Advances in Diagnosis and Evaluation of Bronchiectasis

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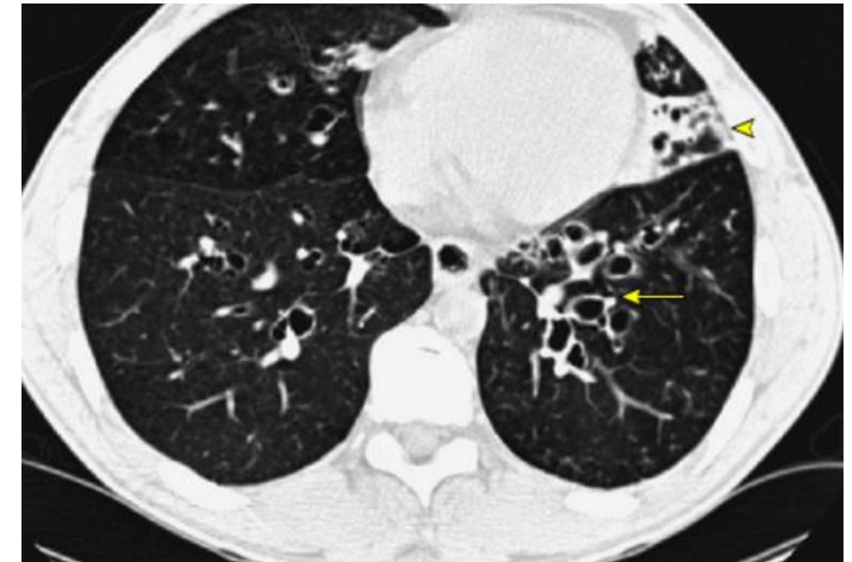
Vicious cycle of bronchiectasis pathogenesis

Neutrophil Inflammation (Proteases)

Airway Destruction and Distortion (Bronchiectasis)

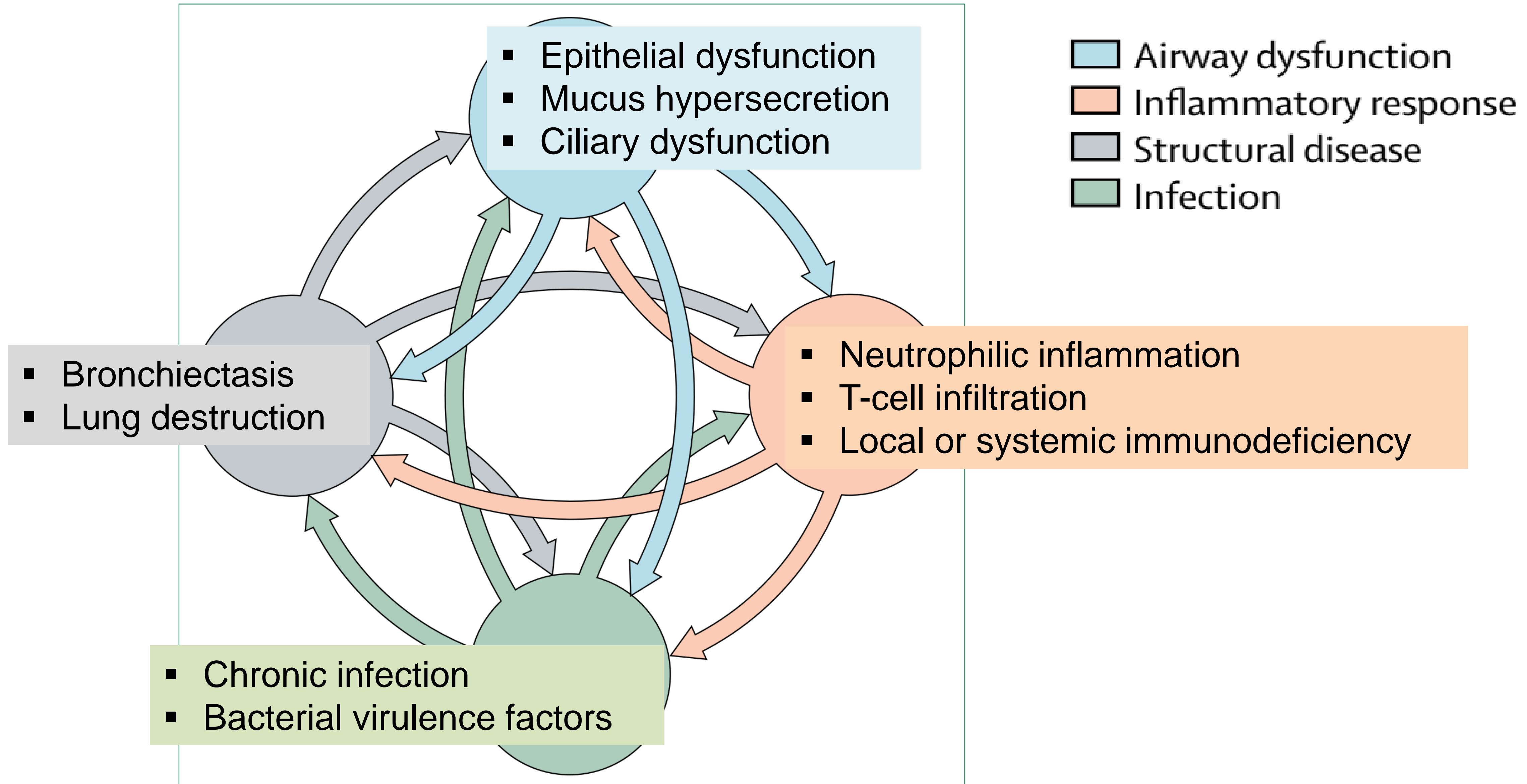
Abnormal Mucus Clearance

Bacterial Colonization



McShane PJ, et al. Am J Crit Care Med 2013;188(6):647-656.

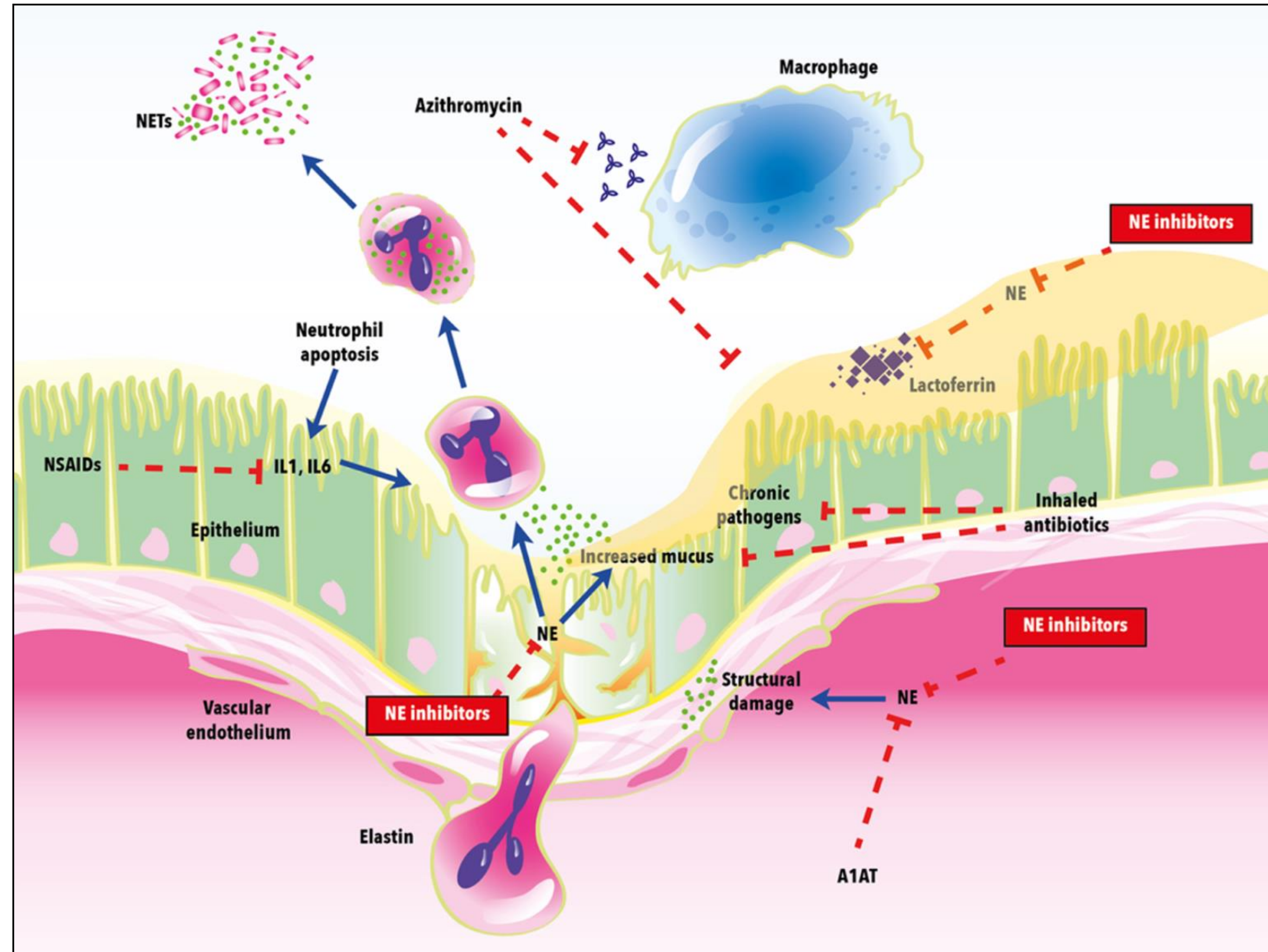
Recent model for pathogenesis of bronchiectasis



Flume PA, et al. Lancet 2018;392:880-890.

Neutrophil elastase in bronchiectasis

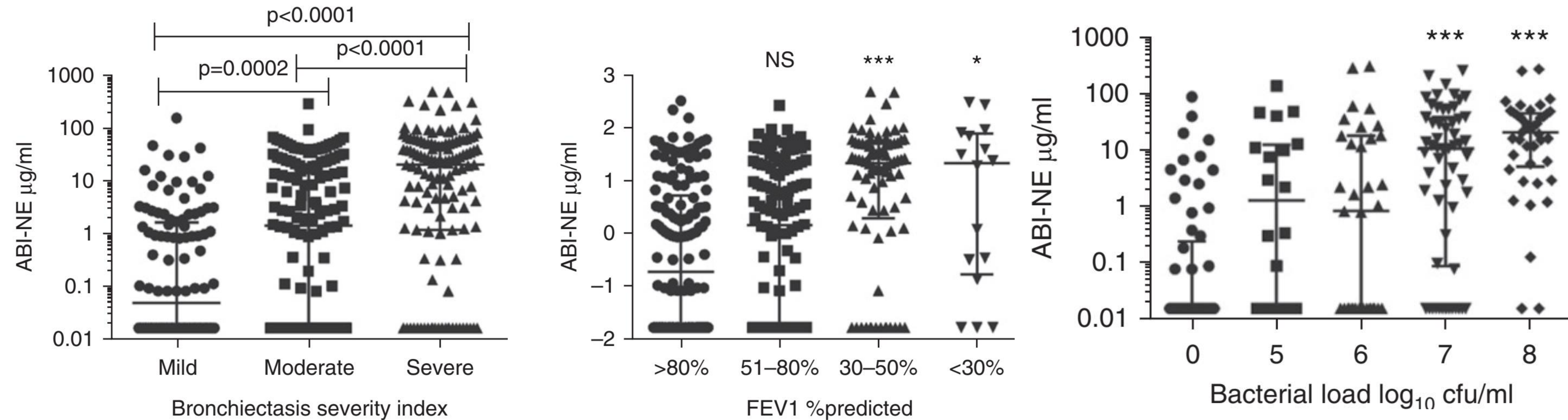
- Proteolytic enzyme belonging to the chymotrypsin-like family of the serine-proteinases
- Roles in both impaired mucus clearance and chronic bacterial infections leading to a serious neutrophilic activation
- Key determinant of tissue damage



Gramegna A, et al. Respir Res 2017;18(1):211.

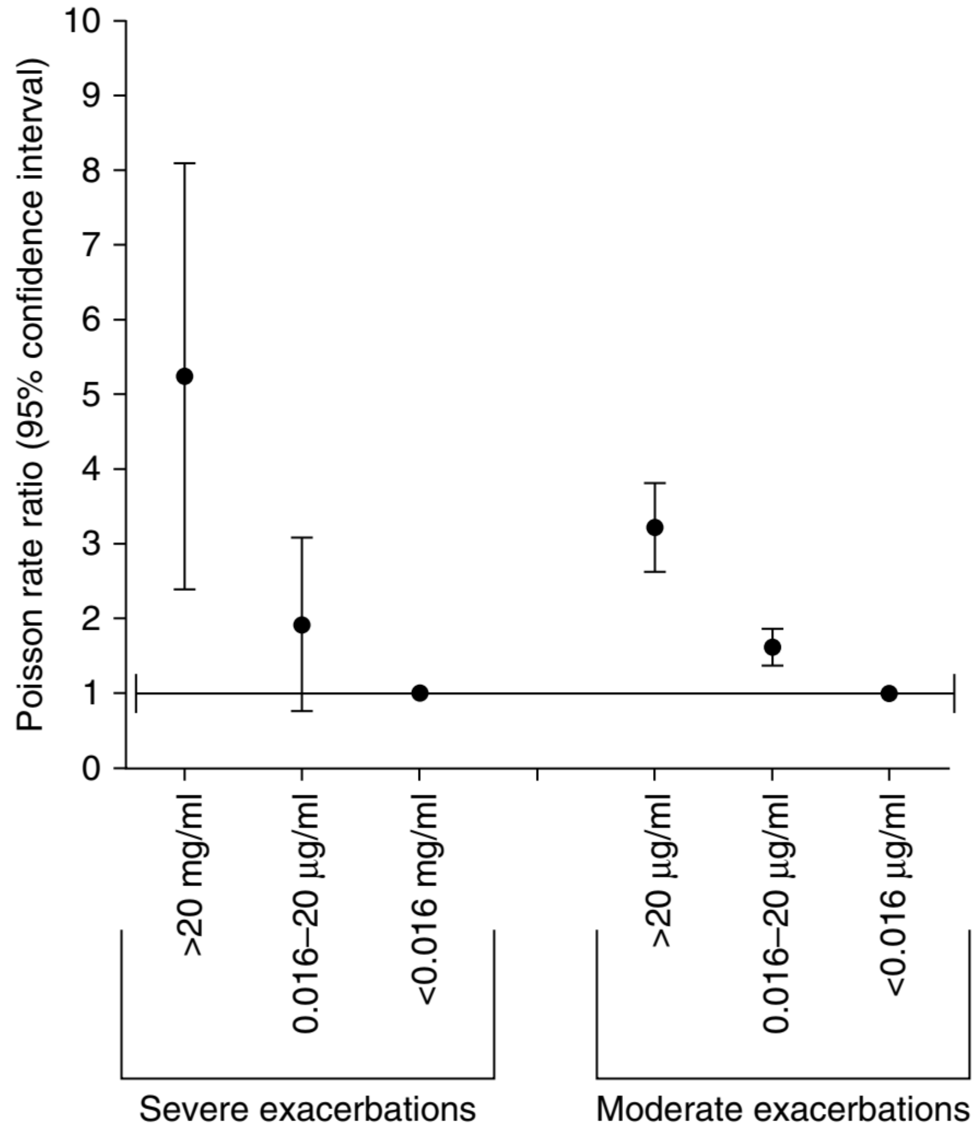
NE activity and disease severity

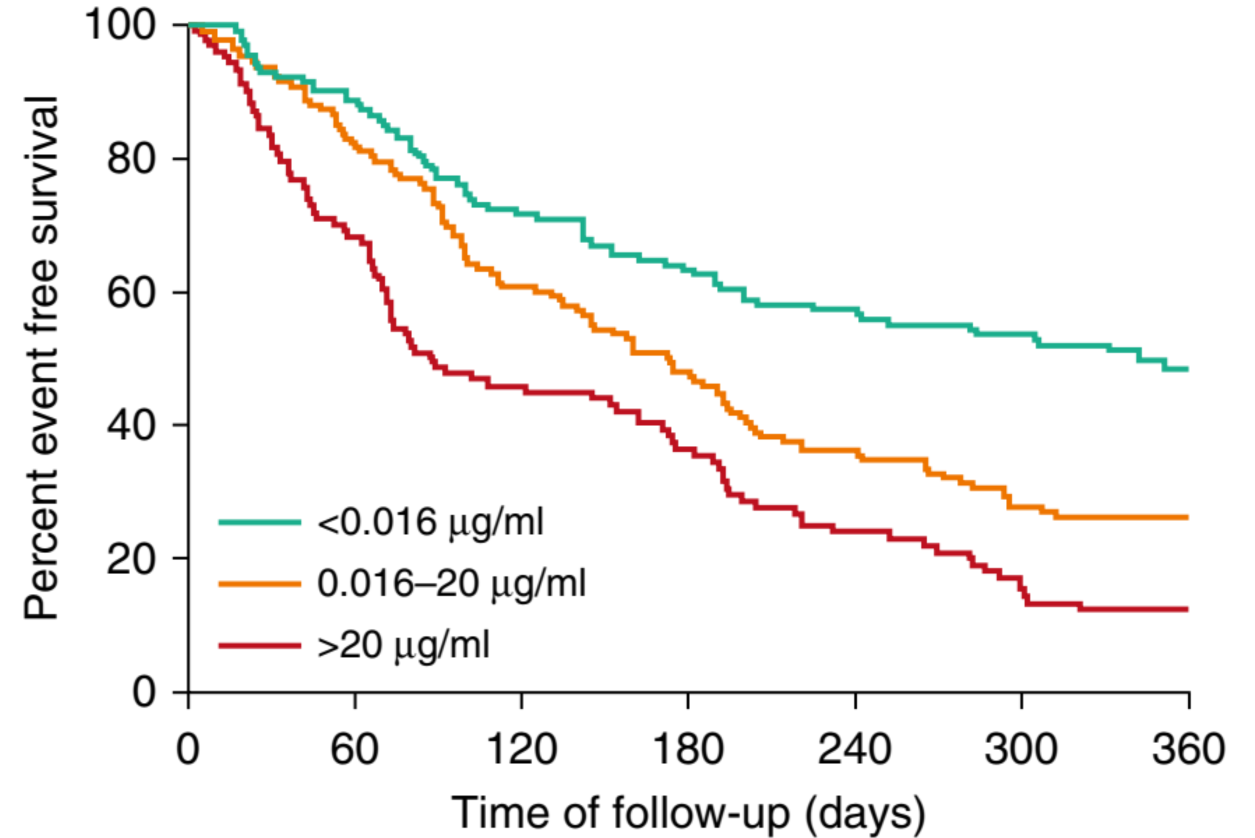
- 433 bronchiectasis patients from UK prospective cohort
- sputum NE activity using ProteaseTag active NE immunoassay



Chalmers JD, et al. Am J Respir Crit Care Med 2017;195(10:1384-1393.

NE activity and clinical course





Chalmers JD, et al. Am J Respir Crit Care Med 2017;195(10:1384-1393.

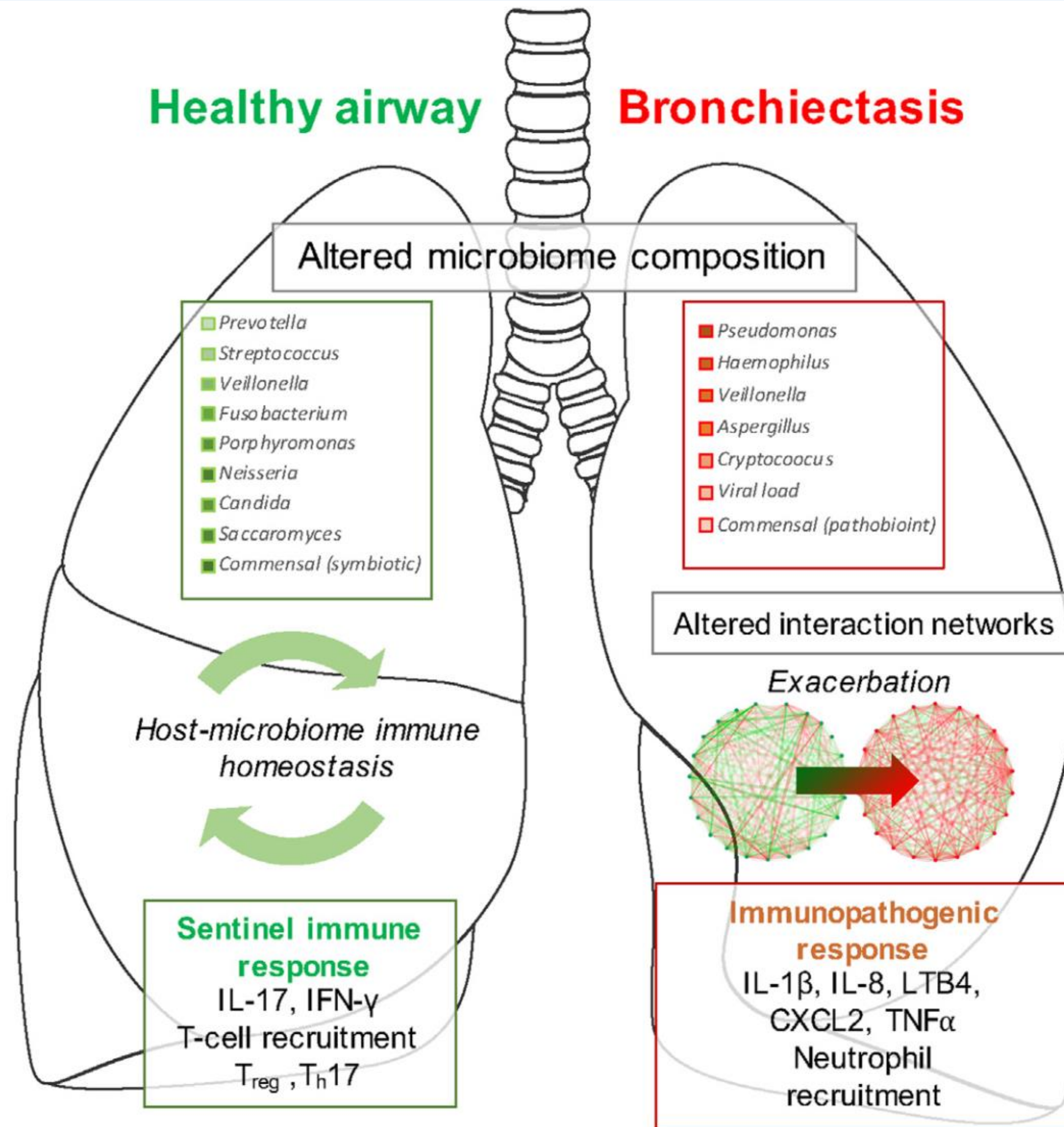
Clinical characteristics according to sputum NE level

- 266 bronchiectasis patients from Southern European cohort

	Sputum NE level			P-value
	Low (0-6㎍/㎖)	Medium (7-20㎍/㎖)	High (>30㎍/㎖)	
Age	65 (51-75)	63 (53-73)	64 (54-74)	0.45
Bronchiectasis severity index	6 (4-9)	7 (4-10)	8 (5-12)	0.009
Sputum volume	6 (5-20)	15 (5-50)	25 (7-75)	<0.001
QoL respiration	74.1 (66.7-81.5)	70.4 (59.3-77.8)	66.7 (51.9-74.1)	0.04
Chronic infection with *P.aeruginosa*	12 (14.0)	21 (27.6)	44 (47.3)	<0.001
FEV1 <50% predicted	8 (8.9)	9 (12.0)	22 (23.2)	0.02

Gramegna A, et al. Eur Respir J 2020;56:2001702.

