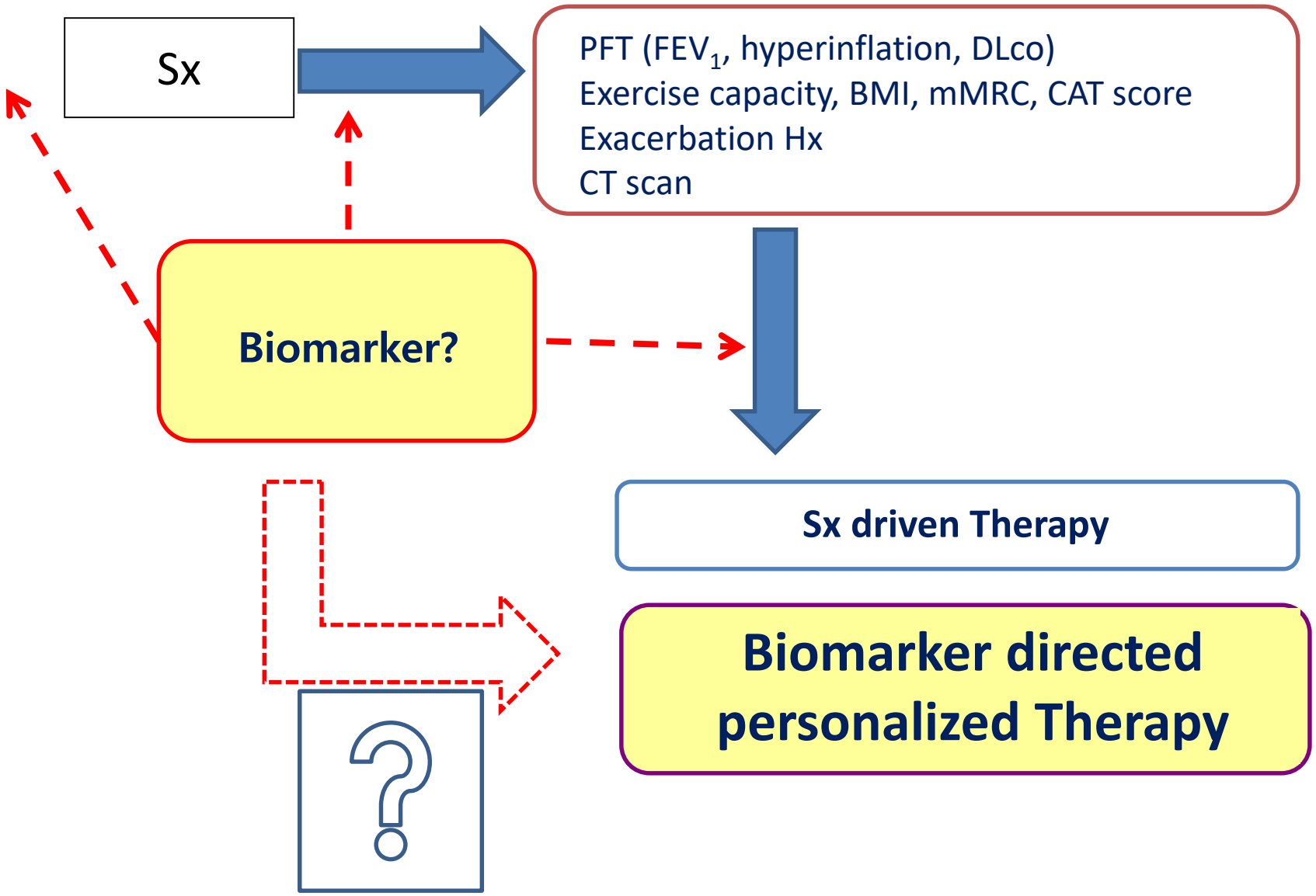
2016. 5.28

성균관의대 강북삼성병원 호흡기내과
임 성용

Algorithm for lung cancer today



Algorithm for COPD in the future?



Definitions

- **Disease Activity**
  - Level of activation of the **biological processes** that **drive disease progression**
- **Disease Severity**
  - Extent of functional impairment of the target organs
- **Disease Impact**
  - Effect on patient centered outcomes (PRO)
    - Symptoms
    - Physical activities of daily living
    - Exacerbations
    - Death

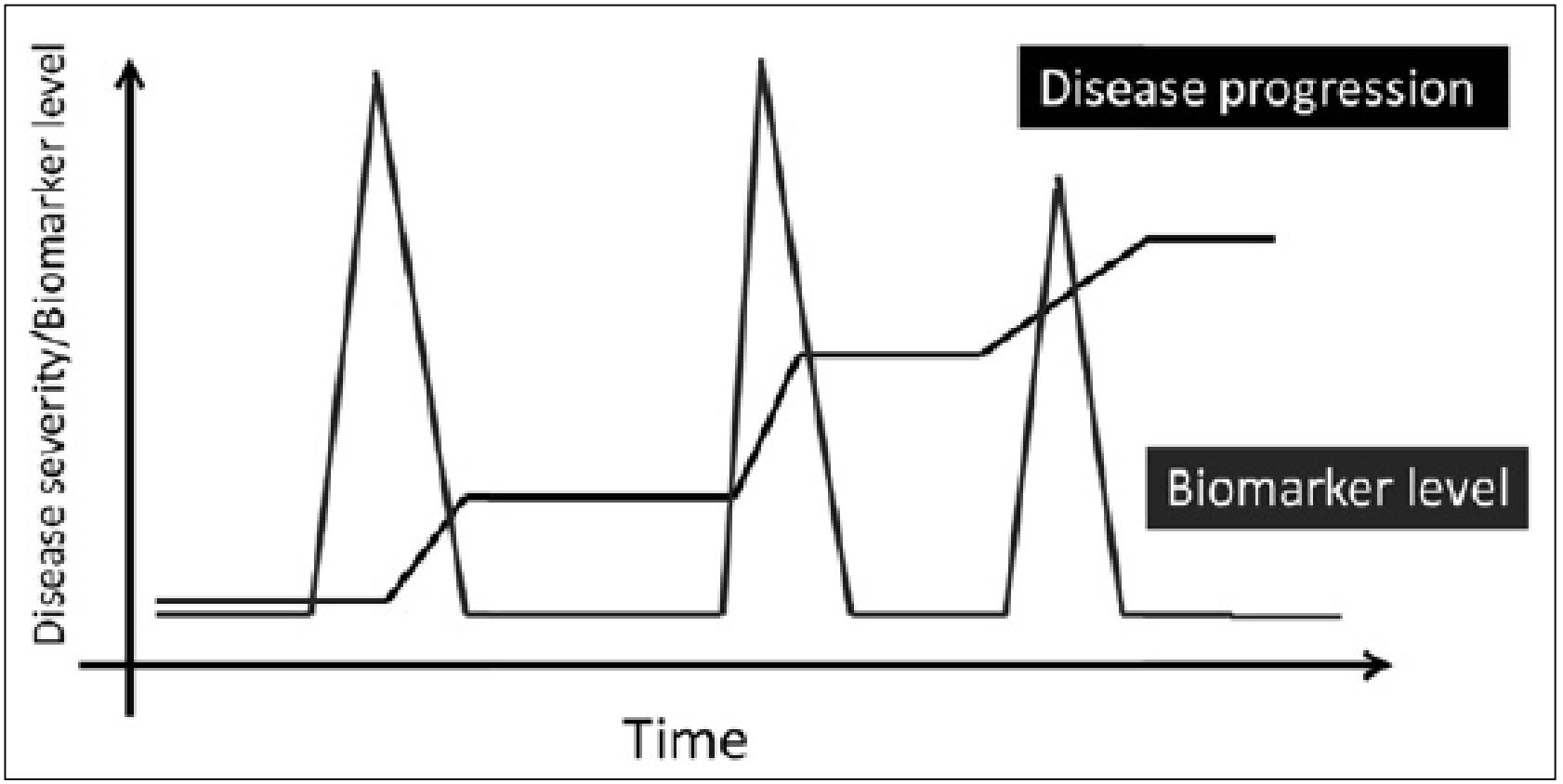
ATS/ERS document 2015

Disease activity: lack of validated activity markers

- Related to the balance between the pulmonary and systemic inflammatory responses to inhalational injury and the subsequent repair process
- **Potential markers of disease activity** include:
  - **Clinical markers**: worsening dyspnea and health status, loss of exercise capacity, cough and sputum production, active smoking, appearance or worsening of comorbidities, weight loss, and frequency of AECOPD
  - **Functional markers**: FEV_1 decline, DLCO deterioration, progressive hyperinflation
  - **Structural markers**: progression of emphysema, worsening of airway dimensions, appearance or worsening of bronchiectasis
  - **Biological markers**: lung, circulating blood, exhaled air, and/or urine

