Overview of Alpha-1 Antitrypsin Deficiency

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Disclosures

- None related to this topic

Objectives

- Understand the pathophysiology and clinical presentation of alpha 1 antitrypsin deficiency
- Understand the genetic background of the disorder
- Discuss the disease from a patient perspective
- Discuss the current available treatments for the disease
- Discuss the ongoing research trials related to the disease

History of the Disease

- Discovered in 1962 by Dr. Carl-Bertil Laurell and Dr. Sten Eriksson at the University of Lund in Sweden.
- 6 patients with absence of alpha-1 bands on electrophoresis gels.
- 4 of the 6 patients had emphysema

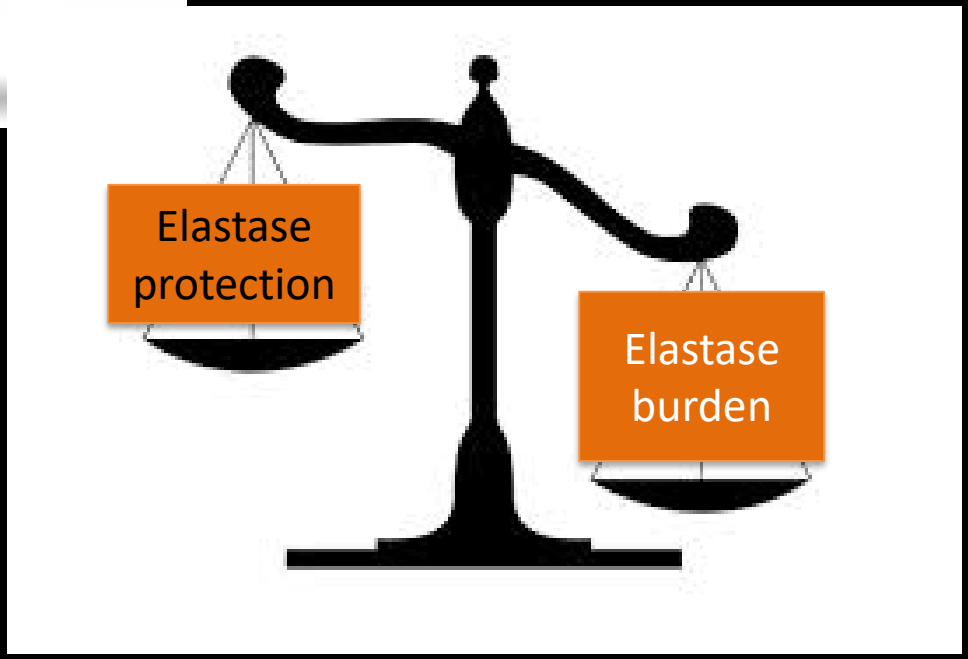
Pathophysiology of the Disease

- Normal Alpha 1 Antitrypsin protein phenotype is “M”
- 95% is made in the liver
- Main function is to control neutrophil elastase, a potent proteolytic enzyme able to damage the elastin matrix of the lungs
- Autosomal co-dominant inheritance

James K. Stoller; Loutfi S. Aboussouan; *Am J Respir Crit Care Med* 2012 185:246-259

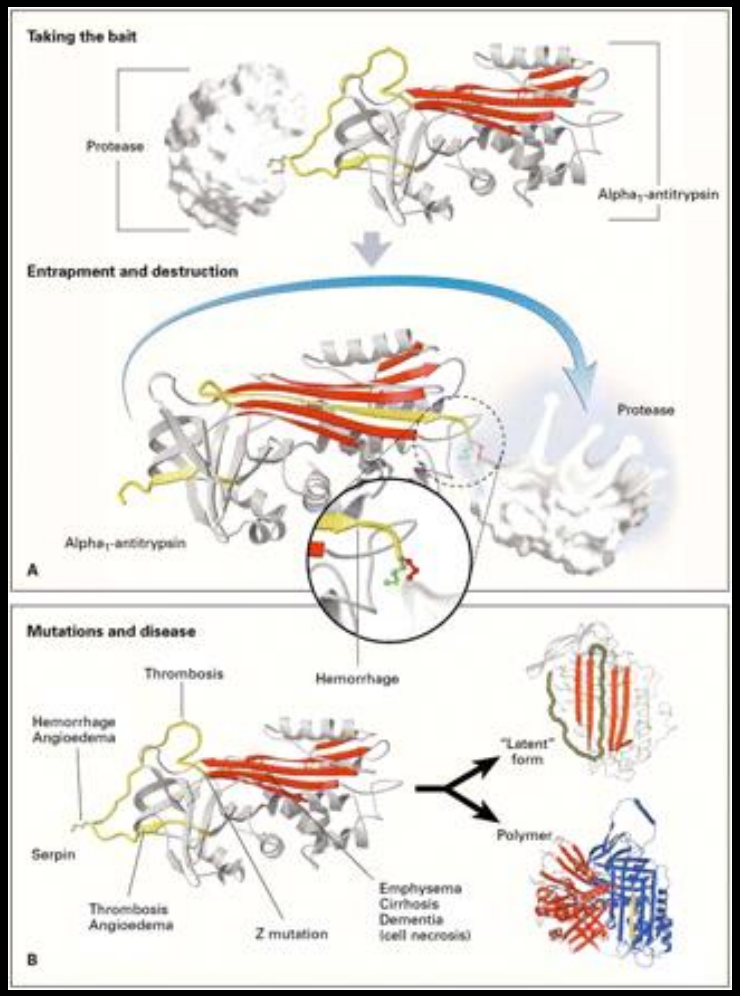
Normal Alpha-1 antitrypsin levels

Low Alpha-1 antitrypsin levels

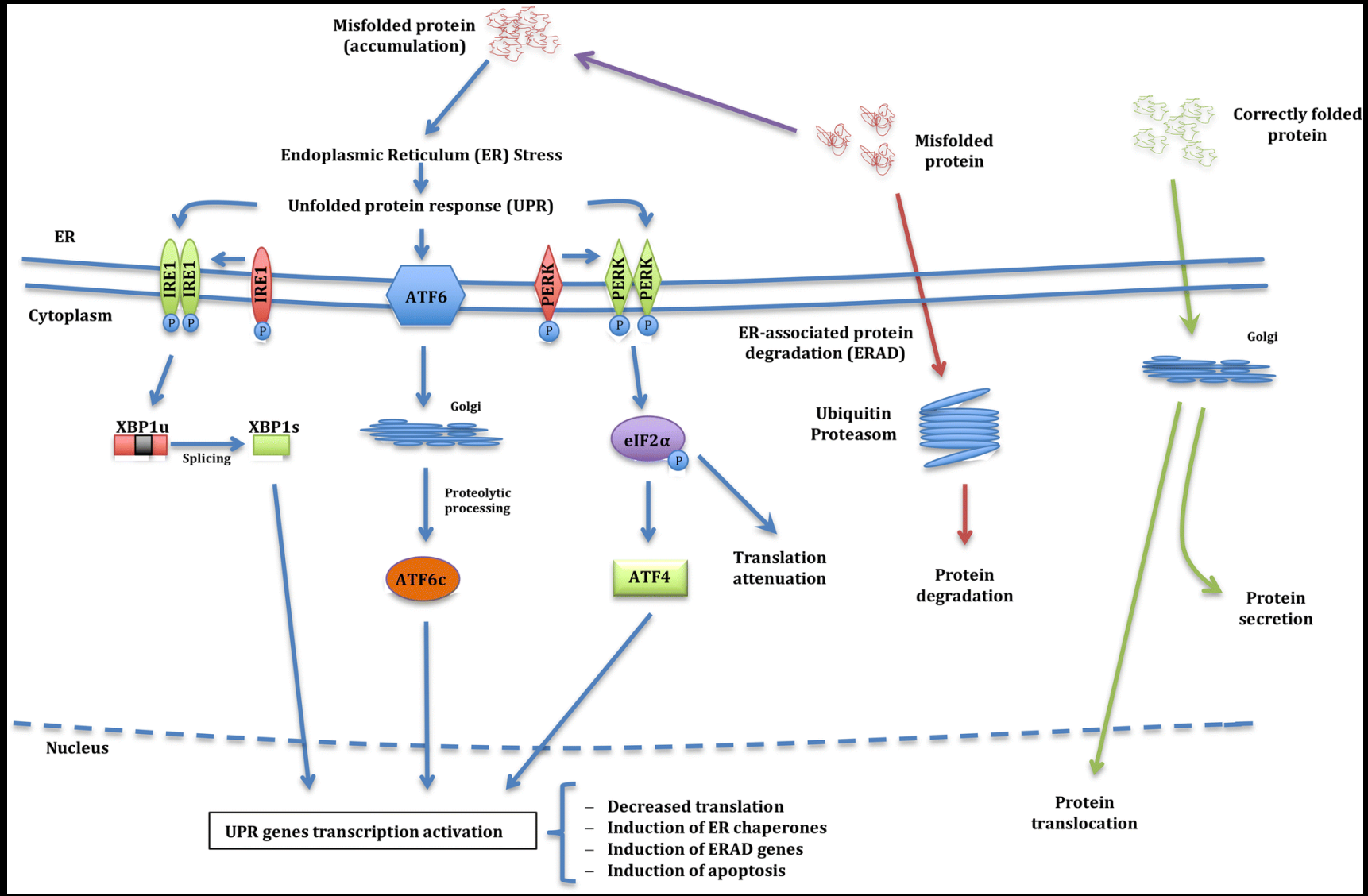


Genetics of AAT deficiency

- M allele – Normal
- Z allele
  - Most common cause of clinical illness (95%)
  - Results from a single point mutation in 1 amino acid
  - (lysine substituted for glutamic acid)
- S allele
  - Milder variant
- Null allele
  - Complete absence of alpha 1 antitrypsin
- Multiple other rare alleles
  - F, Mmalton, etc…
  - Account for 11% of alpha 1 deficient variants in an Italian Registry



