Biomarkers in COPD

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Financial Disclosure

- Consultant: AstraZeneca, Boehringer Ingelheim, Chiesi, Contrafect, Novartis, Roche-Genentech, GlaxoSmithKline, Merck, Verona, Mylan, Theravance, AbbVie, Kiniksa, BristolMyersSquibb, Galderma, Kamada, Pulmonx, Kinevant, Puretech

- Advisory Board Member: Arrowhead, Chimerix

- Research grants: AstraZeneca, Sanofi, Boehringer-Ingelheim, Verona

Learning Objectives

- Upon completion of this learning activity, participants should be able to define the difference between a biomarker and a surrogate (or intermediate) endpoint.
- Upon completion of this learning activity participants should be able to use clinically relevant biomarkers to predict risk of exacerbation in patients with COPD.

Goals of presentation

- Define biomarkers and their diverse uses
- Distinguish biomarkers from intermediate outcomes
- Review some biomarkers in COPD

No two people define biomarker the same

"Like Love, everyone recognizes a biomarker when they see it, but nobody would trust another person's definition"

Definition of Biomarkers (FDA-NIH Biomarker working group)

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.
- Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.
- A biomarker is not an assessment of how an individual feels, functions, or survives.

BEST (Biomarkers, EndpointS, and other Tools) Resource

FDA-NIH Biomarker Working Group.

Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016-.

https://www.ncbi.nlm.nih.gov/books/NBK326791/

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Distinction between a biomarker and a surrogate outcome

The single most common and serious error in the evaluation of biomarkers is the assumption that a correlation between the measured level of a biomarker and a clinical outcome means that the biomarker constitutes a valid surrogate.

…to qualify as a surrogate, the biomarker must not only be correlated with the outcome, but the change in the biomarker must “explain” the change in the clinical outcome.

The term “explains” invokes statistical inference, which can only be made with confidence if the observation is made in multiple therapies that all change the biomarker. This high bar means that the overwhelming majority of biomarkers are not valid surrogates; further, even when a surrogate is validated, that validation only pertains to a specific context of use

Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood). 2018 Feb;243(3):213-221

Types of Biomarkers

- Chemical
- Physiologic
- Radiographic
- Digital / Senor
- Patient reported

Uses of biomarkers

- Susceptibility/risk biomarker
- Diagnostic biomarker
- Monitoring biomarker
- Prognostic biomarker
- Predictive biomarker
- Therapeutic response biomarker
- Safety biomarker
- Composite biomarker

Distinction between predictive, prognostic, diagnostic biomarkers

- Predictive biomarkers are used to predict whether an individual will more likely develop a disease or condition
- Prognostic biomarkers are used to predict whether an individual with a disease will show progression or worse outcomes
- Diagnostic biomarkers are used to establish the presence of a disease

Distinction between predictive, prognostic, diagnostic biomarkers

- Predictive (susceptibility) biomarkers are used to predict whether an individual has an increased risk to develop a disease or condition

Example: A1AT Deficiency and Emphysema

Example: TERT (telomerase) mutations and Emphysema

Distinction between predictive, prognostic, diagnostic biomarkers

- Prognostic biomarkers are used to predict whether an individual with a disease will show progression or worse outcomes

Example: Eosinophil count and exacerbations

Example: CRP and exacerbations

Distinction between predictive, prognostic, diagnostic biomarkers

- Diagnostic biomarkers are used to establish the presence of a disease

Example: FEV1/FVC and COPD

Example: CT densitomtry (<-950 HU) and Emphysema

Biomarkers accepted by FDA as “qualified” biomarkers for COPD

- Fibrinogen
  - Associated with increased risk of exacerbations and death
  - May be used as an “enrichment” biomarker selecting patients for clinical trials with exacerbation or mortality as an outcome measure.

https://www.fda.gov/media/92567/download

Biomarker Validation – American Heart Association

- Differentiates subjects with/without condition
- Predicts development of condition
- Adds information to established risk markers
- Provides information to guide treatment
- Use of marker Improves clinical outcomes
- Cost-effective – improved outcomes justify added costs and burden