ATS/ERS document 2015

Biomarker of dis activity vs dis severity

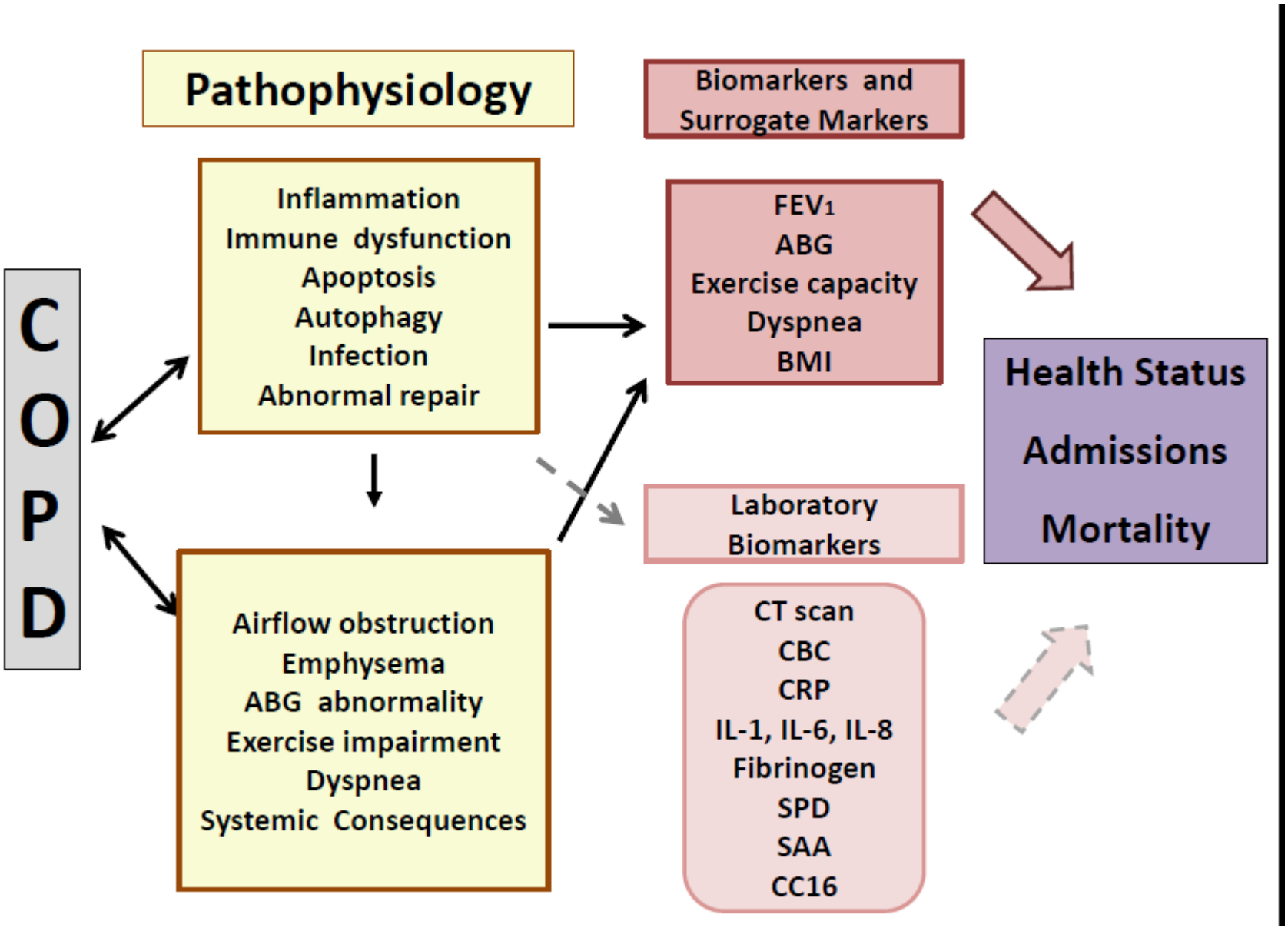


As a tool for **predicting progression, a biomarker of disease activity is more suitable** than a biomarker that solely reflects the current disease state

Disease activity: ATS/ERS recommendation

- To **validate the biomarkers as clinically useful measures of disease activity**, by relating potential biomarkers to patient-centered outcomes
- To evaluate the **impact of disease activity on treatment response** and, conversely, the **effects of treatment on disease activity**

ATS/ERS document 2015



Celli BR, 2014

Disease severity

- Extent of **functional impairment of the target organs**
- Disease severity markers:
  - FEV_1
  - Dyspnea
  - BMI
  - PaO_2

Composite Index	Components
BODE	BMI, FEV_1, mMRC, 6MWD
mBODE	BMI, FEV_1, mMRC, peak V_{O_2}
eBODE	BMI, FEV_1, mMRC, 6MWD, exacerbation rate
BODEx	BMI, FEV_1, mMRC, exacerbation rate
Inflammatory BODE	BODE, inflammatory biomarkers, age, and hospitalization history
ADO	Age, mMRC, FEV_1
DOSE	mMRC, FEV_1, smoking status, exacerbation rate
CODEx	Comorbidity, obstruction, dyspnea, and previous severe exacerbations

Disease severity: ATS/ERS recommendation

- To determine **which of them best stratifies patients** for the purposes of **determining disease severity** or for **recommending treatment**

- To study if short-term changes in these indices (or other measures like CT findings, biomarkers) are **useful surrogate markers of medium- or long-term patient-centered outcomes**, thus shortening the time needed to complete therapeutic trials

ATS/ERS document 2015

Biomarkers

- **"a measurement of any molecule or material (eg, cells, tissue) that reflects the disease process**
  - Excludes functional (or imaging) measurements from the more general concept of a marker

- **Role**
  - early detection
  - improving the diagnosis of acute or chronic syndromes
  - stratifying patients' risk
  - selecting the most appropriate therapy for a given patient
  - monitoring disease progression and response to therapy

Clin Chest Med 2014

Biomarkers: Requirements

(1) Relevance : related to a specific underlying disease mechanisms

(2) Sensitivity : able to detect clinically relevant differences

(3) Specificity: not influenced by confounding variables

(4) reliability : the capacity to perform consistently in different settings

(5) consistency: similar instruments produce similar results

(6) repeatability: it only changes when disease changes

(7) interpretability: translate into clinically interpretable results (QoL score)

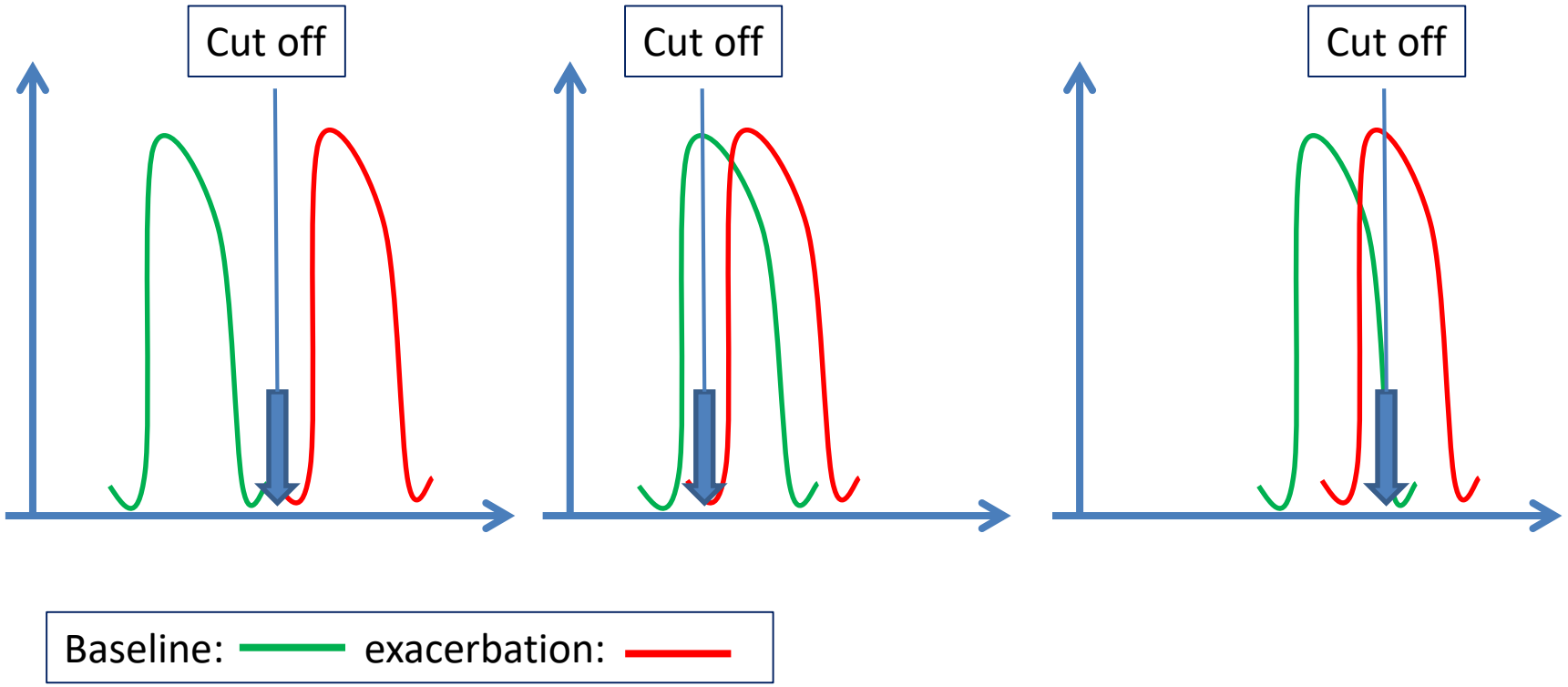
(8) simplicity: feasible in routine clinical practice

(9) cost-effective: its cost is lower that the savings it produces

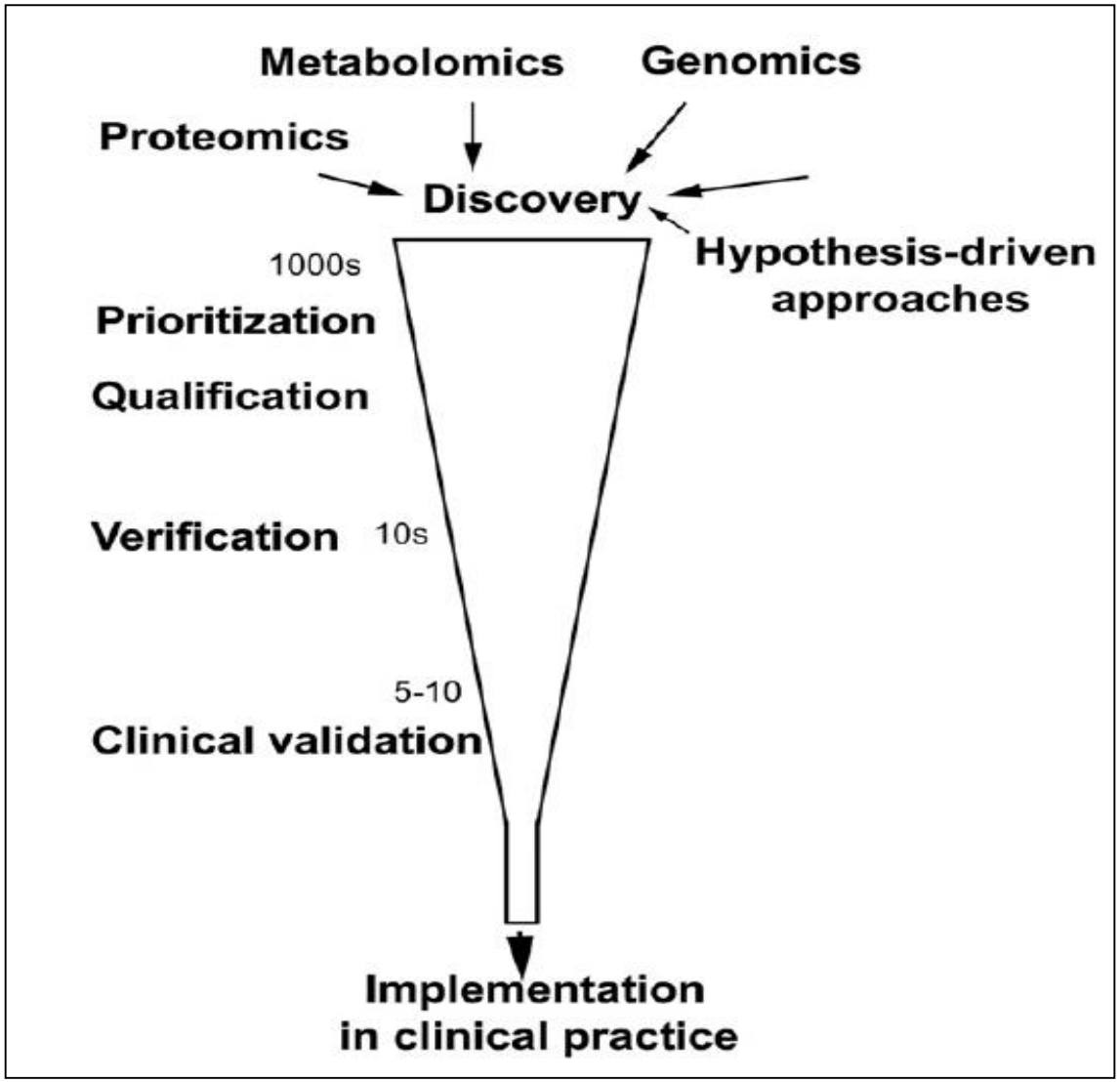
Clin Chest Med 2014

Good biomarker

- Easily obtained
- Easy and cheap to measure
- Reproducible and sensitive and/or specific