Microbiome in bronchiectasis

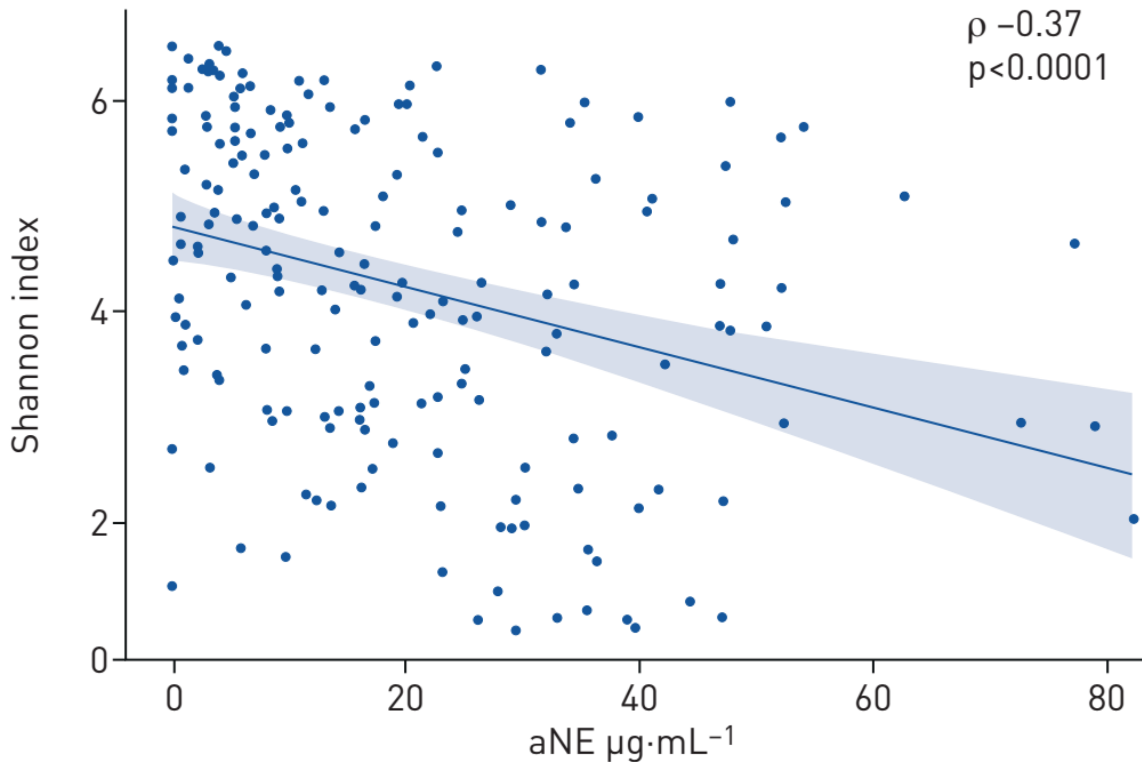


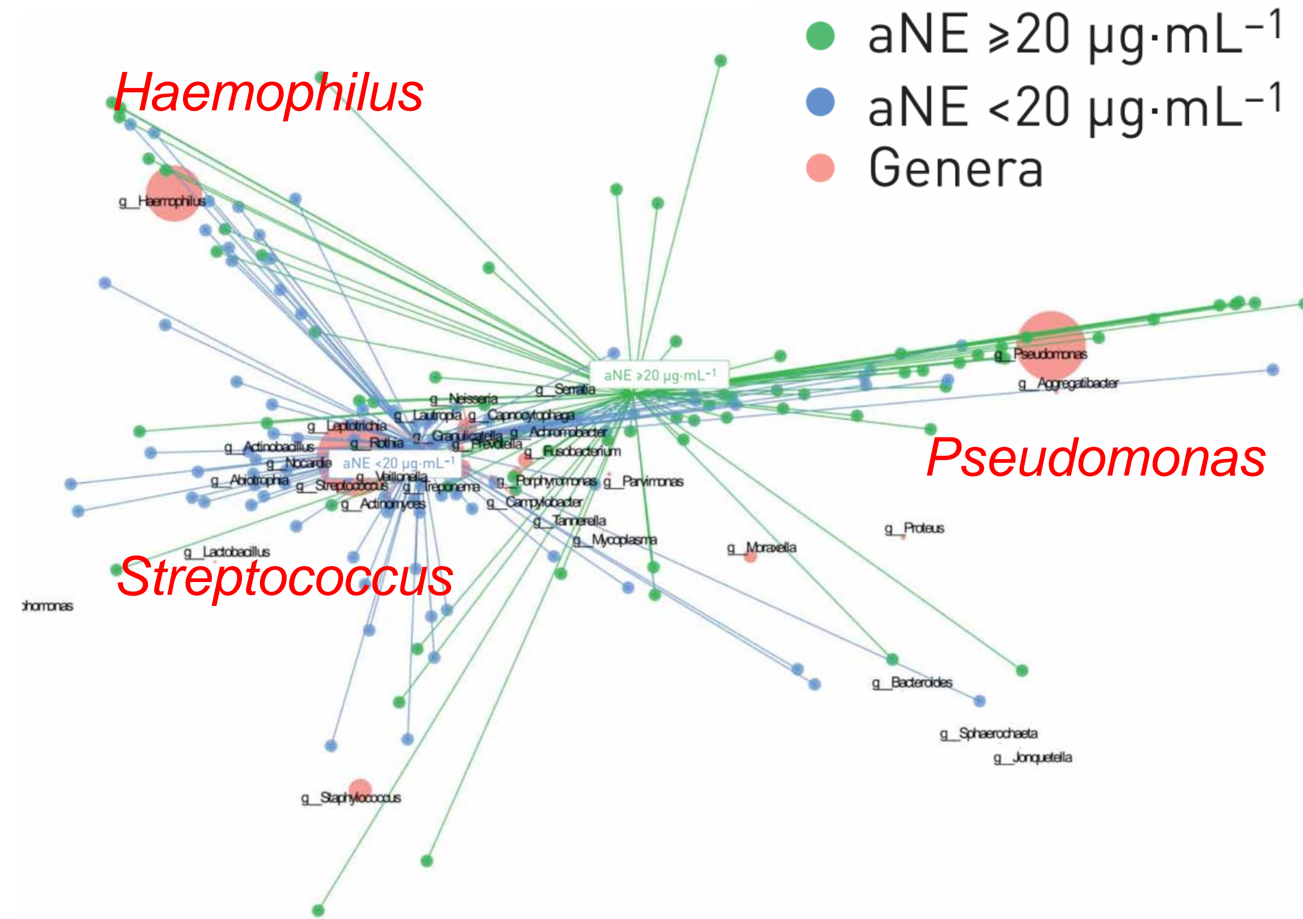
Aogain MM, et al. Clin Chest Med 2022;43(1):23-34.

Sputum NE activity and microbiome

- 185 adult bronchiectasis patients with clinical stable status, Italy
- Sputum NE level measurement and microbiome analysis

Microbiome α-diversity

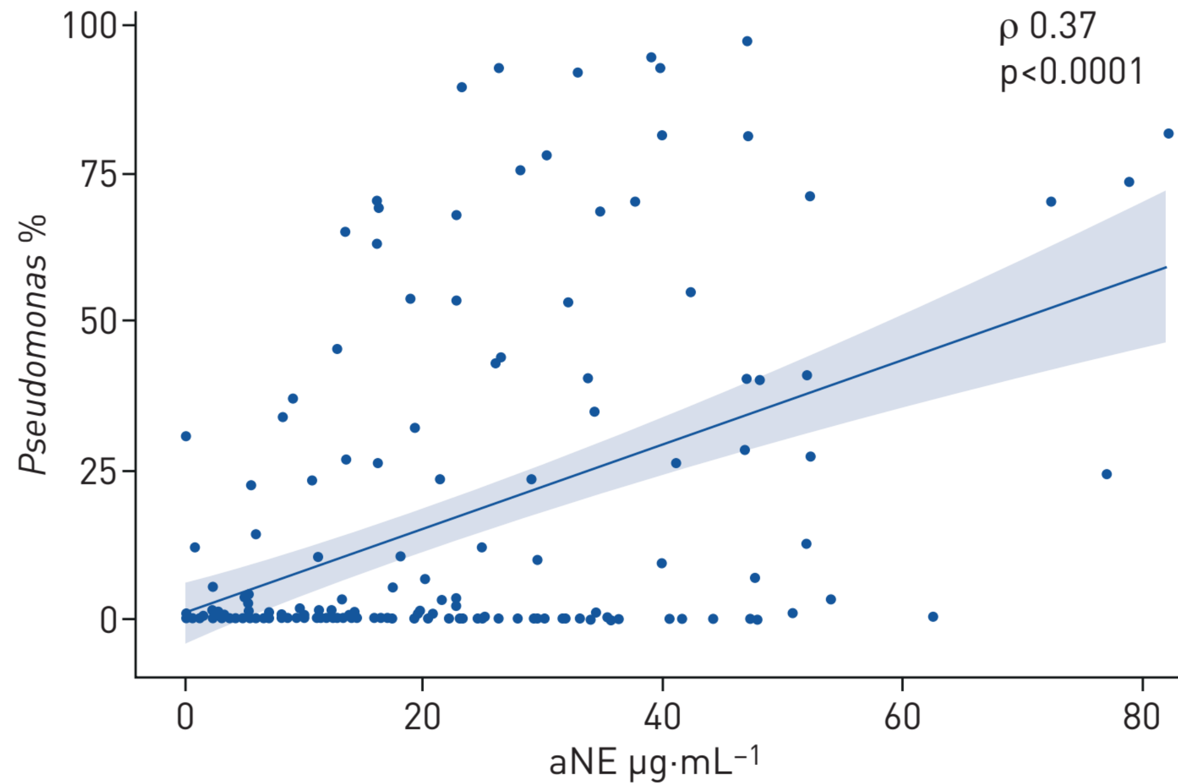




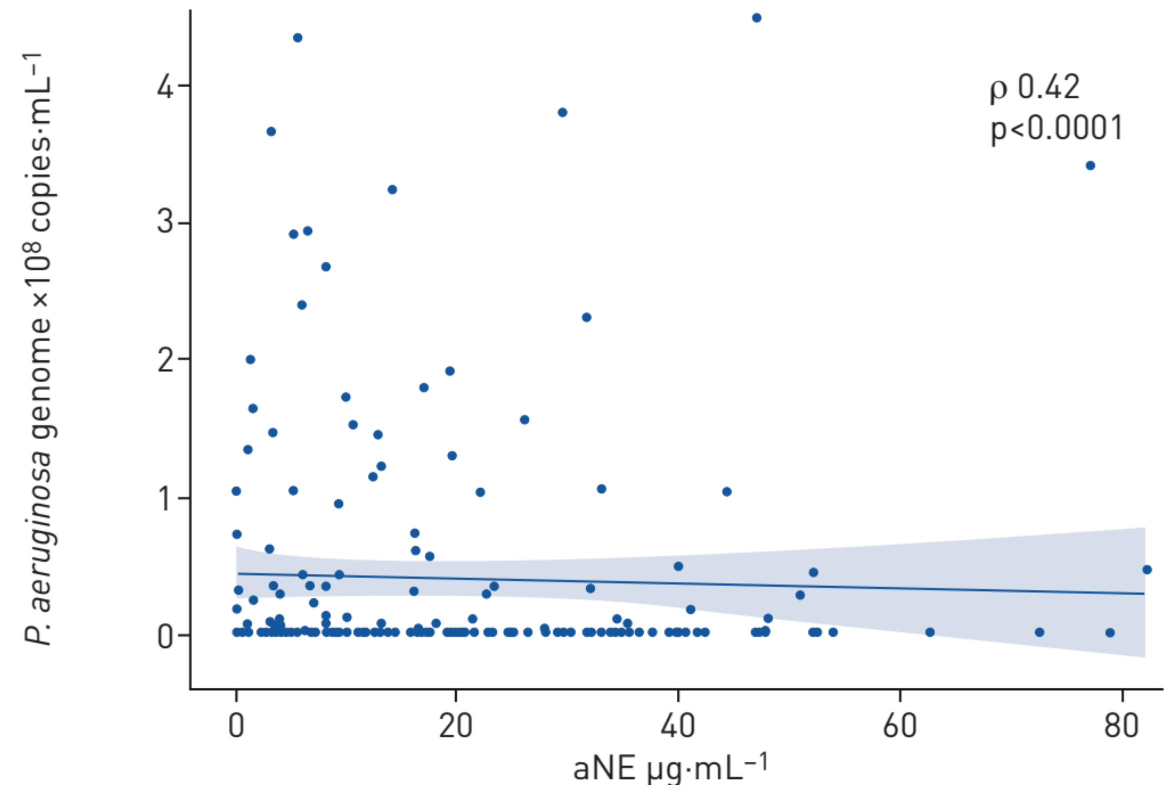
Oriano M, et al. Eur Respir J 2020;56(4):2000769.

Sputum NE activity and microbiome

Relative abundance of *P. aeruginosa*



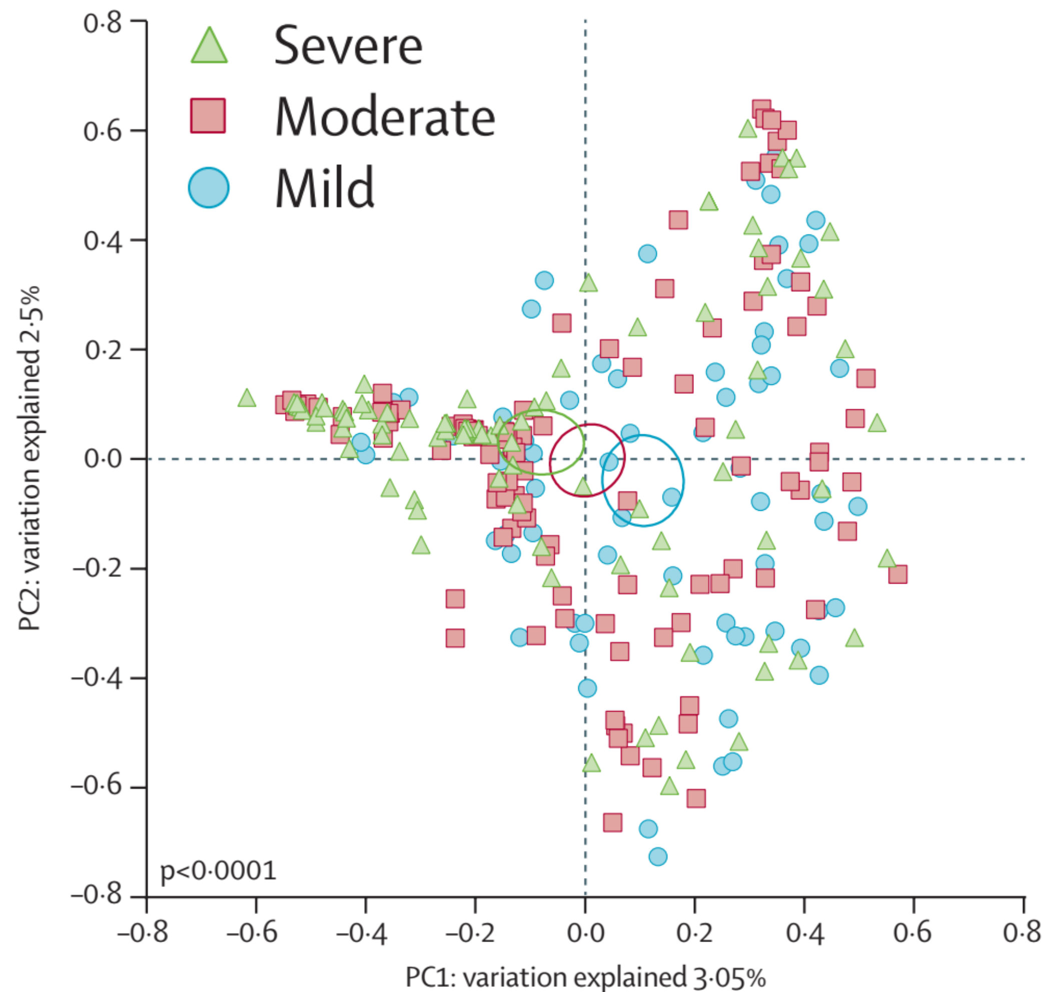
Bacterial burden of *P. aeruginosa*

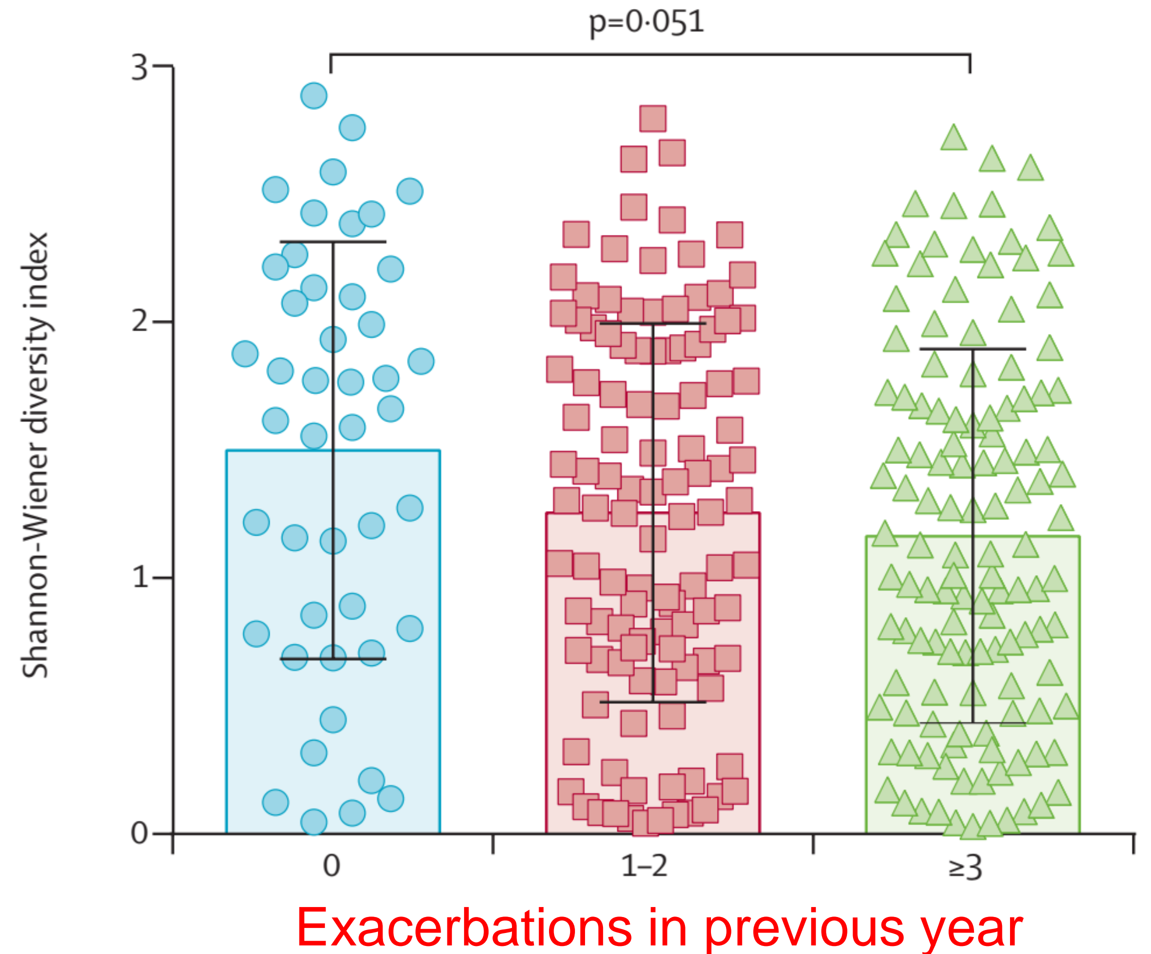


Oriano M, et al. Eur Respir J 2020;56(4):2000769.