Hlatky MA et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119:2408–2416

Percent of variance of clinical outcome explained by serum biomarkers added to clinical features

Biomarker	FEV_1	FEV_1 Decline	Emphysema	Emphysema Progression	Mortality
Clinical markers	N/A	34%	53%	49%	31%
1. CC16	2%	3%	5%	0.5%	2%
2. SP-D	3%	8%	4%	0.8%	3%
3. sRAGE	10%	4%	18%	4%	3%
4. CRP	9%	0%	4%	0.6%	1%
5. Fibrinogen	11%	2%	13%	0.6%	2%
6. IL-6	4–5%	N/A	N/A	Low	N/A

COPDgene n = 2746
Eclipse n = 1465

Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic Obstructive Pulmonary Disease Biomarkers and Their Interpretation. Am J Respir Crit Care Med. 2019 May 15;199(10):1195-1204.

Zemans RL, Jacobson S, Keene J, Kechris K, Miller BE, Tal-Singer R, Bowler R. Multiple biomarkers predict disease severity, progression and mortality in COPD. Respir Res 2017;18:117

Conclusion about serum biomarkers

"Therefore, the field must acknowledge that statistically significant associations between biomarkers and outcomes that can be observed in large cohorts may be largely inadequate to explain remaining variance after strong clinical covariates are included in the models."

Zemans RL, Jacobson S, Keene J, Kechris K, Miller BE, Tal-Singer R, et al. Multiple biomarkers predict disease severity, progression and mortality in COPD. Respir Res 2017;18:117

Clinical Predictive Biomarkers

Outcome	Model	Covariates
Severity of Emphysema (% LAA ≤ -950 HU)	Ordinal Regression	FEV_1, Age, Smoking Status, Gender, BMI, Race, Scanner
FEV_1 (% Predicted)	Linear Regression	Race
FEV_1/FVC	β-regression	Age, Gender, Asthma, Race
Prospective Exacerbations	Zero Inflated Negative Binomial	FEV_1, GERD, SGRQ, Prior Exacerbations, Race
All Cause Mortality	Cox Proportional Hazards	BODE, Age^2, Age, Gender, Severe Exacerbations
Decline in FEV_1 (ml)	Linear Mixed	Age, Time, Gender, Height, Smoking Status, Pack Years, Age^2, $Height^2$
Decline in CT Density (%LAA)	Linear Mixed	FEV_1, Age, Time, Smoking Status, Gender, BMI, Scanner
Previous Exacerbations	Zero Inflated Negative Binomial	FEV1, GERD, SGRQ, Gender, Race

