MONACO
15 - 17 January 2016

3rd INTERNATIONAL WORKSHOP ON LUNG HEALTH

Asthma & COPD: converging or diverging chronicity?

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3rd INTERNATIONAL WORKSHOP ON LUNG HEALTH

Asthma & COPD: converging or diverging chronicity?

Alpha-1 antitrypsin deficiency (AATD) and Non-cystic fibrosis bronchiectasis (NCFBE) survey

Monaco, 16th January 2016

Sponsored by

GRIFOLS

DETAILS OF THE STUDY (1)

AIM OF THE STUDY:

The aim of the survey is to learn the physicians practices and experiences related to Alpha-1 antitrypsin deficiency (AATD) and Non-Cystic fibrosis bronchiectasis (NCFBE).

CONTENTS OF THE STUDY:

- ✓ **Alpha-1 antitrypsin deficiency (AATD):**
  - AATD testing
  - Augmentation therapy treatment
  - Interest in learning more about AATD

- ✓ **Non-Cystic Fibrosis Bronchiectasis (NCFBE):**
  - NCFBE patients
  - Pseudomonas aeruginosa colonization in NCFBE patients
  - NCFBE and antibiotic perception
  - Interest in learning more about NCFBE disease and patient management

DETAILS OF THE STUDY (2)

TARGET:

Doctors interested in attending the 3rd International Lung Congress 2016

FIELDWORK DATES:

From 2nd to 18th December 2015

METHODOLOGY:

Online self-completion questionnaire

QUESTIONNAIRE LENGTH:

8 minutes

UNIVERSE

352 individuals opened the newsletter sent by the organization

134 opened the survey webpage

SAMPLE

63 respondents participated in the survey (14 partial answers)

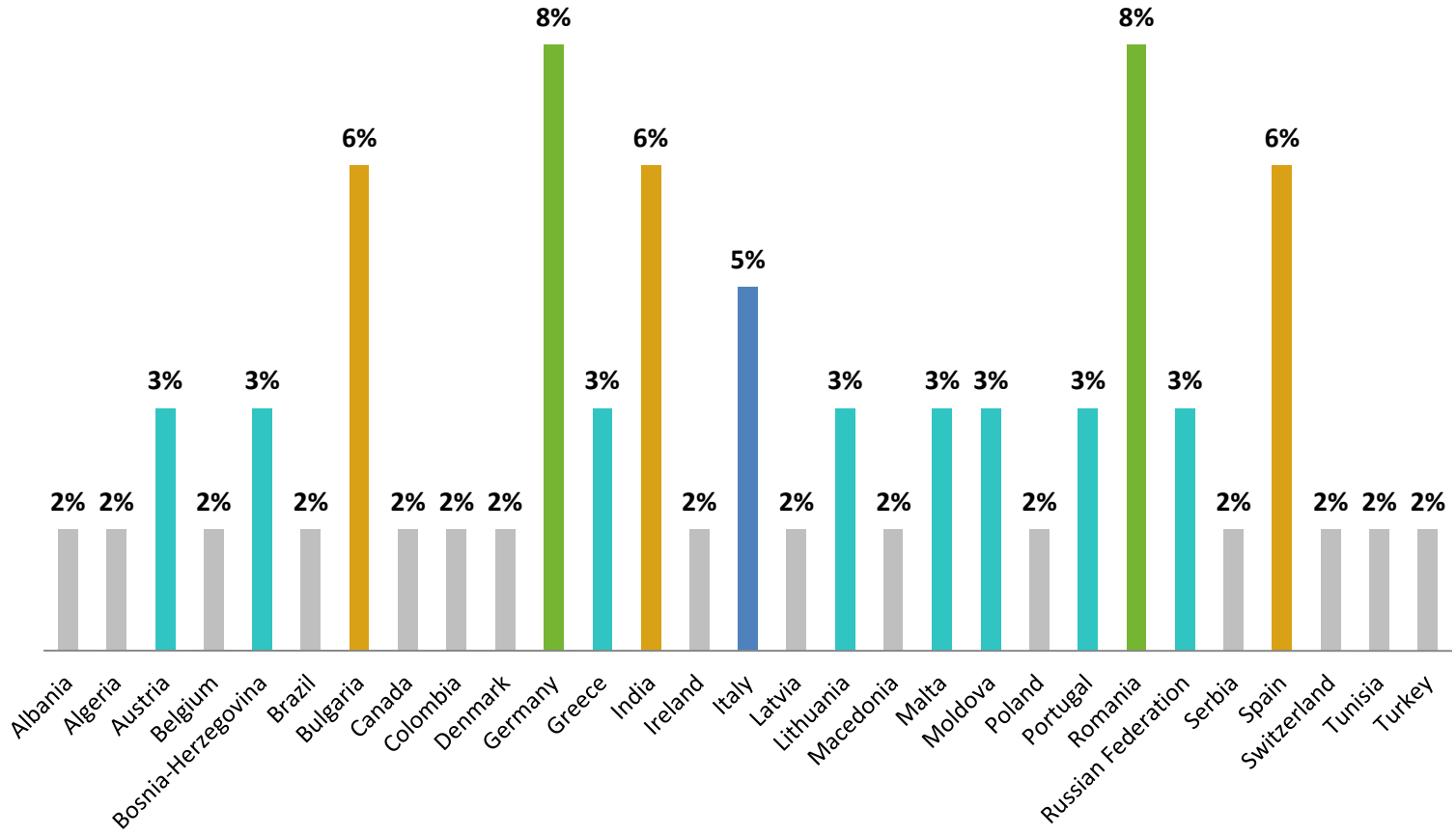
49 full completion questionnaires

RESPONSE RATE

13,9%

The countries with more individuals participating in the survey are Germany and Romania

Countries participating in the survey



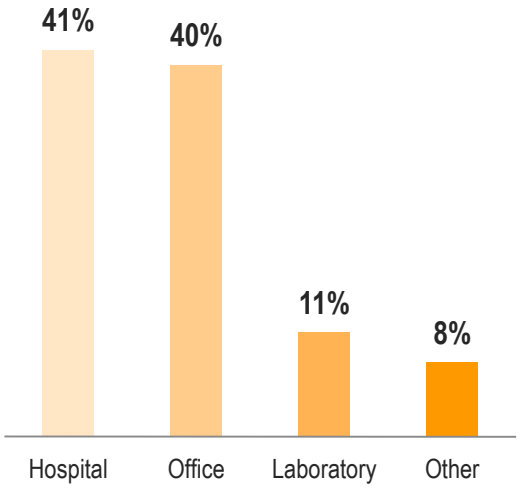
Base:(63)

Q1. In what country do you mainly practice?

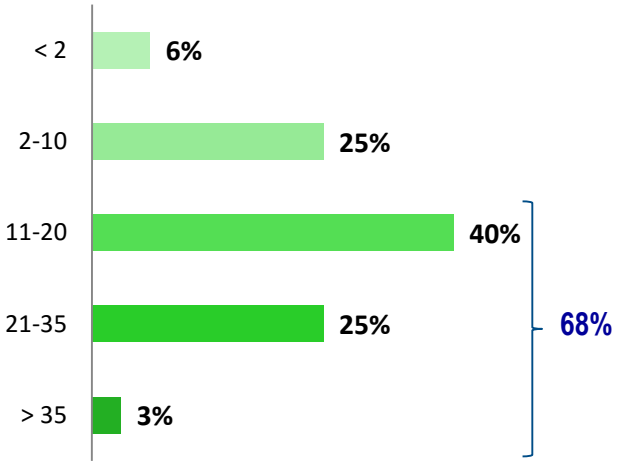
The vast majority of the respondents have more than 10 years of clinical experience and are mainly located at office or hospital

Sample profile

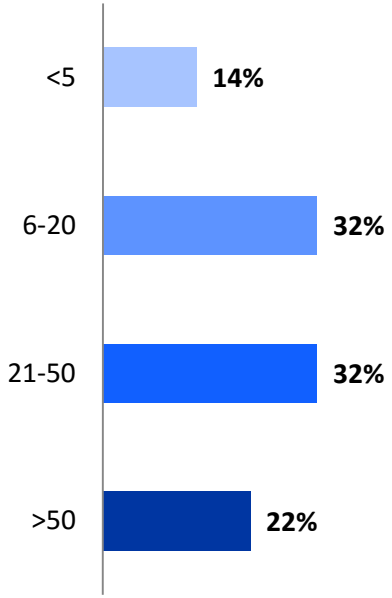
Physician location



Years of clinical experience



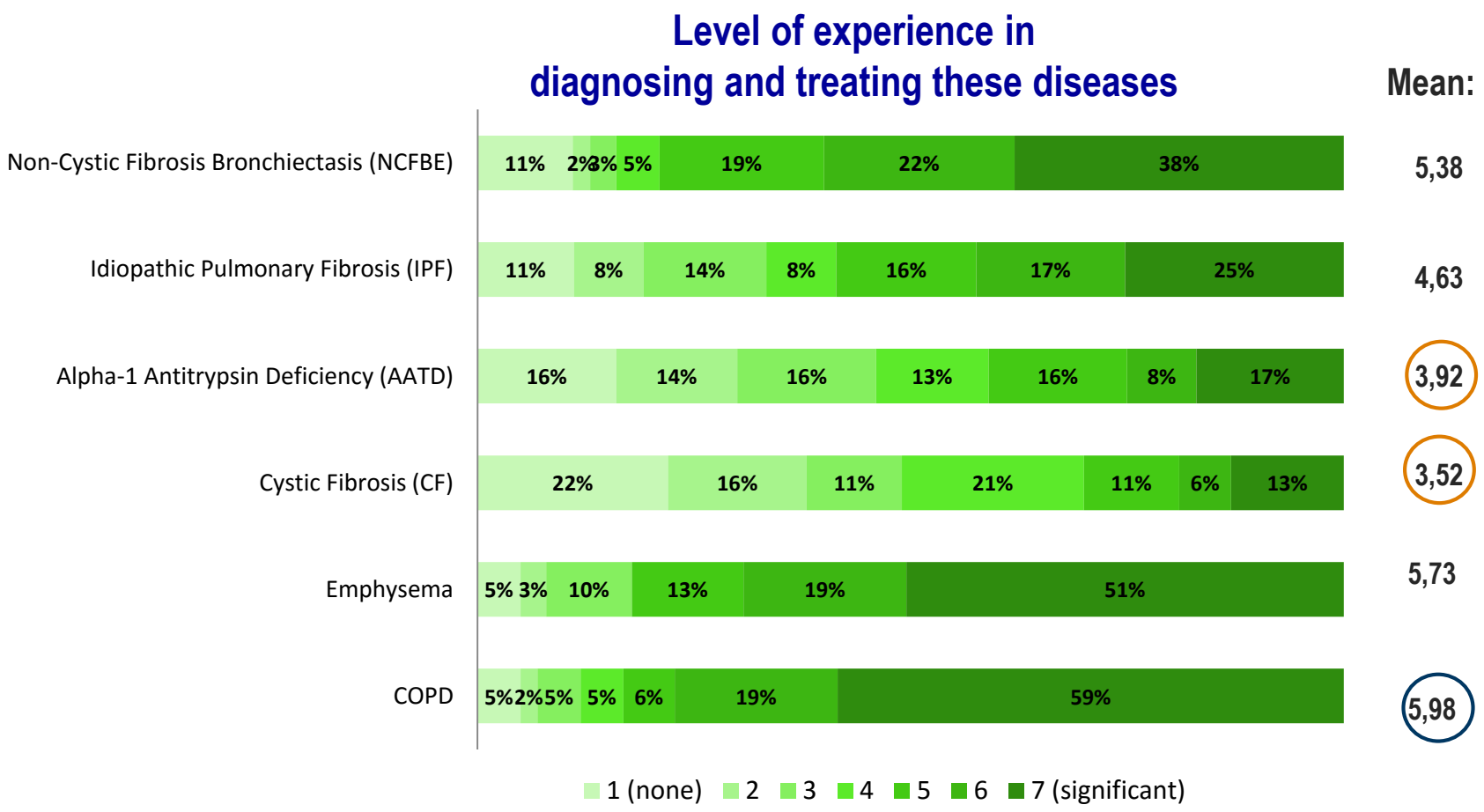
Number of COPD patients treated per month



Base: (63)

Q.2 .Where are you primarily located?
Q.3 How many years of clinical experience do you have?
Q.4 How many COPD patients do you treat per month?