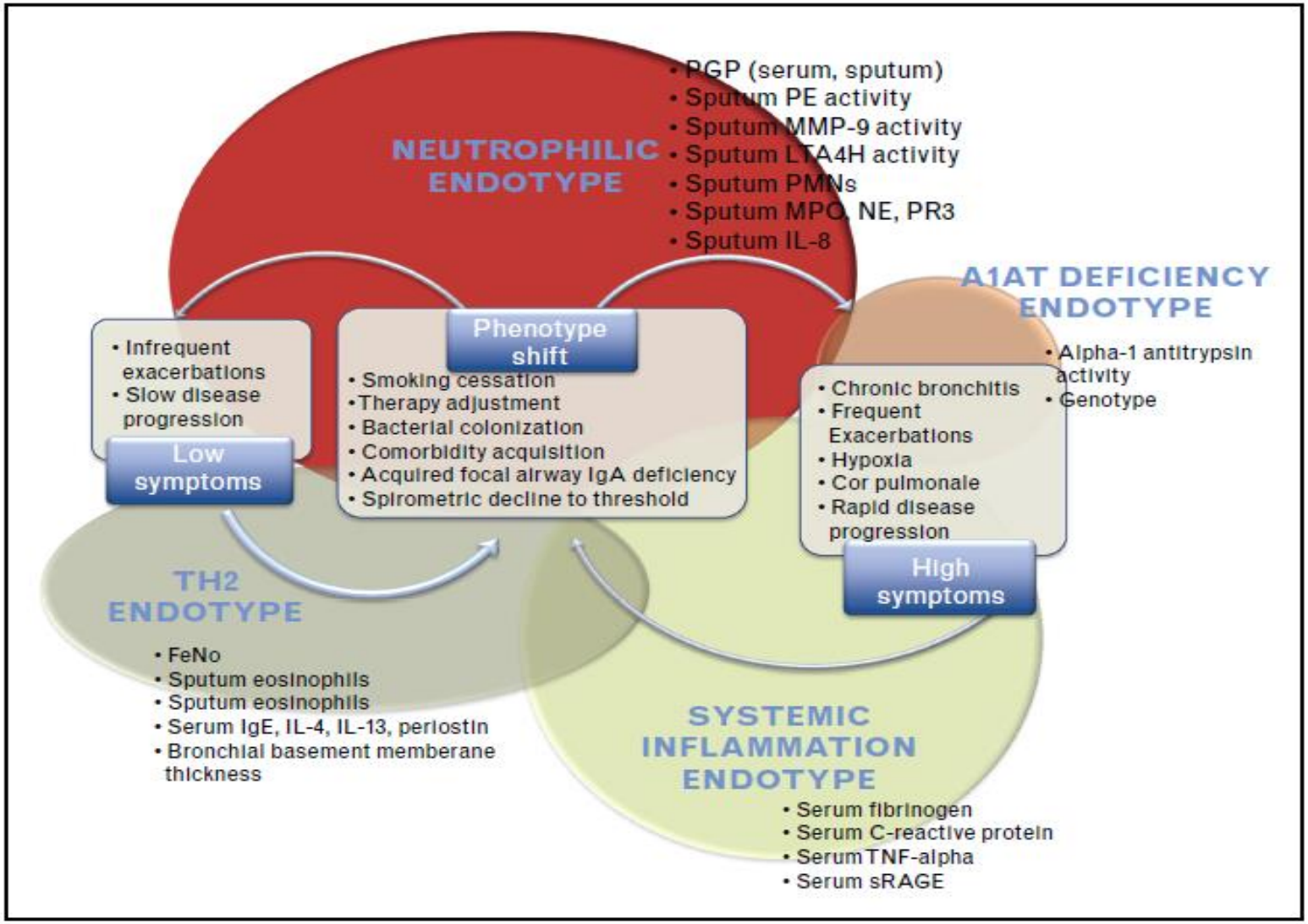


Biomarker development pipeline



FRANGOGIANNIS. Trans Res, 2012

Endotypes in COPD



Russell et al, COPM, 2016

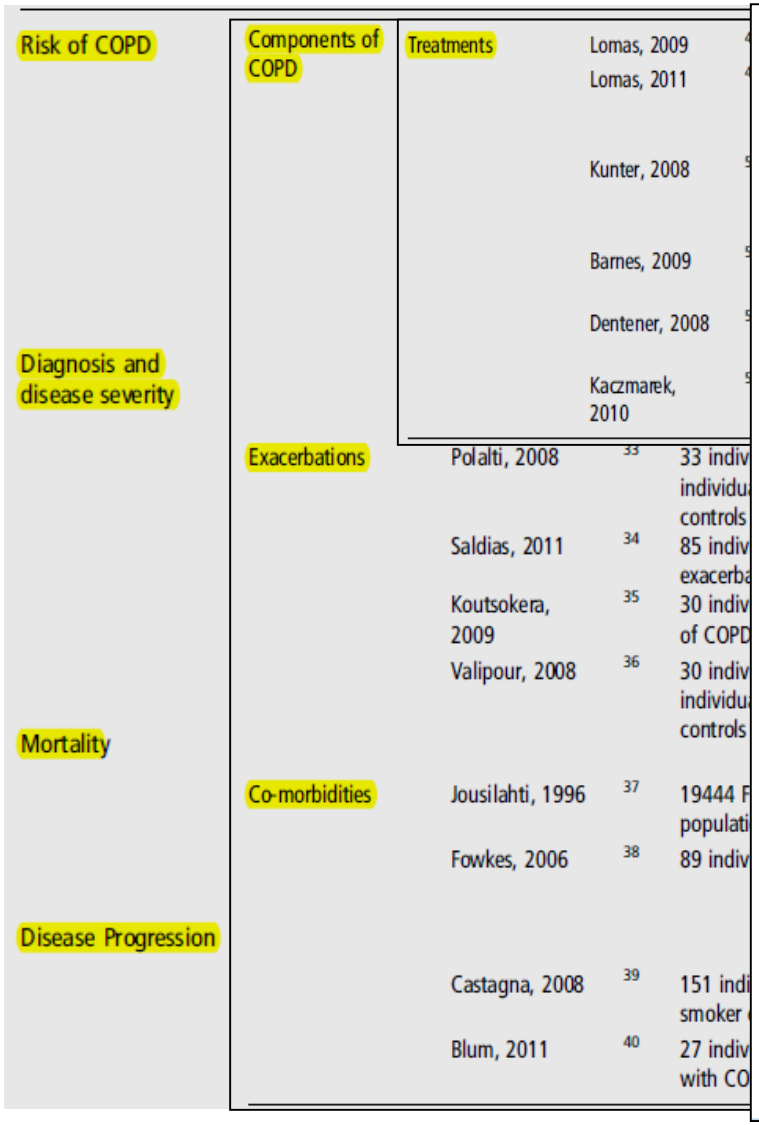
Lessons from ECLIPSE: a review of COPD biomarkers

Type of biomarker	Main findings
Cellular biomarkers	
Sputum neutrophils	3.5% variability at 1-year follow-up[3]
Sputum neutrophils	Weak/absent association with FEV_1%, SGRQ, emphysema, systemic inflammatory markers, exacerbation frequency or lung function decline[3]
Circulating WBC	Associated with persistent systemic inflammation,[4] frequent exacerbations[5] and mortality[6]
Blood protein biomarkers	
Fibrinogen	Significantly associated with symptoms, exercise capacity, exacerbation rate and BODE index.[6 10] Currently undergoing a regulatory qualification process[11]
CC16	Weakly associated with lung function decline, emphysema and depression[12–15]
SP-D	Weak association with COPD exacerbations[5 16]; sensitive to treatment with oral and inhaled corticosteroids[16]
CCL18 (PARC)	Increased risk of cardiovascular hospitalisation or mortality[17]
sRAGE	Lower circulating sRAGE levels are associated with emphysema severity, and genetic polymorphisms in the AGER locus are associated with circulating sRAGE levels[22]
Inflammome*	Patients with persistent systemic inflammation (16%) had higher mortality and exacerbation rate than patients without inflammation (30%).[4] Systemic inflammation was also associated with heart disease, hypertension and diabetes[18]
Adipokines	Leptin and adiponectin levels were (+) and (–) related to CRP, respectively; BMI and gender were the strongest determinants of both adipokines[20]
Vitamin D	Low levels of vitamin D were related to emphysema, 6MWD, airways reactivity and CC-16 levels[21]

Faner et al, Thorax, 2014

Blood protein biomarker: Fibrinogen

- First COPD biomarker approved by FDA & COPD Biomarker Qualification Consortium -



Risk of COPD	Components of COPD	Treatments	Lomas, 2009	4	
			Lomas, 2011	4	
			Kunter, 2008	5	
			Barnes, 2009	5	
			Dentener, 2008	5	
Diagnosis and disease severity			Kaczmarek, 2010	5	
	Exacerbations		Polalti, 2008	33	33 indiv individu controls
			Saldias, 2011	34	85 indiv exacerb
			Koutsokera, 2009	35	30 indiv of COPD
			Valipour, 2008	36	30 indiv individu controls
Mortality					
	Co-morbidities		Jousilahti, 1996	37	19444 F populati
			Fowkes, 2006	38	89 indiv
Disease Progression					
			Castagna, 2008	39	151 indi smoker
			Blum, 2011	40	27 indiv with CO

FDA Approves First COPD Biomarker: Paving Way for New, Improved Treatments and Cures

July 09, 2015 09:00 AM Eastern Daylight Time

WASHINGTON--(BUSINESS WIRE)--The COPD Foundation is extremely pleased to announce that a new clinical biomarker, plasma fibrinogen, has been approved for use in interventional clinical trials in patients with chronic obstructive pulmonary disease, the nation's 3rd leading cause of death. This is the first COPD biomarker to receive qualification by the U.S. Food and Drug Administration (FDA) and is the result of six years of work by the COPD Biomarker Qualification Consortium (CBQC).

"Individuals working in the pharmaceutical industry, universities and the patient community have spent several million dollars and countless hours assembling and analyzing data that has led to the FDA's monumental decision to approve this first COPD biomarker. Ultimately this clinical biomarker will enable future drug development to benefit patients."