Sputum microbiome and bronchiectasis severity

- 281 bronchiectasis patients with clinical symptom
- Repeated sputum samples at stable and exacerbation visits



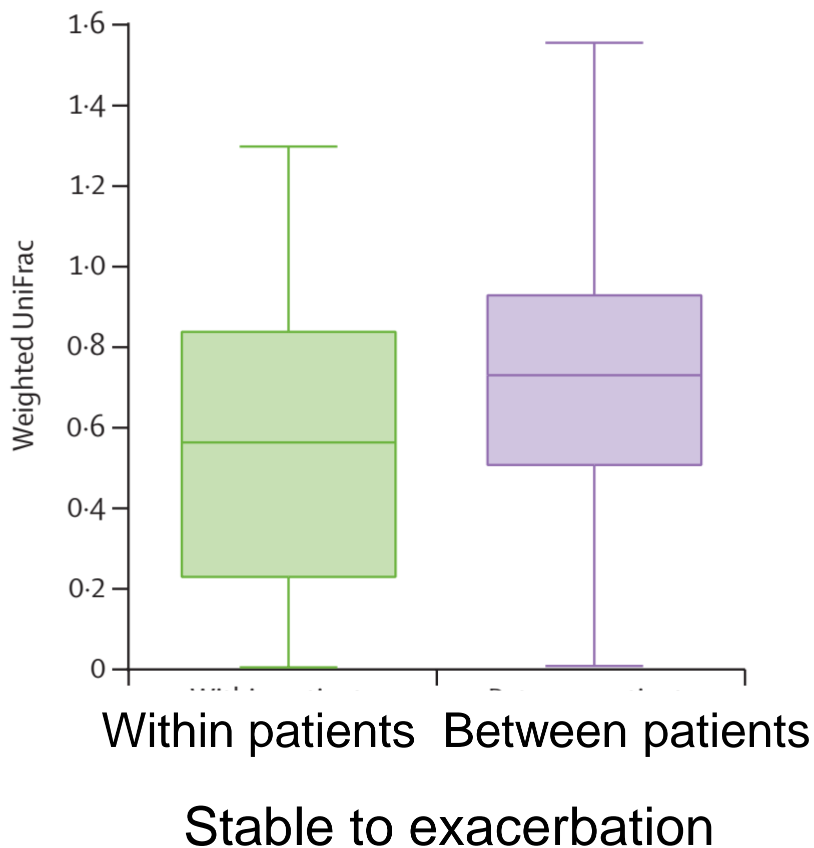


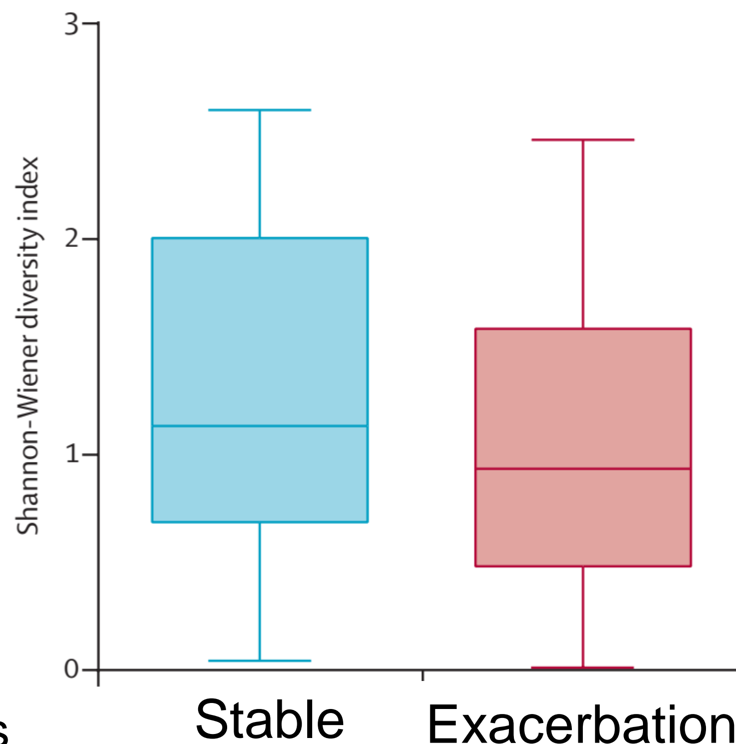
Exacerbations in previous year

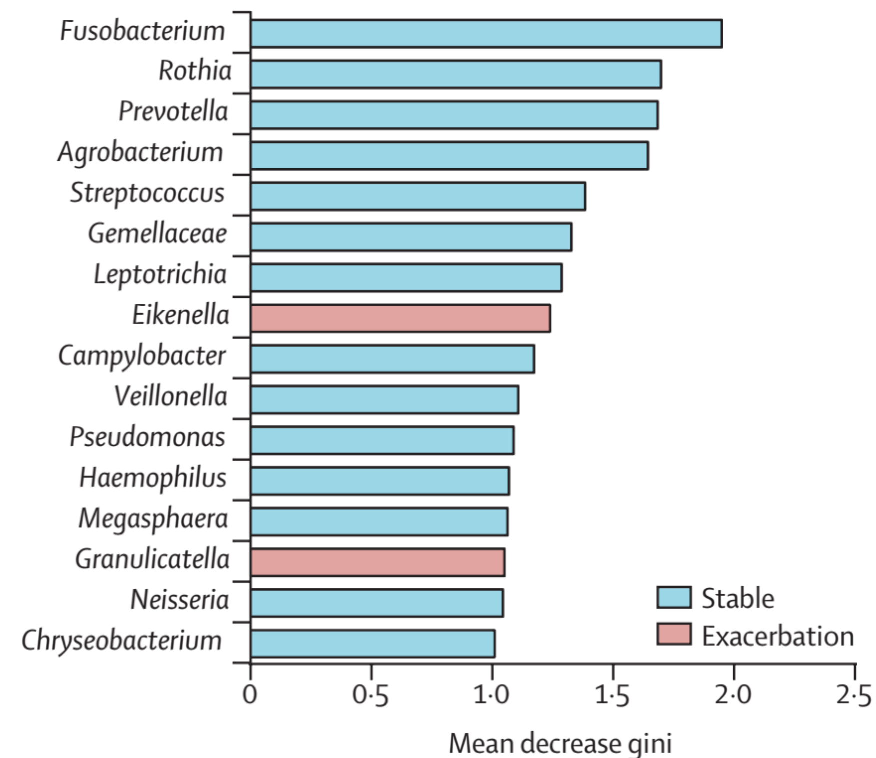
Dicker AJ, et al. Lancet Respir Med 2021;9:885-896.

Sputum microbiome according to exacerbation

Differences in the microbiome between stable state and exacerbation



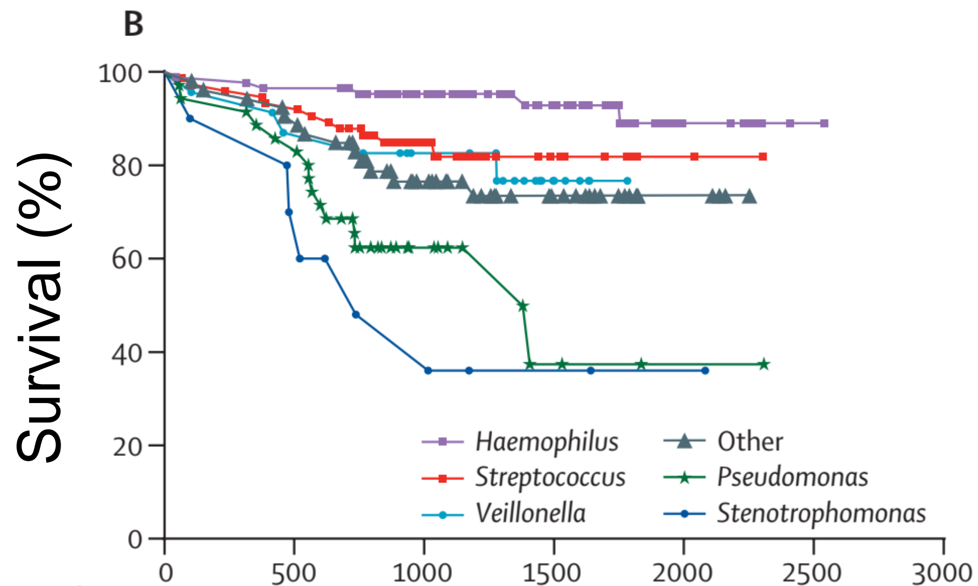




Dicker AJ, et al. Lancet Respir Med 2021;9:885-896.

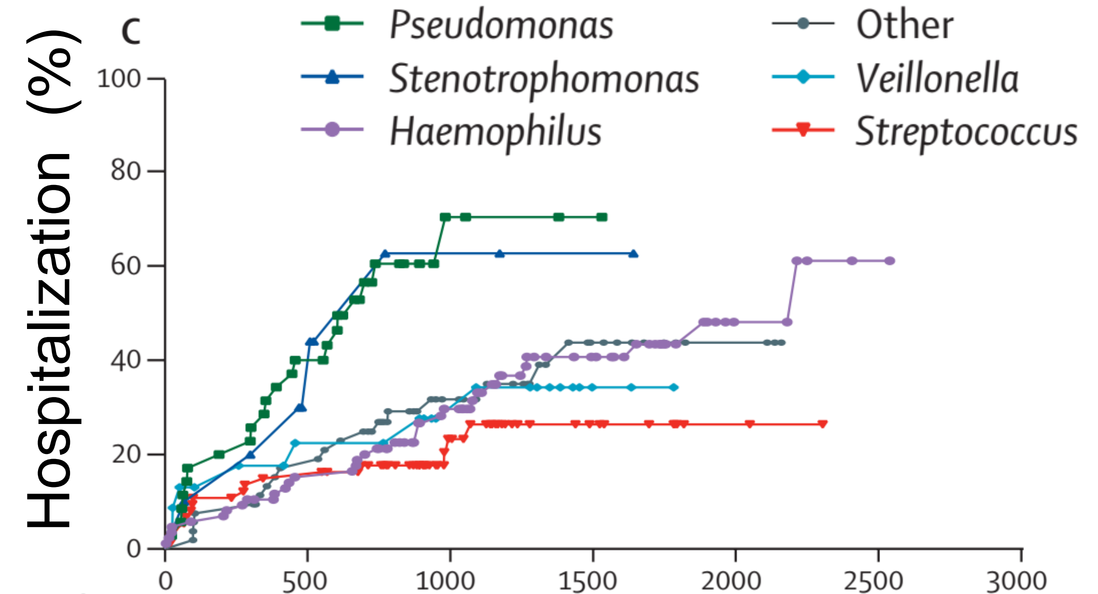
Microbiome profile and longitudinal outcome

Based on the dominant organism identified at baseline sampling



Number at risk (number censored)

	0	500	1000	1500	2000	2500	3000
Haemophilus	86 (0)	83 (0)	58 (24)	35 (22)	7 (27)	1 (6)	0 (1)
Streptococcus	74 (0)	69 (0)	30 (33)	10 (19)	2 (8)	0 (2)	0 (0)
Veillonella	23 (0)	20 (0)	16 (3)	6 (9)	0 (6)	0 (0)	0 (0)
Other	53 (0)	48 (0)	31 (10)	16 (14)	4 (12)	0 (4)	0 (0)
Pseudomonas	35 (0)	30 (0)	9 (13)	3 (4)	1 (2)	0 (1)	0 (0)
Stenotrophomonas	10 (0)	7 (0)	4 (1)	2 (1)	1 (1)	0 (1)	0 (0)



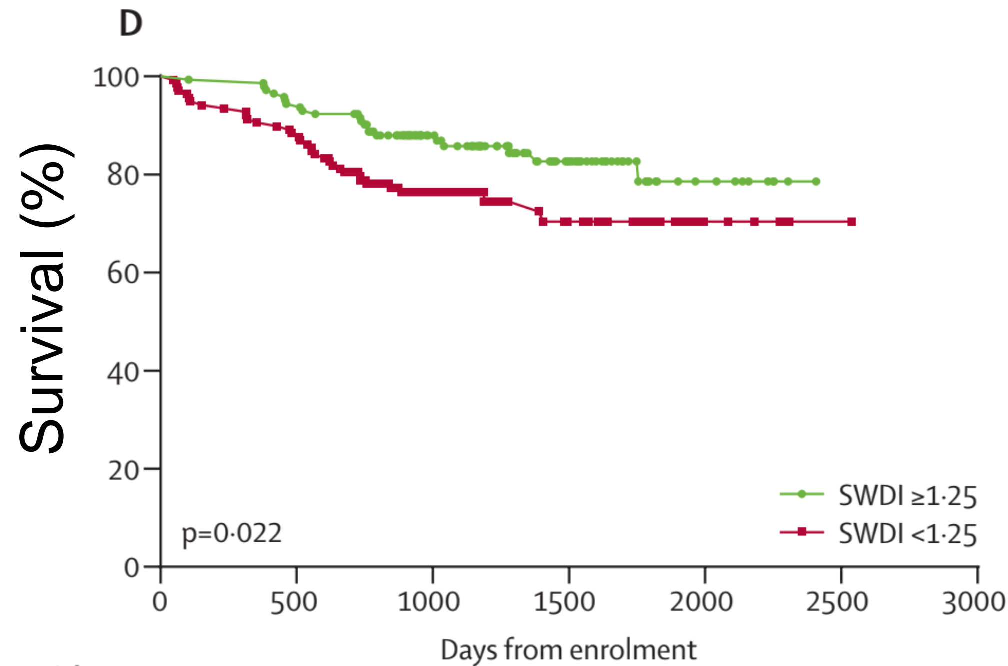
Number at risk (number censored)

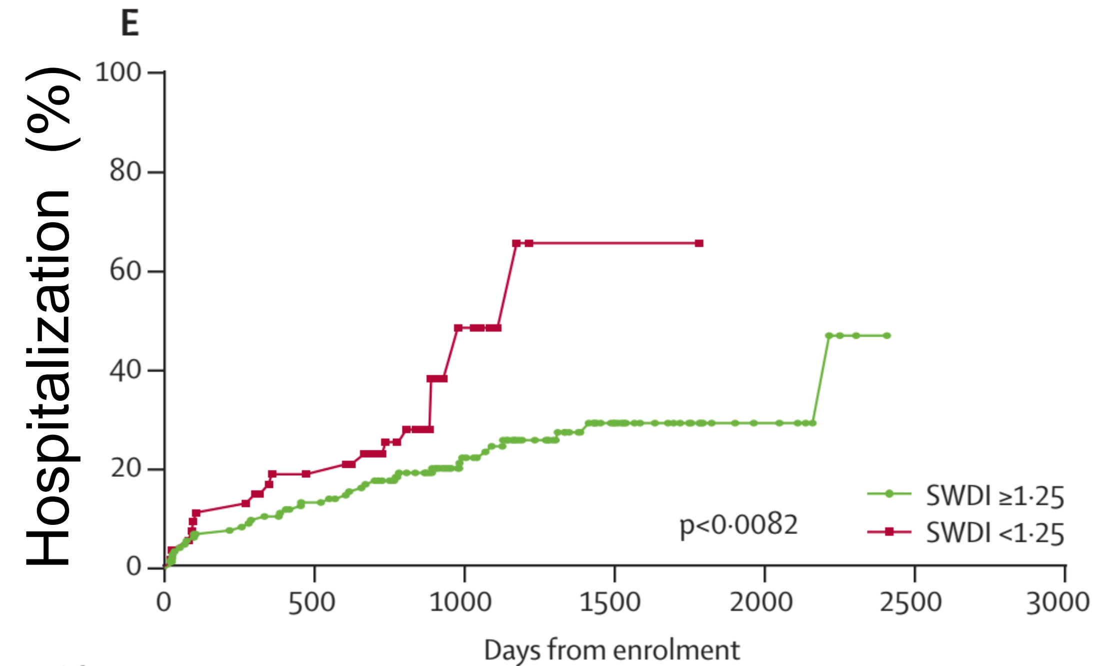
	0	500	1000	1500	2000	2500	3000
Pseudomonas	35 (0)	21 (0)	3 (11)	1 (2)	0 (1)	0 (0)	0 (0)
Stenotrophomonas	10 (0)	5 (2)	2 (1)	1 (1)	0 (1)	0 (0)	0 (0)
Haemophilus	86 (0)	71 (2)	47 (13)	26 (15)	5 (19)	1 (3)	0 (1)
Other	53 (0)	43 (1)	25 (11)	10 (12)	3 (7)	0 (3)	0 (0)
Veillonella	23 (0)	16 (2)	11 (4)	3 (7)	0 (3)	0 (0)	0 (0)
Streptococcus	74 (0)	62 (1)	27 (31)	9 (17)	2 (7)	0 (2)	0 (0)

Dicker AJ, et al. Lancet Respir Med 2021;9:885-896.

Microbiome profile and longitudinal outcome

Based on the microbiome α-diversity (Shannon-Wiener diversity index)

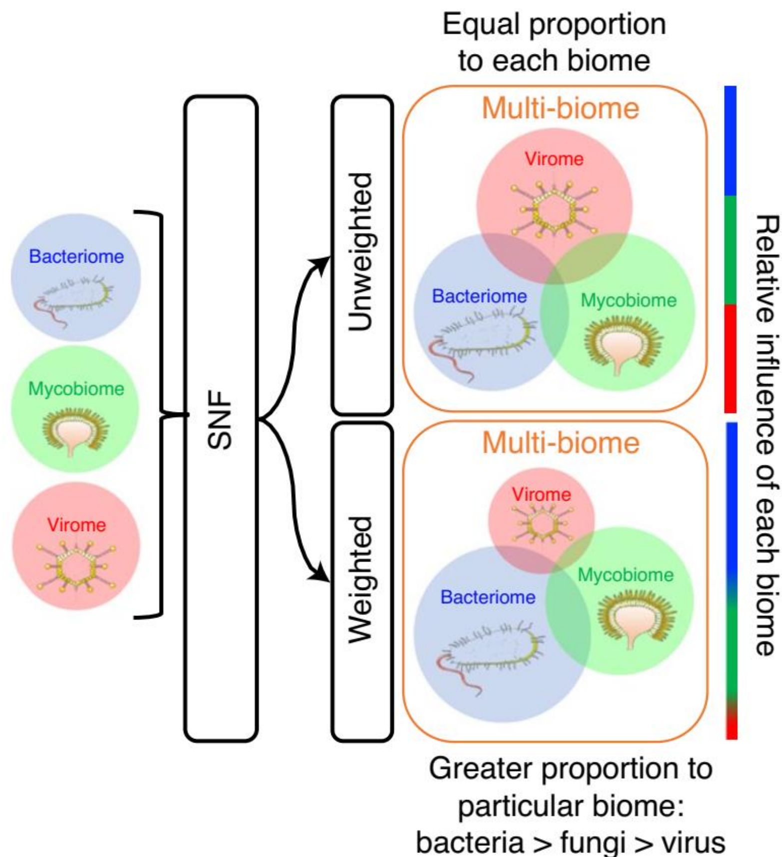




Dicker AJ, et al. Lancet Respir Med 2021;9:885-896.

Multi-biome intergration in bronchiectasis exacerbation

- 217 bronchiectasis patients from Asian and European cohort (CAMEB)
- Respiratory samples with integrated multi-biome analysis (bacteriome/mycobiome/virome)



1
2
0.5
0
Similarity
Patients with bronchiectasis
Patients with bronchiectasis

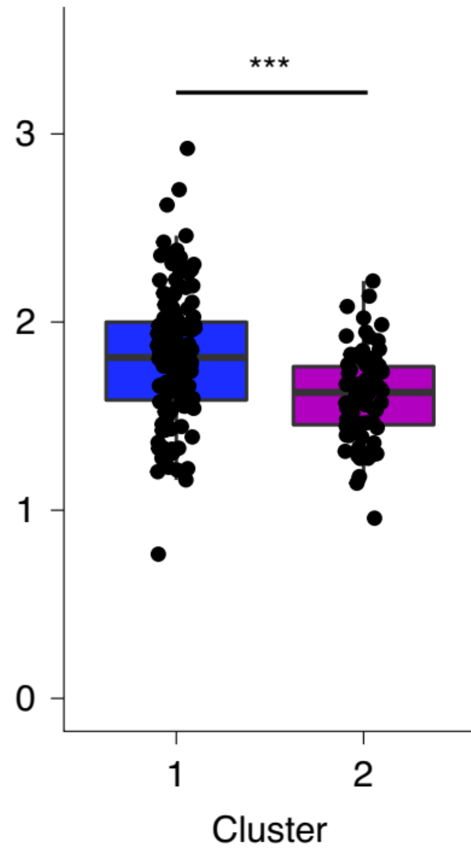
Clustering for frequent exacerbator phenotype

V_Human parainfluenzavirus 3
B_Pseudomonas
B_Neisseria
F_Aspergillus
B_Klebsiella
V_Human parainfluenzavirus 4
B_Prevotella
B_Porphyromonas
B_Actinobacillus
F_Trechispora
F_Perenniporia
B_Corynebacterium
B_Staphylococcus
B_Leptotrichia
F_Trichosporon
B_Acinetobacter
B_Gemella
B_Veillonella
F_Penicillium
F_Issatchenkia
B_Fusobacterium
F_Botrytis
F_Cryptococcus
F_Wickerhamomyces
F_Clavispora
F_Saccharomyces
V_Rhinovirus
B_Rothia
B_Haemophilus
F_Candida
B_Streptococcus
−6 −4 −2 0 2 4 6
LDA score ($\log_{10}$)

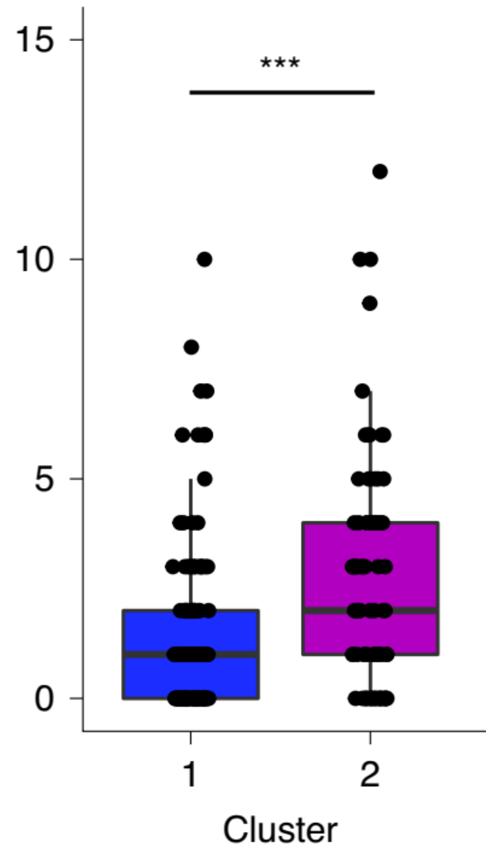
Mac Aogain M, et al. Nat Med 2021;27(4):688-699.