Along with Cystic Fibrosis, AATD is the disease with the least current level of experience while respondents have the highest expertise with COPD



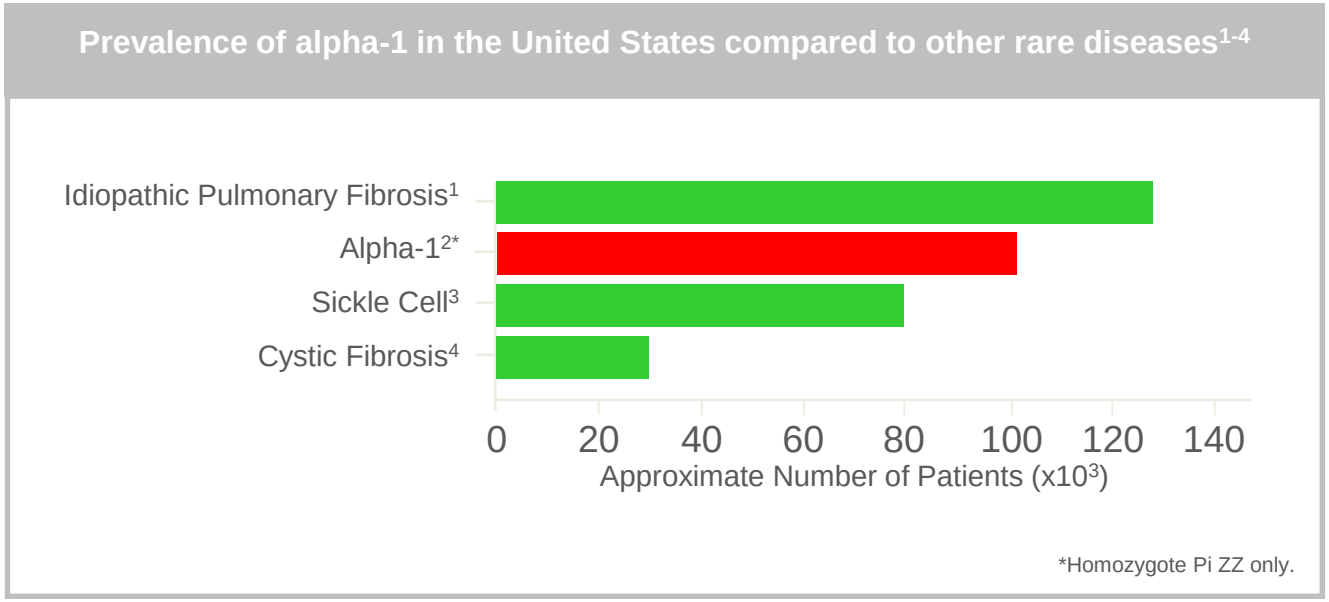
Base: (63)

Q.5 Please rate your current level of experience in diagnosing and treating the following diseases? (Where 1 is none and 7 is significant: please select one option for each disease

Alpha-1 antitrypsin deficiency (AATD)

Epidemiology of AATD

- AATD may be among the most common hereditary disorders in the world

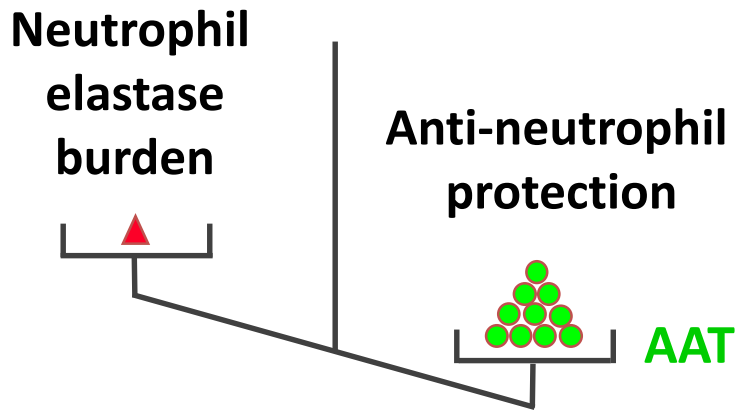


- ~ 1 in 9000 in the USA[3]
- ~ 1 in 5000 in Europe[4]

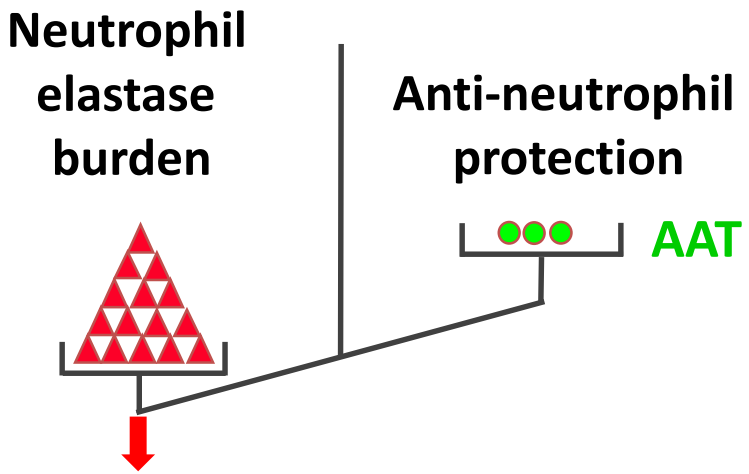
[1]Campos MA, et al. *Chest* 2005;128(3):1179–1186. Abboud RT, et al. *Can Respir J* 2001;8(2):81−88. De Serres FJ, et al. *Mon Arch Chest Dis* 2007;67: 4, 184–208. [4]Blanco I, et al. *Eur Respir J* 2006;27: 77–84, 1179–1186.

AAT is an “anti-enzyme” for Neutrophil Elastase

Functional AAT



Deficient or non-functional



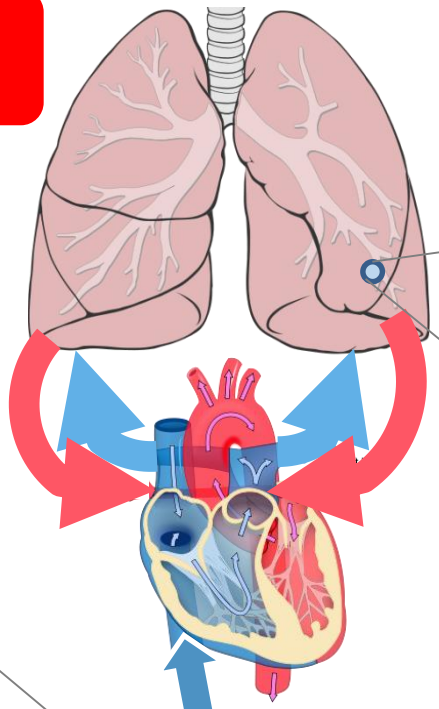
Tissue damage from excess NE can result from inadequate AAT function

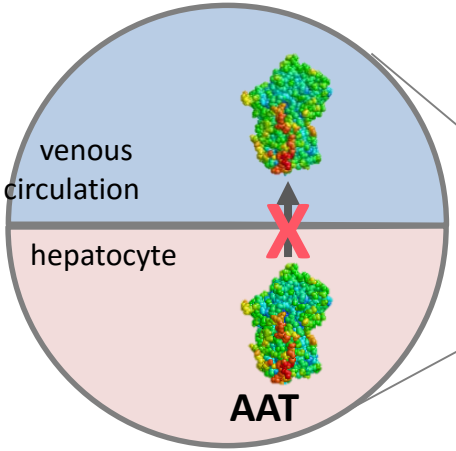
Adapted from American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168:818-900.
Adapted from Köhnlein T, Welte T. *Alpha-1 Antitrypsin Deficiency: Clinical Aspects and Management.* Bremen, Germany: UNI-MED Verlag AG; 2007.

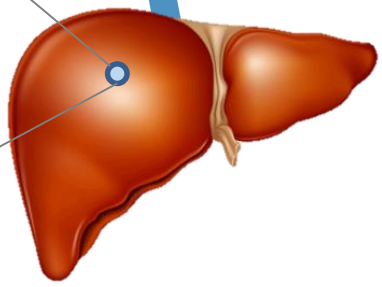
Deficient or Abnormal AAT Cannot Protect the Lung

Deficient

Abnormal AAT does not effectively enter circulation, is not produced or is otherwise non-functional