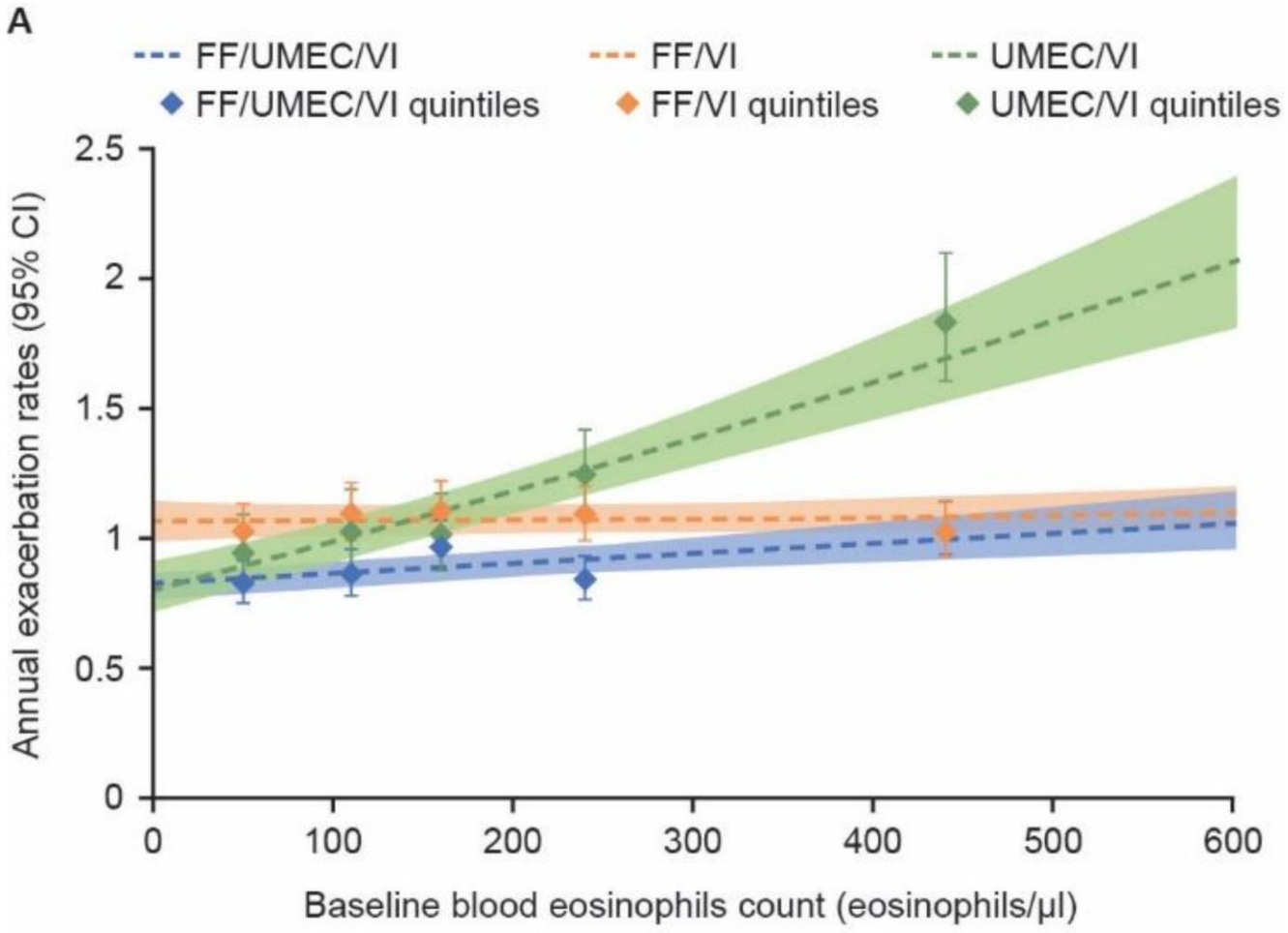
Zemans RL, Jacobson S, Keene J, Kechris K, Miller BE, Tal-Singer R, et al. Multiple biomarkers predict disease severity, progression and mortality in COPD. Respir Res 2017;18:117

Clinically Important Predictors

Exacerbations	FEV1, GERD, SGRQ, Prior Exacerbation, Race
Mortality	BODE, Age, Gender, Severe Exacerbations
FEV1 decline	Age, Gender, Height, Smoking status, Pack Years
Emphysema progression	FEV1, Age, Smoking status, Gender, BMI

Zemans RL, Jacobson S, Keene J, Kechris K, Miller BE, Tal-Singer R, et al. Multiple biomarkers predict disease severity, progression and mortality in COPD. Respir Res 2017;18:117