Ferrarotti I, Baccheschi J, Zorzetto M*, et al*; *Journal of Medical Genetics* 2005;**42:**282-287
James K. Stoller; Loutfi S. Aboussouan; *Am J Respir Crit Care Med* 2012 185:246-259



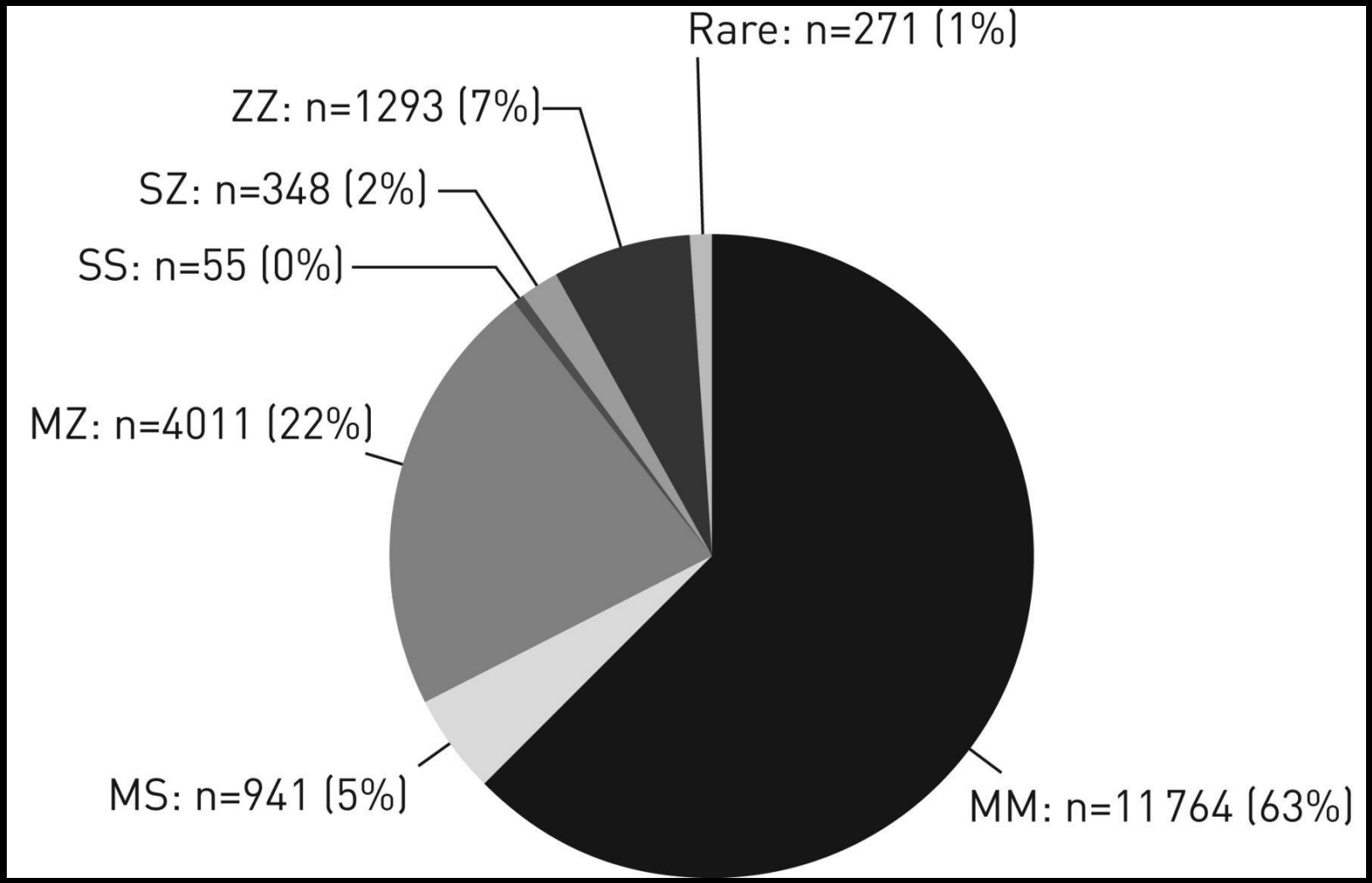
Torres-Durán, M., Lopez-Campos, J.L., Barrecheguren, M. *et al.* Alpha-1 antitrypsin deficiency: outstanding questions and future directions. *Orphanet J Rare Dis* **13,** 114 (2018)

Genetics of AAT deficiency

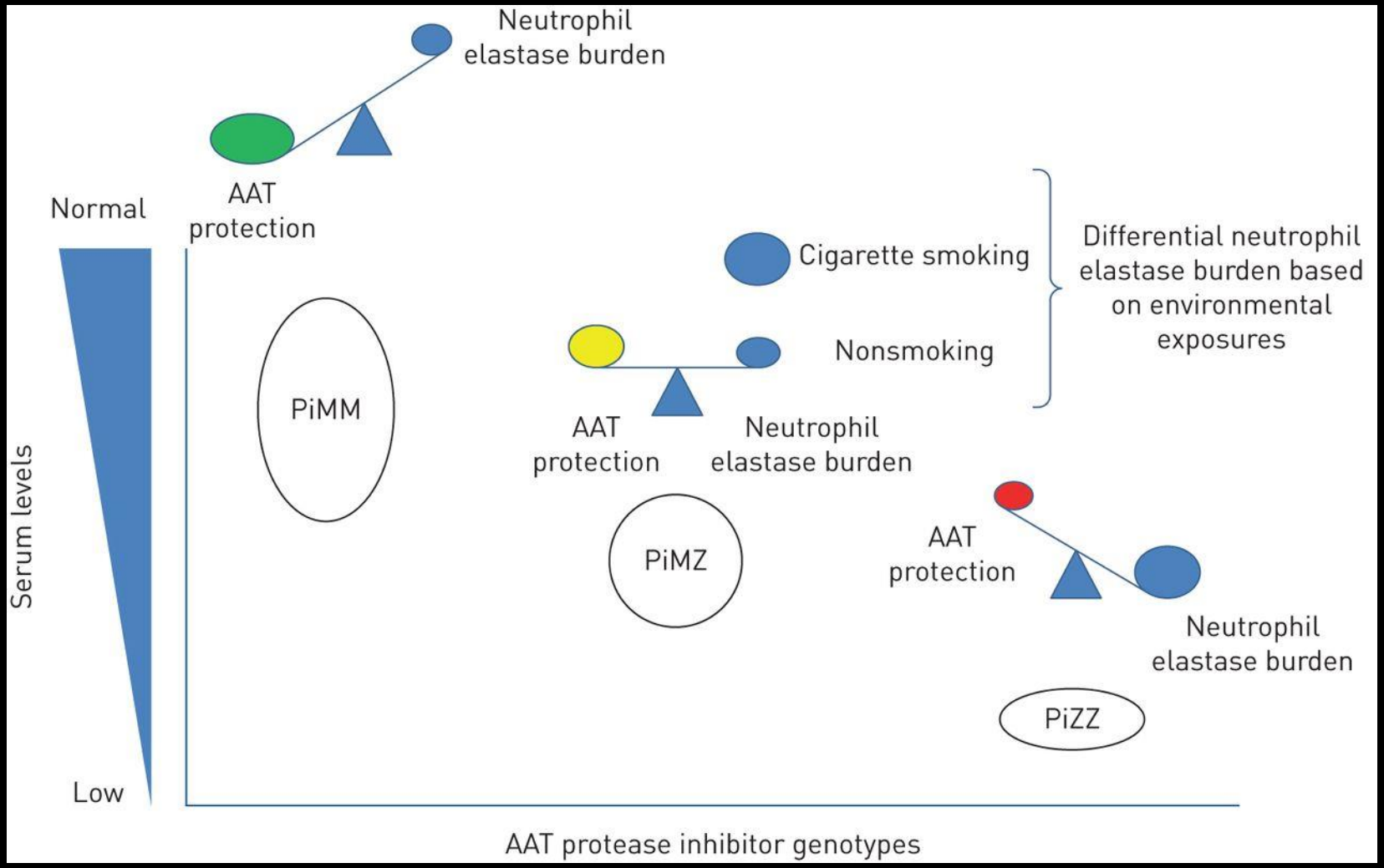
- **Pi*MM**
  - **Does not have disorder**
- **Pi*MZ**
  - **Mild to moderate A1AT deficiency**
  - **Possible link to emphysema and liver disease**
- **Pi*MS**
  - **Most likely no increased risk**