Tweet this

The CBQC, which includes representatives and resources from university and government research, pharmaceutical and patient communities, was created by the COPD Foundation in 2010, with encouragement from the FDA and the National Heart, Lung and Blood Institute, to develop a "biomarker qualification process" for COPD. Biomarkers are medical processes that researchers use to measure disease severity or to determine if a new drug or treatment is effective. Being able to use a biomarker qualified by the FDA assures drug developers that any potential new drug applications will not be rejected simply because of how the drug's efficacy was measured or how patients were selected.

"This is a major triumph and, on behalf of the entire COPD community, I extend a heart-felt thank you to the FDA and congratulate the CBQC on its commitment and tireless leadership that allowed us to reach this significant milestone," said John W. Walsh, co-founder and president of the COPD Foundation. "Individuals working in the pharmaceutical industry, universities and the patient community have spent several million dollars and countless hours assembling and analyzing data that has led to the FDA's monumental decision to approve this first COPD biomarker. Ultimately this clinical biomarker will enable future drug development to benefit patients."

COPD causes serious long-term disability and as many as 24 million Americans have the disease, but approximately half of them remain undiagnosed. On average, one American dies from COPD every 4 minutes yet in the last 3 decades, only one new class of drug has been approved for COPD.

For more information on the CBQC, visit http://copdf.co/CBQC-Biomarker.

Duvoix A, et al. Thorax 2013

However, usefulness of biomarkers in real field ?


STATISTICS AND MEDICINE

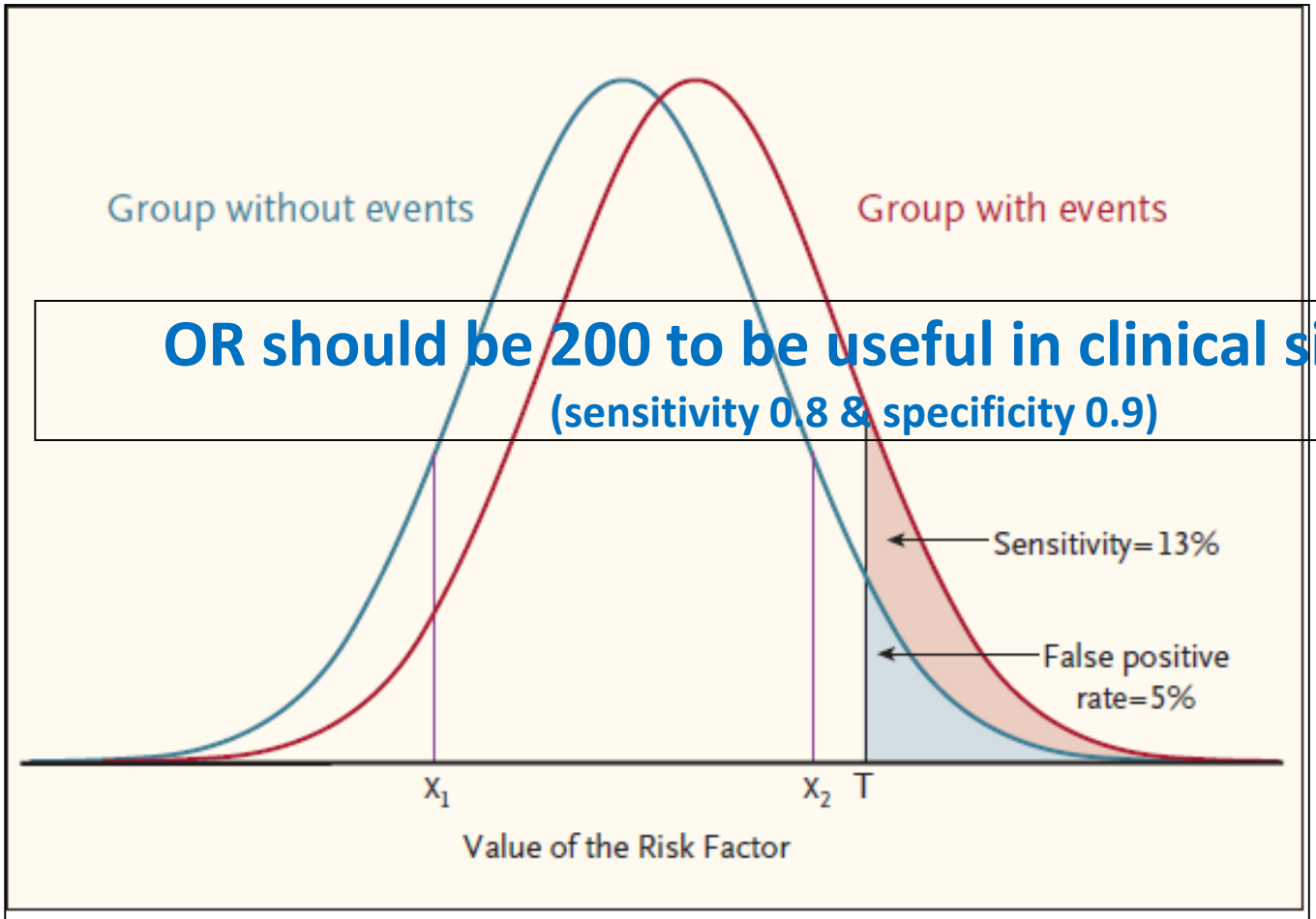
The Limitations of Risk Factors as Prognostic Tools

James H. Ware, Ph.D.

- Prediction model for an event (ex. exacerbation)
  - Even small differences in values of a biomarker bet those with and without a future event will result in statistical significance if the numbers are high
- In order to be useful in individual prediction (high sensitivity and specificity)
  - There should be a substantial separation between distribution (mean values) of biomarker in those with and without the event

Ware et al, NEJM 2006

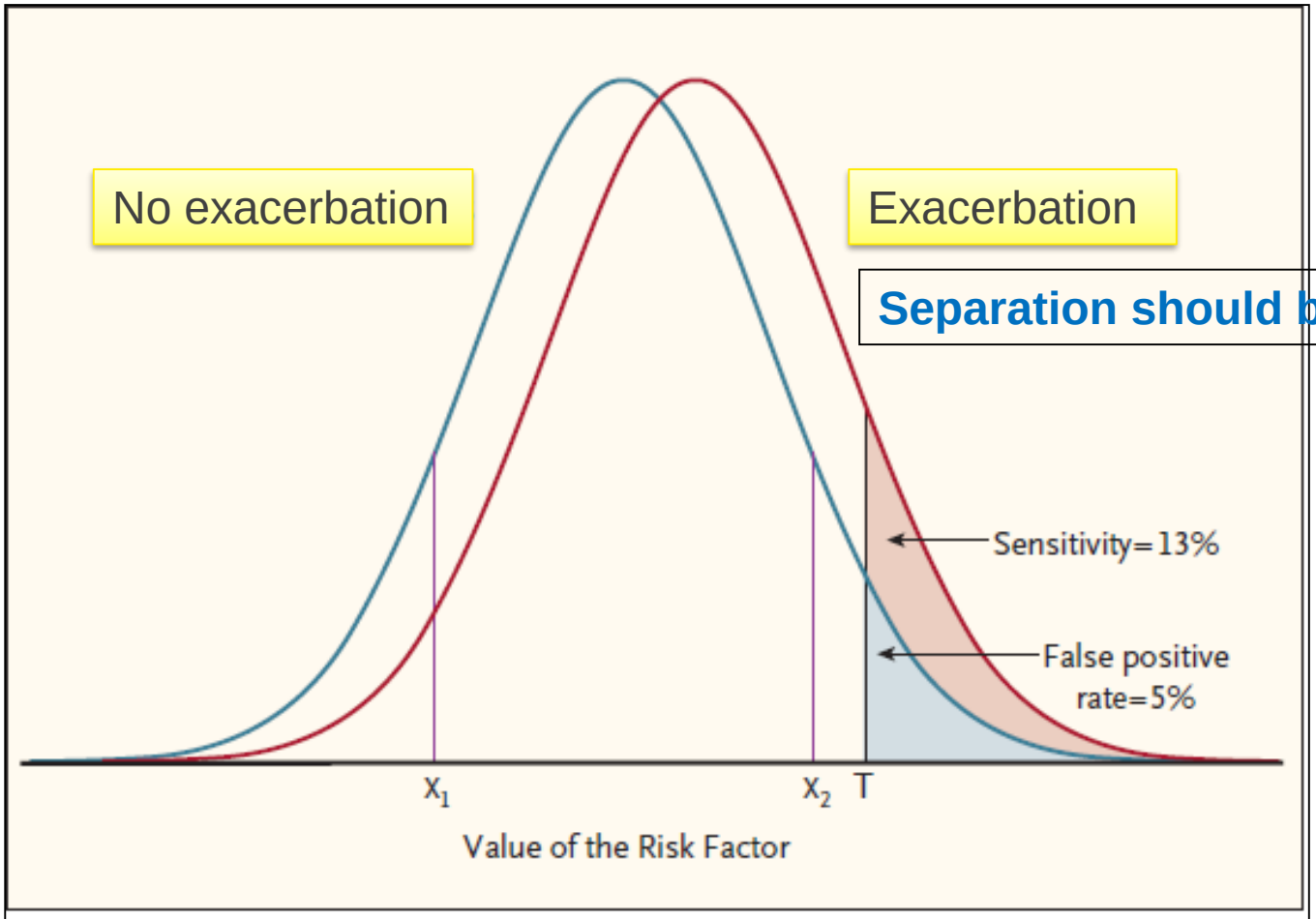
Ex) Mean 0.5 SD differ corresponds to OR 3.6



OR should be 200 to be useful in clinical situation
(sensitivity 0.8 & specificity 0.9)

Normal Probability Density Functions of the Risk Factor among Persons Who Will Not Have the Event (Blue) and among Those Who Will (Red).

Prediction for individual patients



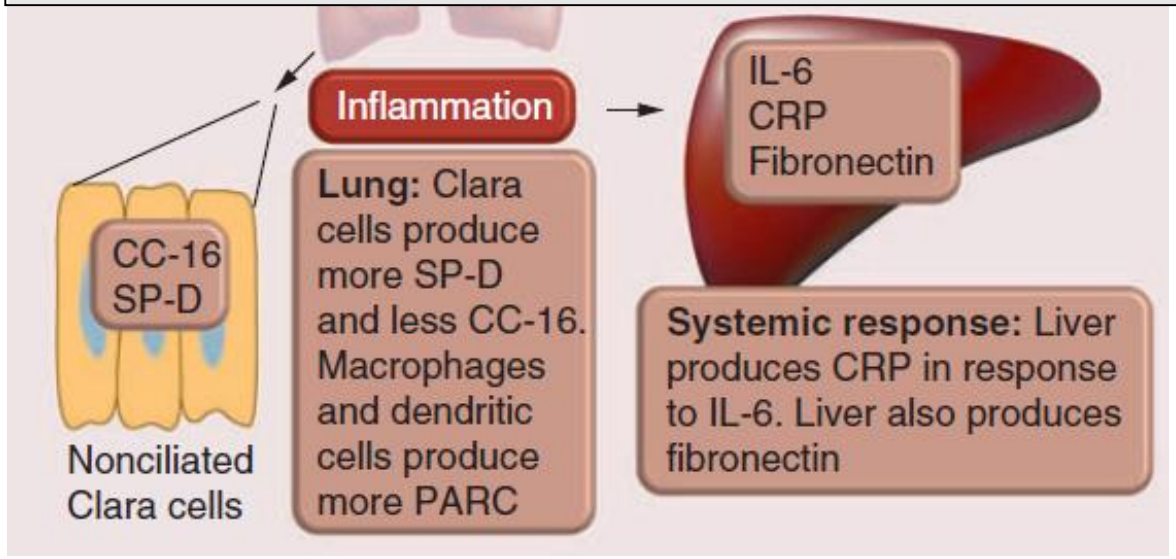
Normal Probability Density Functions of the Risk Factor among Persons Who Will Not Have the Event (Blue) and among Those Who Will (Red).