Eosinophilia predicts exacerbation risk and response to ICS

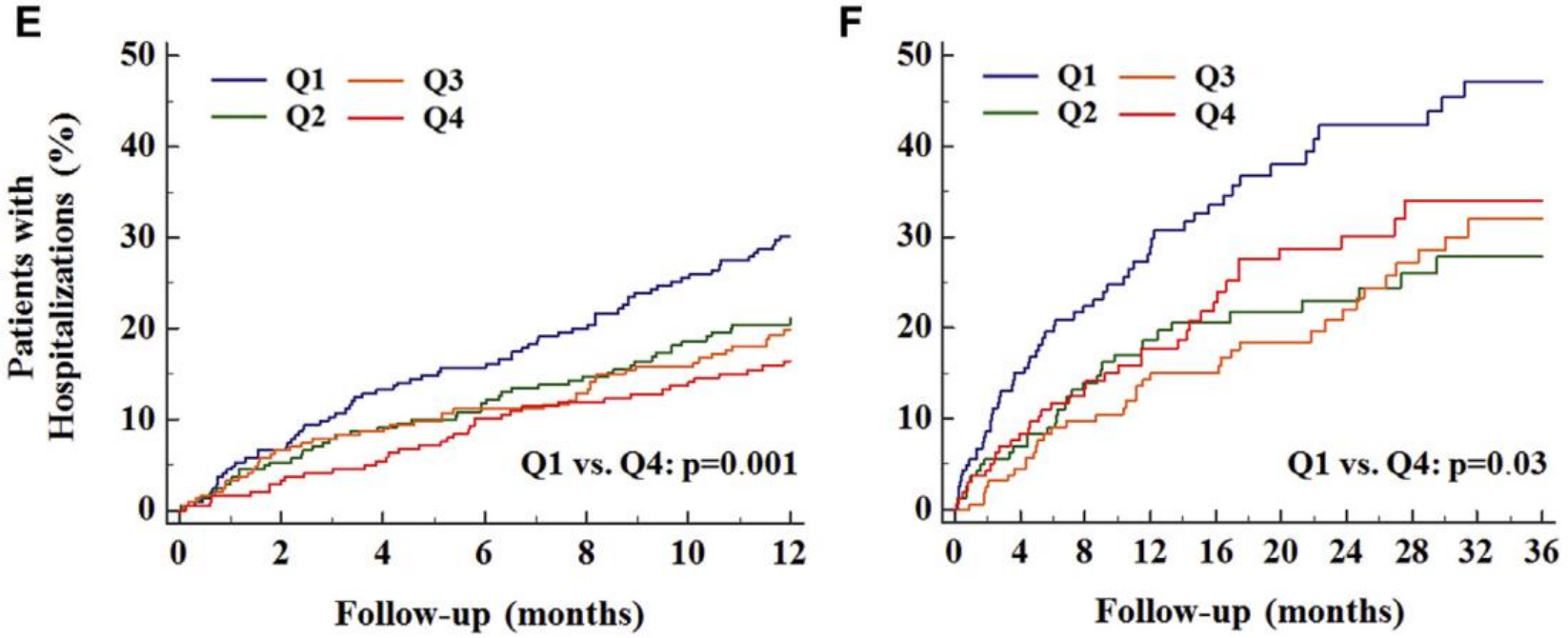


Pascoe S et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med. 2019 Sep;7(9):745-756.