Genetics of AAT deficiency

- Pi*SZ
  - Moderate to severe deficiency
- Pi*ZZ
  - Moderate to severe disease
- Pi*SS
  - Most likely no increased risk of disease
- Pi*Null
  - Early onset of lung disease.
  - Less likely liver disease



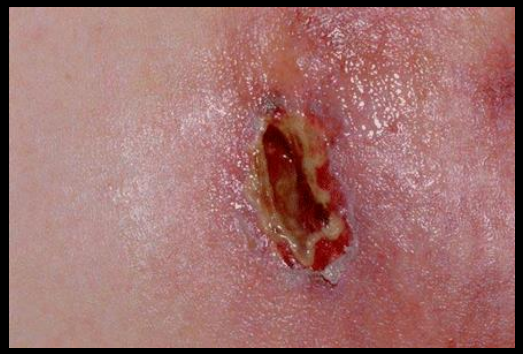
Haitham S. Al Ashry, and Charlie Strange Eur Respir Rev 2017;26:170068



Haitham S. Al Ashry, and Charlie Strange Eur Respir Rev 2017;26:170068

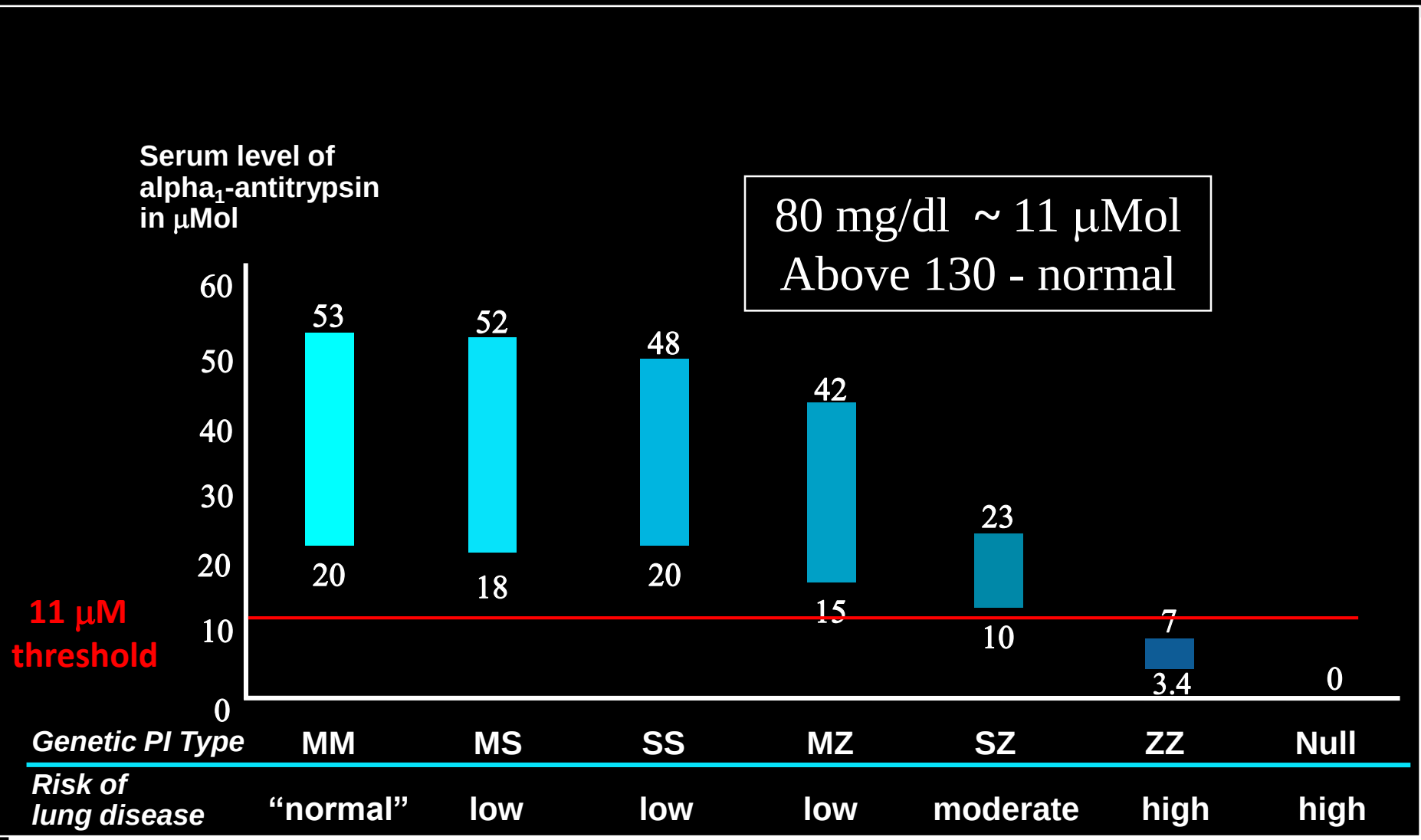
Manifestations of PiZ A1AT deficiency

- Lung disease (emphysema)
  - About 80% develop emphysema
- Liver cirrhosis
  - 12-34%
- Panniculitis
  - 1:1000 A1AT deficient people
- Vasculitis (PR3 ANCA)
  - 5.6-17.6%



James K. Stoller; Loutfi S. Aboussouan; *Am J Respir Crit Care Med* 2012 185:246-259
Larsson C. *Acta Med Scand* 1978; 204:345-351

Inheritance – Diagnostic Levels



In which of the following subjects should A1AT deficiency be considered?

1. All subjects with chronic obstructive pulmonary disease
2. All patients with asthma
3. Family members of A1AT deficient patients
4. All of the above
5. 1 and 3

Who should be tested?

- COPD (3% have A1AT deficiency)
- Asthma with spirometry that does not normalize with treatment
- Family history of A1AT deficiency
- Chronic liver disease
- Adults with bronchiectasis without evident etiology
- Unexplained panniculitis
- Anti-proteinase-3 vasculitis

ATS/ERS statement 2003

Sandhaus RA, Turino G, Brantly ML, et al. *Chronic Obstr Pulm Dis*. 2016; 3(3): 668-682

What is the estimated frequency of A1AT deficiency in the US?

1. 1:300
2. 1:3,000
3. 1:30,000
4. 1:300,000

Prevalence of Alpha-1

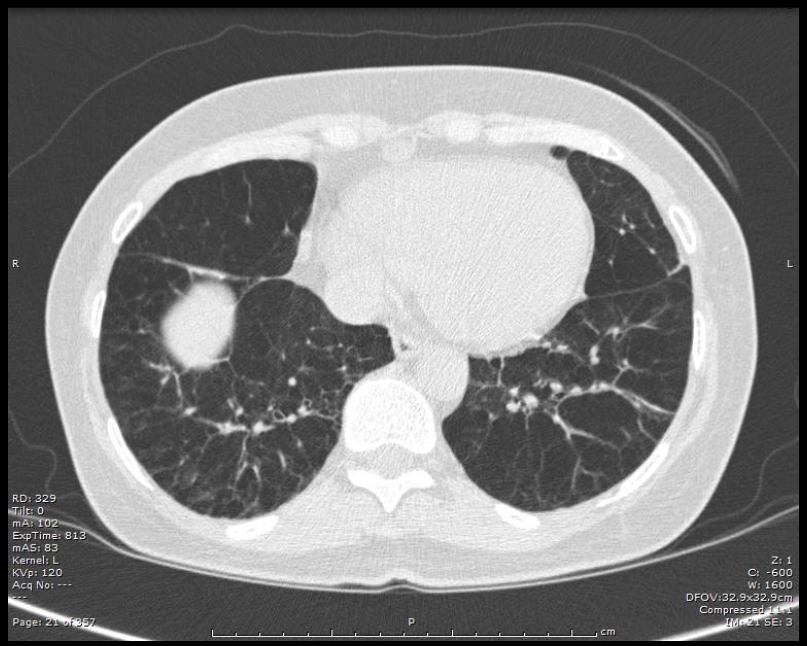
- A figure of 1:2857 means that
  - Over 100,000 Americans have severe deficiency
  - An estimated 25 million carry deficient genes
  - Less than 10% diagnosed