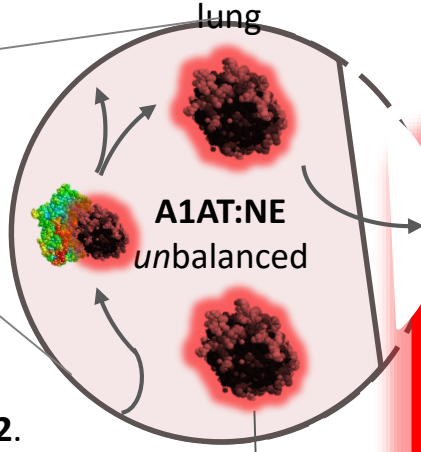






4. Undestroyed excess **Elastase** remains in the lung

3. Available A1AT binds and destroys some **Elastase**

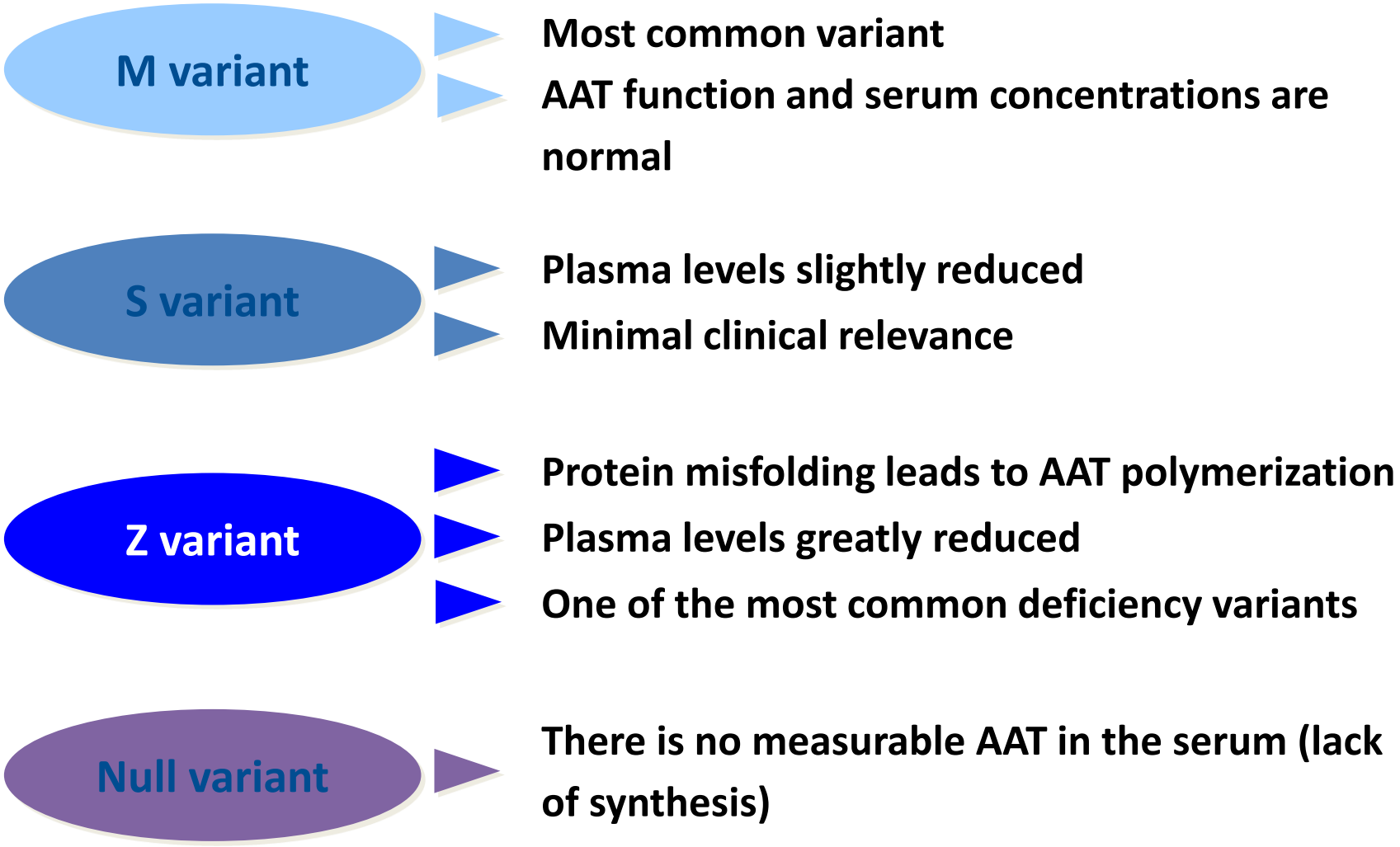


5. Elastase irrepairably damages lung tissue, possibly resulting in eventual emphysema

2. insufficient **A1AT** enters lung

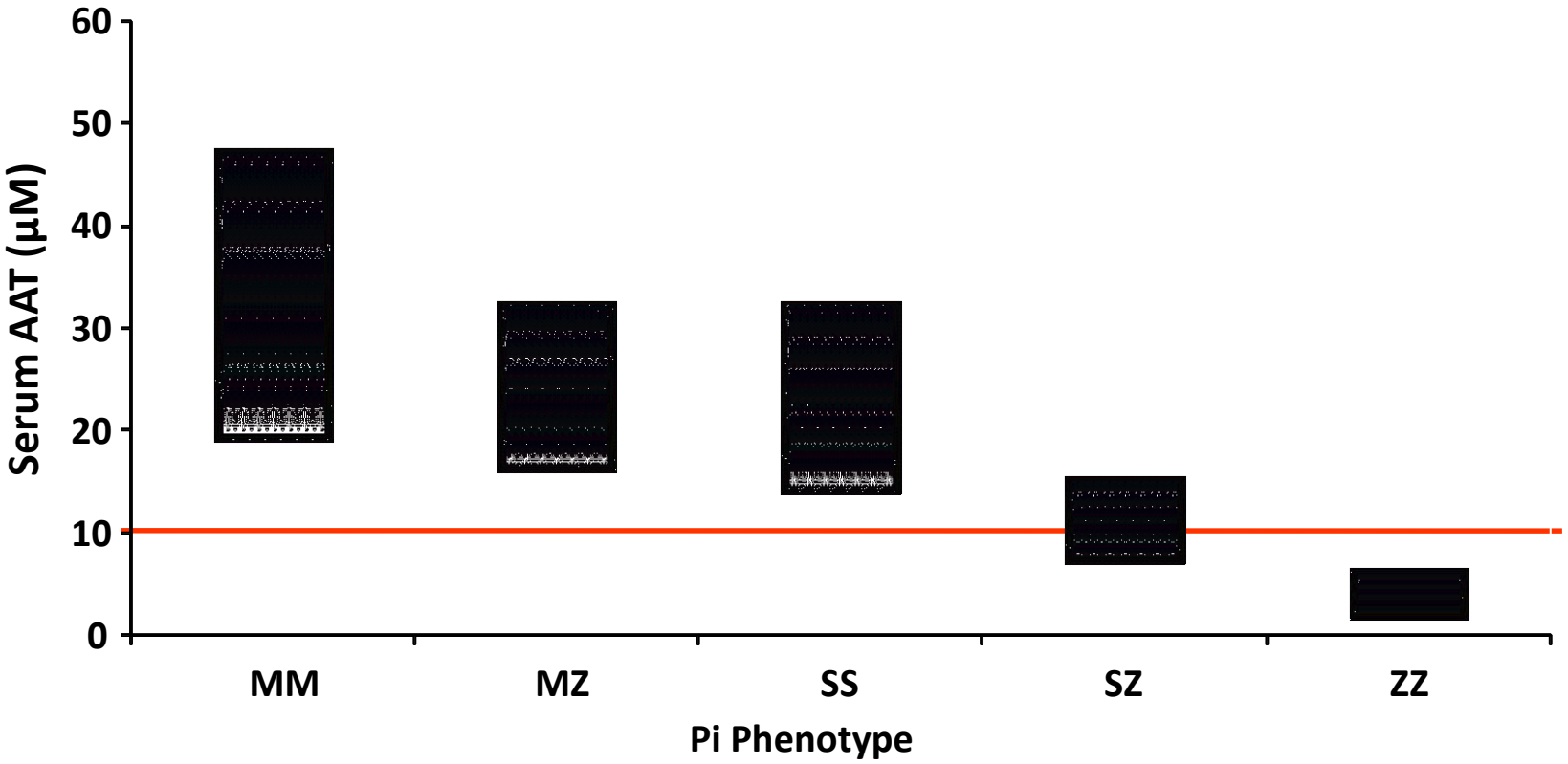
1. Neutrophil Elastase released into lung as part of pro-inflammatory immune response

Review of Alpha$_1$-Antitrypsin Variants



American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med* 2003;168(7):818–900.

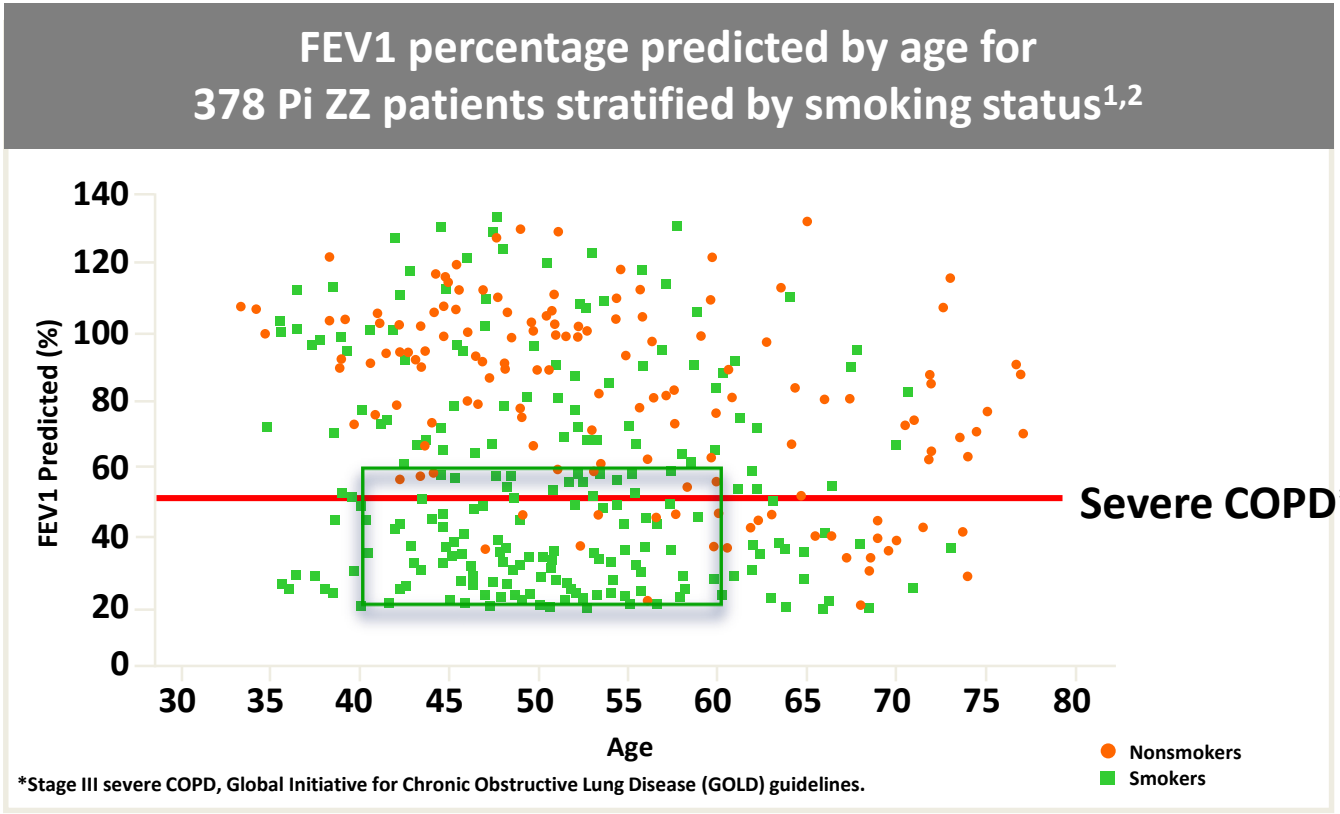
Alpha$_1$-Antitrypsin Serum Levels by Phenotype



A level of less than 11 µM (80 mg/dL if measured by radial immunodiffusion; 50 mg/dL if measured by nephelometry) is associated with an increased risk for emphysema.

American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med* 2003;168(7):818–900.

Age, Smoking History, or Severity of FEV_1 Decline Should NOT Define Which COPD Patients to Test



Remember that only a laboratory test can confirm the presence of alpha-1 antitrypsin deficiency

[1]DeMeo DL, et al. *Thorax.* 2007;62(9):806-813. Image reproduced with permission from BMJ Publishing Group Ltd.
[2]Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD diagnosis, management, and prevention. 2013:1-32.

ATS/ERS guidelines recommend testing all COPD patients

No	Recommendation
1	Confirmation of absent alpha-1 antitrypsin peak on serum protein electrophoresis
2	Early-onset pulmonary emphysema (regardless of smoking history)
3	Family members of known alpha-1 antitrypsin–deficient patients
4	Dyspnea and cough occurring in multiple family members in same or different generations
5	Liver disease of unknown cause
6	All subjects with chronic obstructive pulmonary disease
7	Adults with bronchiectasis without evident etiology should be considered for testing
8	Patients with asthma whose spirometry fails to return to normal with therapy
9	Unexplained panniculitis and anti–proteinase-3 vasculitis

Adapted from: ATS/ERS Guidelines

American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003 Oct 1;168(7):818-900

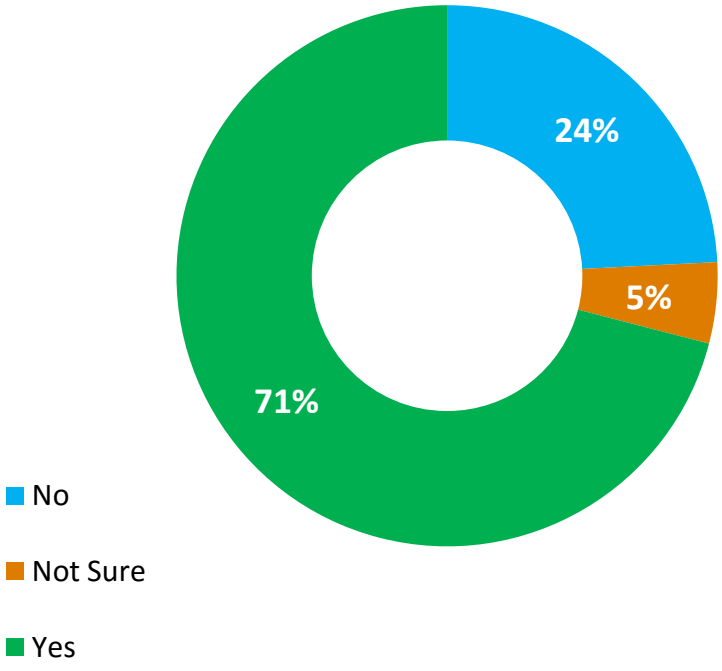
For analysis purposes, countries have been separated related to Augmentation therapy reimbursement

Augmentation therapy is reimbursed
Austria
Brazil
Canada
Colombia
Germany
Greece
Portugal
Spain
Switzerland
USA

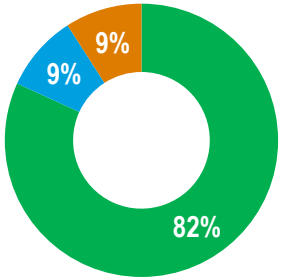
Augmentation therapy is NOT reimbursed	
Albania	Malta
Algeria	Moldova
Belgium	Poland
Bosnia-Herzegovina	Romania
Bulgaria	Russian Federation
Denmark	Serbia
India	Tunisia
Ireland	Turkey
Latvia	Ukraine
Lithuania	United Kingdom
Macedonia	

The vast majority (71%) test for AATD currently, although the percentage is higher (82%) in those countries where the augmentation therapy is reimbursed.