Separation should be at least 2 SD

Do inflammatory biomarkers predict mortality?

- Inflammome -

Biomarker	Origin	Action
C-reactive protein	Liver	Acute-phase protein secreted in infection, inflammation or tissue injury
Fibronectin	Liver	Promotes wound repair
Pulmonary and activation-regulated chemokine; CC-chemokine ligand-18	Monocytes/macrophages and dendritic cells of the lungs	Unclear
Clara cell secretory protein-16	Clara cells in the lung	Immunosuppressant and has been thought to provide protection from oxidative stress and carcinogenesis
Surfactant protein-D	Endoplasmic reticulum of type II pneumocytes and the secretory granules of Clara cells	Role in surfactant homeostasis and pulmonary immunity
IL-6	Liver	Proinflammatory



Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease

Bartolome R. Celli[1], Nicholas Locantore[2], Julie Yates[2], Ruth Tal-Singer[3], Bruce E. Miller[3], Per Bakke[4], Peter Calverley[5], Harvey Coxson[6], Courtney Crim[2], Lisa D. Edwards[2], David A. Lomas[7], Annelyse Duvoix[7], William MacNee[8], Stephen Rennard[9], Edwin Silverman[1], Jørgen Vestbo[10,11], Emiel Wouters[12], and Alvar Agustí[13,14], for the ECLIPSE Investigators

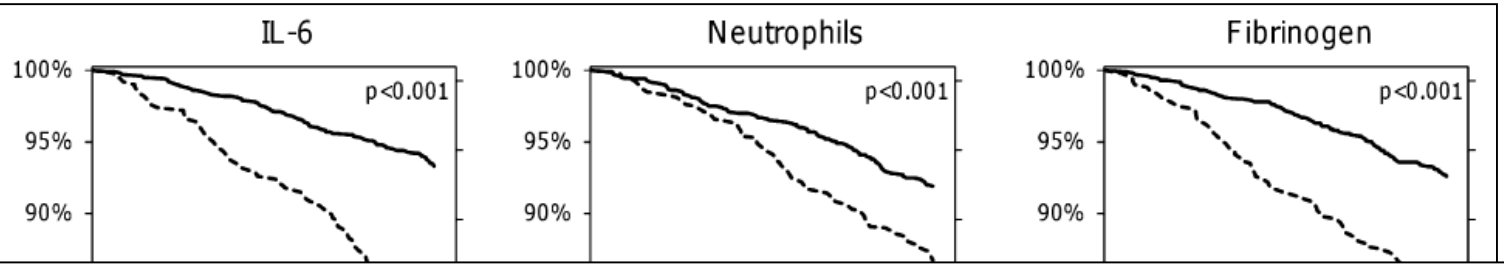


TABLE 3. C STATISTIC VALUE FOR THE PREDICTION OF DEATH

Model	C Statistic	Difference from Base	95% Confidence Interval for Difference from Base Model	*P* Value Versus Reference
Age + BODE + COPD Hosp	0.686			
+ IL-6	0.708	0.023	(0.003 to 0.043)	0.027
+ Neutrophils	0.699	0.013	(−0.001 to 0.028)	0.078
+ White blood cells	0.698	0.012	(−0.003 to 0.028)	0.119
+ CRP	0.697	0.012	(−0.005 to 0.028)	0.168
+ Fibrinogen	0.698	0.012	(−0.007 to 0.031)	0.207
+ SP-D	0.692	0.006	(−0.006 to 0.018)	0.309
+ IL-8	0.690	0.005	(−0.005 to 0.013)	0.371
+ All biomarkers	0.726	0.041	(0.014 to 0.067)	0.003
Sensitivity Model (n = 1,579)				
Age + BODE + COPD Hosp	0.697			
+ CCL-18/PARC	0.706	0.009	(−0.008 to 0.026)	0.294
+ All biomarkers	0.742	0.045	(0.010 to 0.079)	0.011

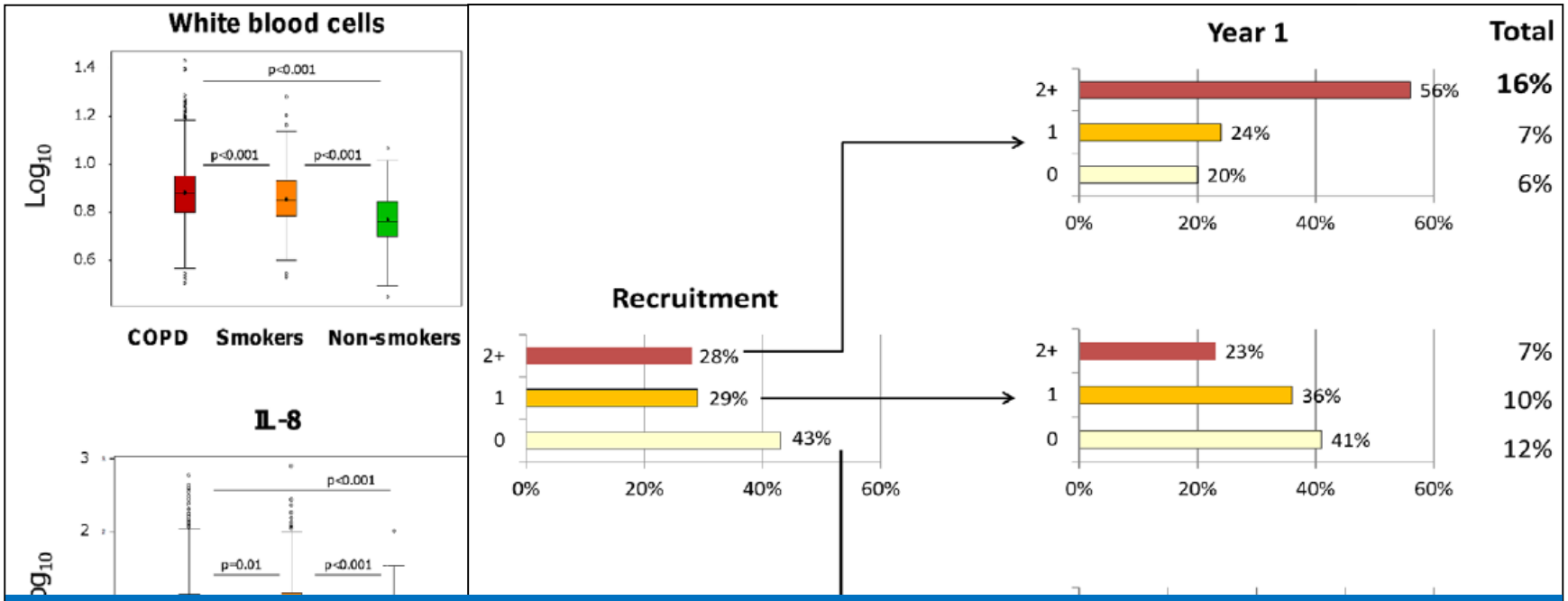
Celli et al, AJRCCM 2012

OPEN ACCESS Freely available online

PLoS one

Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype

Alvar Agustí[1,2]*, Lisa D. Edwards[3], Stephen I. Rennard[4], William MacNee[5], Ruth Tal-Singer[6], Bruce E. Miller[6], Jørgen Vestbo[7,8], David A. Lomas[9], Peter M. A. Calverley[10], Emiel Wouters[11], Courtney Crim[3], Julie C. Yates[3], Edwin K. Silverman[12], Harvey O. Coxson[13], Per Bakke[14], Ruth J. Mayer[3], Bartolome Celli[12], for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators



persistently inflamed patients during follow-up had significantly **increased all-cause mortality** (13% vs. 2%, p,0.001) & **exacerbation** (1.5 vs. 0.9/yr, p,0.001) compared to non-inflamed COPD patients

Agusti A et al, PLOSone 2012

Biochemical biomarker panel can improved traditional mortality prediction -PROMISE COPD study-

•combination of **three biomarkers (adrenomedullin, arginine vasopressin and atrial natriuretic peptide)** assessed in plasma samples of 385 patients in Predicting Outcome using Systemic Markers in Severe Exacerbations of COPD (PROMISE-COPD) study

Number of increased biomarkers

TABLE 5 ROC AUC, negative and positive likelihood ratios, and net reclassification improvement for death prediction at 3 years and maximum follow-up time according to the number of increased biomarkers in the derivation and validation cohort

	Derivation cohort	Validation cohort
Subjects n	142	243
ROC AUC		
Clinical basic model#	0.711	0.715
Clinical basic model + 3 biomarkers	0.744	0.729
BODE		0.616
BODE + 3 biomarkers		0.669
Likelihood ratio at 3 years negative/positive		
3 biomarkers *versus* none	0.89 (0.80–1.00)/3.06 (1.08–8.71)	0.73 (0.55–0.97)/5.01 (2.02–12.42)
BODE 7–10 vs 1–6		0.87 (0.73–1.02)/2.53 (1.15–5.55)
Likelihood ratio at 5 years negative/positive		
3 biomarkers *versus* none	0.95 (0.87–1.05)/1.71 (0.60–4.89)	0.84 (0.71–0.98)/3.66 (1.39–9.66)
BODE 7–10 *versus* 1–6		0.88 (0.78–0.99)/2.74 (1.26–5.96)
Net reclassification improvement at 3 years %		
Clinical basic model + 3 biomarkers *versus* clinical basic model	89.4 (53.0–100)	40.9 (9.4–71.5)
BODE + 3 biomarkers *versus* BODE		57.9 (21.7–92.4)
Net reclassification improvement at 5 years %		
Clinical basic model + 3 biomarkers *versus* clinical basic model	89.4 (51.7–100)	38.7 (10.7–64.7)
BODE + 3 biomarkers *versus* BODE		45.9 (13.9–75.7)

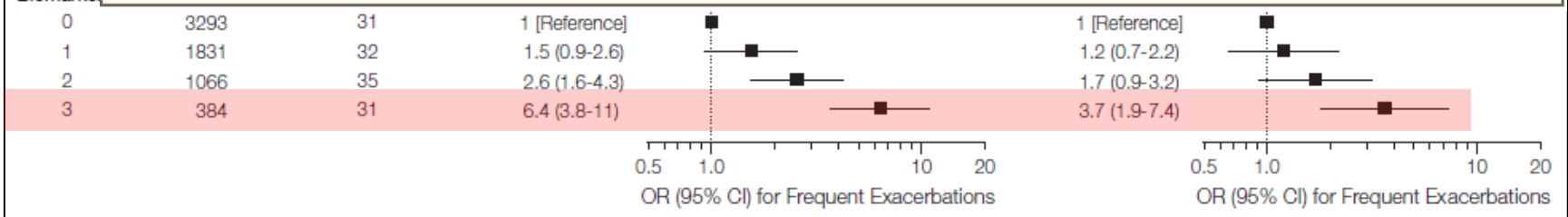
Stolz et al, ERJ 2014

Inflammatory Biomarkers and risk of AECOPD

ECLIPSE: Fibrinogen, hsCRP, CCL-18, SP-D – role a/w frequent AECOPD??? (NEJM 2010)

Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.*

Factor	Number of Exacerbations						P Value for Overall Model
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	1.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007



Plasma C-reactive protein and fibrinogen and blood leukocyte count were defined as high or low according to cut points of 3 mg/L, 14 μmol/L, and 9 $\times10^9$/L, respectively. The first model was multivariable adjusted for age, sex, forced expiratory volume in 1 second percent predicted, smoking, use of any inhaled medication, and body mass index (trend $P=3\times10^{-11}$), while the second model also included adjustment for history of frequent exacerbations and time since most recent prior exacerbation (trend $P=2\times10^{-5}$). COPD indicates chronic obstructive pulmonary disease; OR, odds ratio.