Pi*ZZ Prevalence

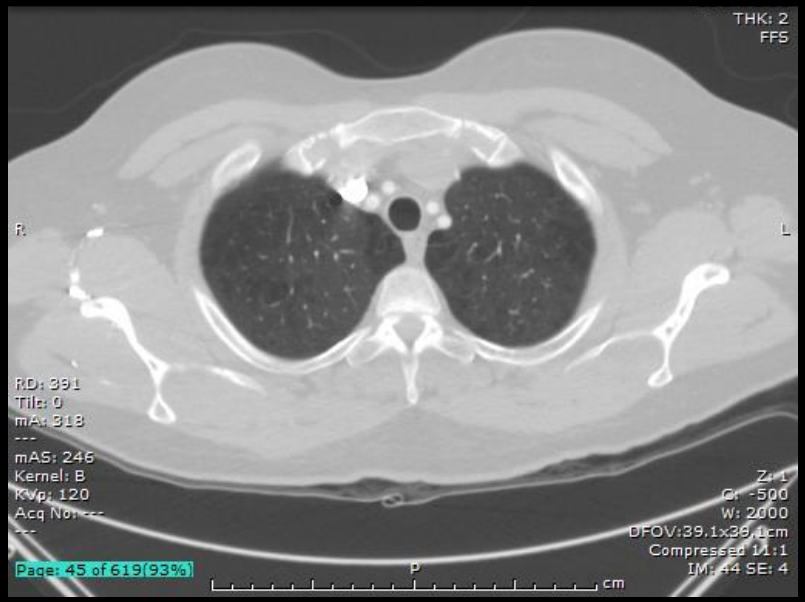
Disorder	Prevalence
AAT deficiency (PI*ZZ)	Over 100,000
Cystic Fibrosis	30,000
Huntington's Disease	30,000
Spina Bifida	166,000
Idiopathic Pulmonary Fibrosis	128,000
Testicular Cancer	196,000
Ovarian Cancer	177,000
Hodgkin's Lymphoma	164,000
Cervical Cancer	243,884