Multi-biome and clinical outcome

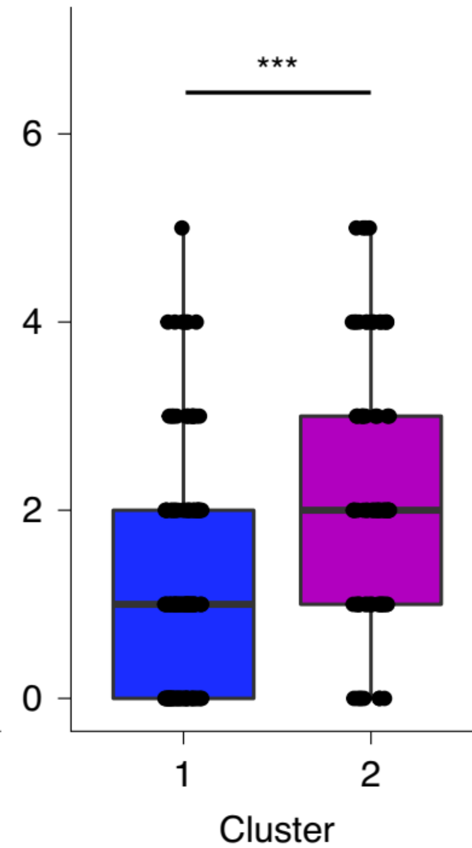
Shannon diversity index



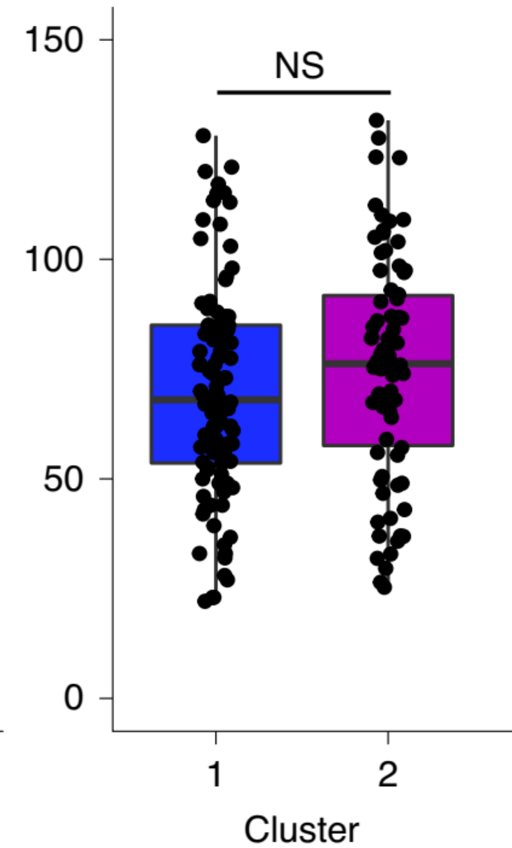
Exacerbations



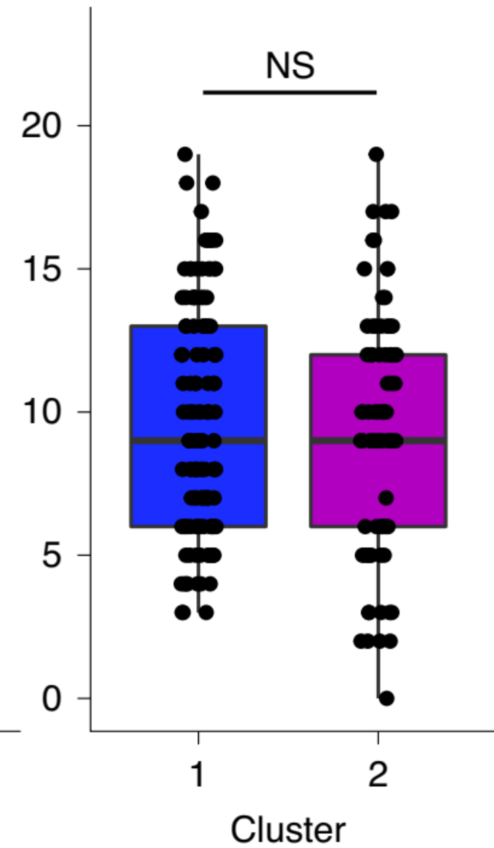
mMRC score



FEV1(% predicted)

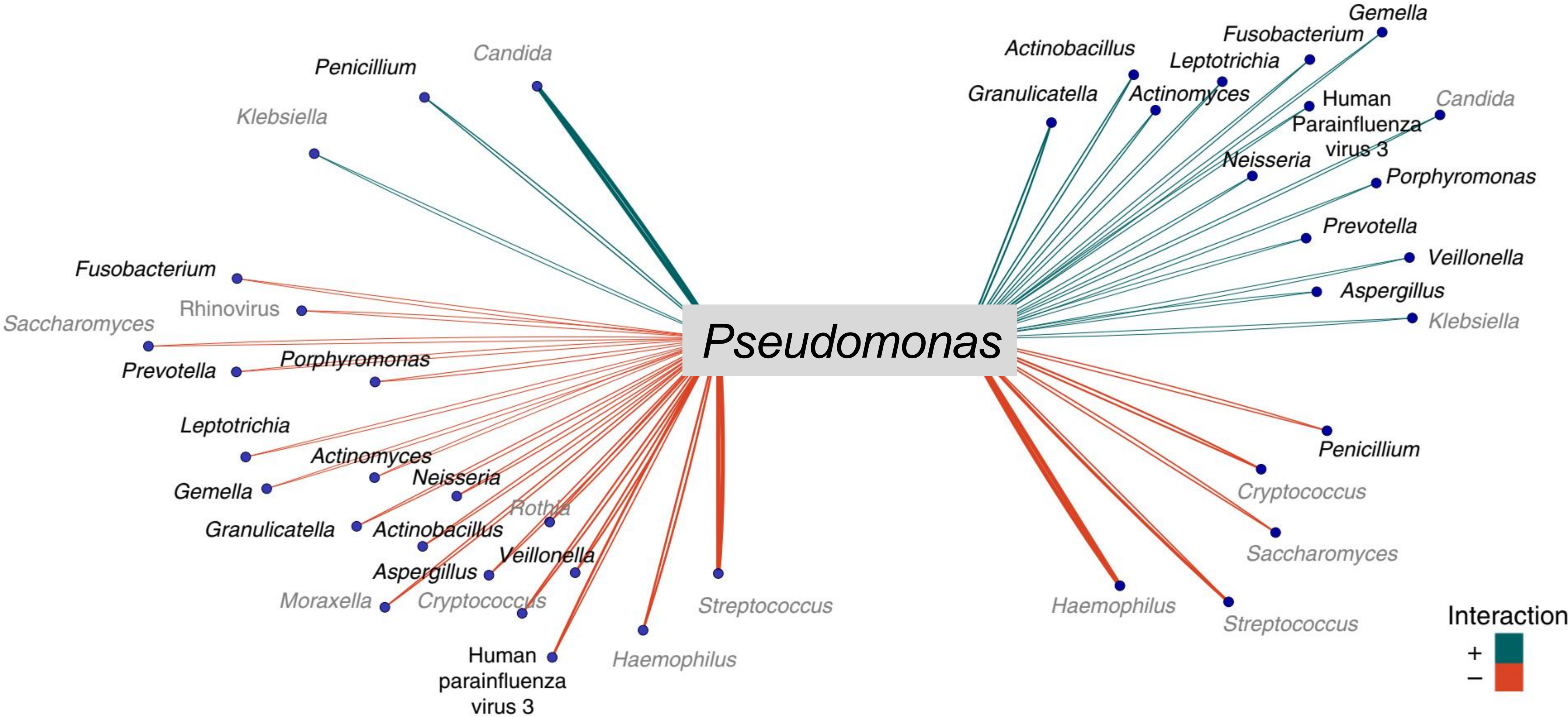


BSI



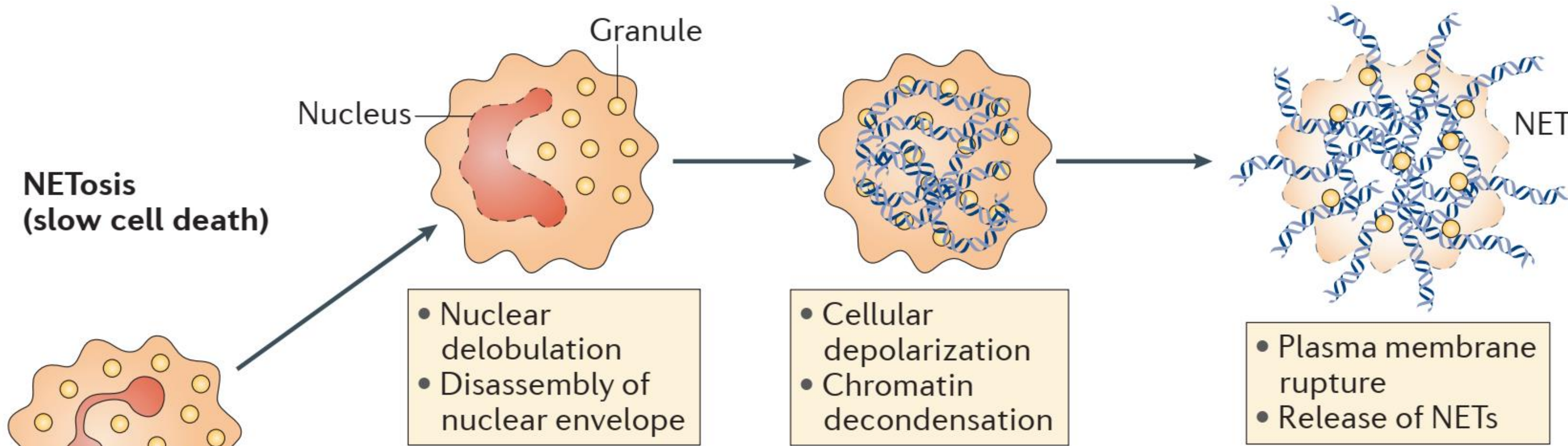
Mac Aogain M, et al. Nat Med 2021;27(4):688-699.

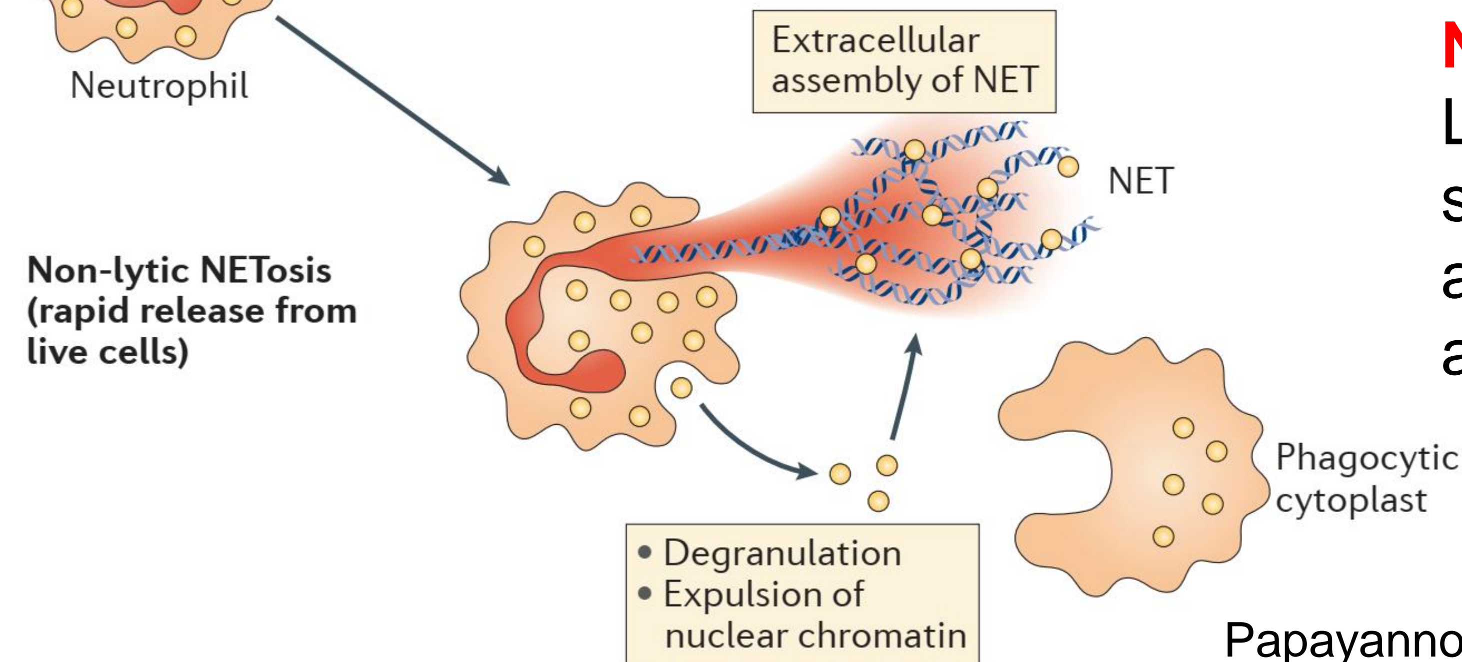
Pseudomonas-interaction network in exacerbation clustering



Mac Aogain M, et al. Nat Med 2021;27(4):688-699.

Neutrophil extracellular traps in immunity





NET formation pathways

Large, extracellular, web-like structures composed of cytosolic and granule proteins, assembled on a scaffold of decondensed chromatin

Papayannopoulos V. Nat Rev Immunol 2018;18(2):134-147.

NET in respiratory disease

NETosis

Translocation

MPO
Elastase
PAD4

NET casting

NET

Calprotectin

Fungi

ROS production & granule membrane disintegration

Nuclear membrane disintegration & chromosome decondensation

NETs trap viruses, bacteria & fungi

MPO

Elastase
Histones

Bacteria

Viruses

Neutrophil

Degranulation

Phagocytosis

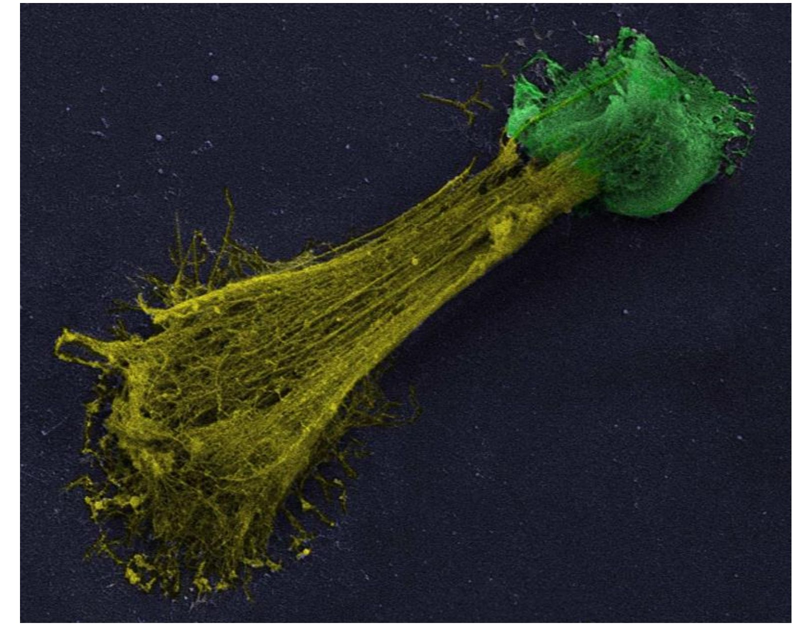
Toxic granule proteins are released

Deactivation and killing of pathogens

Opsonized pathogens and infected cells are phagocytized

Immunoglobulins
Complement

Opsonization

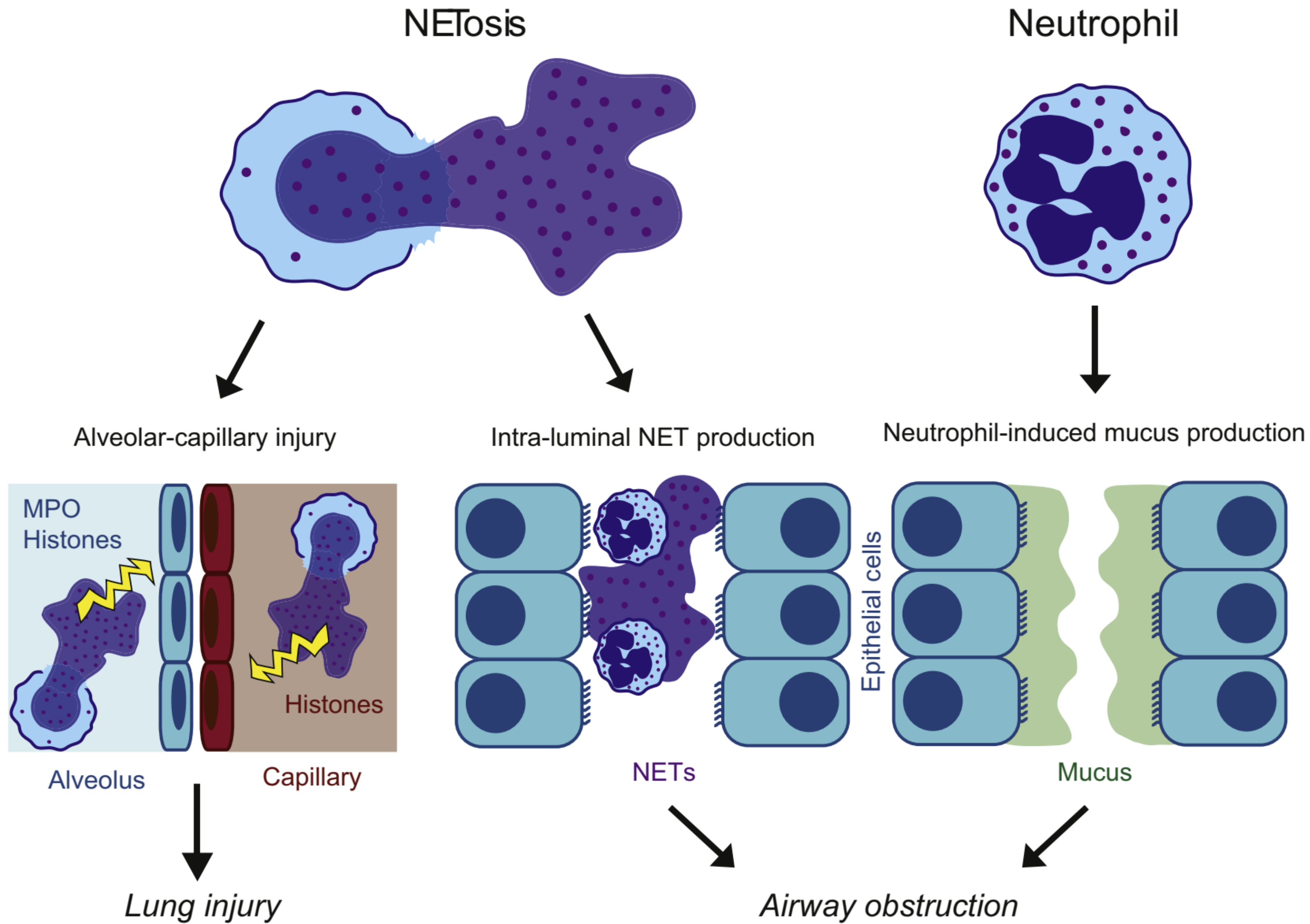


NETosis

- NET release occuring primarily through a cell death process
- To trap and/or neutralize pathogens

Cortjens B, et al. Paediatr Respir Rev 2017;21:54-61.