Recovery, Recurrence of AECOPD: CRP

Nonrecovered AECOPD at day 35 had a persistently higher serum CRP

recurrent AECOPD had a significantly higher serum CRP at 14 days

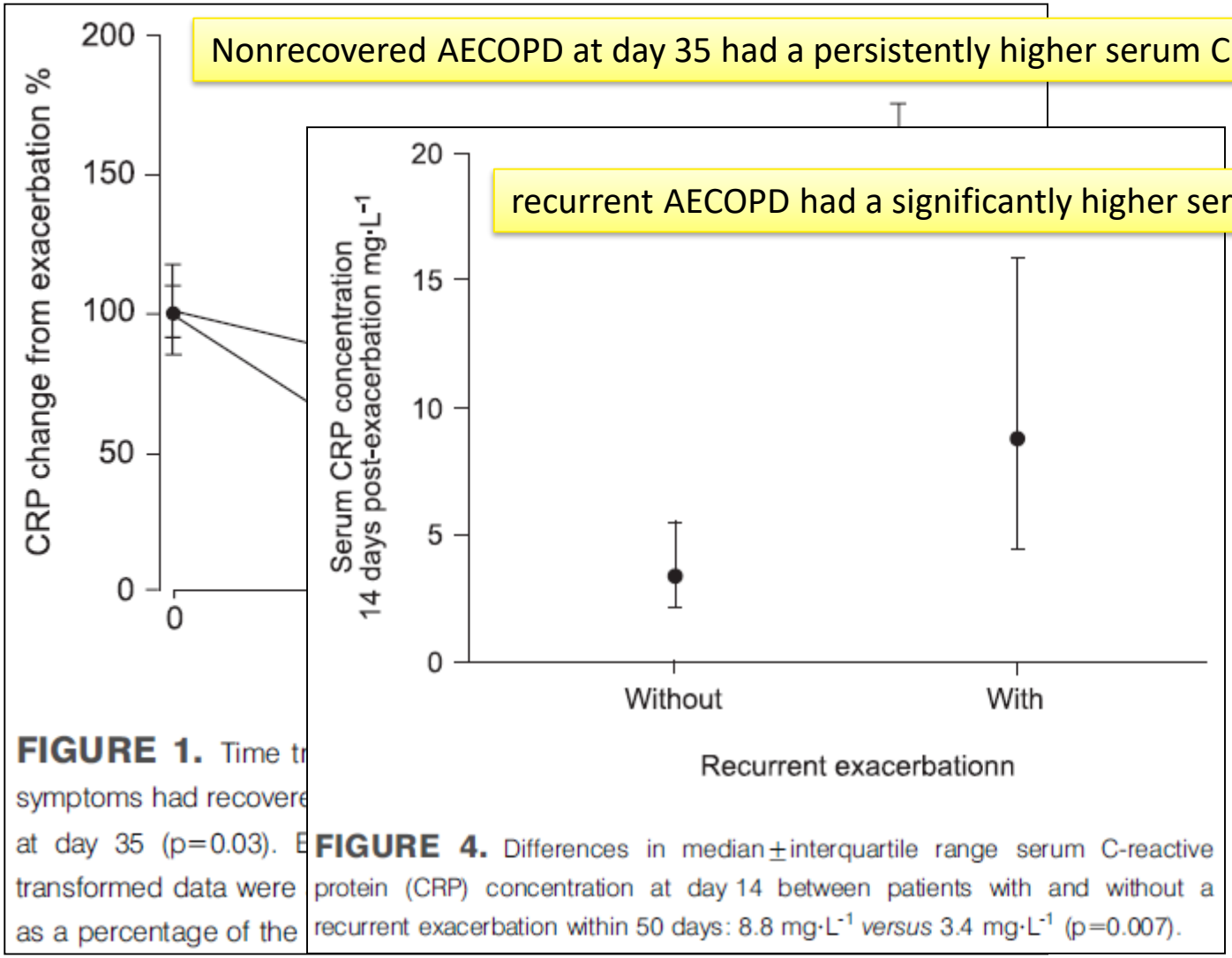


FIGURE 1. Time tr
symptoms had recovere
at day 35 (p=0.03). E
transformed data were
as a percentage of the

FIGURE 4. Differences in median ± interquartile range serum C-reactive protein (CRP) concentration at day 14 between patients with and without a recurrent exacerbation within 50 days: 8.8 $mg \cdot L^{-1}$ *versus* 3.4 $mg \cdot L^{-1}$ (p=0.007).

Major candidate systemic biomarkers in COPD of potential clinical use in AECOPD

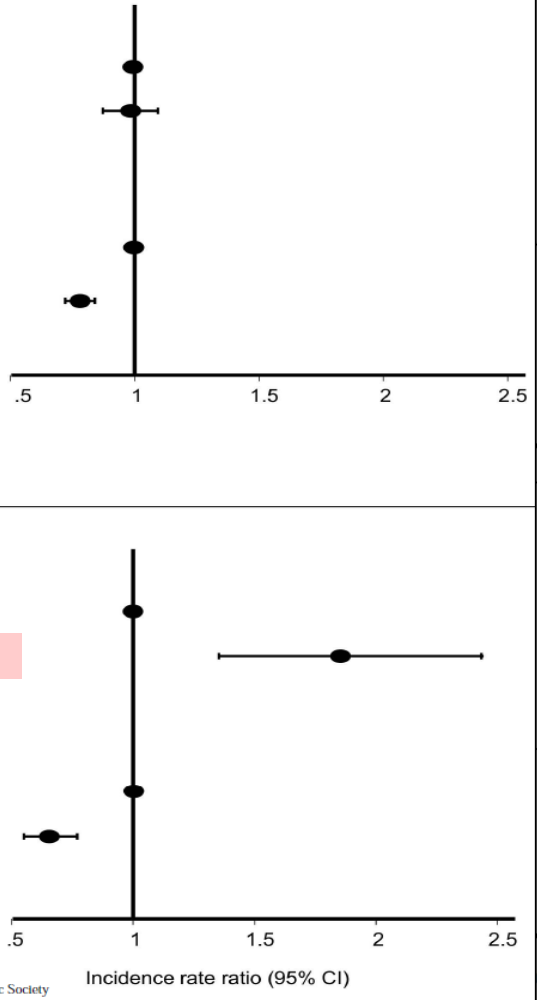
Biomarker	Clinical Implication
CRP	Increased in Anthonisen type I [80]; may improve the diagnosis of AECOPD when added to major symptoms [100]; identification of patients with late recovery and risk of recurrent AECOPD [111]
SAA	More sensitive than CRP in the identification of moderate/severe AECOPD [102]; may identify bacterial infections [108]
IP-10	May help in diagnosis of HRV infection [107]
CXCL10	Identification of viral infections [108]
Blood eosinophils	Identification of AECOPD with sputum eosinophilia [108]
Copeptin	Association with length of hospitalization and death during hospitalization [80]
Pro-adrenomedullin	Association with length of hospitalization [81]
Pro-endothelin-1	Association with length of hospitalization [81]
Albumin	Association with length of hospitalization [109]
Troponin-T	Association with length of hospitalization [110] and 30-day mortality [86]

AECOPD: acute exacerbations of COPD; CRP: C-reactive protein; CXCL10: chemokine (C-X-C motif) ligand 10; HRV: human rhinovirus; IP-10: interferon-gamma-inducible protein 10; SAA: serum amyloid A.

Blood eosinophil levels: marker of AECOPD risk

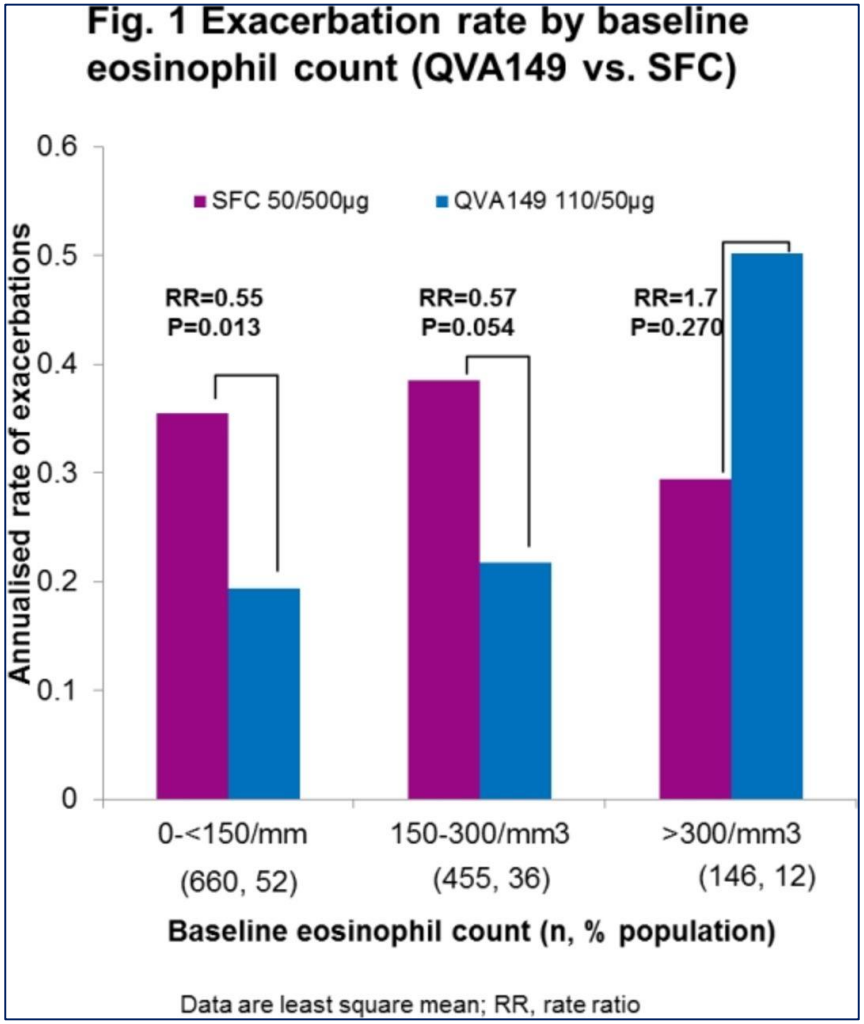
- Copenhagen general population & clinical COPD -