Patient Presentations

57 year old F with Pi*ZZ genotype

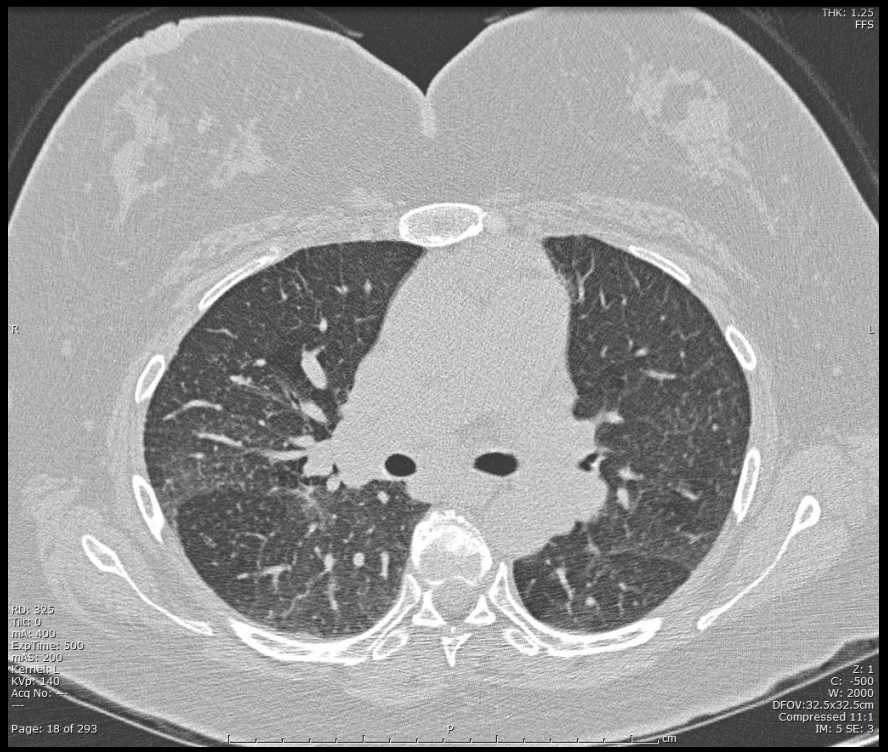


41 year old F with Pi*ZZ genotype

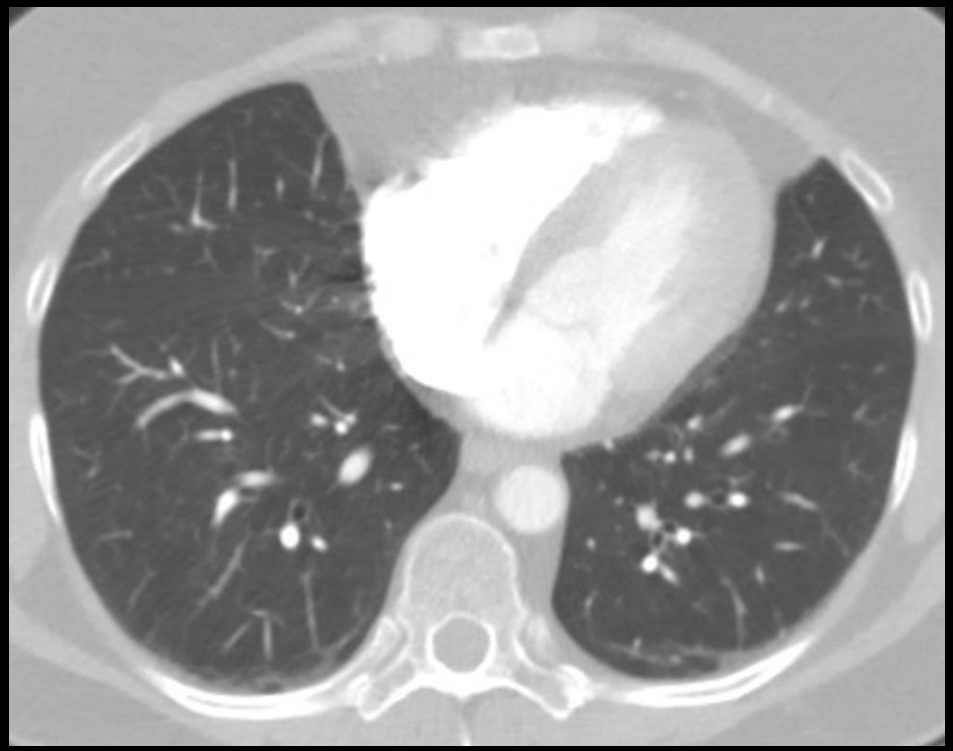


Patient Presentations

49 year old Pi*SZ with shortness of breath and granulomatous hepatitis



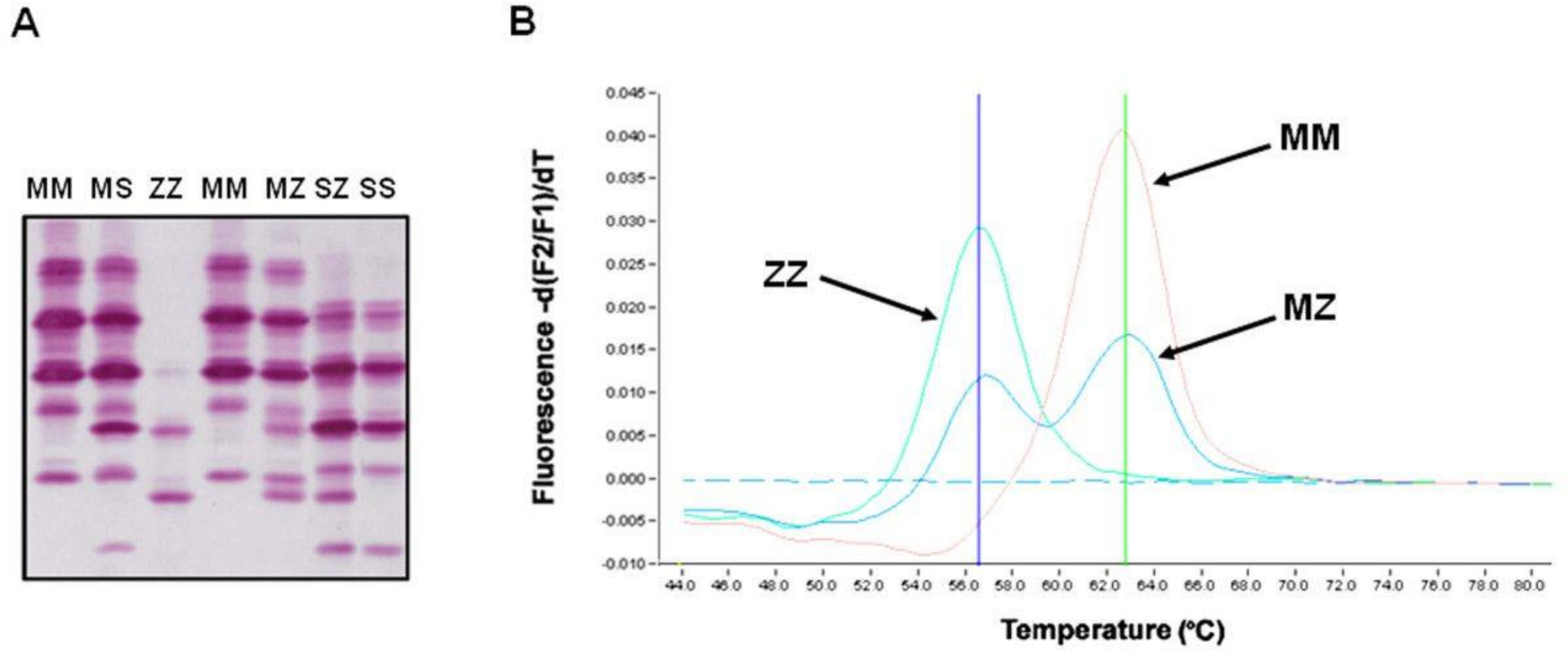
50s year old female with Pi*MZ with severe asthma in the setting of tobacco use



Diagnosis

- Average Alpha-1 patient has symptoms for 7.2 to 8.3 years before a diagnosis is made.
- It may take 3 different doctors to get a diagnosis
- I would send both the level and the genotype when checking for alpha-1
- Testing via fingerstick or blood test
  - Genotyping vs isoelectric gel analysis

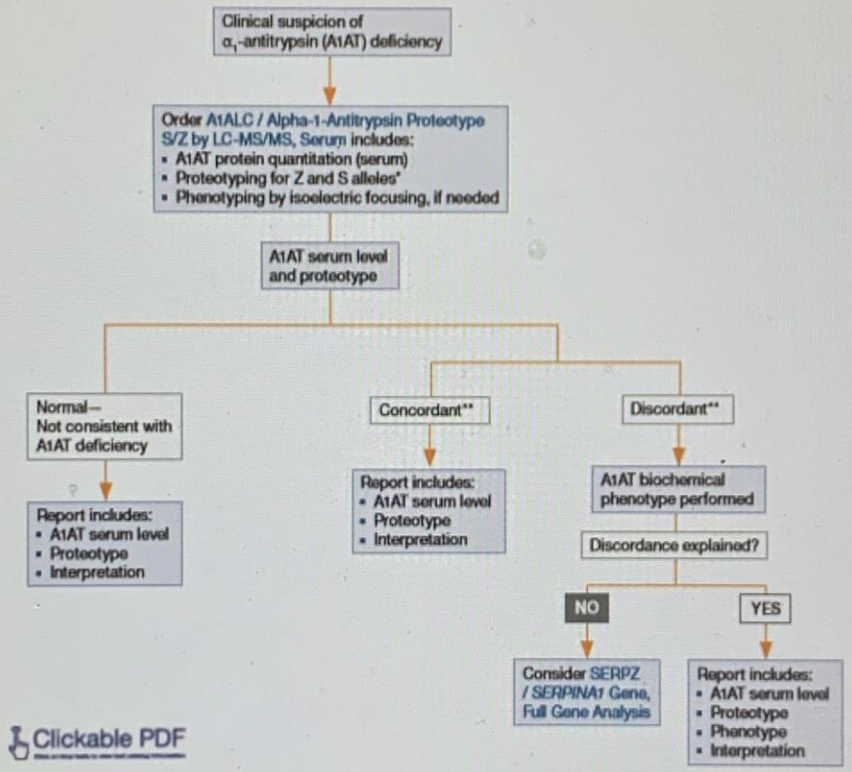
Stoller JK, Smith P, Yang P, Spray J. Physical and social impact of alpha-1 antitrypsin deficiency: results of a survey. *Cleve Clin J Med* 1994;61:461–467



Carroll, T.P., O'Connor, C.A., Floyd, O. *et al.* The prevalence of alpha-1 antitrypsin deficiency in Ireland. *Respir Res* **12,** 91 (2011)

MAYO CLINIC LABORATORIES

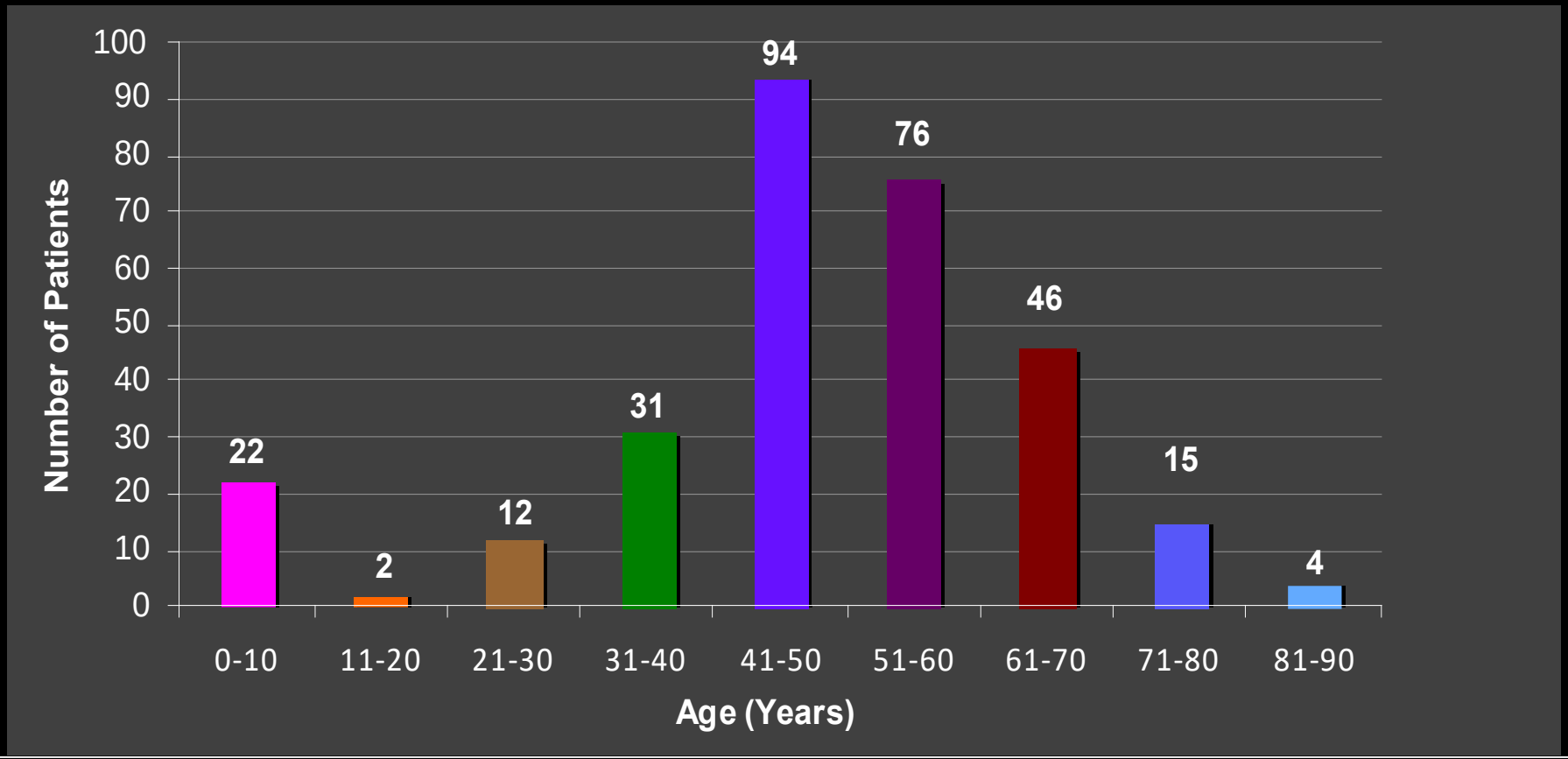
Alpha$_1$ Antitrypsin—A Comprehensive Testing Algorithm



*Chen Y, Snyder MR, Zhu Yi, et al: Simultaneous phenotyping and quantification of alpha-1-antitrypsin by liquid chromatography-tandem mass spectrometry. Clin Chem 2011;57(8):1161-1168

**For each of the possible A1AT proteotypes there is an expected range for the total serum level of A1AT. However, a number of factors can influence either the A1AT serum level or the A1AT proteotype results, including acute illness (A1AT is an acute phase reactant), protein replacement therapy, the presence of other rare variants and/or the presence of DNA polymorphisms. As noted above in the algorithm, when the serum level differs from what is expected for that proteotype (discordant), additional studies are performed in order to ensure the most appropriate interpretation of test results. Additional follow-up may include A1AT phenotyping by isoelectric focusing (IEF), obtaining additional clinical information, and/or DNA sequencing.