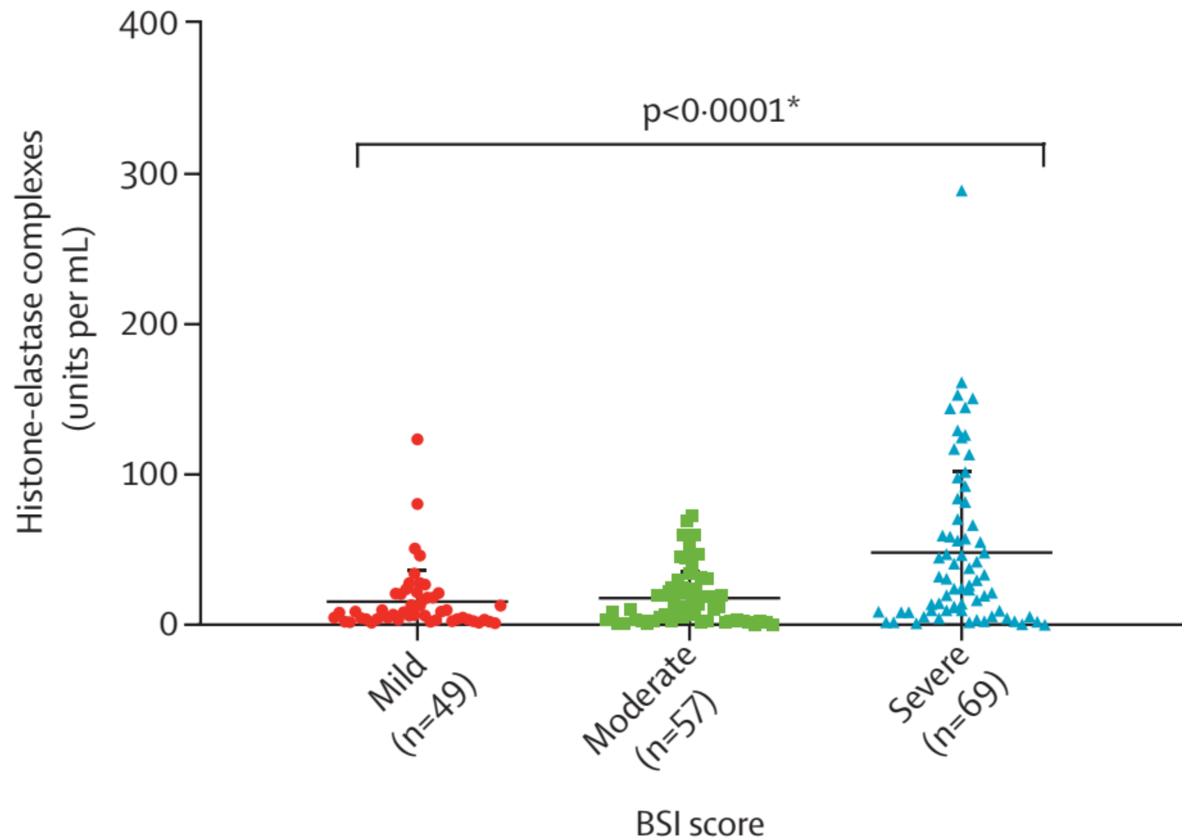
Potential immunopathological roles of NETs

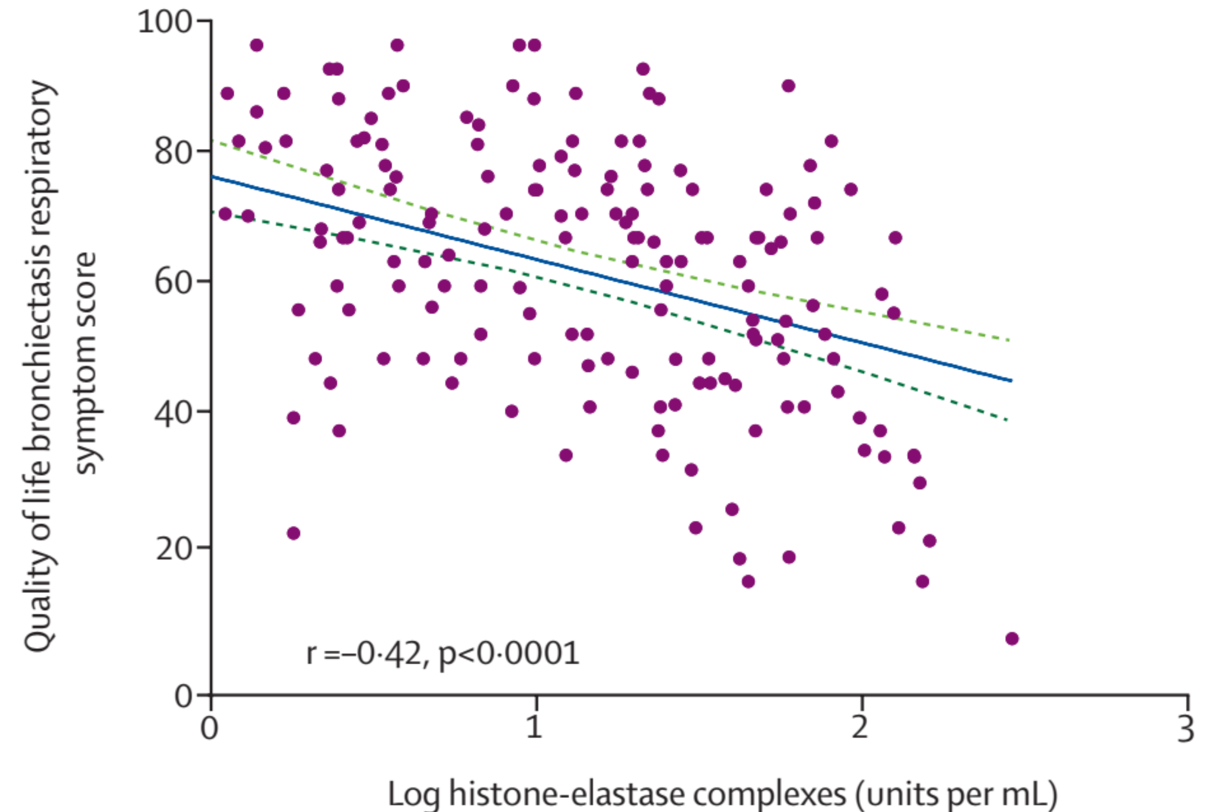


Cortjens B, et al. Paediatr Respir Rev 2017;21:54-61.

NET and bronchiectasis severity

- ➢ Patients with clinically stable, CT-confirmed idiopathic or post-infective bronchiectasis, without antibiotic treatment for 4 weeks before enrollment
- ➢ Sputum samples for proteomic analysis
  - ✓ NET quantification with immunoassay for histone-elastase complexes

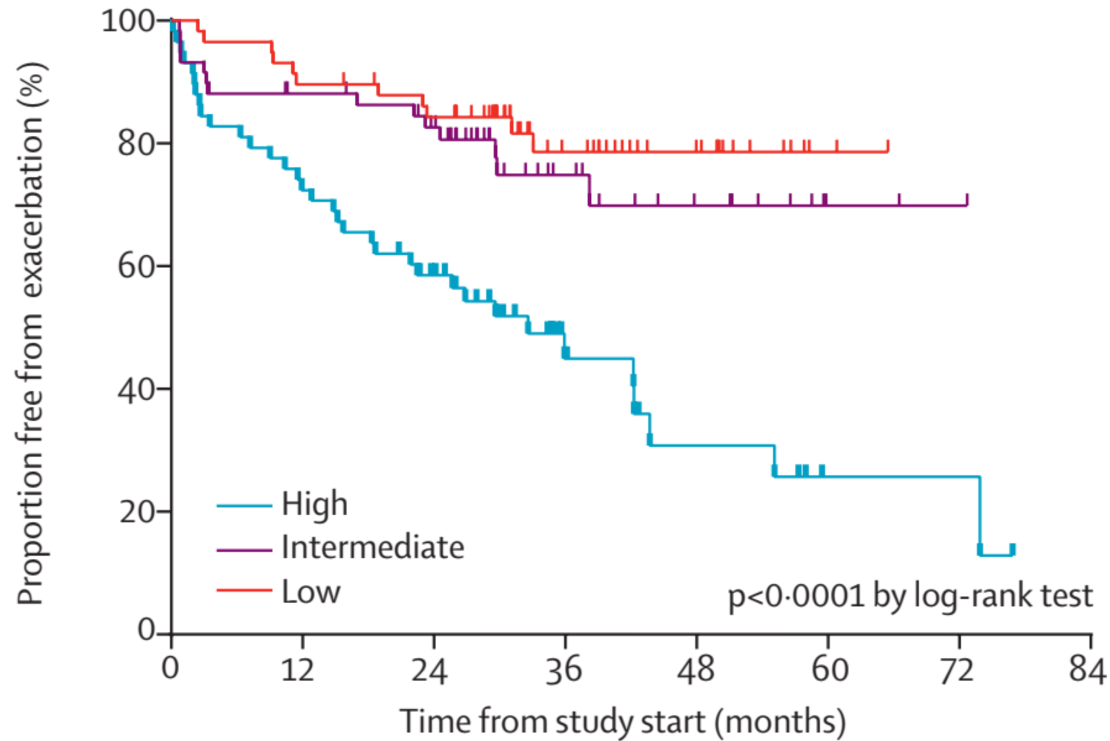


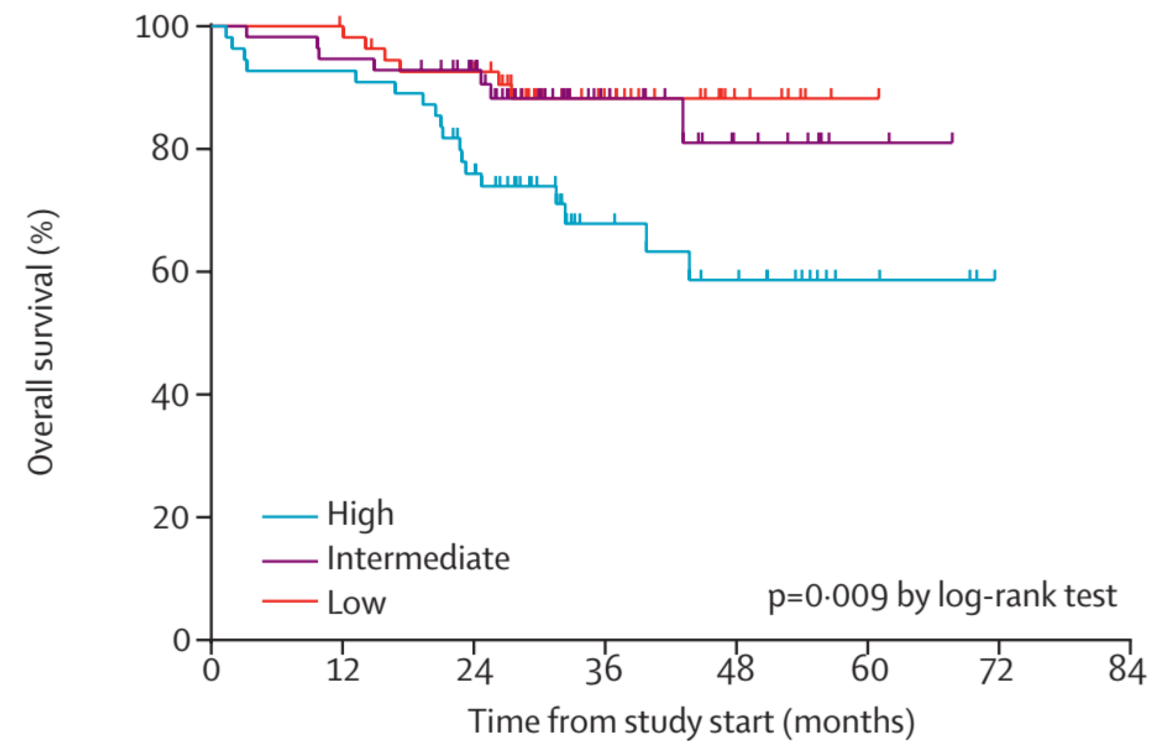


Keir HR, et al. Lancet Respir Med 2021;9:873-884.

NET and longitudinal outcome

- Association with severe bronchiectasis, symptoms, frequent exacerbations, and future outcomes





Number at risk (number censored)

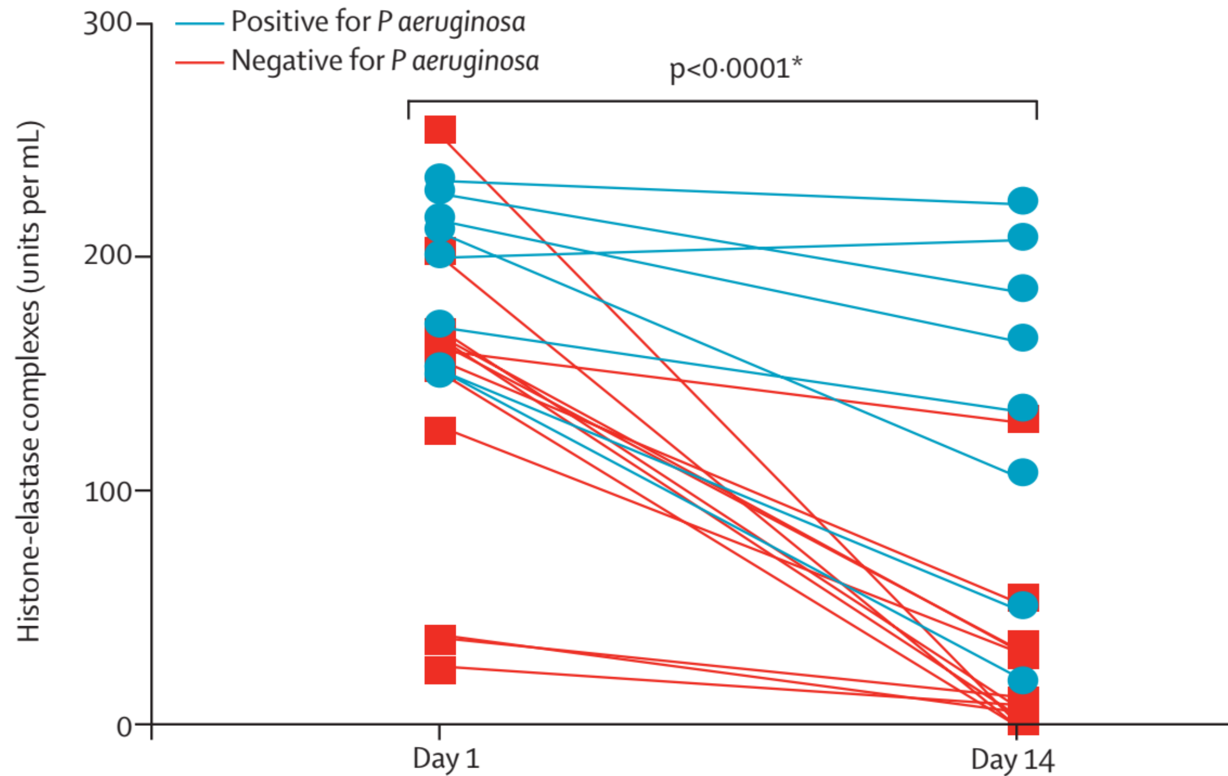
	0	12	24	36	48	60	72	84
High	58 (0)	43 (0)	31 (4)	12 (18)	7 (20)	3 (23)	3 (23)	0 (24)
Intermediate	59 (0)	50 (3)	44 (6)	18 (29)	10 (36)	3 (43)	2 (44)	0 (45)
Low	58 (0)	53 (0)	48 (2)	25 (23)	14 (34)	3 (45)	1 (47)	0 (47)

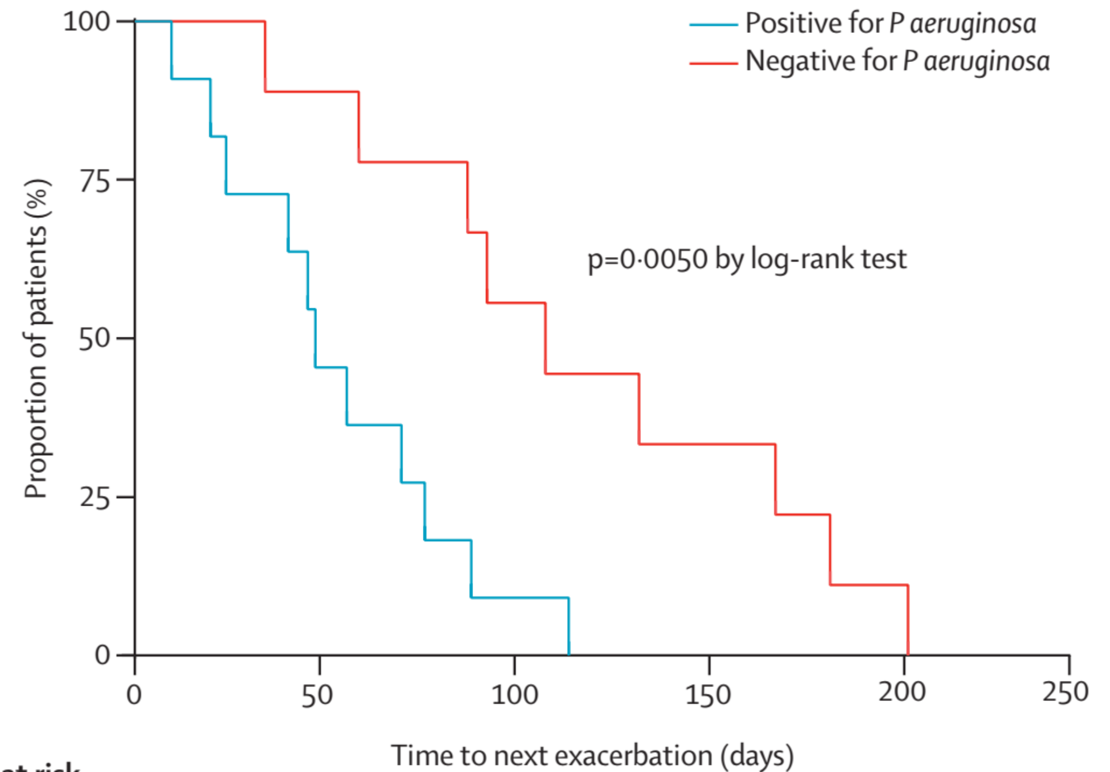
	0	12	24	36	48	60	72	84
High	58 (0)	55 (0)	48 (24)	19 (26)	14 (34)	7 (37)	4 (40)	0 (40)
Intermediate	59 (0)	57 (0)	53 (4)	21 (33)	12 (41)	4 (49)	2 (51)	0 (52)
Low	58 (0)	58 (0)	53 (2)	27 (26)	14 (39)	3 (50)	1 (52)	0 (52)

Keir HR, et al. Lancet Respir Med 2021;9:873-884.

NET change and antibiotic response

- Antibiotic treatment reduces NETs
- Patients with *P aeruginosa* infection: higher baseline NETs and less of a reduction in NETs, which correlates with a worse clinical outcome



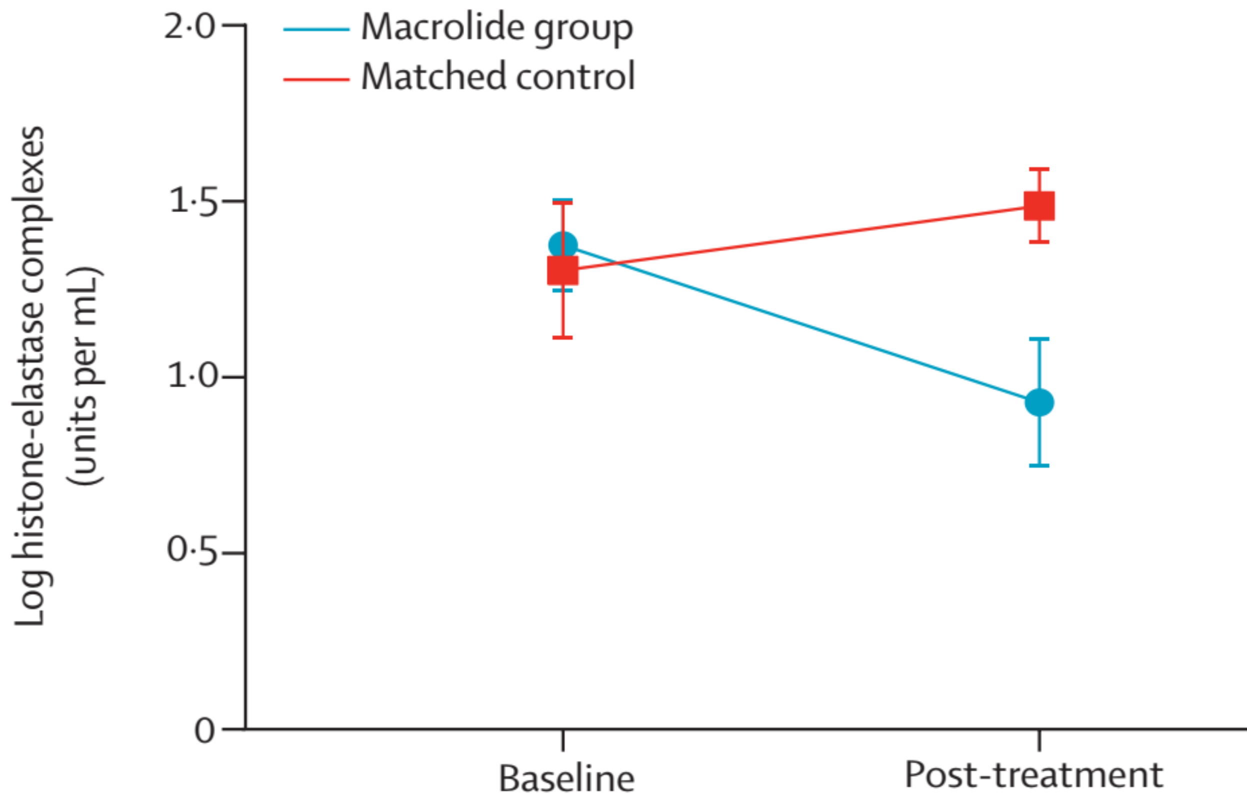


Keir HR, et al. Lancet Respir Med 2021;9:873-884.

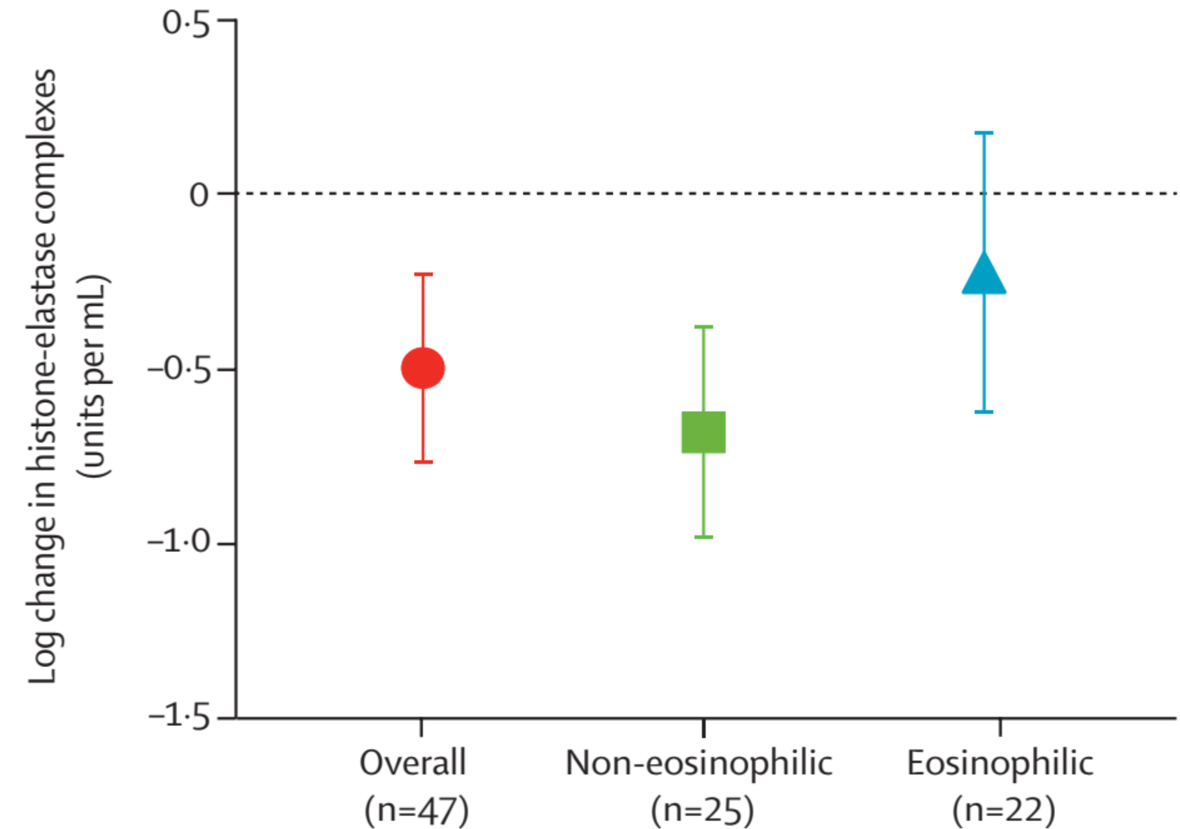
NET change according to macrolide therapy

- Changes in NET concentrations in response to long-term macrolide therapy in bronchiectasis and asthma

Bronchiectasis group



Asthma group



Keir HR, et al. Lancet Respir Med 2021;9:873-884.