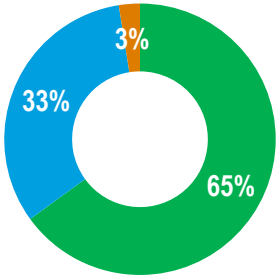
Current testing for AATD (% of respondents)



Augmentation therapy is reimbursed



Augmentation therapy is NOT reimbursed



Base: Sample (62)
Augmentation therapy is reimbursed (22)
Augmentation therapy is not reimbursed (40)

Q.6. Do you currently test for Alpha-1 Antitrypsin Deficiency (AATD)?

The main reason for not testing for AATD is that physicians think that serum level test is too expensive. There is also opportunity to improve awareness of AATD testing methods.

Reasons for not testing for AATD

1st top reasons	2nd top reasons	3rd top reasons
AUGMENTATION THERAPY IS REIMBURSED		
Testing Alpha-1 Protein serum level is too expensive (25%)	**Testing Alpha-1 Protein serum level is too expensive** (50%)	**Testing Alpha-1 Protein serum level is too expensive** (25%)
I am not aware of the testing methods (25%)	Patients refuse testing (25%)	
AUGMENTATION THERAPY IS NOT REIMBURSED		
Augmentation therapy (Alpha-1 Proteinase Inhibitor replacement via infusion) for AATD doesn't exist in my country, so there is no reason to test(36%)	**Testing Alpha-1 Protein serum level is too expensive** (36%)	**It takes too long to get test results and to follow up with patients** (29%)
Testing Alpha-1 Protein serum level is too expensive (36%)	Patients refuse testing (21%)	My peers do not recommend testing (21%)

Base: Augmentation therapy is reimbursed (4)* *Caution low base*
Base: Augmentation therapy is not reimbursed sample (14)

Q.7. If you do not currently test for AATD (answered "no" in Question 6), what are the top 3 reasons why you do not test? (Please Pick 3)

It seems that do not believe in augmentation therapy is not a reason for not testing at all

Reasons for not testing for AATD (2)

Nobody mentioned the following reason for not testing in any country:

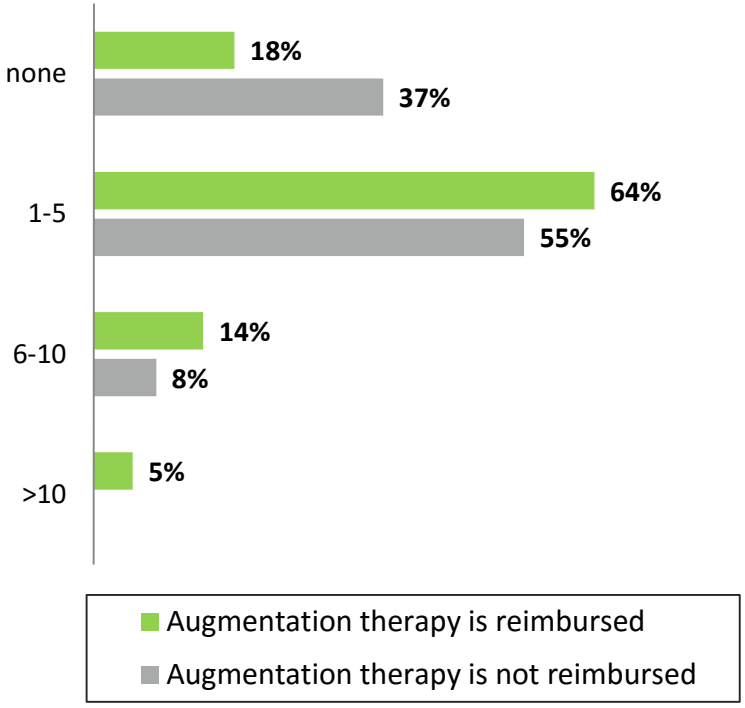
- I do not believe augmentation therapy is beneficial, so there is no reason to diagnose AATD

Base: Sample (18)
Augmentation therapy is reimbursed (4)* *Caution low base*
Augmentation therapy is not reimbursed (14)

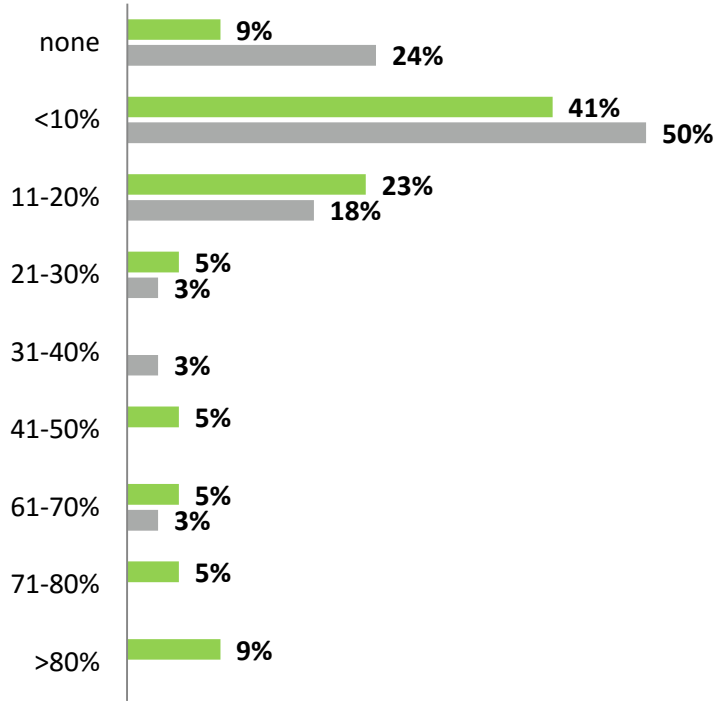
Q.7. If you do not currently test for AATD (answered "no" in Question 6), what are the top 3 reasons why you do not test? (Please Pick 3)

In general, respondents perform between none and 5 tests per month. Most physicians have tested less than 10% of their COPD patients in all countries.

AATD tests performed per month



Percentage of COPD patients ever tested for AATD

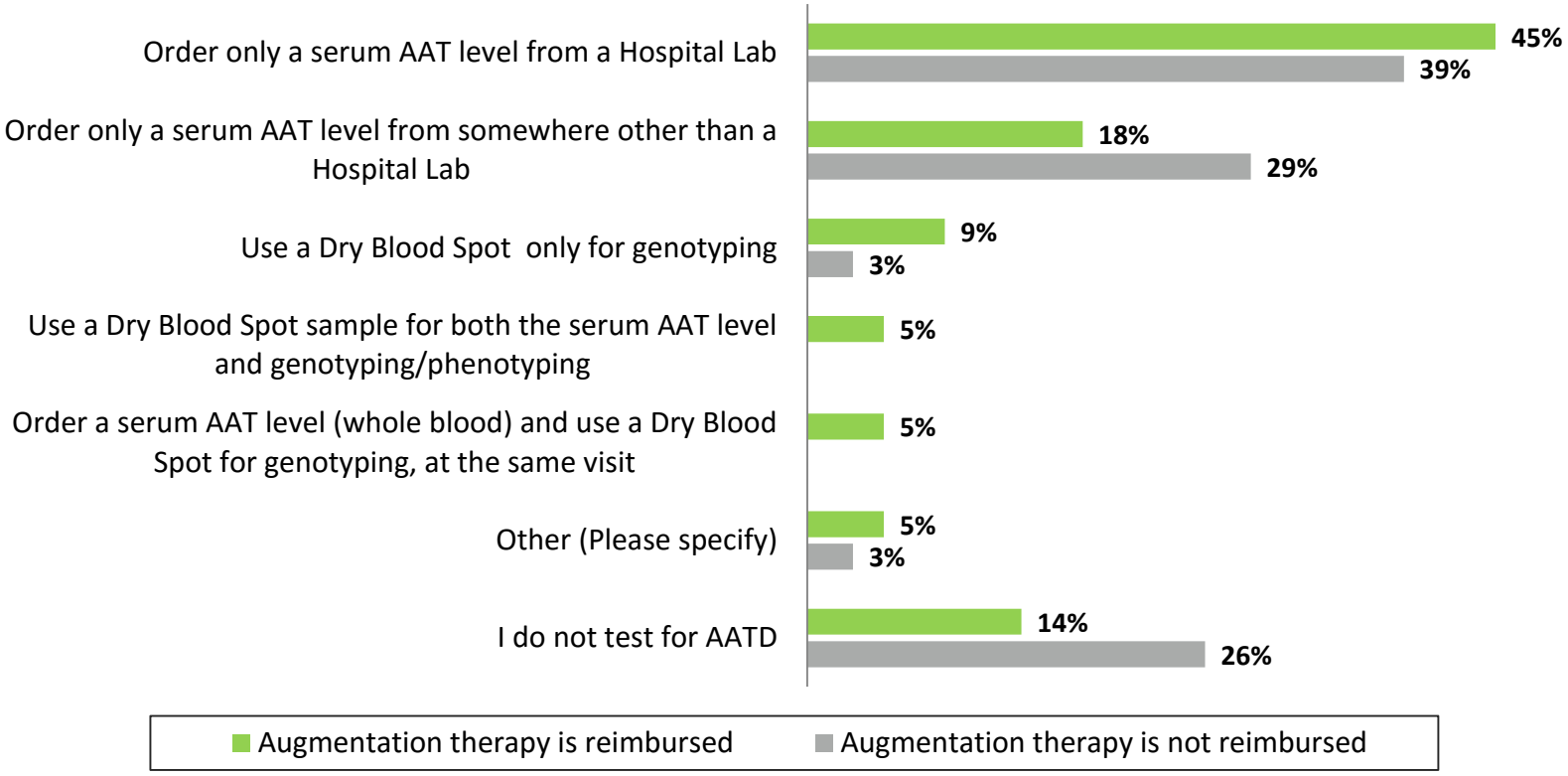


Base: Sample (60)
Augmentation therapy is reimbursed (22)
Augmentation therapy is not reimbursed (38)

Q.8. How many tests for AATD do you perform per month?
Q.9. What percent of your COPD patients have ever been tested (by anyone) for AATD?

Serum AAT level test in a hospital lab is most often the first step in testing. Genotyping/phenotyping is rarely done as a first step.