Average Age at Diagnosis



Based on 302 patients with PiZZ out of 26,520 patients tested.
M Brantly, U of Florida

The patient is diagnosed with Alpha-1. What does he/she do now?

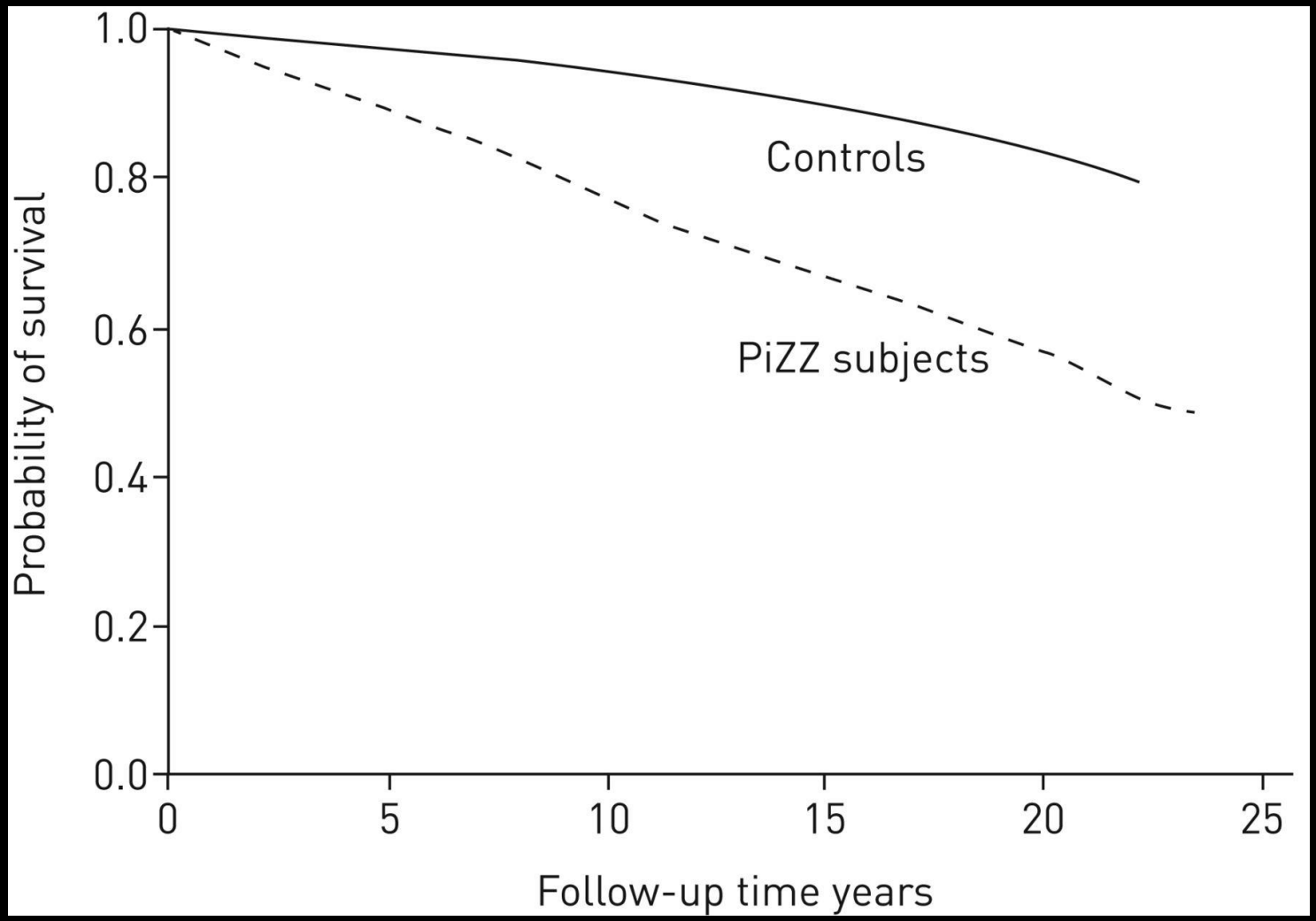
Questions that Patients Ask

- How do I get educated about this disease?
- Are there any specialized alpha-1 centers in my community?
- What is my genotype of alpha-1 antitrypsin deficiency?
- What are my personal goals?
- How will this diagnosis affect my survival?
- How will this diagnosis affect my finances?
- What will the impact be on my family members?

AATD and Survival

- Median survival in smokers – 49 years
- Median survival in non-smokers – 69 years
- Lung disease diagnosed after age 50 in non-smokers

Kaplan–Meier curve illustrating survival in 1585 PiZZ subjects and 5999 population-based controls.



Hanan A. Tanash et al. Eur Respir J 2017;50:1700198

	Ever-smokers		Never-smokers	
	PiZZ	Controls	PiZZ	Controls
Subjects n	301	445	172	302
Respiratory	182 (60)	34 (8)	63 (36)	3 (1)
Hepatic	35 (12)	10 (2)	37 (22)	5 (2)
Cirrhosis/complications	21 (7)	5 (1)	21(12)	2 (1)
Primary liver carcinoma	12 (4)	5 (1)	14(8)	3 (1)
Cholangiocarcinoma	2 (1)	0	2	0
Cardiovascular disease	35 (12)	169 (38)	39 (23)	113 (37)
Cancer	32 (11)	146 (33)	19 (11)	101 (33)
Pulmonary carcinoma	3 (1)	29 (7)	3 (2)	4 (1)
Gastrointestinal	9 (3)	8 (2)	4 (2)	2 (1)
Others	8 (2)	78 (17)	10 (6)	78 (26)

Main causes of death among 473 PiZZ subjects and 747 population-based controls

Hanan A. Tanash et al. Eur Respir J 2017;50:1700198

Major Resources

- Alpha-1 Foundation
  - Alpha1.org
  - https://www.alpha1.org/Newly-Diagnosed/Living-with-Alpha-1/Find-an-Alpha-1-Specialist
- AlphaNet
  - Big Fat Reference Guide
  - www.alphanetbfrg.org

Education and Support

- **Education Days**
  - https://www.alpha1.org/Alphas-Friends-Family/Education/Education-Days
- **Support Groups**
  - https://www.alpha1.org/Alphas-Friends-Family/Support/Support-Groups

Genetic Counseling

- https://www.alpha1.org/Alphas-Friends-Family/Support/Genetic-Counseling
- **1-800-785-3177**

Treatment

- **Smoking Cessation**
- Pulmonary rehabilitation
- Inhalers
  - LAMAs
  - LABAs
  - LAMA/LABA combinations
  - Inhaled steroids
- Vaccinations
- Oxygen
- Lung Transplant

Intravenous Augmentation Therapy

- Plasma derived
- Goals
  - Increase serum and epithelial lining fluid alpha 1 antitrypsin concentration
  - Decrease elastase burden leading to lung protection
- To be used ONLY in patients with severe alpha 1 antitrypsin deficiency (<11 microM) AND emphysema