Excerbation as a prognostic factor

- Key events in the natural history of bronchiectasis
- **Exacerbation**
  - ✓ Requirement for antibiotics in the presence of one or more symptoms of increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnea, increased fatigue/malaise, fever, and hemoptysis
- **Severe exacerbation**
  - ✓ Unscheduled hospitalizations or emergency department visits for exacerbations or complications

Excerbation as a prognostic factor

- 2,572 bronchiectasis patients in Europe and Israle, up to 5 years of follow-up

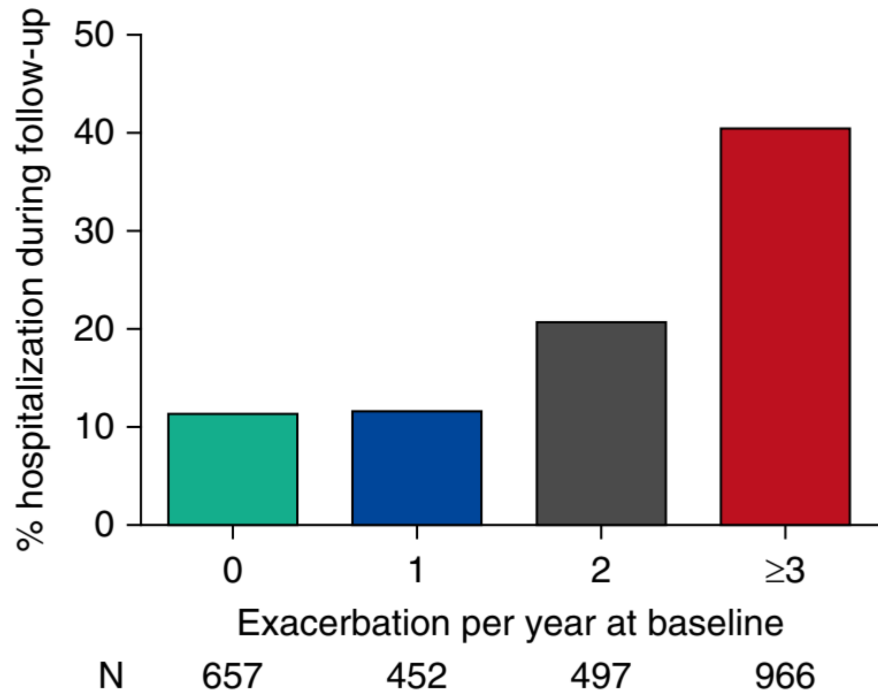
Incident rate ratios for exacerbation frequency during follow-up

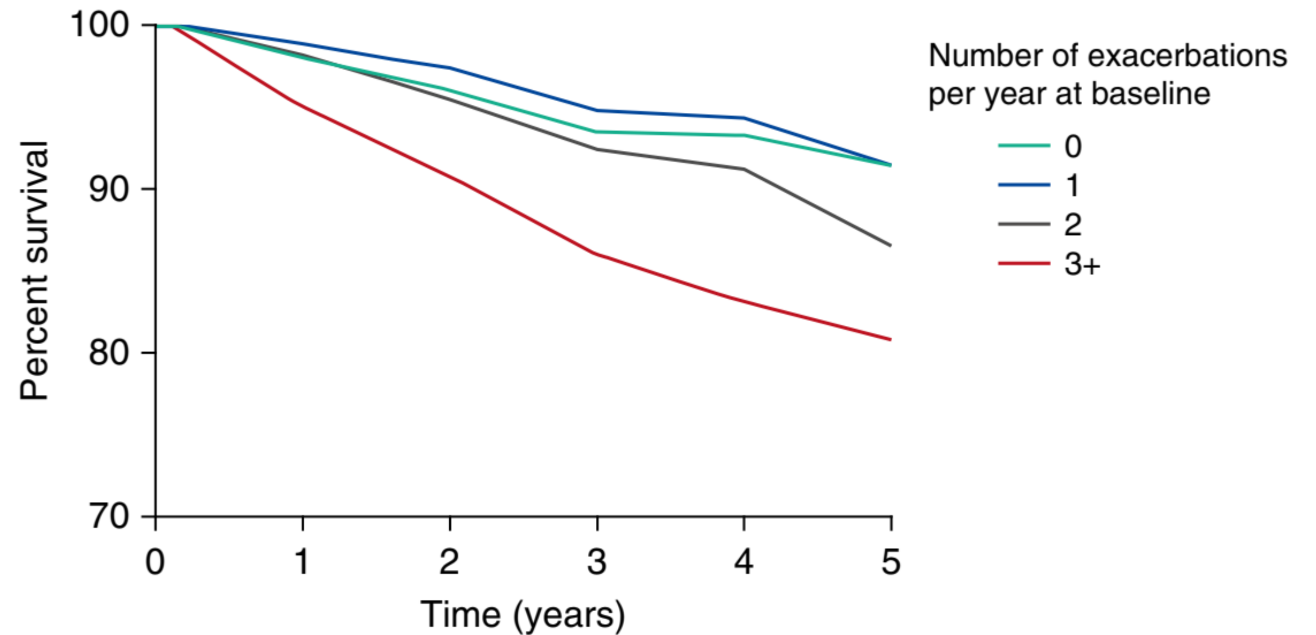
	aIRR (95% CI)	P-value
0 Past history of exacerbations	**1.0 (ref)**	
1 Past history of exacerbations	**1.81 (1.54-2.12)**	**<0.001**
2 Past history of exacerbations	**3.07 (2.62-3.60)**	**<0.001**
3 Past history of exacerbations	**5.18 (4.51-5.95)**	**<0.001**
FEV1 % predicted (per 10%)	0.96 (0.94-0.98)	0.001
Haemophilus influenzae	1.13 (1.01-1.28)	0.040
Pseudomonas aeruginosa	1.20 (1.04-1.40)	0.010
COPD	1.43 (1.22-1.67)	<0.001

Chalmers JD, et al. Am J Respir Crit Care Med 2018;197(11):1410-1420.

Excerbation as a prognostic factor

Follow-up hospitalization rates and annual survival in groups on the basis of baseline exacerbations





Numbers at risk

0	657	654	600	554	522	153
1	452	444	402	381	351	134
2	497	490	437	407	376	196
3 or more	966	958	836	771	694	365

Chalmers JD, et al. Am J Respir Crit Care Med 2018;197(11):1410-1420.

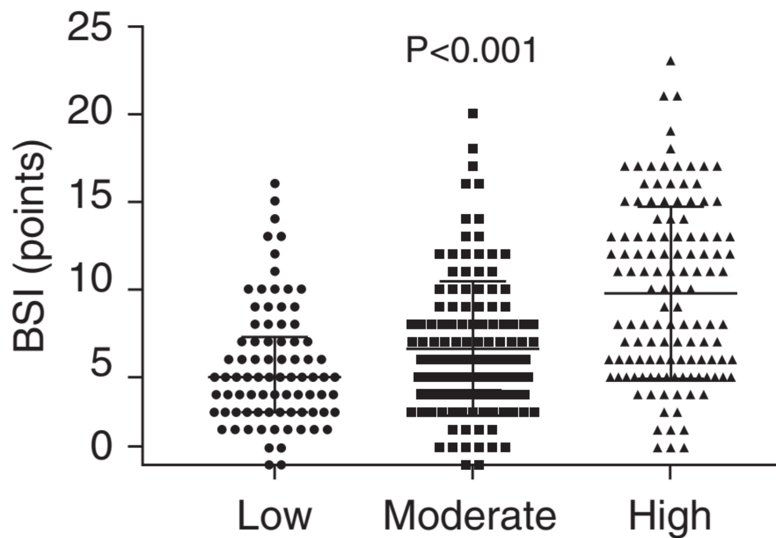
Symptom burden and disease severity

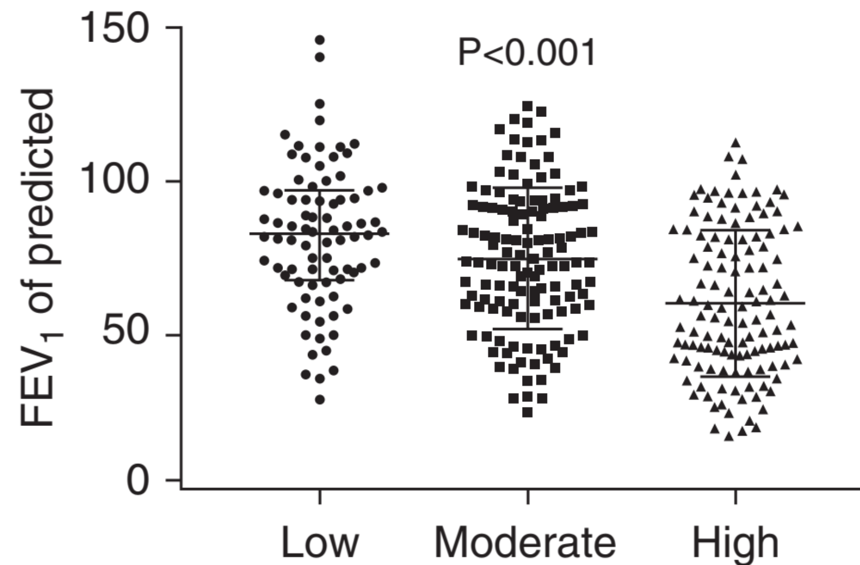
- 333 bronchiectasis, observational cohort in Scotland
- Measurement of daily symptom burden using SGRQ symptom score
  - ✓ Low, <40 points; Moderate, 40-70 points; High, >70 points

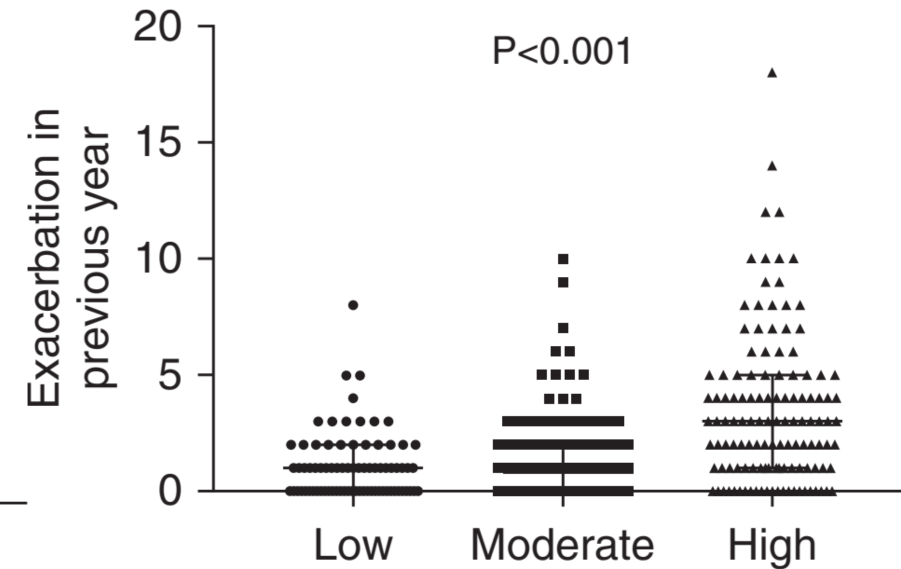
Bronchiectasis severity index

FEV1 % predicted

Exacerbation in previous year







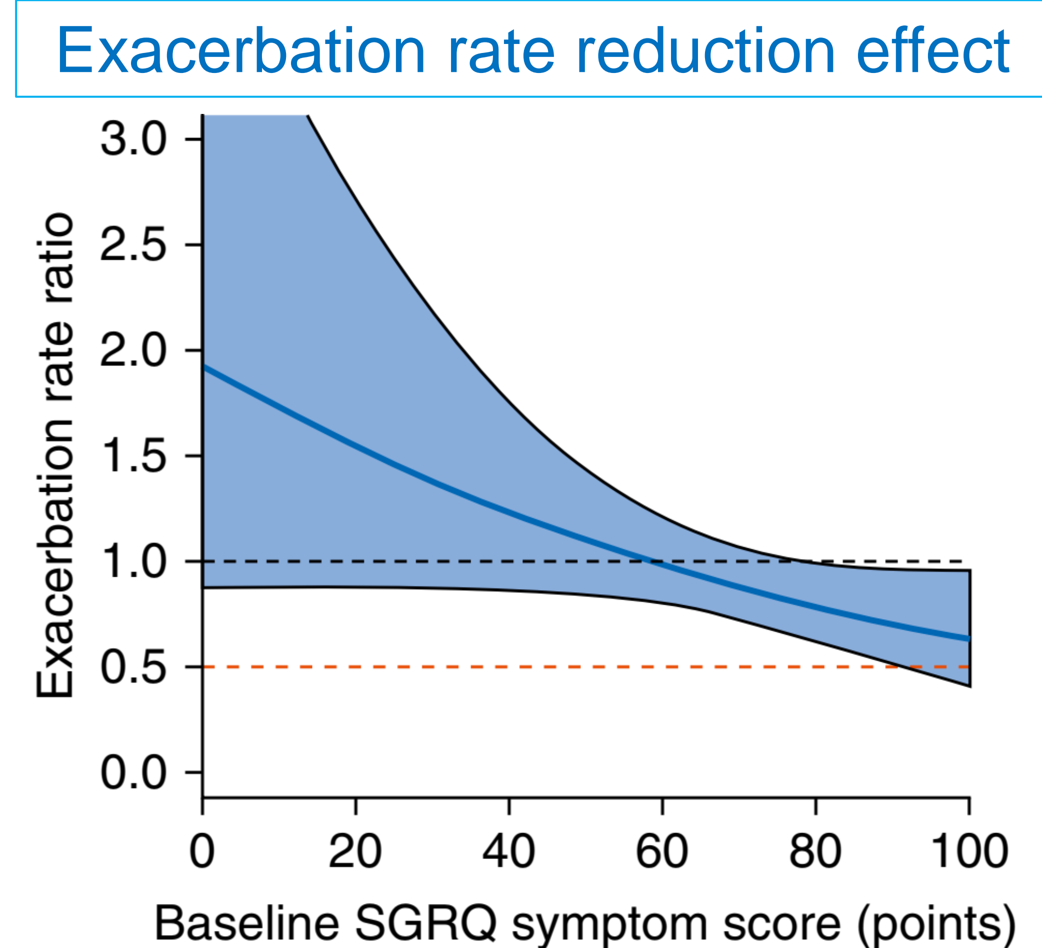
Gao Y, et al. Am J Respir Crit Care Med 2020;201(12):1499-1507.

Symptom burden and exacerbation risk

- *Post hoc* analysis of RCT of inhalaed dry power mannitol treatment
  - ✓ Inhaled mannitol 400mg bid vs. low-dose control, 1:1, 52wk

SGRQ Symptom Score	Exacerbation		Time to first exacerbation	
	aRR (95% CI)	P-value	aRR (95% CI)	P-value
Uncategorized	1.09 (1.02-1.17)	0.017	1.09 (1.02-1.15)	0.009
Categorized				
Low	1 (ref)		1 (ref)	
Moderate	1.50 (0.92-2.45)	0.10	1.73 (1.07-2.80)	0.03
High	1.75 (1.07-2.86)	0.03	1.78 (1.09-2.90)	0.02

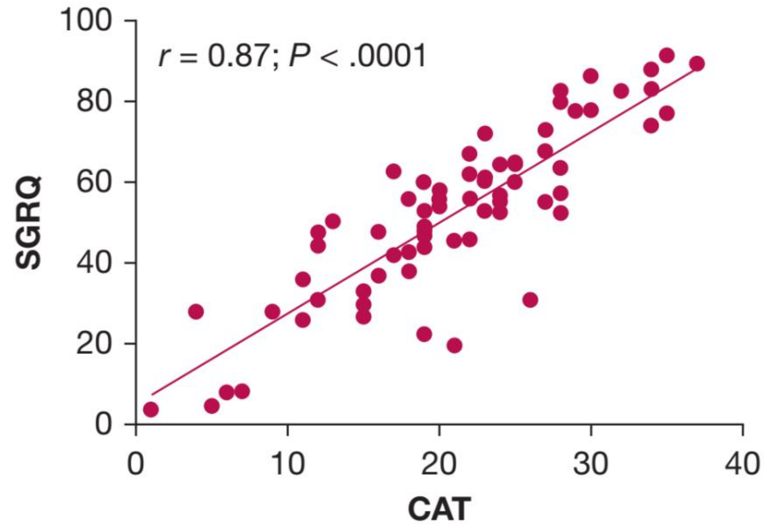
Exacerbation rate reduction effect

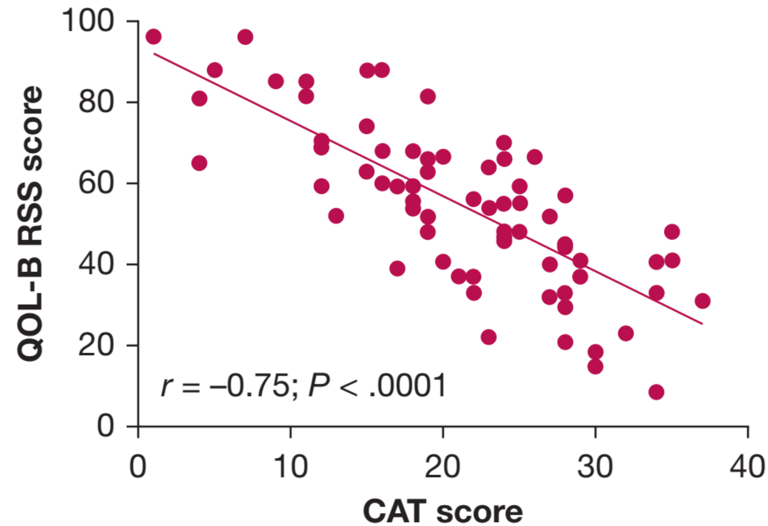


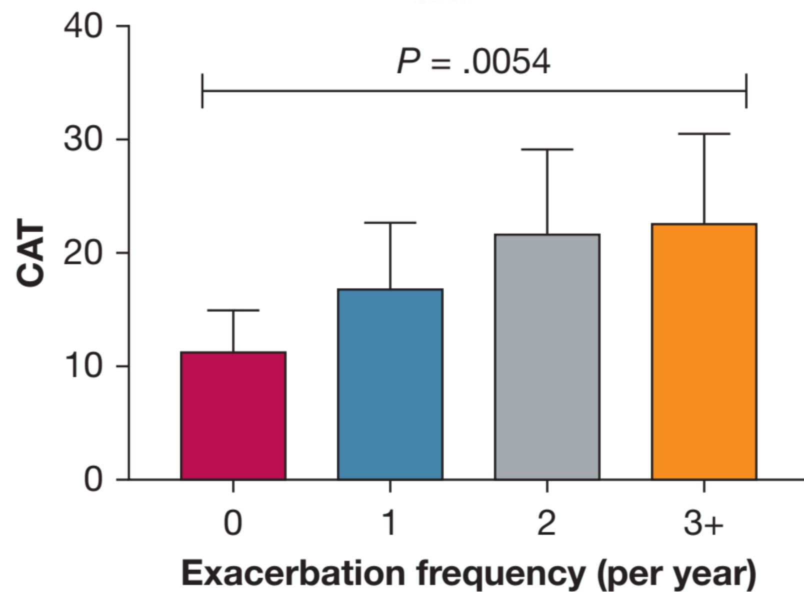
Gao Y, et al. Am J Respir Crit Care Med 2020;201(12):1499-1507.