IgG quartiles and exacerbation risk: Time to Severe Exacerbation

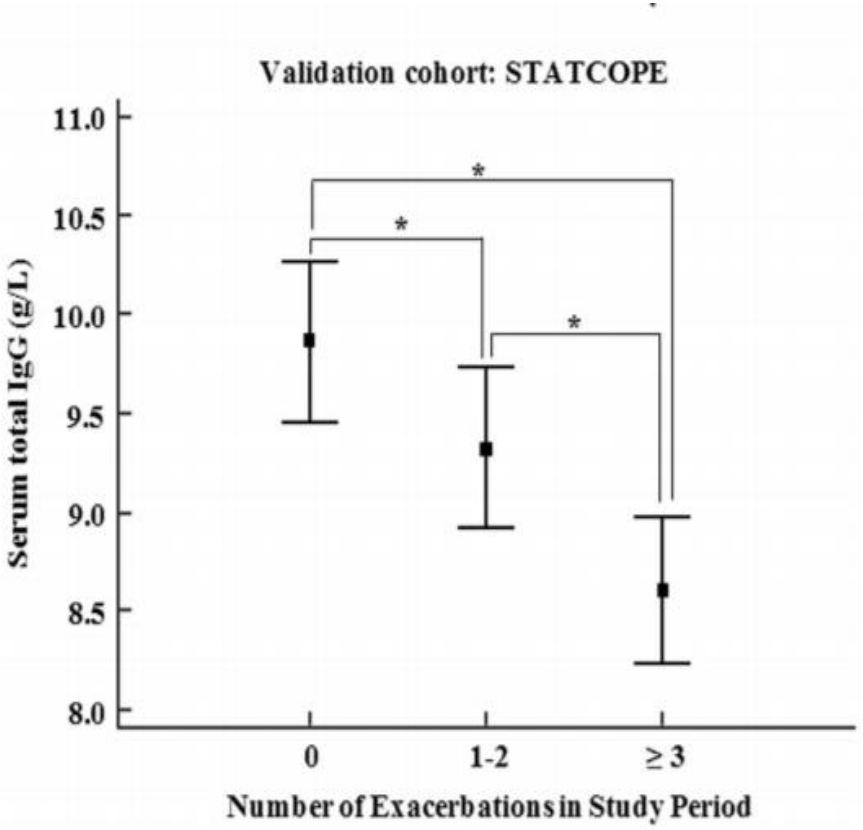
MACRO

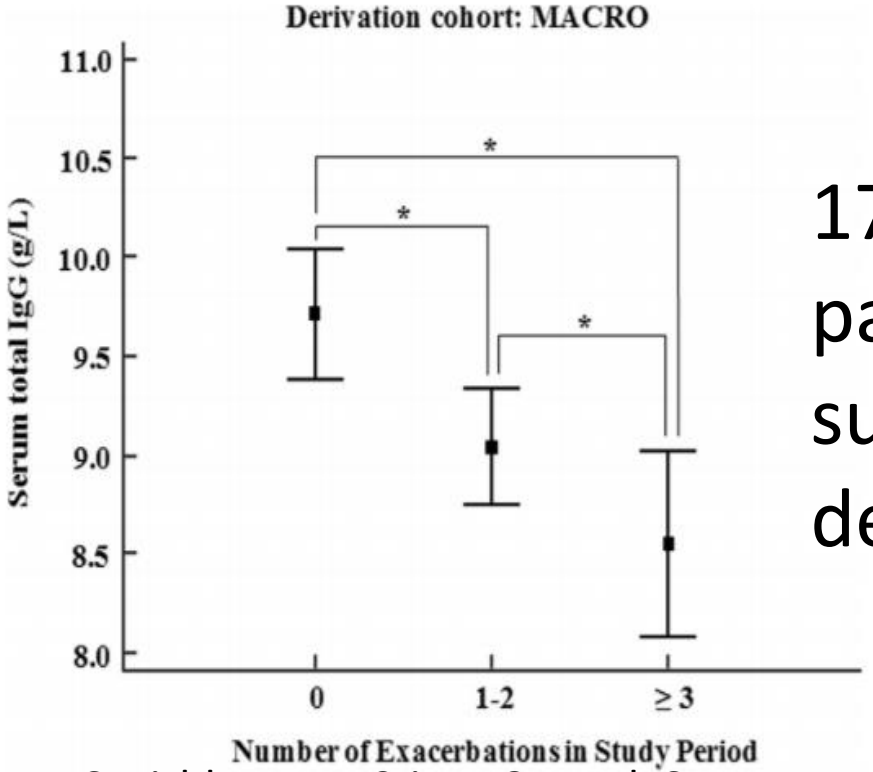
STATCOPE



Leitao Filho FS, Won Ra S, Mattman A, Schellenberg RS, Fishbane N, Criner GJ et al. Serum IgG and risk of exacerbations and hospitalizations in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2017 Oct;140(4):1164-1167.