Initial Test for AATD

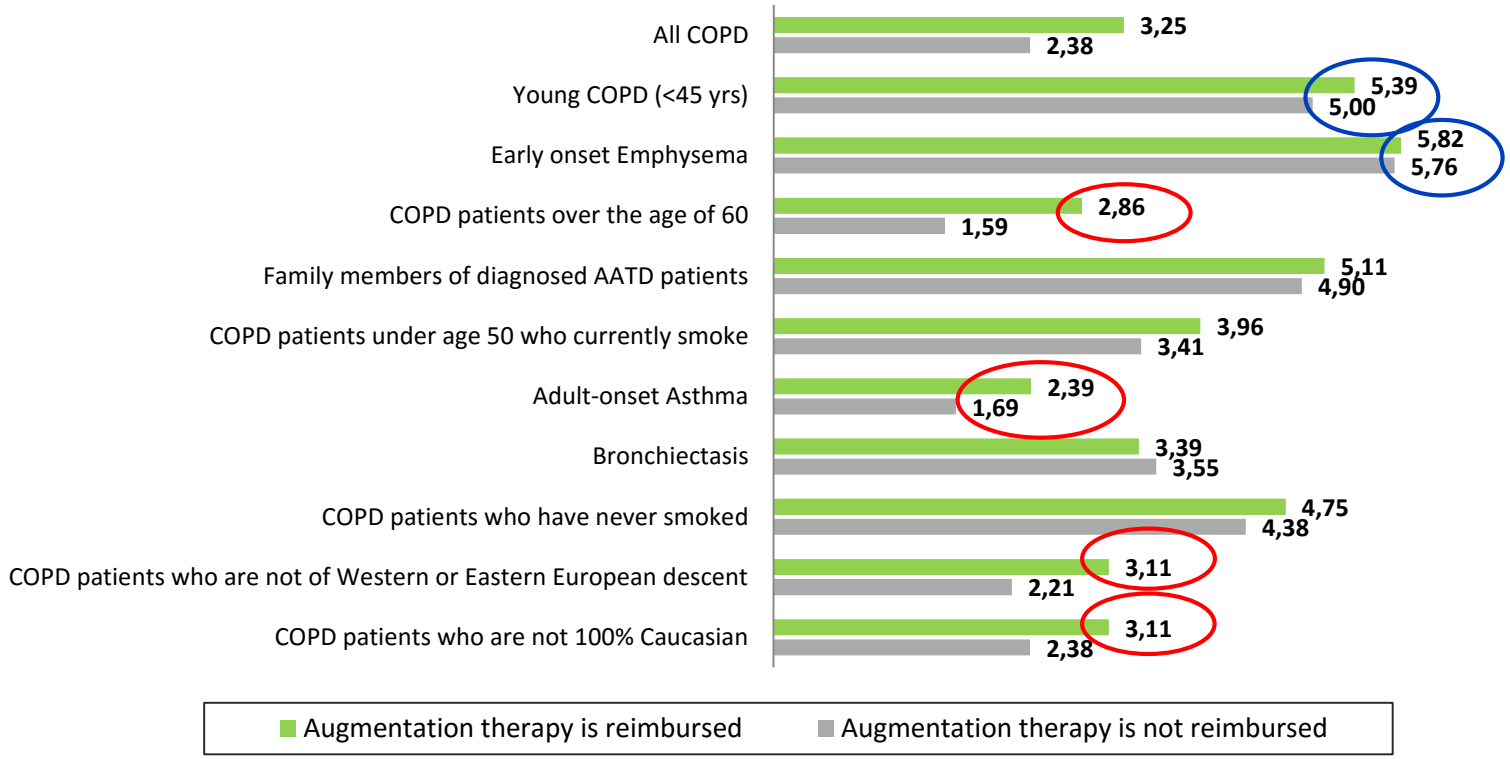


Base: Sample (60)
Augmentation therapy is reimbursed (22)
Augmentation therapy is not reimbursed (38)

Q.10. How do you most often do the initial test for AAT Deficiency?

Young COPD patients (<45 y.o.) and those with early onset Emphysema are most often tested for AATD. Patients with adult-onset asthma, COPD patients over 60 y.o., and COPD patients who are not of European descent or not 100% Caucasian are less likely to get tested.

Who is tested for AATD? (Mean)



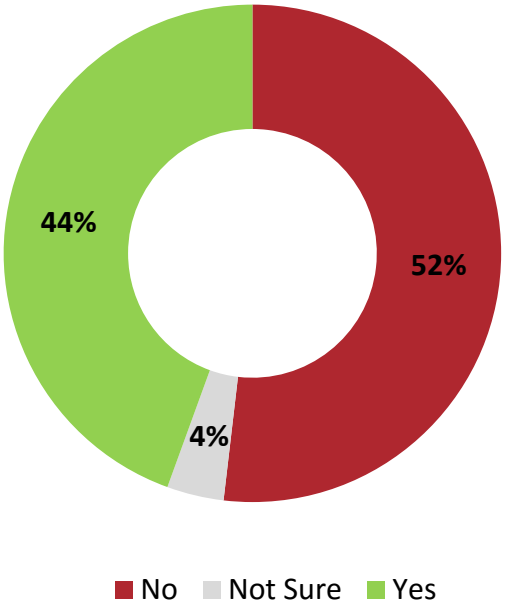
Base: (57)
Augmentation therapy is reimbursed sample (21)
Augmentation therapy is not reimbursed sample (36)

Q.11. Using a scale of 1 to 7, where 1=never and 7=always, please indicate how often you test each of the following patient types for AATD?

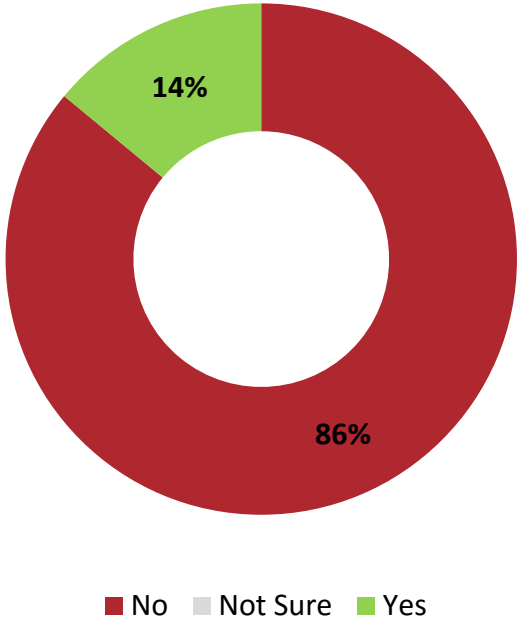
About half of the respondents from countries with AAT reimbursement have never prescribed augmentation therapy while the percentage increases dramatically where it is not reimbursed.

% of respondents who have prescribed Augmentation therapy for AATD

Augmentation therapy is reimbursed



Augmentation therapy is NOT reimbursed

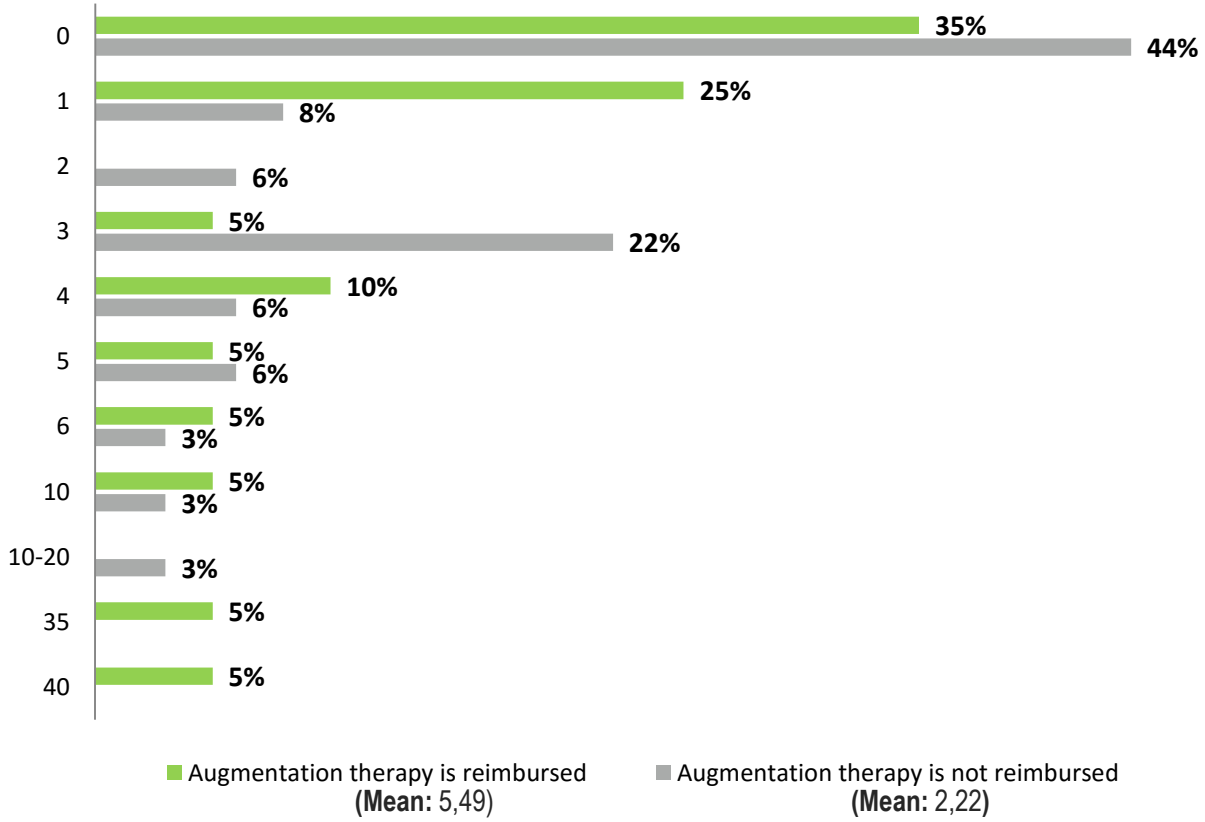


Base: Sample (56)
Augmentation therapy is reimbursed (20)
Augmentation therapy is not reimbursed (36)

Q.12. Have you ever prescribed augmentation (Alpha-1 Proteinase Inhibitor replacement) therapy for patients with AATD?

In the countries with AAT reimbursement, roughly 75% of physicians have less than 5 severe AATD patients while where there is not reimbursement the percentage is about 85%

Severe AATD patients care

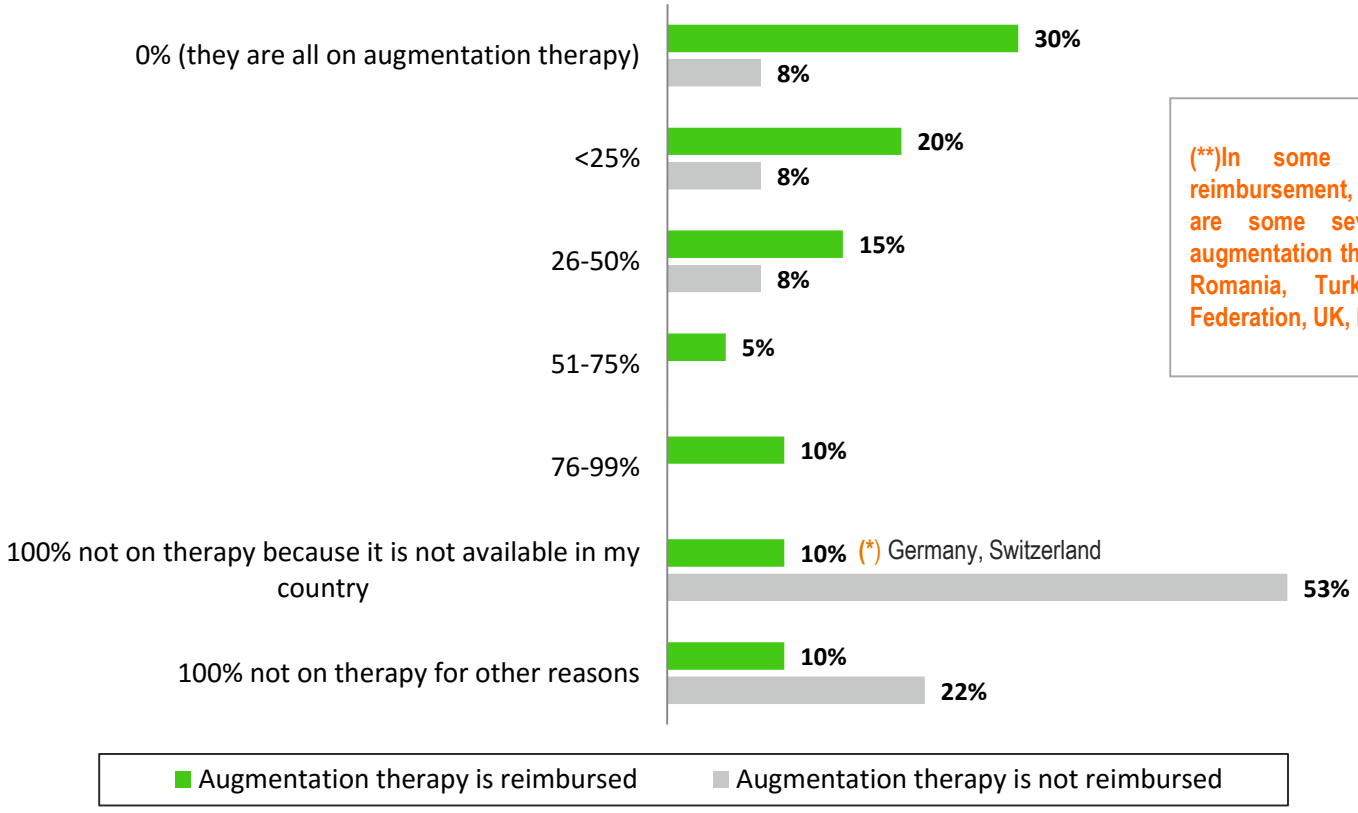


Base: Sample (56)
Augmentation therapy is reimbursed (20)
Augmentation therapy is not reimbursed (36)

Q.13. How many patients with severe AAT deficiency do you currently have under your care ?