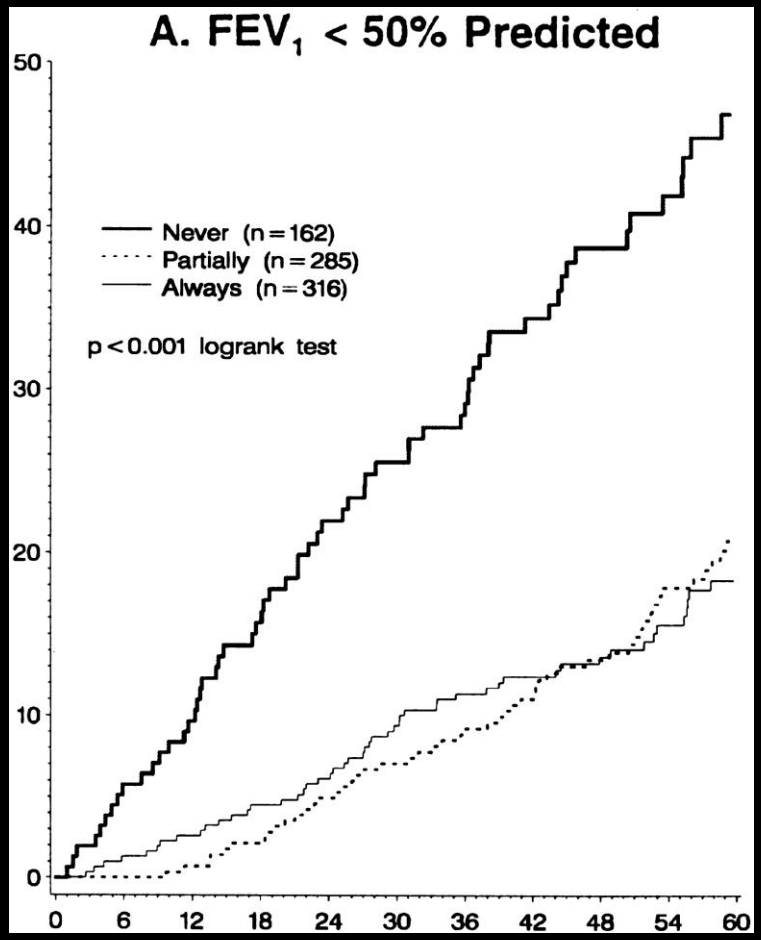
Available Formulations

- Multiple formulations
  - Prolastin
  - Prolastin C
  - Aralast
  - Aralast NP
  - Zemaira
  - Glassia

NHLBI Registry

- Severe ZZ patients with levels <11 microM
- Followed over time (1988-1996)
- Average rate of FEV1 decline 54 ml/year

The Alpha-1-Antitrypsin Deficiency Registry Study Group. *AJRCCM* 1998; 158: 49-59.



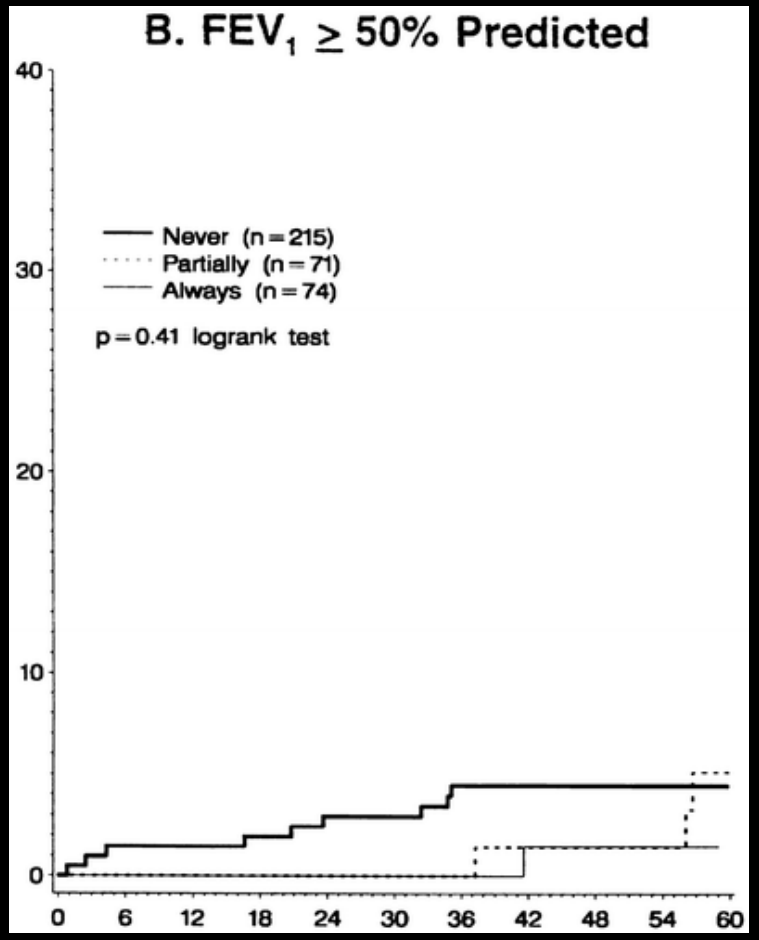
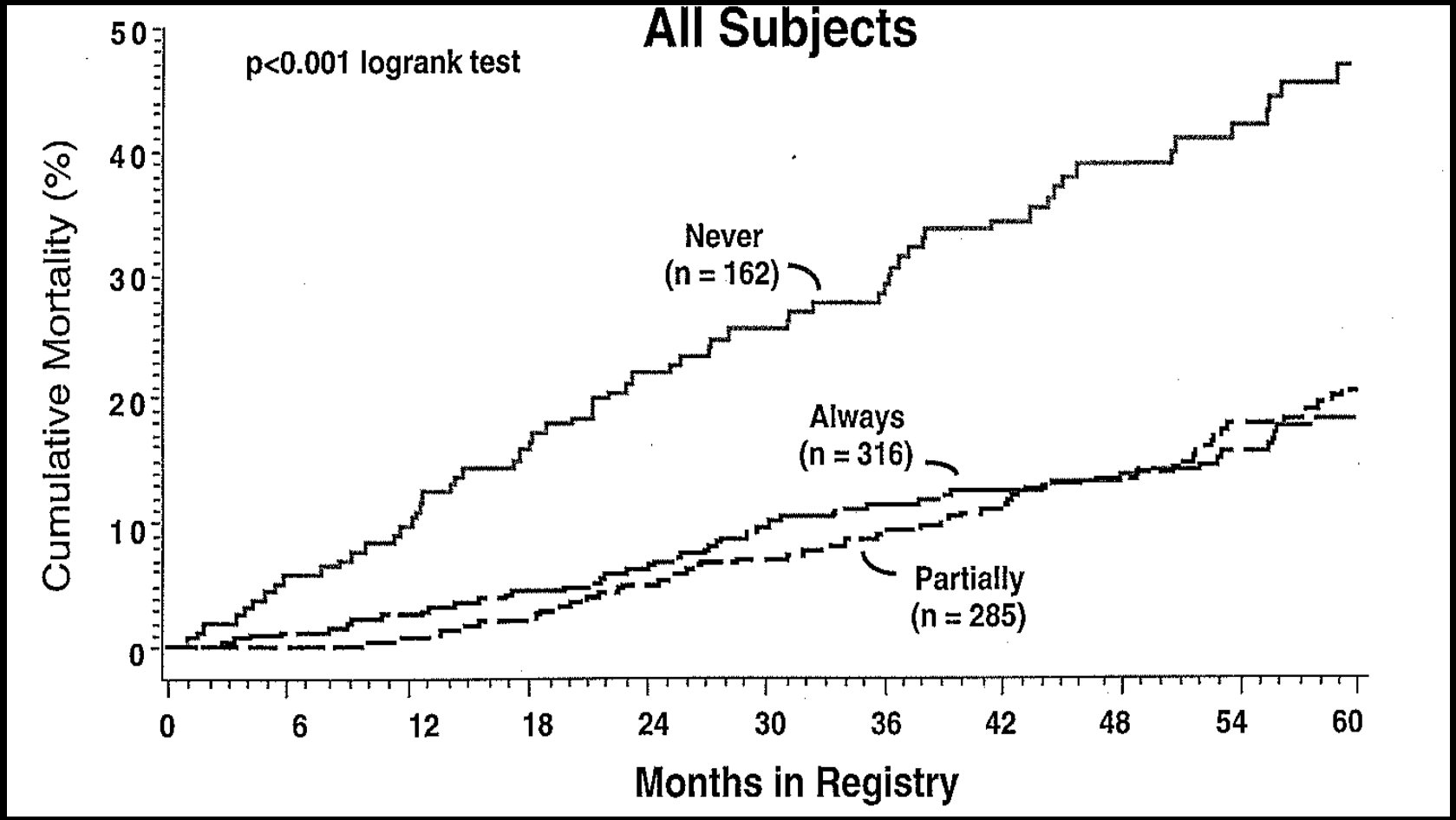


Fig. 1. Kaplan–Meier cumulative mortality curves based on all eligible patients and deaths, plotted for subjects with initial FEV1 < 50% predicted and for those with initial FEV1 ⩾ 50% predicted. In each plot, separate curves are shown for subjects classified as never receiving (*thick solid line*), partly receiving (*dotted line*), and always receiving (*narrow solid line*) augmentation therapy. The log-rank p value presented is for a comparison of the subjects never receiving therapy with the combined group of subjects partly or always receiving therapy. (*A* and *B*) Kaplan–Meier plots of survival from time of enrollment using data from all subjects. (*C* and *D*) Similar analysis, but restricted to those subjects who had follow-up contact for at least 6 mo after enrolling in the Registry.