Exacerbations associated with low normal IgG

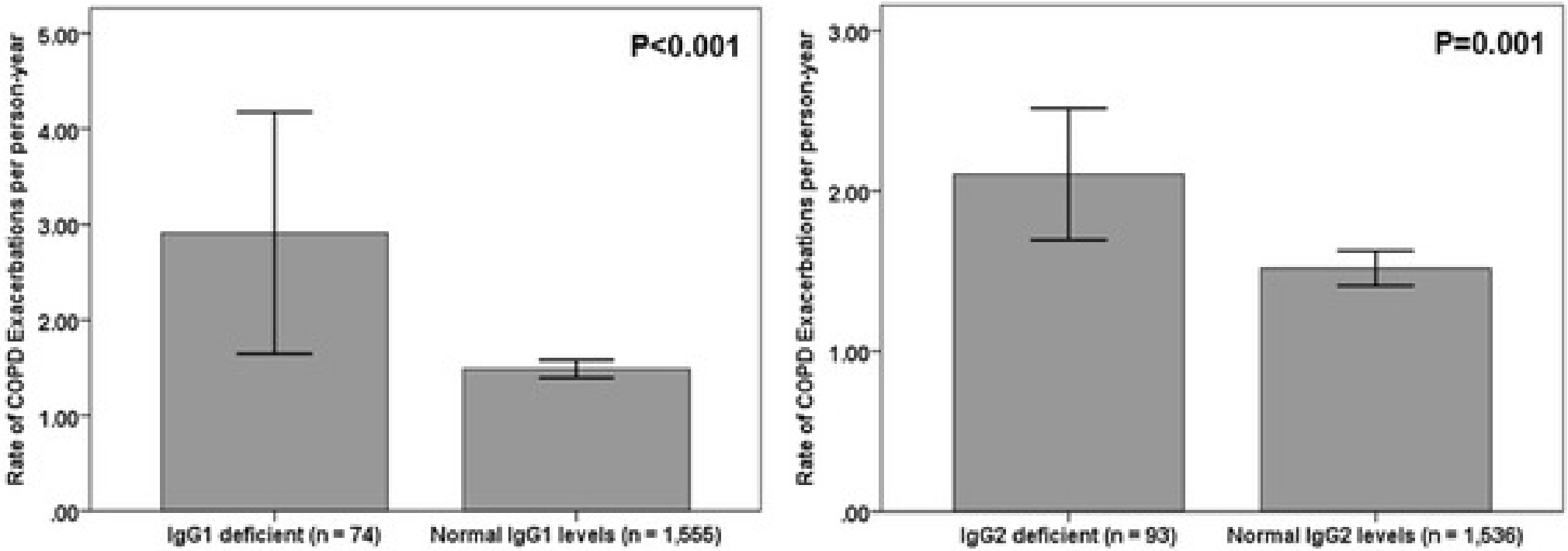




17-20% of COPD patients had IgG subclass deficiency

Leitao Filho FS, Won Ra S, Mattman A, Schellenberg RS, Fishbane N, Criner GJ et al. Serum IgG and risk of exacerbations and hospitalizations in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2017 Oct;140(4):1164-1167.

IgG1 and IgG2 deficiencies are associated with higher rates of exacerbation



Leitao Filho FS, Ra SW, Mattman A, et al. Canadian Respiratory Research Network (CRRN). Serum IgG subclass levels and risk of exacerbations and hospitalizations in patients with COPD. Respir Res. 2018 Feb 14;19(1):30.

The NEW ENGLAND JOURNAL of MEDICINE

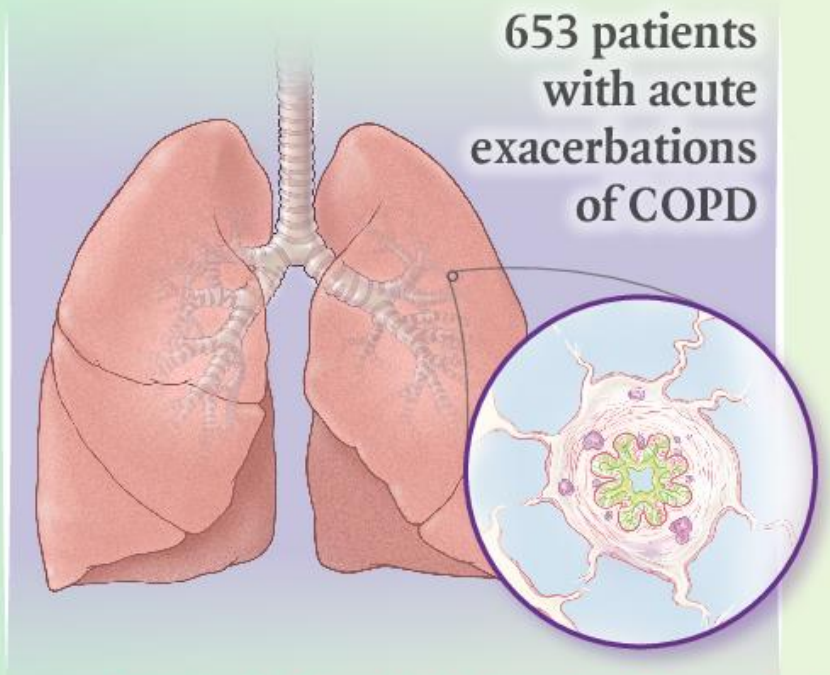
CRP Testing to Guide Antibiotic Prescribing for COPD