Some respondents believe the augmentation therapy is not available in their countries even it is (*). 30% of physicians have all diagnosed AATD patients on augmentation therapy.

Percentage of severe AATD patients are NOT on augmentation therapy



(**)In some countries without AAT reimbursement, respondents say that there are some severe AATD patients on augmentation therapy: Bosnia-Herzegovina, Romania, Turkey, Macedonia, Russian Federation, UK, India, Poland and Tunisia

Base: Sample (56)
Augmentation therapy is reimbursed (20)
Augmentation therapy is not reimbursed (36)

Q.14. What percent of your patients with severe AAT deficiency are NOT on augmentation therapy?

The main reasons for not treating with augmentation therapy where it is reimbursed are that the patient doesn't meet requirement for reimbursement (FEV1 too high) or is still smoking

Reasons for not treating for AATD

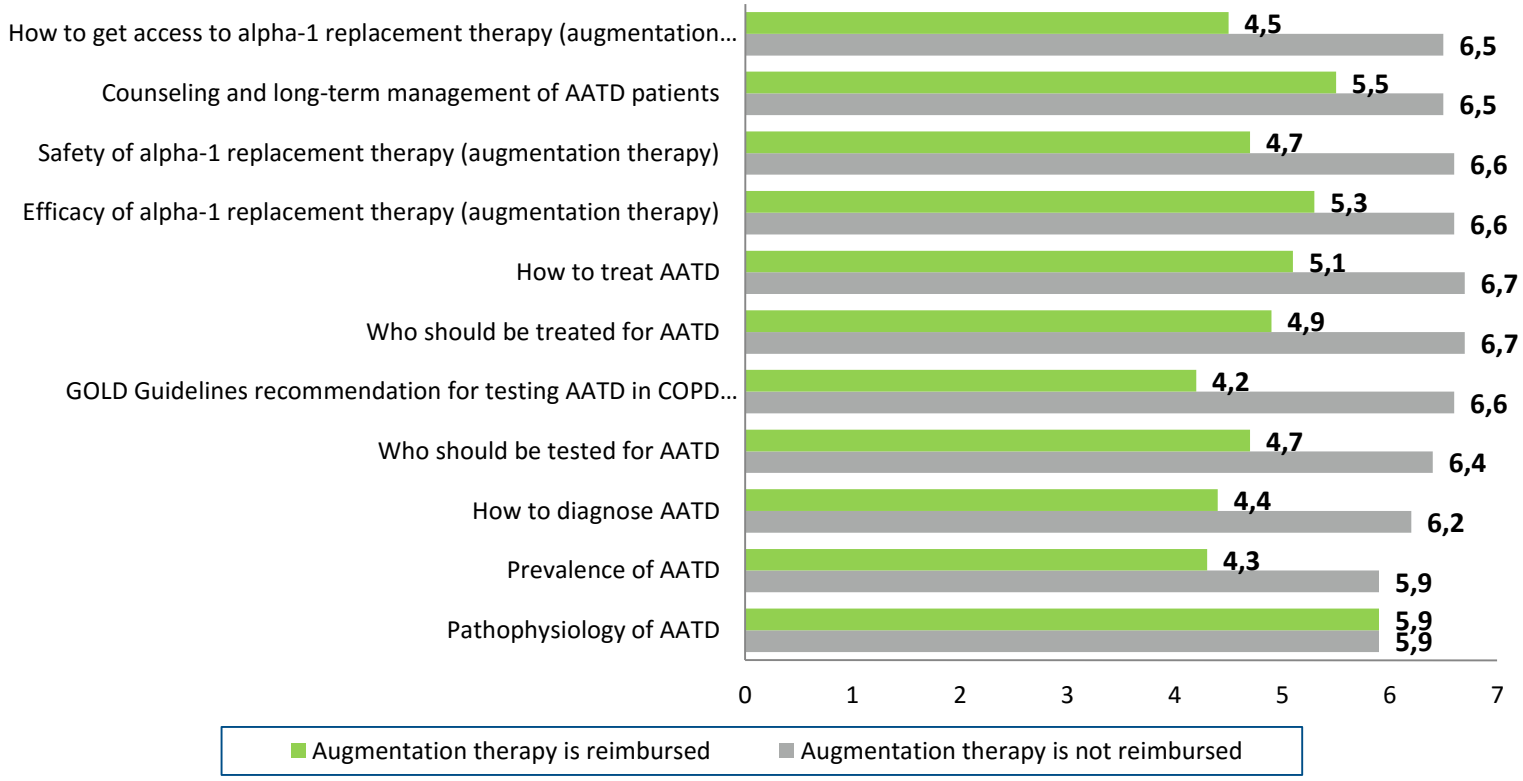
1st top reasons	2nd top reasons	3rd top reasons
AUGMENTATION THERAPY IS REIMBURSED		
Patient doesn't meet requirement for reimbursement - FEV1 too high (35%)	Patient still smoking (30%)	Patient doesn't meet requirement for reimbursement - FEV1 too low (25%)
Patient still smoking (20%)	Patient doesn't meet requirement for reimbursement - FEV1 too high (25%)	Patient doesn't meet requirement for reimbursement - FEV1 too high (20%)
		Patients don't want infusion treatment (20%)
AUGMENTATION THERAPY IS NOT REIMBURSED		
My hospital administration severely restricts the number of patients I can put on therapy (31%)	Local experts do not support treatment (30%)	Local experts do not support treatment (31%)
Local experts do not support treatment (23%)		

Base: Augmentation therapy is reimbursed sample (16)
Augmentation therapy is not reimbursed sample (17)

Q.15. If <100% of severe AATD patients are on augmentation

Where augmentation therapy is reimbursed, respondents have most interest in counseling and long-term management of AATD patients

AATD interest (Mean)



Base: Sample (53)
Augmentation therapy is reimbursed (19)
Augmentation therapy is not reimbursed (34)

Q.16. On a scale of 1 to 7 (with 1=no interest at all and 7=extremely high interest), how interested are you in learning more about AATD disease, testing/diagnosis and patient treatment/management?

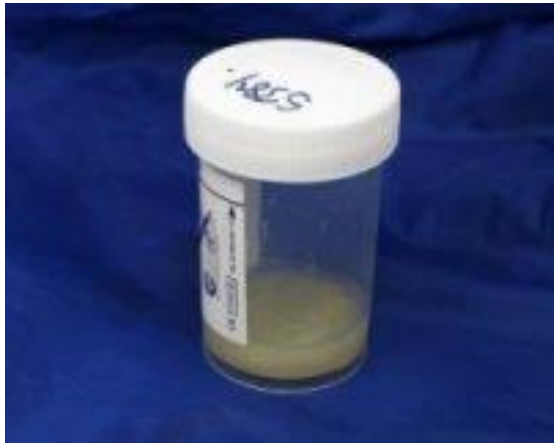
N **BRONCHIECTASIS** CFBE)

Bronchiectasis

Recurrent cough, sputum and respiratory infections

Common- reported prevalence of 52/100,000

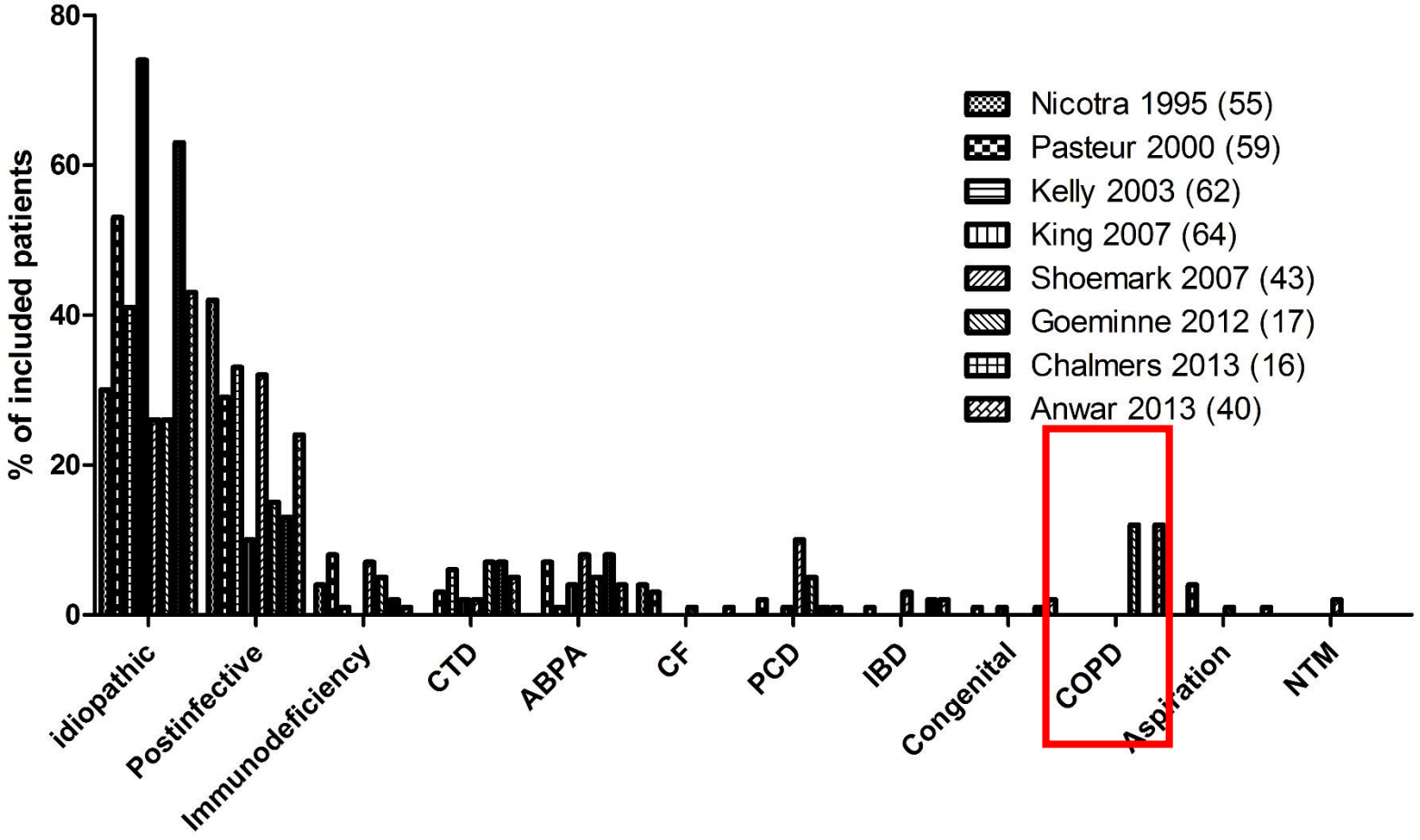
Failed bacterial clearance with chronic bacterial colonisation and neutrophilic airway inflammation



The cause is unknown in >60% of cases

No licensed therapies- Historically neglected

Aetiology


% of included patients
80
60
40
20
0
Nicotra 1995 (55)
Pasteur 2000 (59)
Kelly 2003 (62)
King 2007 (64)
Shoemark 2007 (43)
Goeminne 2012 (17)
Chalmers 2013 (16)
Anwar 2013 (40)
idiopathic
Postinfective
Immunodeficiency
CTD
ABPA
CF
PCD
IBD
Congenital
COPD
Aspiration
NTM

Why should COPD experts and researchers care about bronchiectasis?