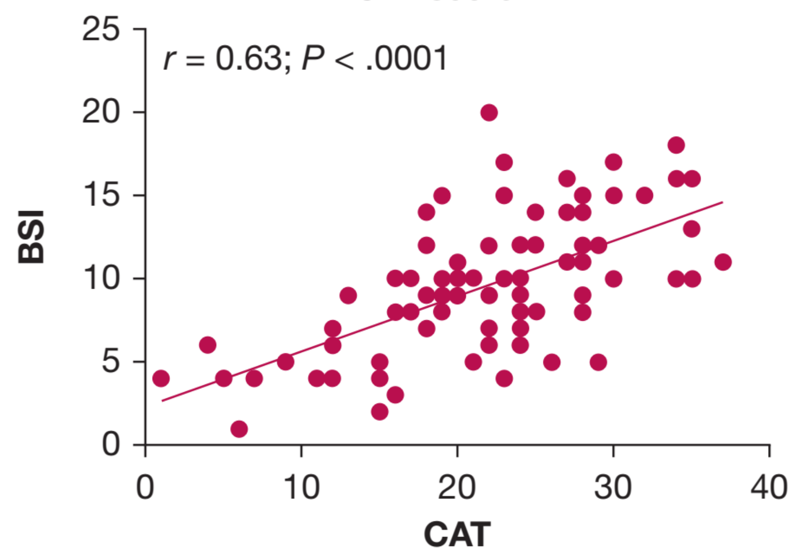
COPD assessment test as an outcome measure

- Bronchiectasis patient without any history of COPD in TRIBE study



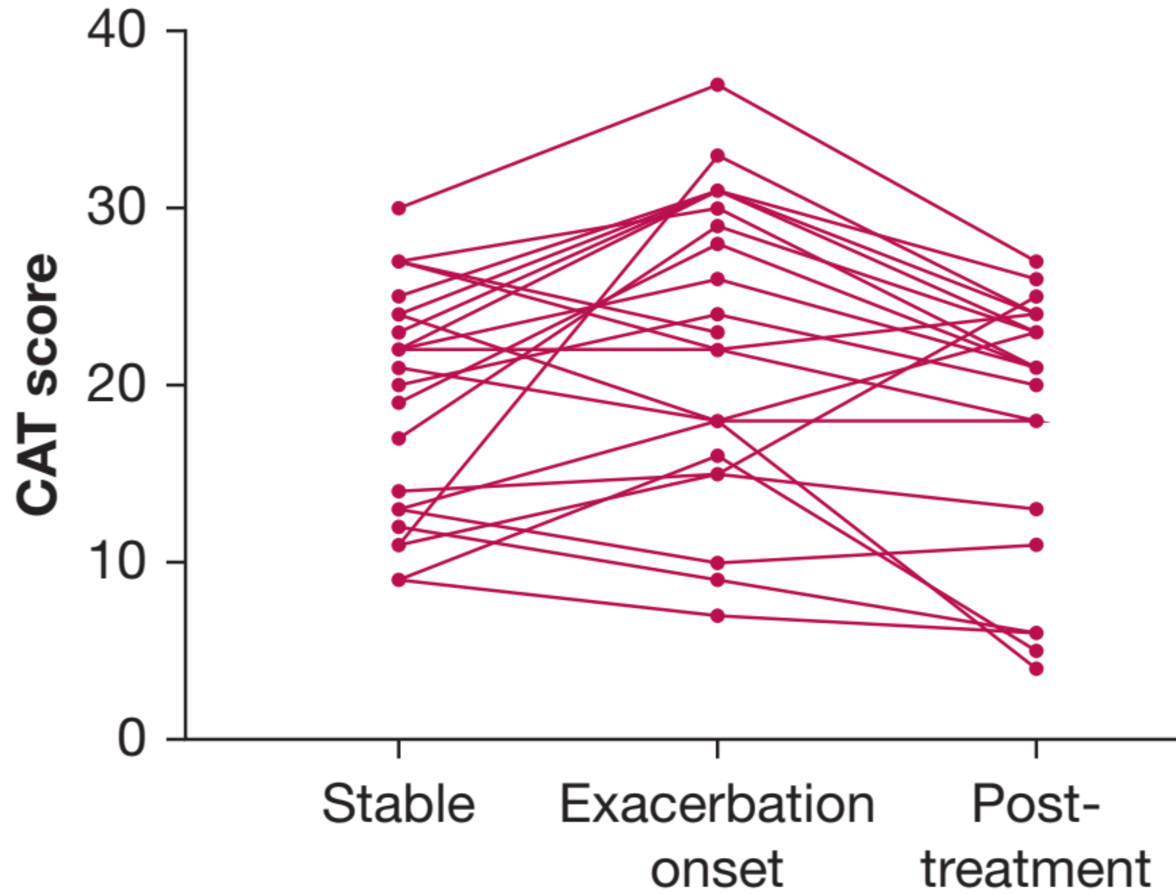




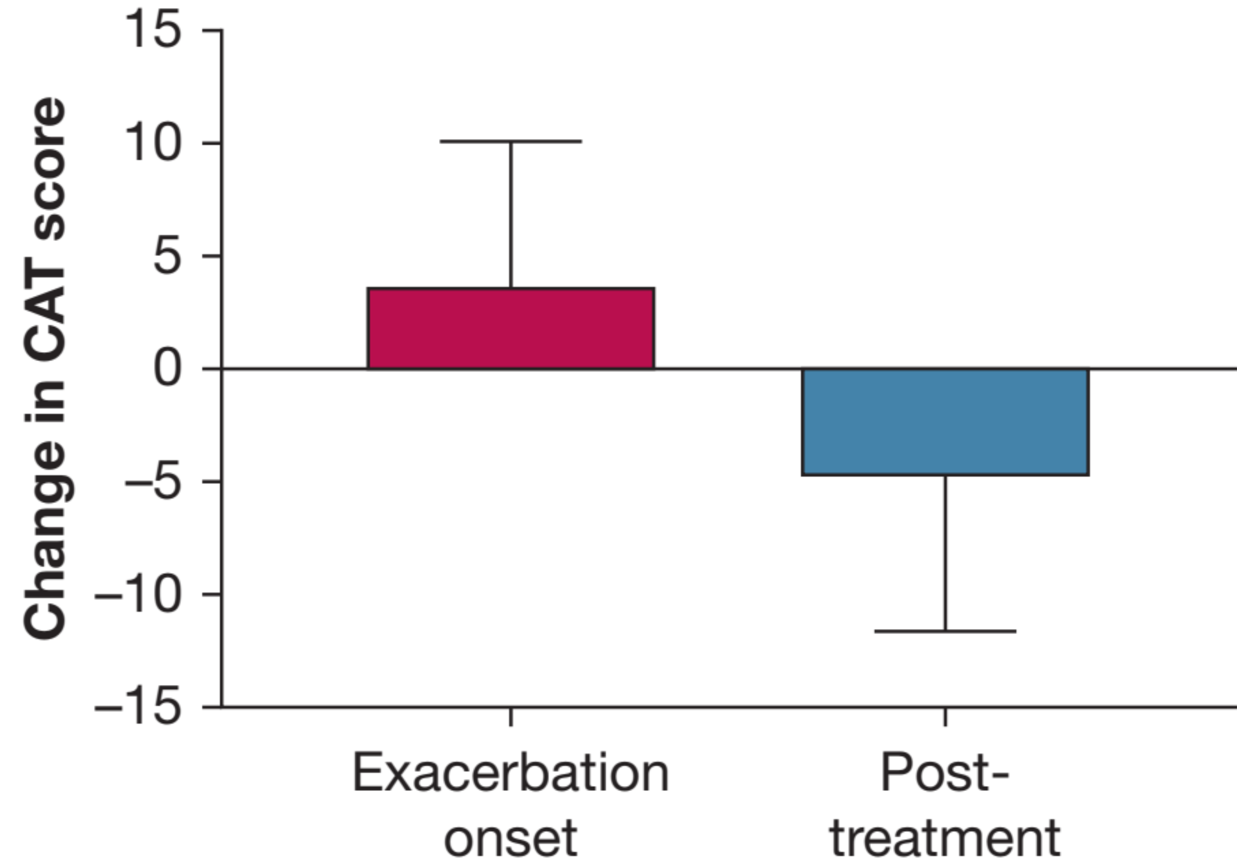


Finch S, et al. CHEST 2020;157(4):815-823.

CAT according to exacerbation



Proposed minimum clinically important difference (MCID): 4 points

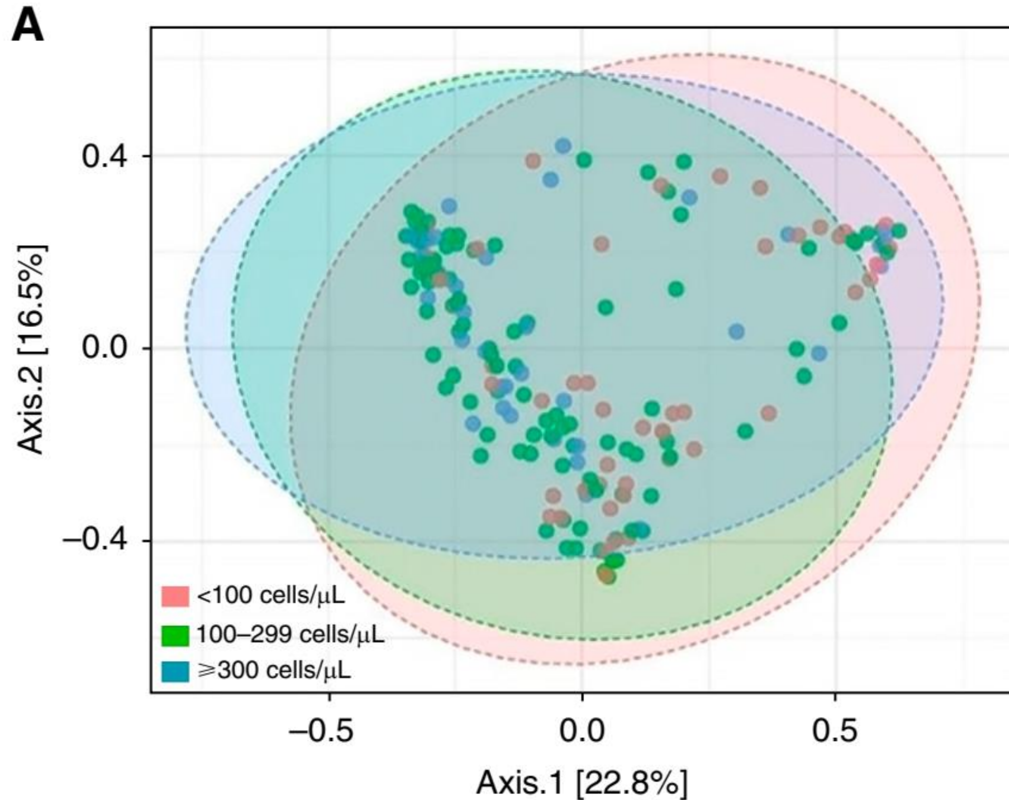


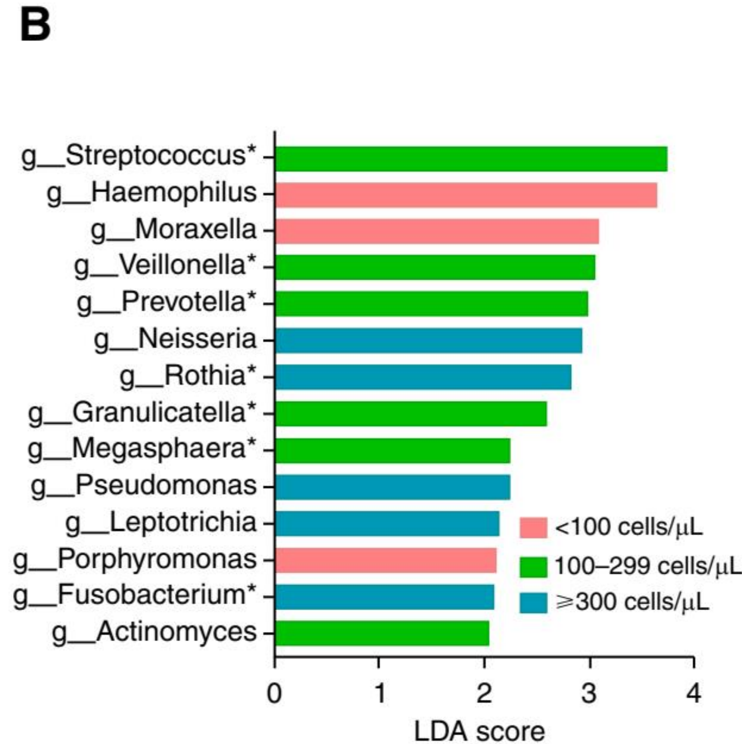
Finch S, et al. CHEST 2020;157(4):815-823.

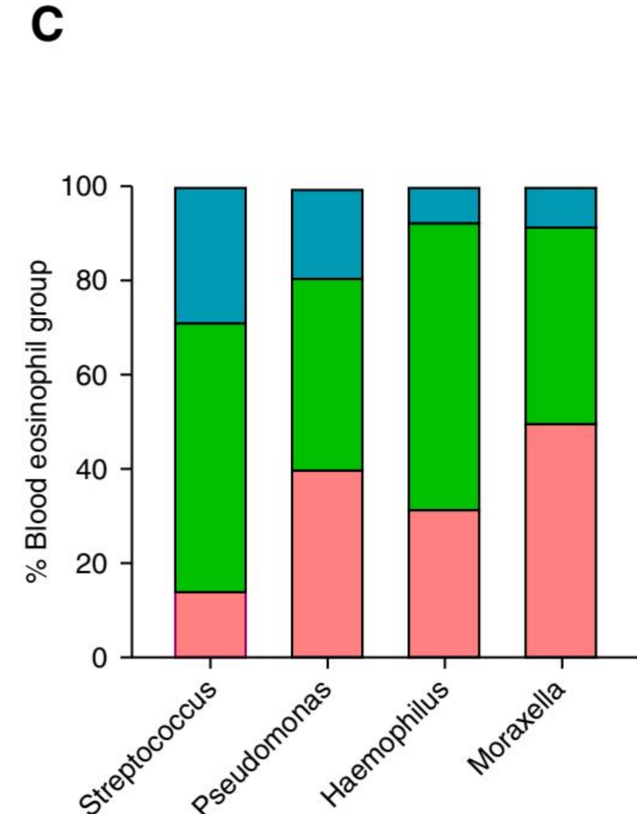
Eosinophilic phenotype

- 1,007 bronchiectasis patients without asthma, European multicohort
- Patients with blood eosinophil counts ≥300 cells/$\mu\ell$: 22.6%

Relationship betweenthe sputum microbiome and blood eosinophil counts

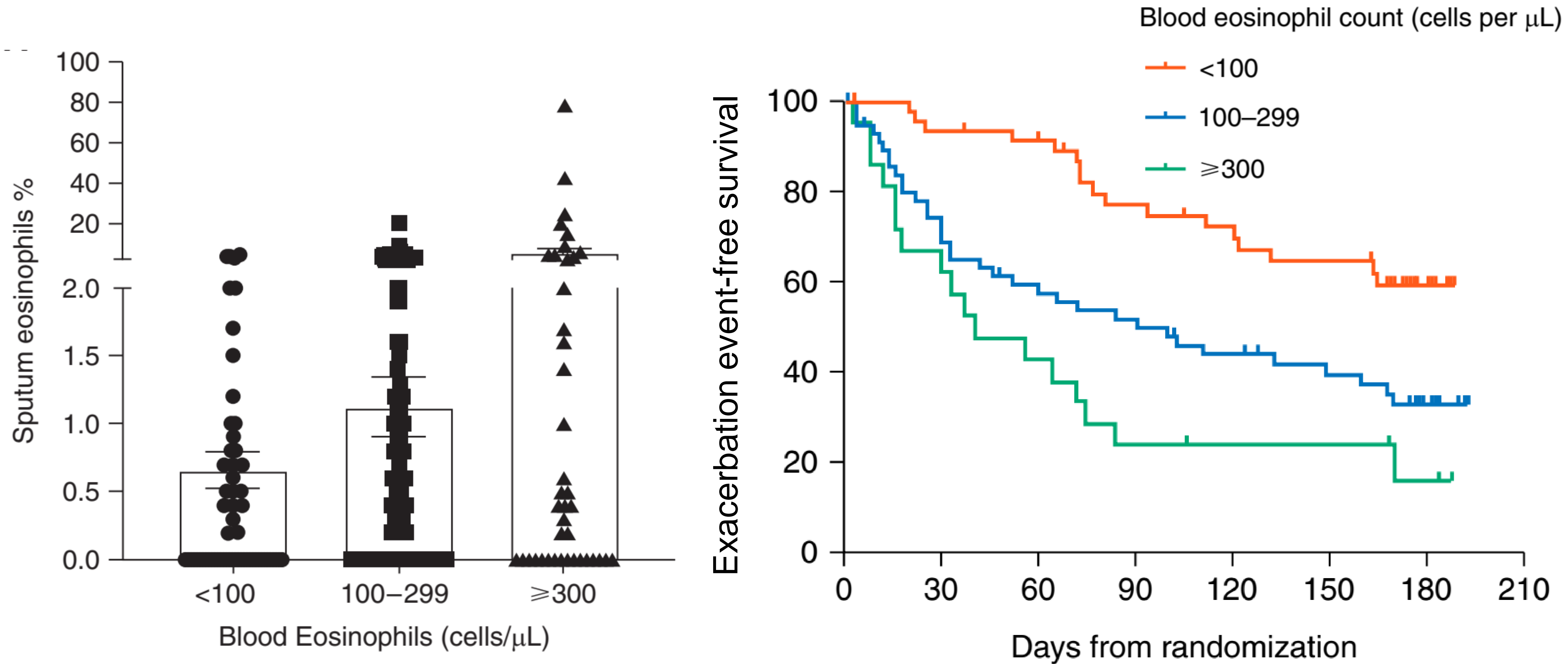






Shoemark A, et al. Am J Respir Crit Care Med 2022;205(8):894-902.

Eosinophilic phenotype and exacerbation



Shoemark A, et al. Am J Respir Crit Care Med 2022;205(8):894-902.

Blood eosinophils and ICS response

- 86 clinically stable bronchiectasis patients without asthma, CF, and ABPA
- Baseline blood eosinophils: low (<3%) vs. high (≥3%)
- ICS (fluticasone propionate) 250μg/500μg 2 times/day vs. no treatment, 6 months

	Low eosinophil group			High eosinophil group		
	FP+ (n=13)	FP- (n=10)	P-value	FP+ (n=44)	FP- (n=19)	P-value
Change SGRQ ≥4 points	4 (33.3)	1 (11.1)	0.34	21 (47.7)	0 (0.0)	<0.001
SGRQ total change	-2.5 (-5.3 to +2.7)	-0.7 (-2.0 to +1.6)	0.54	-3.1 (-8.9 to +2.8)	+1.6 (0.4 to +4.2)	0.003
FEV1 at 6 months %	68.4±19.6	58.5±15.3	0.33	61.4±20.3	72.6±18.5	0.21
MRC (3-4) at 3 months	3 (23.1)	1 (10.0)	0.60	2 (4.6)	4 (21.1)	0.06
Exacerbation at 6 months	7 (70.0)	3 (37.5)	0.34	12 (35.3)	6 (40.0)	0.75

Aliberti S, et al. Eur Respir J 2020;56(2):2000453.

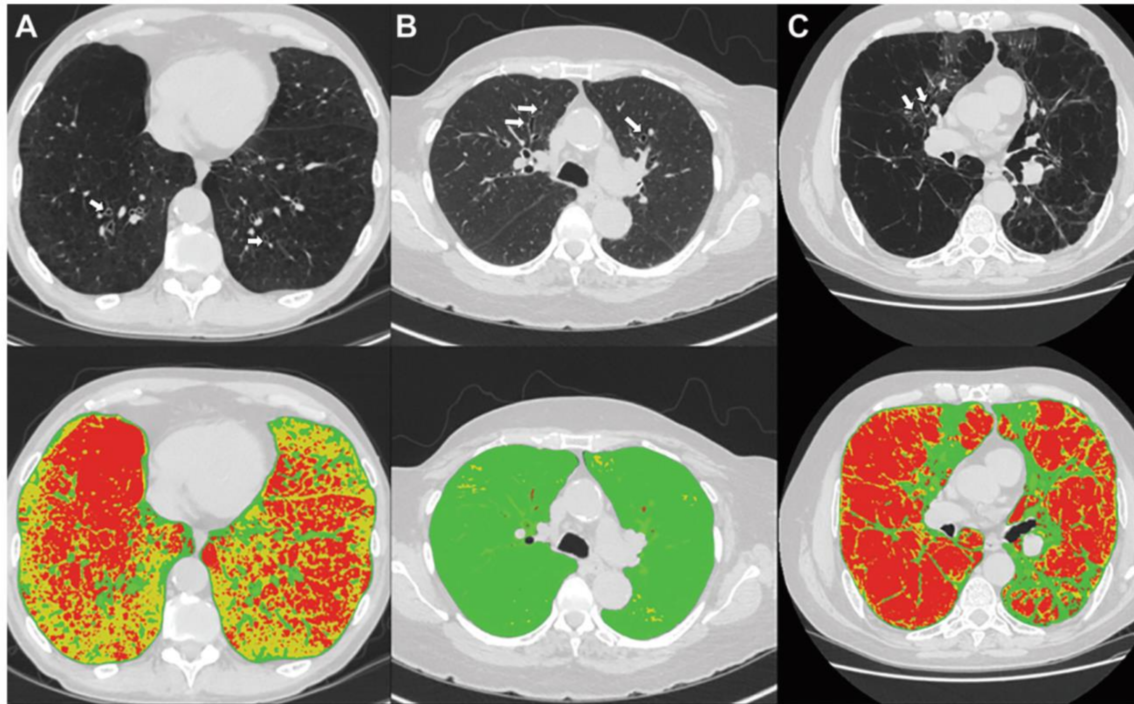
Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations

	Mean scores
Inner airway–artery diameter ratio ≥1·5	3·50/4·00
Outer airway–artery diameter ratio ≥1·5	3·21/4·00
Lack of tapering	3·00/4·00
Visibility of airways in the periphery	2·89/4·00
Inner airway–artery diameter ratio ≥1·1	2·75/4·00
Inner airway–artery diameter ratio ≥1·0	2·71/4·00
Outer airway–artery diameter ratio ≥1·1	2·13/4·00
Outer airway–artery diameter ratio ≥1·0	1·88/4·00

Aliberti S, et al. Lancet Respir Med 2022;10:298-306.