MULTICENTER, RANDOMIZED TRIAL

Patient-reported use of antibiotics within 4 wk after randomization

CRP-Guided Care

57.0%



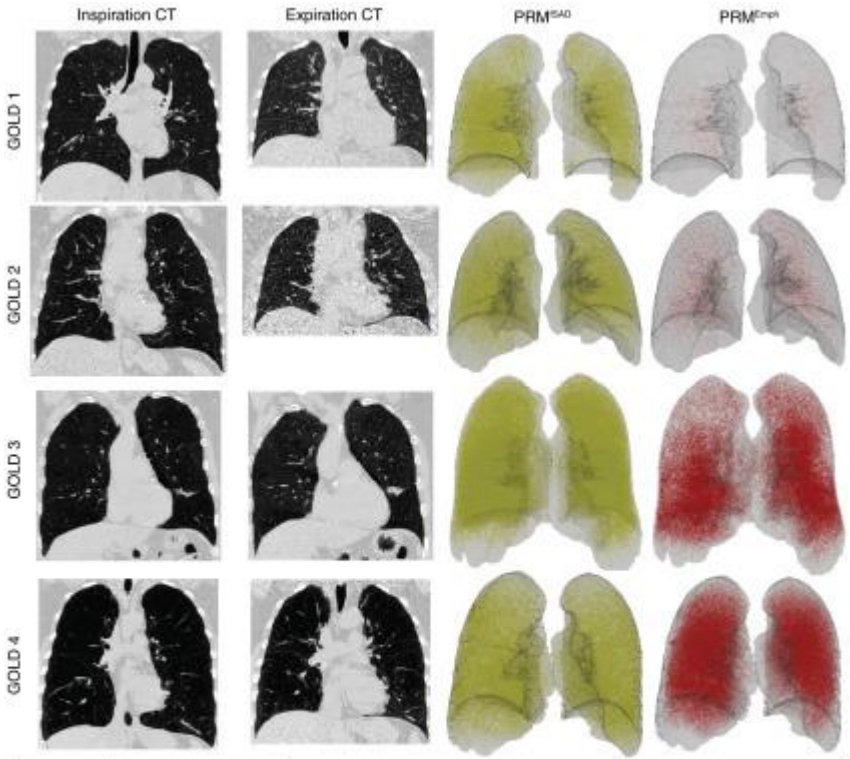
Usual Care

77.4%

Adjusted OR, 0.31 (95% CI, 0.20 to 0.47)

C. C. Butler et al. 10.1056/NEJMoa1803185

Parametric Response Mapping and FEV1 decline



	PRM Normal (%)	PRM Functional Small Airways Disease (%)	PRM Emphysema (%)
GOLD 1	78.8	18.5	0.8
GOLD 2	44.9	41.6	7.0
GOLD 3	28.8	40.8	25.1
GOLD 4	21.8	26.9	43.2

FEV1 decline = --4.5 ml/yr/5% PRM(SAD)
$P < 0.001$

Bhatt SP, et al. COPDGene Investigators. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2016 Jul 15;194(2):178-84.

Conclusions

- Few Biomarkers in COPD reach the level of clinical utility or FDA qualification.
- Eosinophilia and IgG subclasses are promising candidates for exacerbations
- Future directions include composite risk models, advanced imaging, and digital sensors

Thank You