N=3636

Bronchiectasis

20.8%- associated with more exacerbations, worse FEV_1

N=2164

Bronchiectasis

5% GOLD III, 7% GOLD IV

Single centre studies

- 50-60% of patients with moderate to severe COPD
- More bacterial colonisation
- More *P. aeruginosa*
- Independent predictor of death

Stewart et al, AJRCCM 2012; Agusti et al, Respir Res 2012; Martinez et al AJRCCM 2013; Getheral et al COPD 2014

Why should COPD experts and researchers care about bronchiectasis?

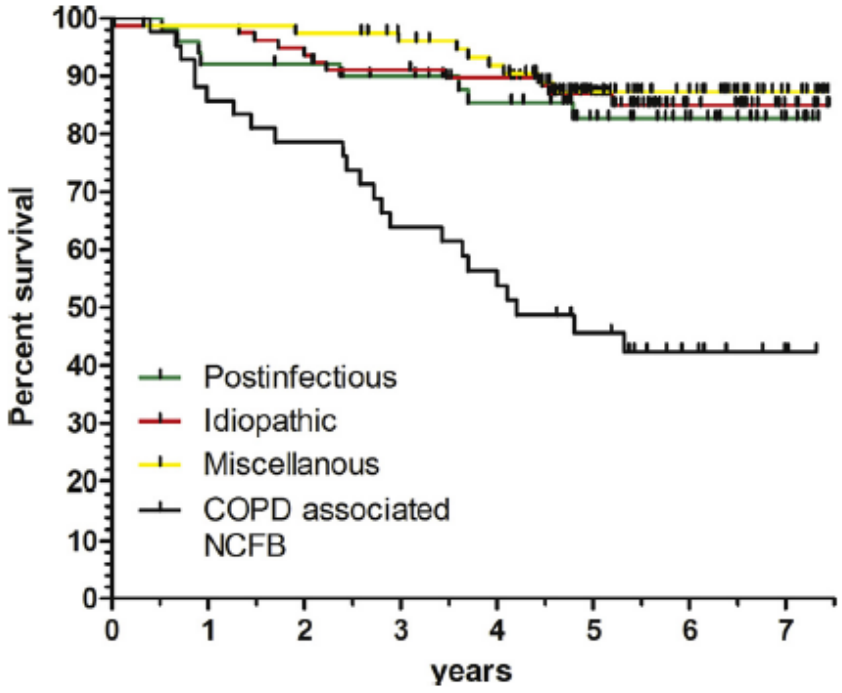
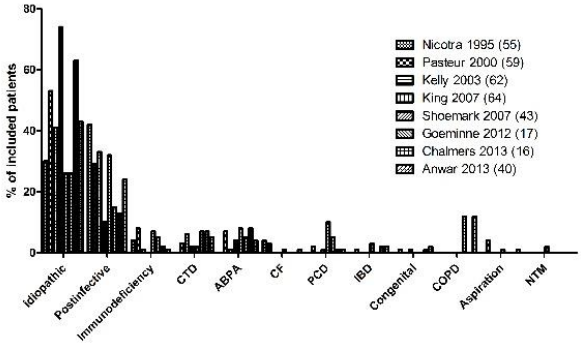


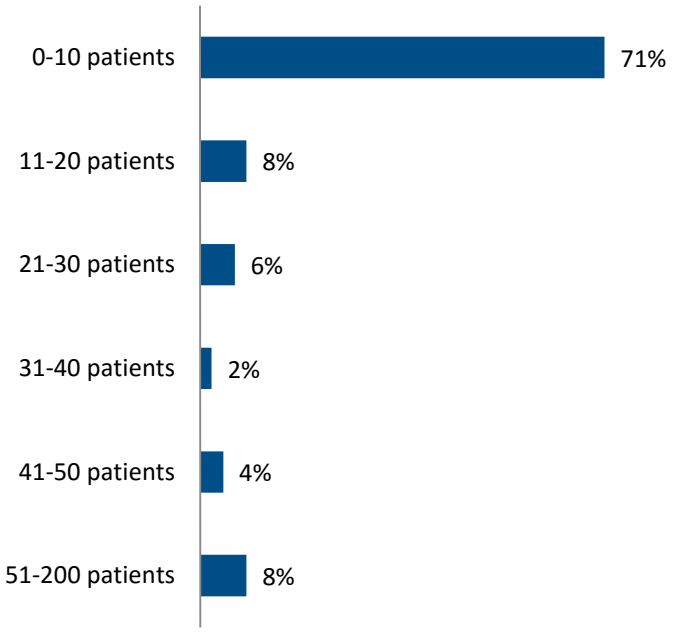
Figure 2 Kaplan–Meier log-rank test survival curve per NCFB etiology over the study period: There was a median follow-up time of 5.18 years and the study period started in June 2006 and ended in November 2013. COPD = Chronic Obstructive Pulmonary Disease; NCFB = Non-cystic fibrosis bronchiectasis.

- **750 million people in Europe**
- **5-10% have COPD**
- **5-50% of these have bronchiectasis**
- **A conservative estimate suggests at least 1m people in Europe have COPD associated bronchiectasis**

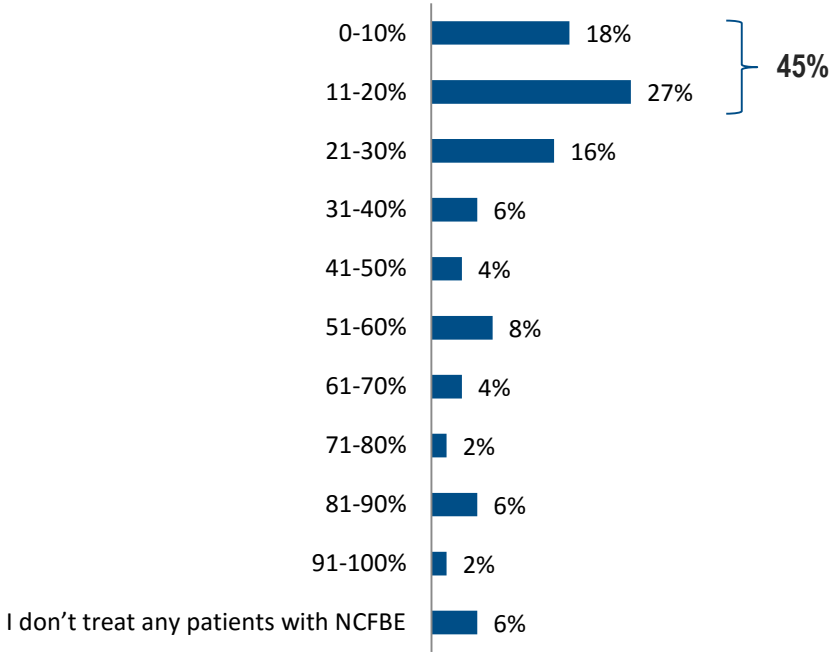


The vast majority have treated ≤10 NCFBE patients in the last 6 months. Almost half of the respondents report that the percentage of NCFBE patients colonized with *Pseudomonas aeruginosa* is ≤20%

Number of NCFBE patients treated in the last 6 months



% of NCFBE patients colonized with *Pseudomonas aeruginosa*



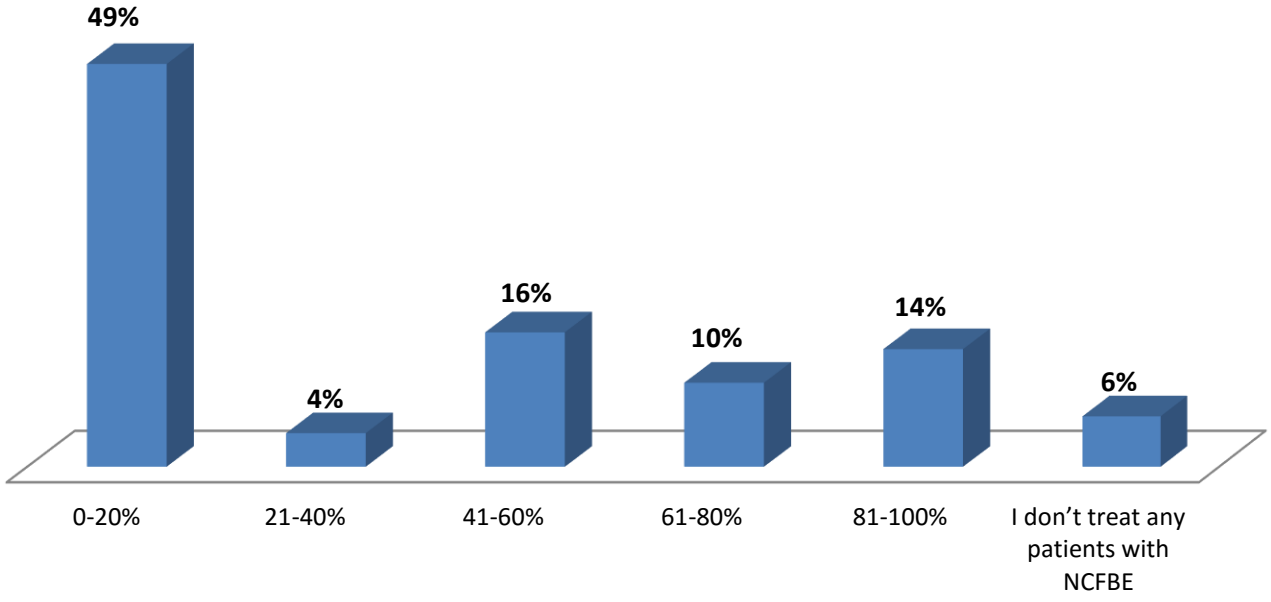
Base: (49)

Q.17. How many NCFBE patients have you treated in the last 6 months? (Please consider each individual as "1 patient" even if seen multiple times)

Q.18. What percent of your NCFBE patients are colonized with Pseudomonas aeruginosa?

Almost half of the respondents report that the percentage of their NCFBE patients colonized with *Pseudomonas aeruginosa* treated with chronic antibiotic is 20% or below

% of NCFBE patients colonized with *Pseudomonas aeruginosa* are on chronic antibiotic

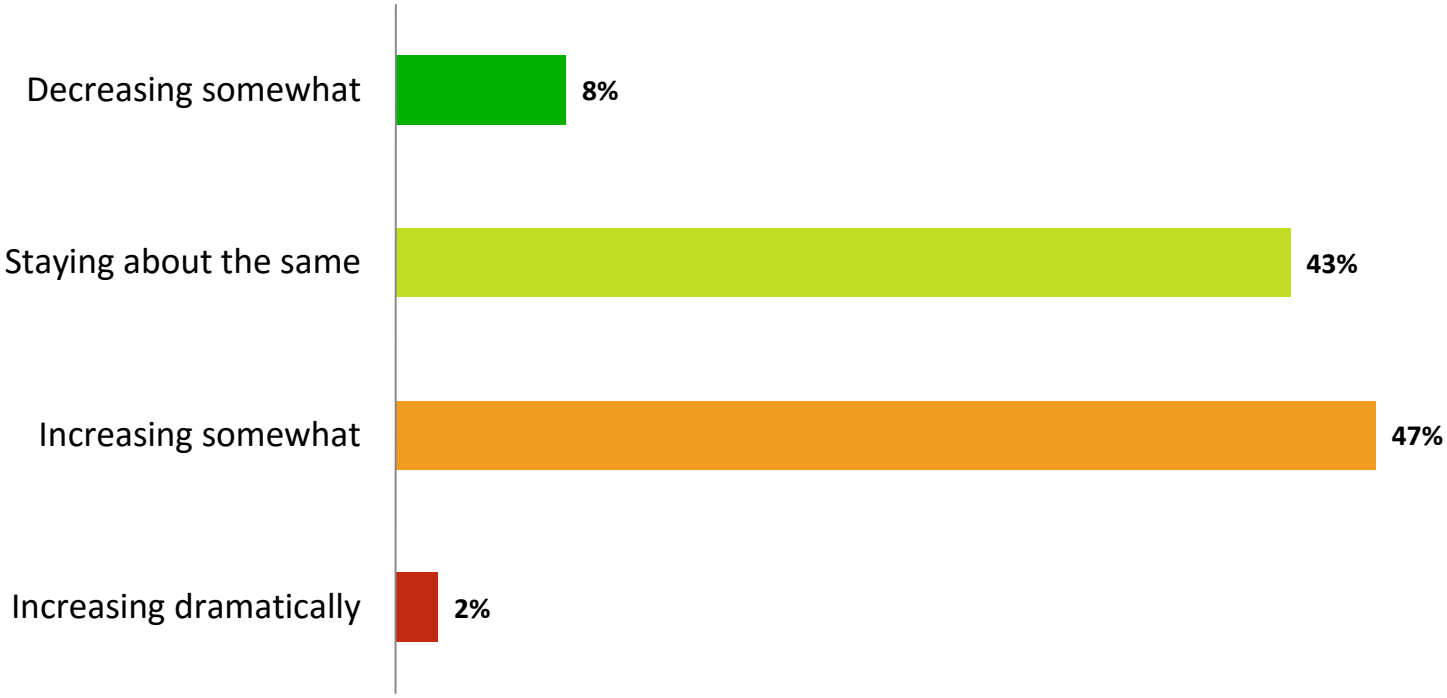


Base: (49)