Blood eosinophils	N/Events	Person years of follow-up	IRR (95% CI)
Severe exacerbations			
< 2% (ref.)	2,618/511	9,529	1.00
≥ 2 %	4,607/928	16,816	0.99 (0.88-1.11)
Moderate exacerbations			
< 2 %	2,618/1,207	9,529	1.00
≥ 2 %	4,607/1,657	16,816	0.78 (0.72-0.84)
Clinical COPD			
Blood eosinophils			
Severe exacerbations			
< 2% (ref.)	69/70	239	1.00
≥ 2 %	134/234	494	1.85 (1.38-2.48)
Moderate exacerbations			
< 2 %	69/282	239	1.00
≥ 2 %	134/376	494	0.64 (0.54-0.75)



Vedel_Krogh et al, AJRCCM 2016

Eosinophil levels: informative marker of differentiate exacerbation reduction with Tx - SFC vs QVA149 -



Pooled analysis
LANTERN/ Illuminate study
SFC vs QVA 149

- **Rate of mod or severe AECOPD significantly lower with QVA149 vs SFC (RR [95% CI]: 0.67 [0.48-0.94]; p=0.021)**

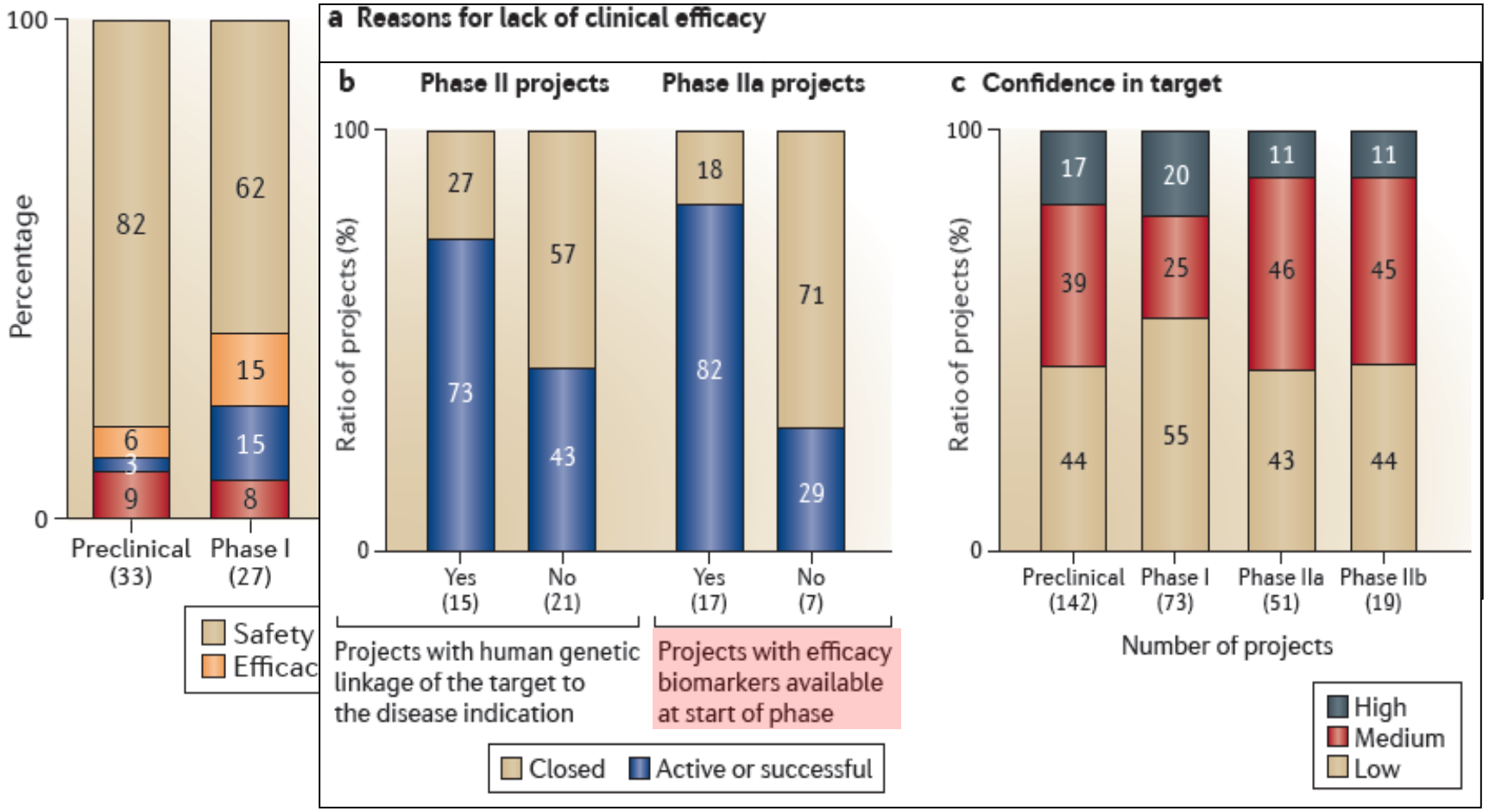
- **EOS <150/mm^3 & 150-300/mm^3**
  QVA149: 45% & 43% reduction AECOPD Vs SFC

- **Eos >300/mm^3 risk of AECOPD was lower with SFC.**

Importance of biomarker-driven selection of patients in drug development clinical trials

Drug develop project 2005-2010
Reasons for closure

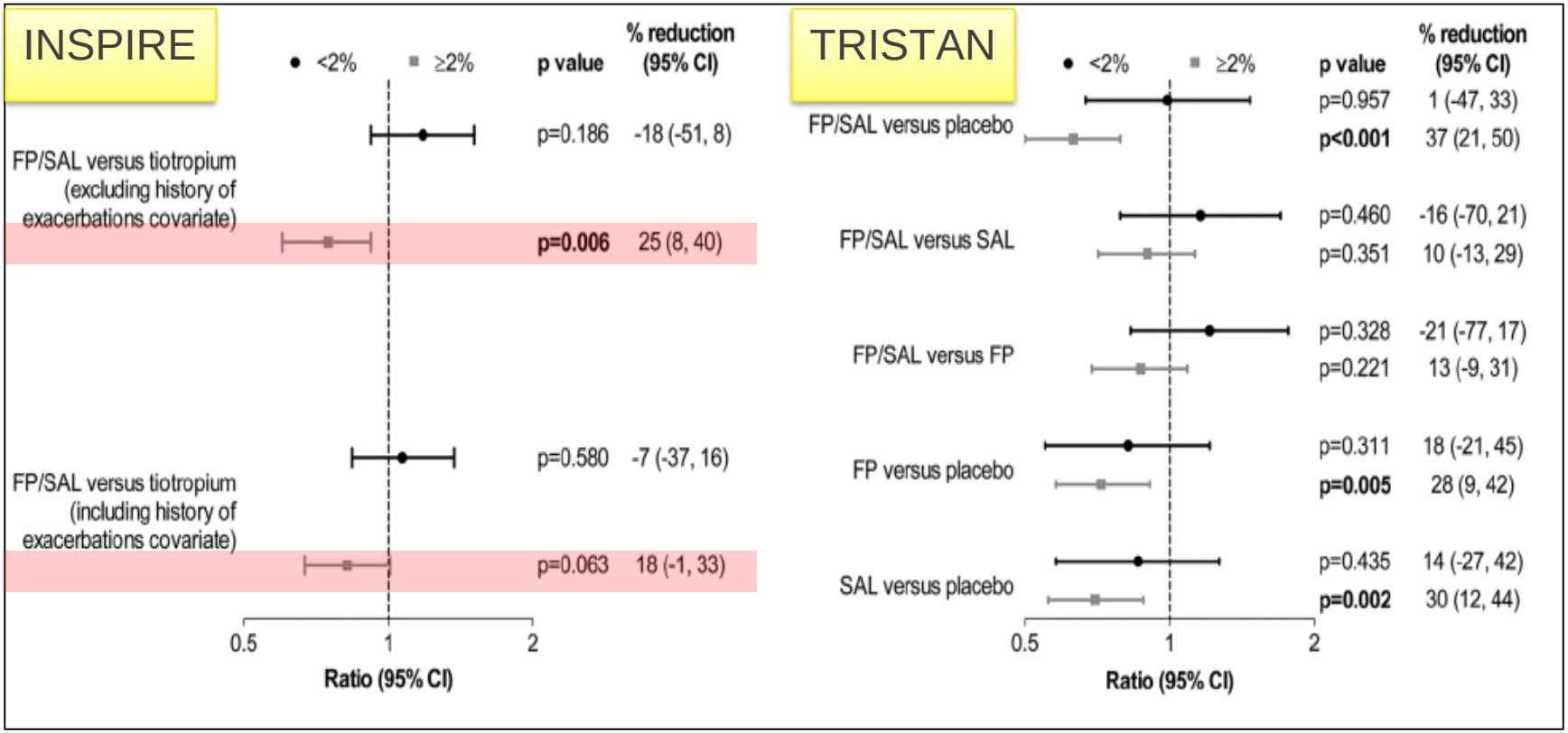
Analysis of project closures due to Efficacy issues



Nat rev drug discov 2014

Eosinophil levels: informative marker for exacerbation reduction with ICS/LABA

- pretreatment blood eos ≥2% (vs <2%) a/w greater reduction in AECOPD w/ ICS/LABA Tx?
- retrospective analysis of data from 3 RCT of at least 1 yr (INSPIRE, TRISTAN, SC030002)



- Blood test for eosinophil levels could be employed as a simple biomarker for clinical decision-making in patients with mod-to-severe COPD and a history of exacerbations.