Small airway disease and emphysema in bronchiectasis

- 737 former and current smokers (387 bronchiectasis) from COPDGene study
- Parametric response mapping on paired expiratory and inspiratory CT scans to identify and quantify the extent of SAD and emphysema



Emphysema: red; SAD: yellow
Normal areas: green

	COPD only	BE without COPD	BE with COPD
PRM^{NORMAL} (%)	66.7 (45.5-79.8)	87.5 (82.0-92.9)	58.6 (42.2-73.8)
PRM^{SAD} (%)	24.8 (16.0-33.6)	9.7 (6.4-13.8)	27.6 (19.2-34.6)
PRM^{EMPHY} (%)	4.1 (1.2-12.6)	0.4 (0.1-1.2)	7.6 (2.6-18.4)
Bronchiectasis severity score		3.0 (2.0-4.0)	3.0 (2.0-4.0)

Maselli DJ, et al. Radiology 2021;300(3):706-714.

SAD/emphysema and exacerbation

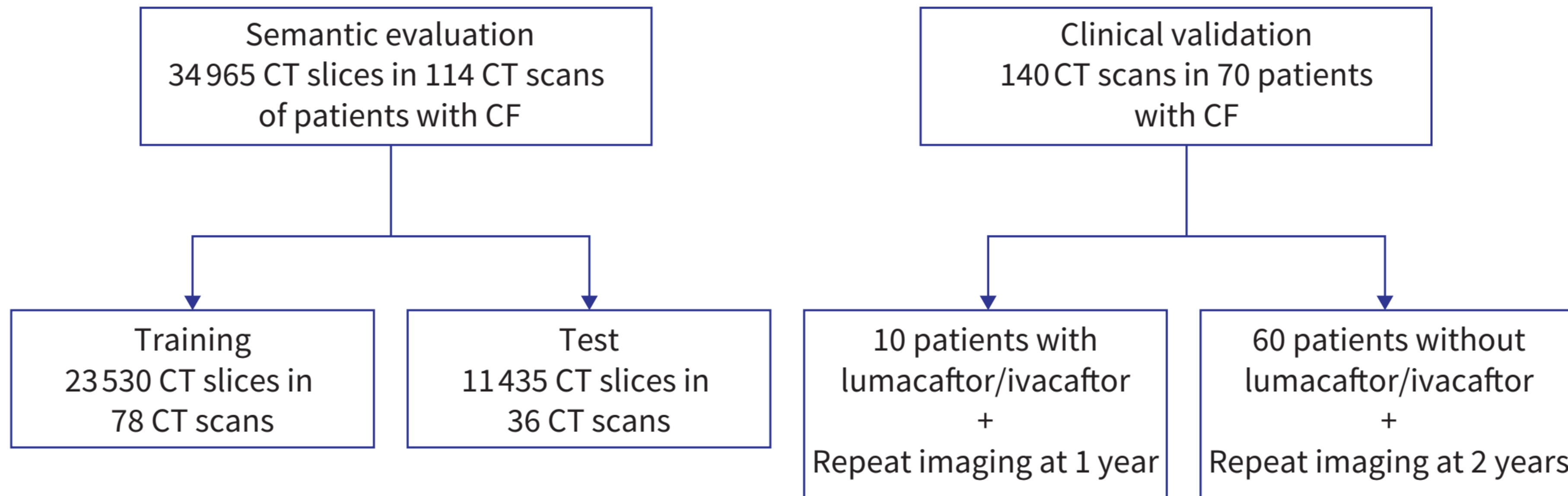
SAD and emphysema at PRM with exacerbation in heavy smokers with bronchiectasis and/or COPD

Group and Parameter	Exacerbation		Severe Exacerbation	
	Relative Risk	*P* Value	Relative Risk	*P* Value
CT-derived bronchiectasis with and without COPD (n = 387)				
PRM^{SAD} ≥15.6% vs <15.6%	1.89 (1.54, 2.33)	<.001	2.02 (1.40, 2.90)	<.001
PRM^{EMPH} ≥5% vs <5%	1.37 (1.13, 1.66)	.001	0.98 (0.69, 1.38)	.89
COPD only (n = 350)				
PRM^{SAD} ≥15.6% vs <15.6%	0.97 (0.82, 1.15)	.72	1.14 (0.82, 1.58)	.45
PRM^{EMPH} ≥5% vs <5%	1.61 (1.38, 1.87)	<.001	1.68 (1.27, 2.22)	<.001
CT-derived bronchiectasis with COPD (n = 197)				
PRM^{SAD} ≥15.6% vs <15.6%	1.67 (1.23, 2.27)	.001	1.83 (1.08, 3.11)	.03
PRM^{EMPH} ≥5% vs <5%	1.51 (1.20, 1.91)	<.001	0.96 (0.64, 1.44)	.84
CT-derived bronchiectasis without COPD (n = 190)				
PRM^{SAD} ≥15.6% vs <15.6%	1.67 (1.16, 2.41)	.007	2.40 (1.20, 4.83)	.01
PRM^{EMPH} ≥5% vs <5%	0.91 (0.27, 3.02)	.87	1.42 (0.17, 11.90)	.75

Maselli DJ, et al. Radiology 2021;300(3):706-714.

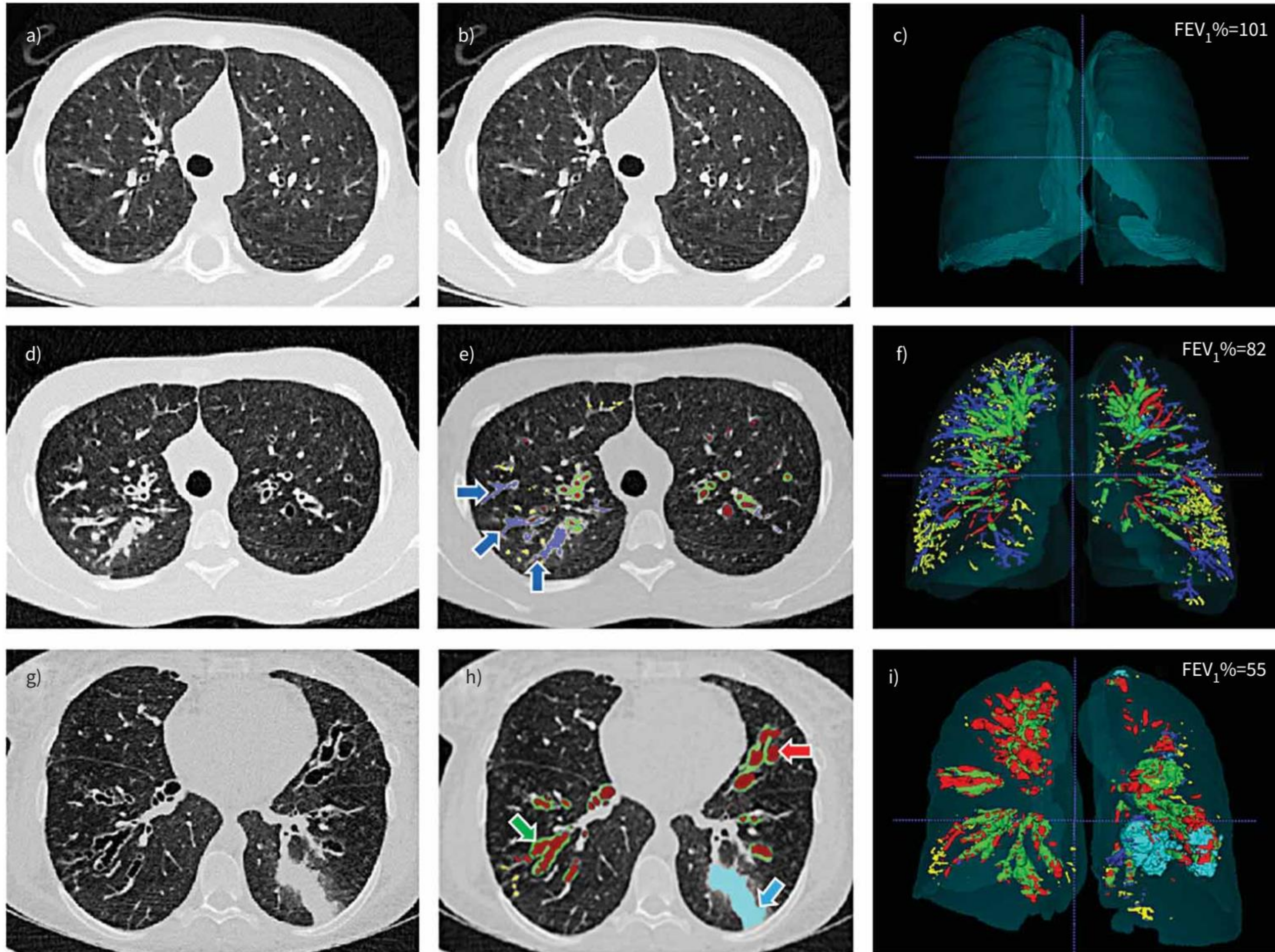
Artificial intelligence for quantifying lung changes

- Cystic fibrosis patients aged 4-54 years with/without lumacaftor/ivacaftor, cystric fibrosis transmembrane conductance regulator (CFTR) modulator
- **AI-driven measurements**: algorithm using three 2D convolutional neural networks trained for the semantic labelling of bronchiectasis, peribronchial thickening, bronchial mucus, bronchiolar mucus and collapse/consolidation



Dournes G, et al. Eur Respir J 2022;59:2100844.

AI-driven semantic labelling

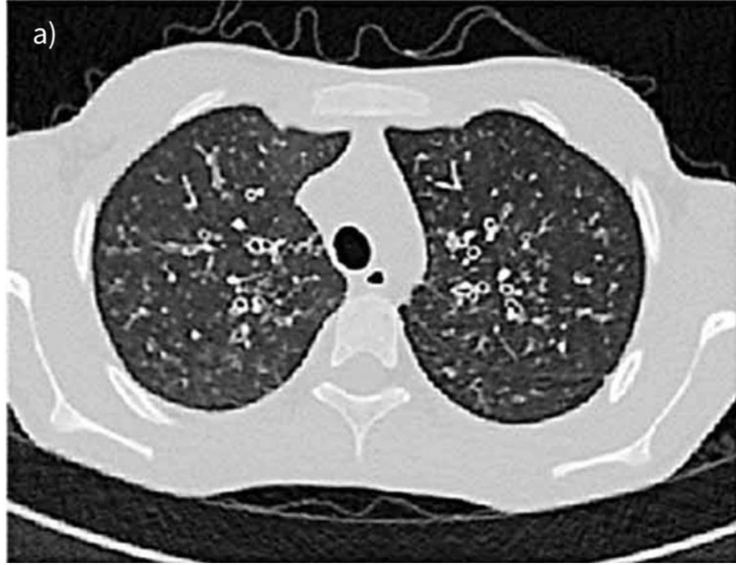


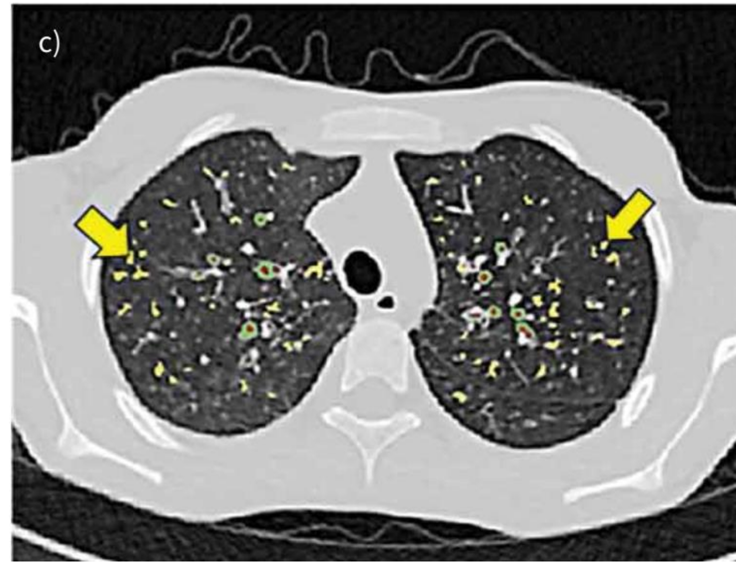
Axial CT slices
→ AI-driven semantic labelling
→ Integration all individual 2D labellings over the entire CT

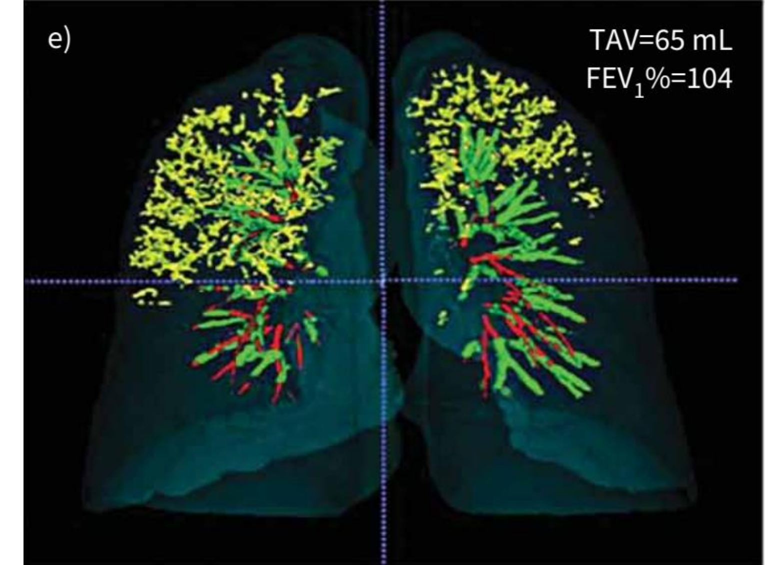
Blue: central mucus plugs
Red: mucus-free lumen dilatations
Green: peribronchial thickening
Cyan: consolidation

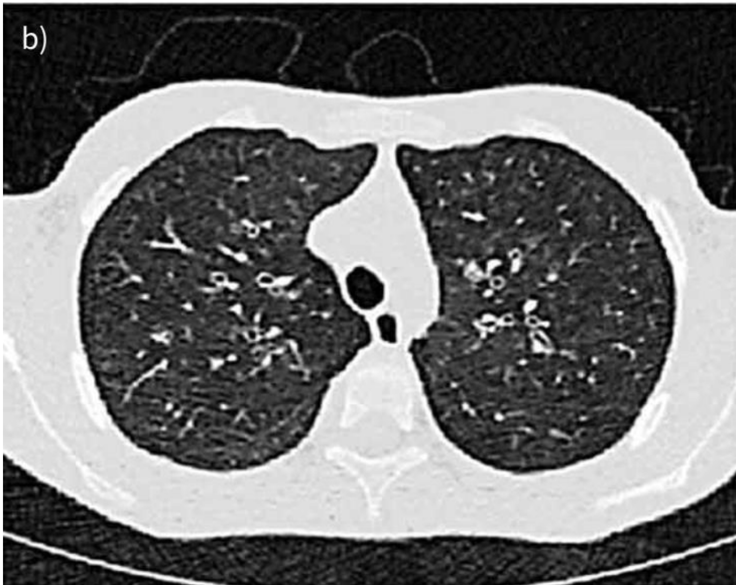
Dournes G, et al. Eur Respir J 2022;59:2100844.

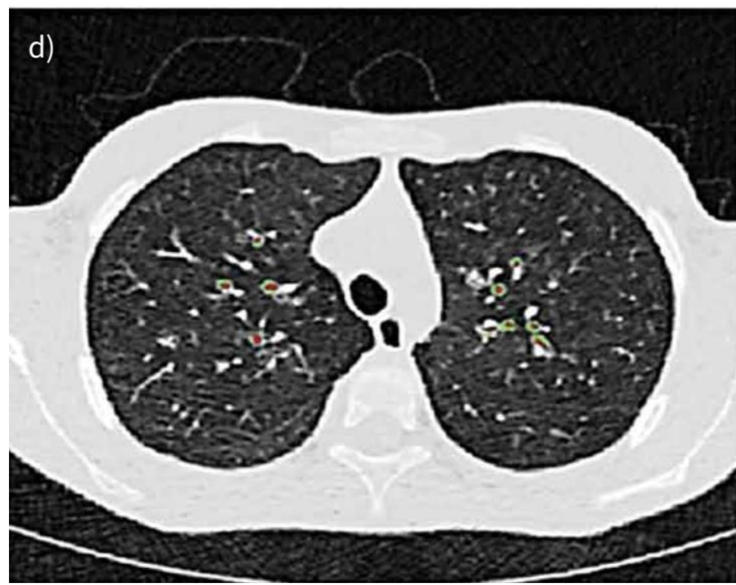
AI-imaging before and after treatment

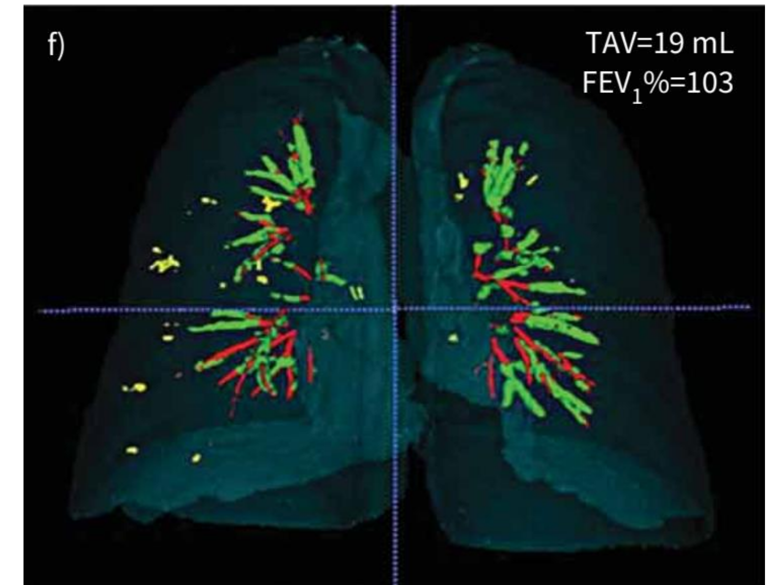






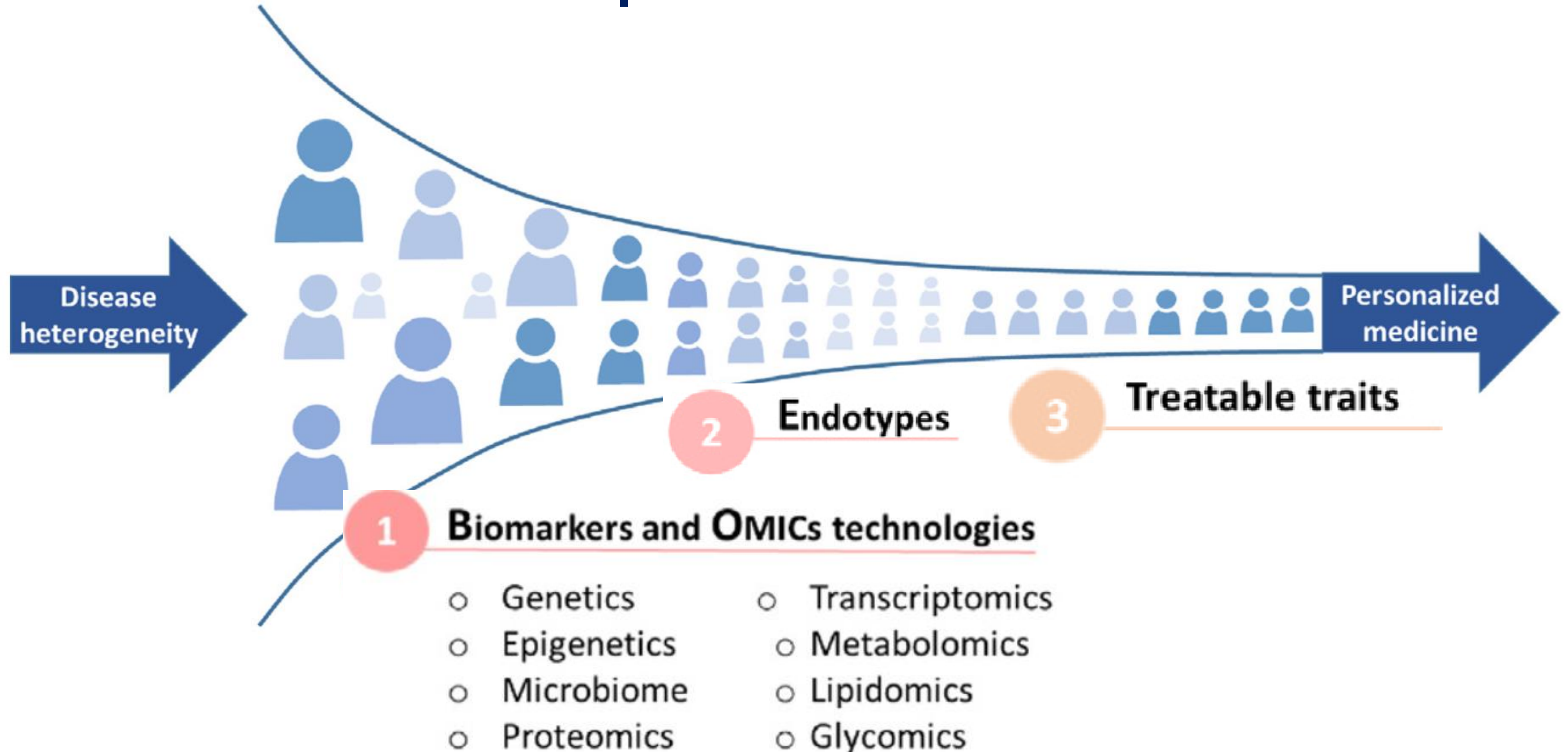






Dournes G, et al. Eur Respir J 2022;59:2100844.

Future directions of bronchiectasis research toward a personalized medicine



Amaro R, et al. Clin Chest Med 2022;43(1):179-187.

Summary

- **Biomarker**
  - ✓ Neutrophil elastase activity
  - ✓ Microbiome
  - ✓ Neutrophil extracellular trap
- **Clinical evaluation**
  - ✓ Exacerbation
  - ✓ Symptom burden
  - ✓ COPD assessment test
  - ✓ Eosinophilic phenotype and ICS response
- **Radiology**
  - ✓ Small airway disease/emphysema
  - ✓ Artificial intelligence for quantification

Thank You for Your Attention