Q.19. Of your patients colonized with Pseudomonas aeruginosa, what percent are on chronic antibiotic treatment (any type of antibiotic)

The perceived NCFBE prevalence seems to be staying about the same or increasing somewhat

Perception of the NCFBE prevalence change

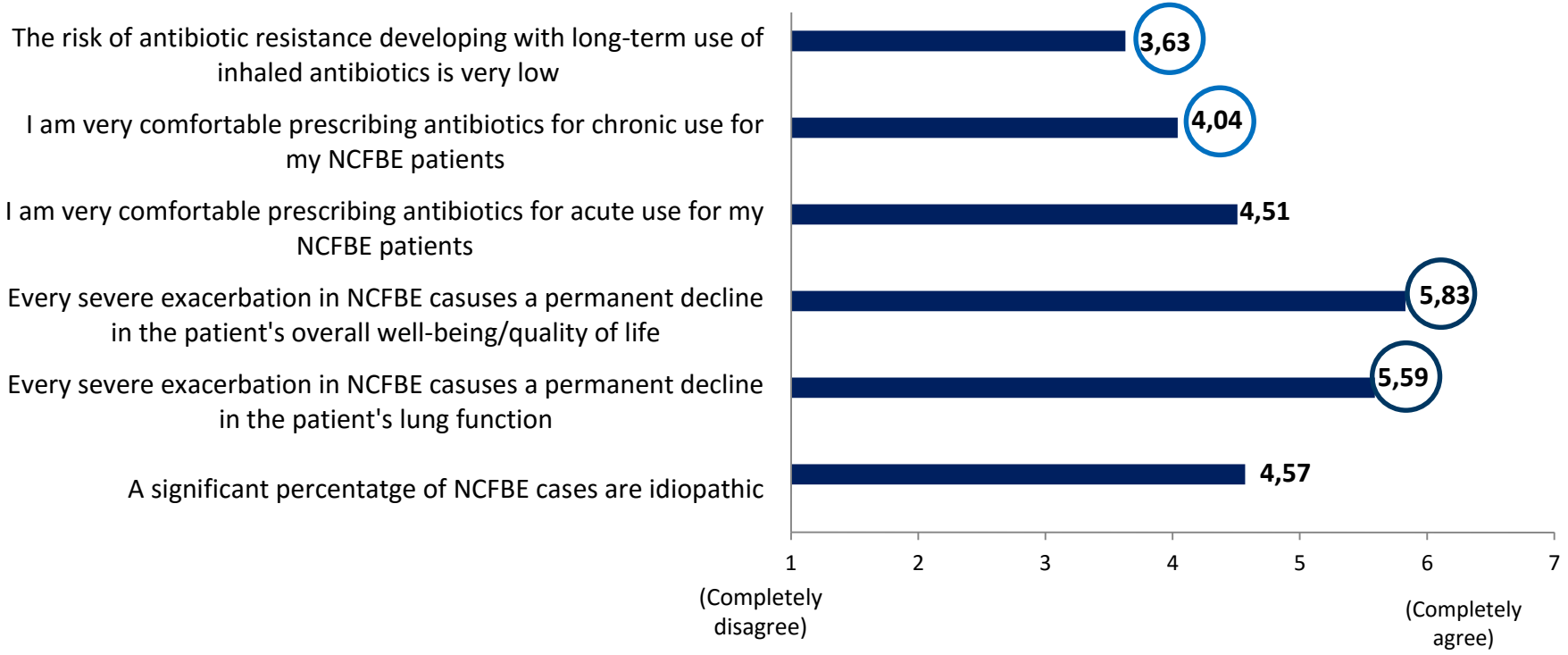


Base:(49)

Q.20.How do you believe the prevalence of NCFBE is changing in your country?

Physicians believe that every severe exacerbation in NCFBE causes a permanent decline in the patient's overall well-being/quality of life and lung function. There is some lack of comfort with chronic use of antibiotics and apparent concern about development of resistance with inhaled antibiotics

Perceptions of NCFBE and antibiotics (1=Completely disagree, 7=Completely agree)



Base:(49)

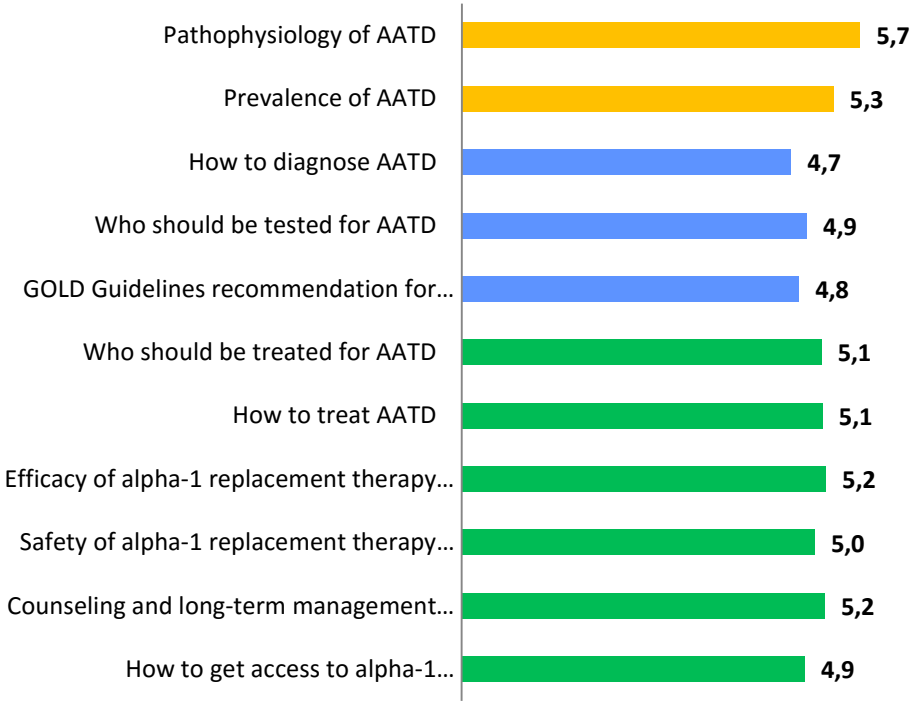
Q.21. On a scale of 1 to 7 (where 1=completely disagree and 7=completely agree), please rate your level of agreement with the following statements:

Interest in knowing more about…

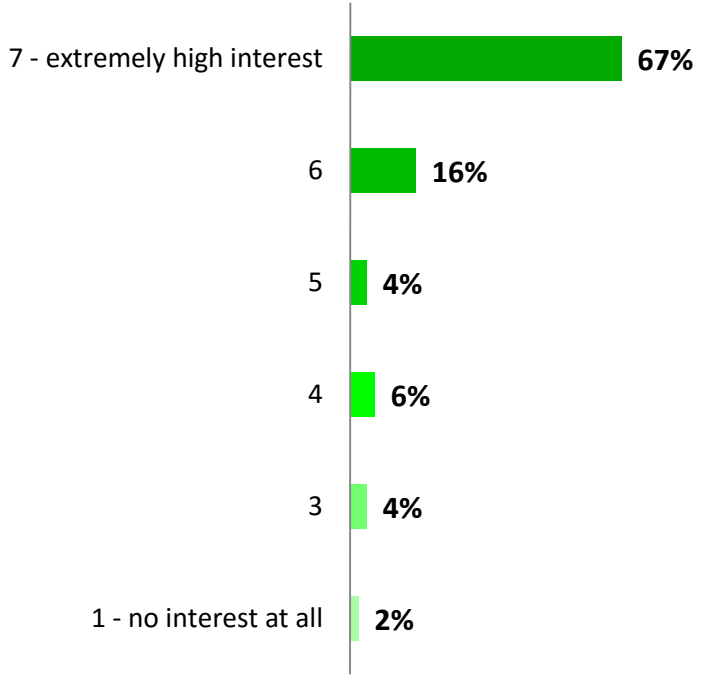
Respondents are highly interested in learning more about AATD and NCFBE diseases, patient treatment and management

Interest in learning more about…

AATD



NCFBE disease and patient treatment/management



Base: AATD (63)
NCFBE disease and patient treatment/management (49)

Q.16. On a scale of 1 to 7 (with 1=no interest at all and 7=extremely high interest), how interested are you in learning more about AATD disease, testing/diagnosis and patient treatment/management?
Q.22. On a scale of 1 to 7 (with 1=no interest at all and 7=extremely high interest), how interest are you in learning more about NCFBE disease and patient treatment/management

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What is EMBARC?

- A pan-European collaborative network to promote research in bronchiectasis
- Funded and supported by the European Respiratory Society as a clinical research collaboration
- An alliance between national networks, expert centres and investigator
- **Open to everyone**

EMBARC
The European Bronchiectasis Registry

ERS EUROPEAN RESPIRATORY SOCIETY

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SOCIETÀ ITALIANA di MEDICINA RESPIRATORIA

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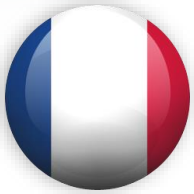
BRONCHIECTASIS RESEARCH REGISTRY
A COPD FOUNDATION INITIATIVE

ELF EUROPEAN LUNG FOUNDATION

BRONCH-UK
The National Bronchiectasis Network



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EMBARC promotes awareness and clinical excellence in bronchiectasis care through educational events, courses and online resources.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Latest News

Call for participation- the Bronchiectasis research roadmap

Jul 9 2014 1:03 PM

The European Bronchiectasis Network (EMBARC) seeks to promote clinical research in bronchiectasis and to build research capacity in Europe. A key task in this will be identifying the areas of …

Latest Research

Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial.

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What can we achieve with a European Bronchiectasis Registry?

ORIGINAL ARTICLE

The Bronchiectasis Severity Index

An International Derivation and Validation Study

James D. Chalmers[1], Pieter Goeminne[2], Stefano Aliberti[3], Melissa J. McDonnell[4,5], Sara Lonni[3], John Davidson[4], Lucy Poppelwell[1], Waleed Salih[1], Alberto Pesci[3], Lieven J. Dupont[2], Thomas C. Fardon[1], Anthony De Soyza[4,5], and Adam T. Hill[6]

[1]Tayside Respiratory Research Group, University of Dundee, Dundee, United Kingdom; [2]Respiratory Medicine, University Hospital Gasthuisberg, Leuven, Belgium; [3]Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Monza, Italy; [4]Adult Bronchiectasis Service and Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne Hospitals, Heaton, Newcastle, United Kingdom; [5]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and [6]Department of Respiratory Medicine Royal Infirmary of Edinburgh and the University of Edinburgh, Edinburgh, United Kingdom

Data from 1310 patients in 4 countries
The first validated prediction rule for bronchiectasis

What EMBARC needs to achieve

- Better understanding of the natural history of bronchiectasis
- Understanding the impact of disease phenotypes
- Promote a higher profile for bronchiectasis research
- Facilitate Clinical Trials

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thank you!