Pavord et al, Thorax 2016

Association of blood eosinophils and plasma periostin with FEV_1 response after 3-month inhaled corticosteroid and long-acting $beta_2$-agonist treatment in stable COPD patients

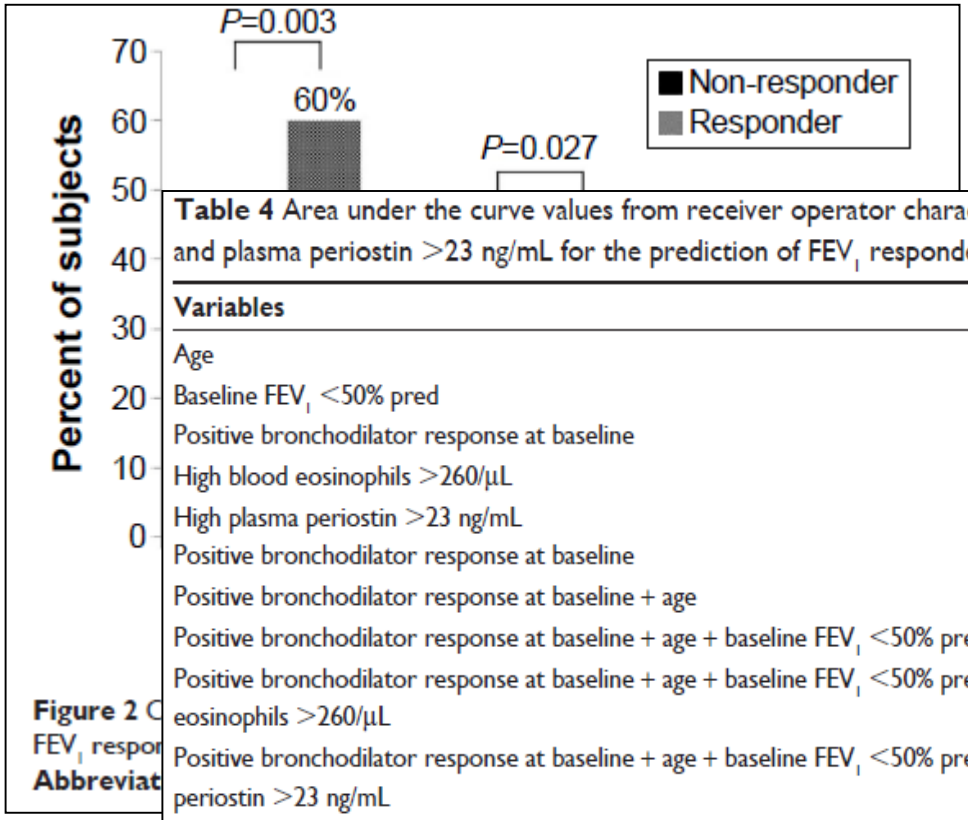


Figure 2 C
FEV_1 respor
Abbreviat

Table 4 Area under the curve values from receiver operator characteristics generated for variables with blood eosinophils >260/μL and plasma periostin >23 ng/mL for the prediction of FEV_1 responders

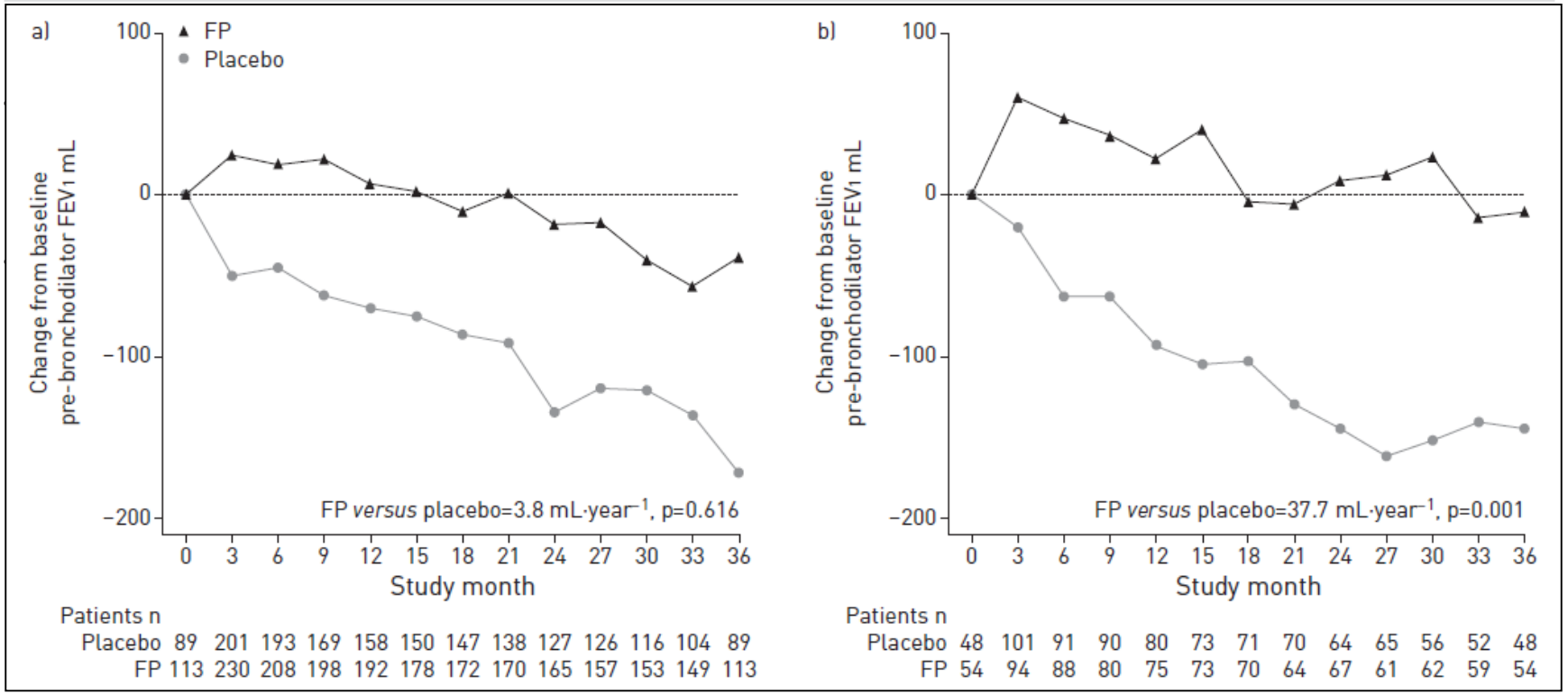
Variables	AUC (95% CI)
Age	0.608 (0.509–0.707)
Baseline FEV_1 <50% pred	0.594 (0.504–0.684)
Positive bronchodilator response at baseline	0.637 (0.548–0.726)
High blood eosinophils >260/μL	0.639 (0.549–0.728)
High plasma periostin >23 ng/mL	0.595 (0.507–0.683)
Positive bronchodilator response at baseline	0.637 (0.548–0.726)
Positive bronchodilator response at baseline + age	0.685 (0.587–0.783) (*P*=0.093)*
Positive bronchodilator response at baseline + age + baseline FEV_1 <50% pred	0.700 (0.602–0.800) (*P*=0.527)*
Positive bronchodilator response at baseline + age + baseline FEV_1 <50% pred + high blood eosinophils >260/μL	0.771 (0.688–0.853) (*P*=0.045)*
Positive bronchodilator response at baseline + age + baseline FEV_1 <50% pred + high plasma periostin >23 ng/mL	0.729 (0.636–0.823) (*P*=0.346)‡
Positive bronchodilator response at baseline + age + baseline FEV_1 <50% pred + combined high blood eosinophils >260/μL and high plasma periostin >23 ng/mL	0.769 (0.682–0.856) (*P*=0.064)‡

Park HY et al., Int J COPD 2015

Eosinophil levels: marker for slower rates of decline in FEV_1 when treated with ICS - ISOLDE study -

- 751 patients (mean postBD FEV_1, 1.4 L: 50% pred) FP 500 µg bid vs placebo for 3 years
- re-analysed by blood eosinophil count to investigate whether eos level predicts ICS benefit

TABLE 2 Rate of decline in post-bronchodilator forced expiratory volume in 1 s (FEV_1) in patients receiving fluticasone propionate 500 µg twice daily (FP) or placebo twice daily according to blood eosinophil level#



Neil C Barnes et al, ERJ 2016

Eosinophil levels: marker of exacerbation risk after withdrawal of ICS – WISDOM *post-hoc* analysis -

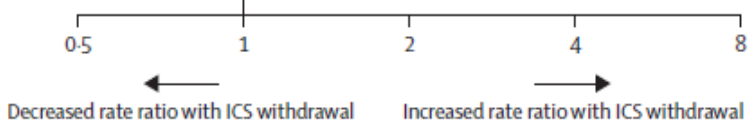
•data from the WISDOM trial to assess whether patients with COPD with higher blood eosinophil counts would be more likely to have exacerbations if ICS treatment was withdrawn

A

	n	Rate ratio (95% CI)	p value
Total			
Baseline eosinophils			
<2%			
≥2%			
Baseline eosinophils			
<3%			
≥3%			
Baseline eosinophils			
<4%			
≥4%			
Baseline eosinophils			
<5%			
≥5%			
Baseline eosinophils			
<6%			
≥6%			
Baseline eosinophils			
<2%			
2 to <3%			
3 to <4%			
4 to <5%			
5 to <6%			
≥6%			

B

	n	Rate ratio (95% CI)	p value
Total	2296	**1·10 (0·96–1·26)**	**0·17**
Baseline eosinophils (<150 cells per µL *vs* ≥150 cells per µL)			
<150 cells per µL	1067	1·08 (0·88–1·32)	0·44
≥150 cells per µL	1172	1·17 (0·97–1·41)	0·094
Baseline eosinophils (<300 cells per µL *vs* ≥300 cells per µL)			
<300 cells per µL	1791	1·04 (0·89–1·21)	0·59
≥300 cells per µL	448	1·56 (1·14–2·13)	0·0055
Baseline eosinophils (<400 cells per µL *vs* ≥400 cells per µL)			
<400 cells per µL	1992	1·07 (0·92–1·23)	0·39
≥400 cells per µL	247	1·73 (1·15–2·62)	0·0090
Baseline eosinophils (mutually exclusive subgroups)			
<150 cells per µL	1067	1·08 (0·88–1·32)	0·44
150 to <300 cells per µL	724	1·00 (0·80–1·27)	0·97
300 to <400 cells per µL	201	1·30 (0·80–2·11)	0·28
≥400 cells per µL	247	1·73 (1·15–2·62)	0·0089



Watz et al, Lancet Resp Med 2016

Biomarkers in COPD: take home messages

- No biomarkers or panel have reported a high enough sensitivity or specificity to be useful for prediction of outcome
- Inflammome or biochemical biomarkers adds prediction value of mortality or exacerbation in COPD
- Blood eosinophil level is useful informative biomarker a/w
  - AECOPD risk
  - Differentiate exacerbation reduction with therapy (ICS/LABA vs LABD)
  - Slower rates of decline in FEV_1 when treated with ICS
  - Exacerbation risk after withdrawal of ICS
- Biomarkers could only replace clinical endpoints if we completely understood the physiology of a biological process, the pathophysiology in the disease state, and effects of intervention – pharmacological, device, or otherwise – on these processes

Stribus K Curr Opin HIV AIDS. 2010 ; 5: 463