Am J Respir Crit Care Med,
https://www.atsjournals.org/doi/abs/10.1164/ajrccm.158.1.9712017

Published in: *Am J Respir Crit Care Med* 1998 15849-59.
DOI: 10.1164/ajrccm.158.1.9712017

NHLBI Registry Mortality Data



The Alpha-1-Antitrypsin Deficiency Registry Study Group. *AJRCCM* 1998; 158: 49-59.

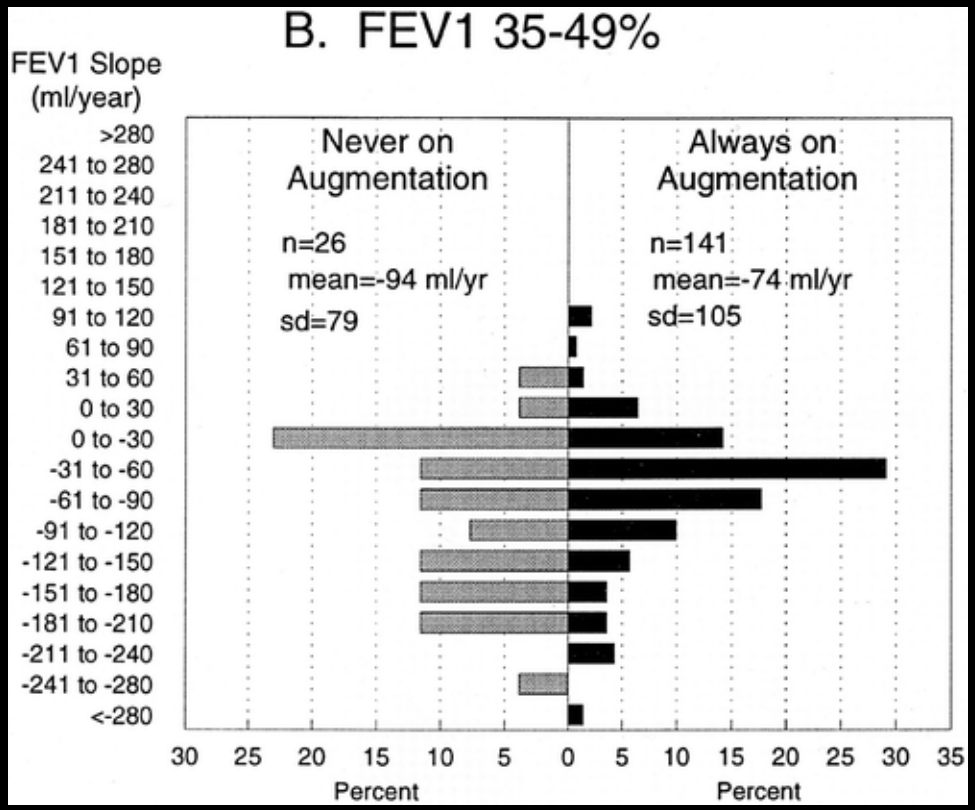


Fig. 2. Histograms of individual rates of FEV1 decline, by augmentation-therapy status and mean FEV1% predicted. Shown is the distribution of the individual least-squares slopes (ml/yr) calculated for individual Registry subjects. These plots include only those subjects who had two or more postbronchodilator measurements of FEV1 at least 1 yr apart while they were continuously receiving or not receiving augmentation therapy. For subjects who were both receiving and not receiving augmentation therapy while in the Registry, the data from the longer period (receiving or not receiving therapy) were used to calculate a slope; the other data were excluded for the purpose of this analysis.

Am J Respir Crit Care Med,
https://www.atsjournals.org/doi/abs/10.1164/ajrccm.158.1.9712017

Published in: *Am J Respir Crit Care Med* 1998 15849-59.
DOI: 10.1164/ajrccm.158.1.9712017

Seersholm et al. ERJ 1997

- Seesholm et al 1997
  - Observational study comparing:
    - Danish subgroup who never received alpha 1 augmentation therapy
    - German subgroup who received weekly alpha 1 augmentation therapy
  - Overall FEV1 decline 53 vs 75 ml/year in treated vs untreated groups
  - FEV1 31-65% predicted
    - FEV1 decline (delta FEV1) slowed by 21 ml/year

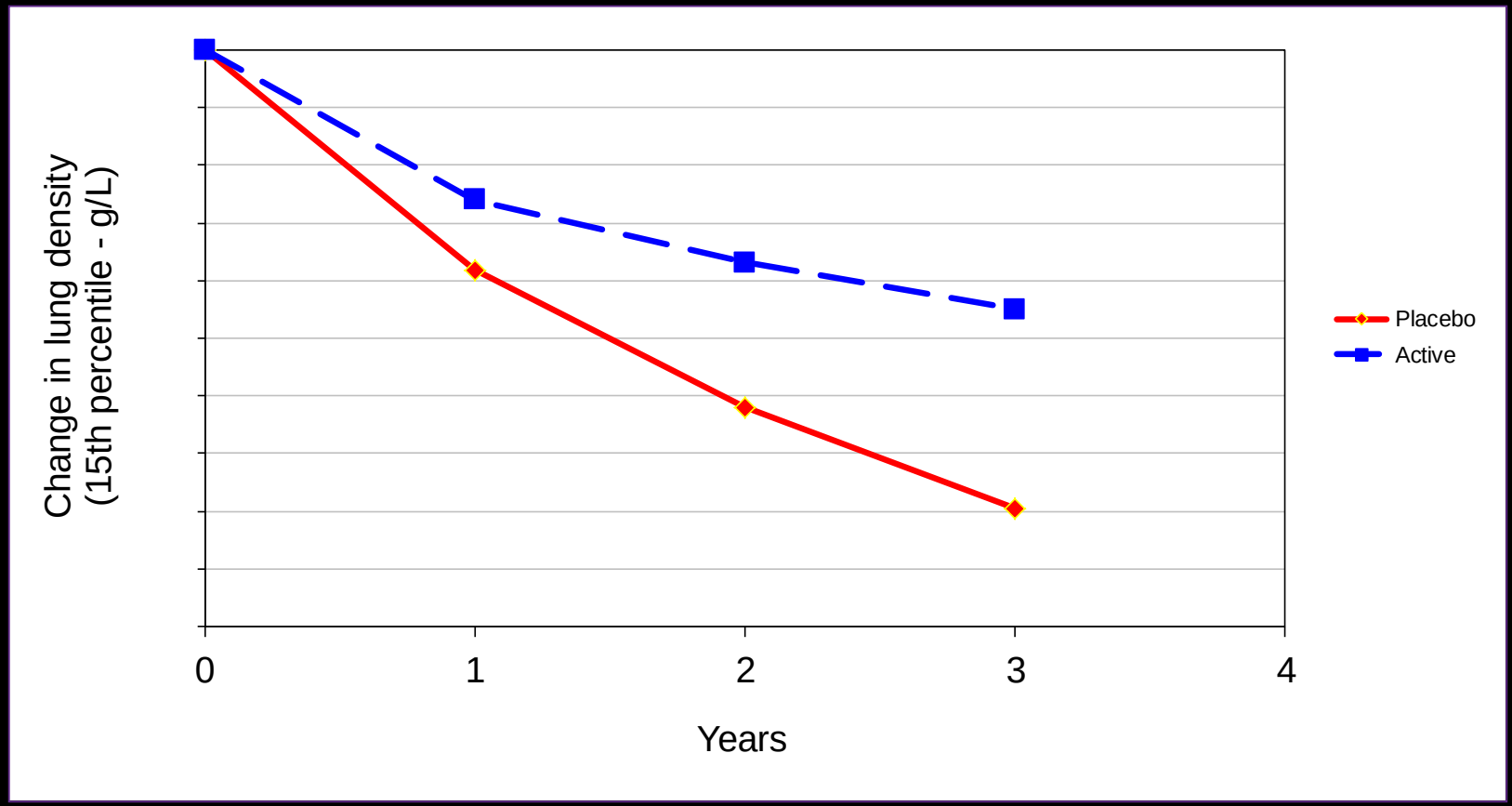
Seersholm N, Wencker M, Banik N, et al. *ERJ* 1997: 10: 2260-2263

Dirksen et al. AJRCCM 1999

- Danish and Dutch Study Group
- Randomised, parallel, double blind, placebo-controlled study
- Alpha 1 infusions 250 mg/kg IV every 4 weeks versus Albumin 625 mg/kg
- 56 patients
  - No change in FEV1 decline
  - Loss of lung tissue 1.5 g/l vs 2.5 g/l

Dirksen A, Dijkman JH, Madsen F, et al. *AJRCCM* 1999; 160: 1468-1472.

Dirksen et al. AJRCCM 1999



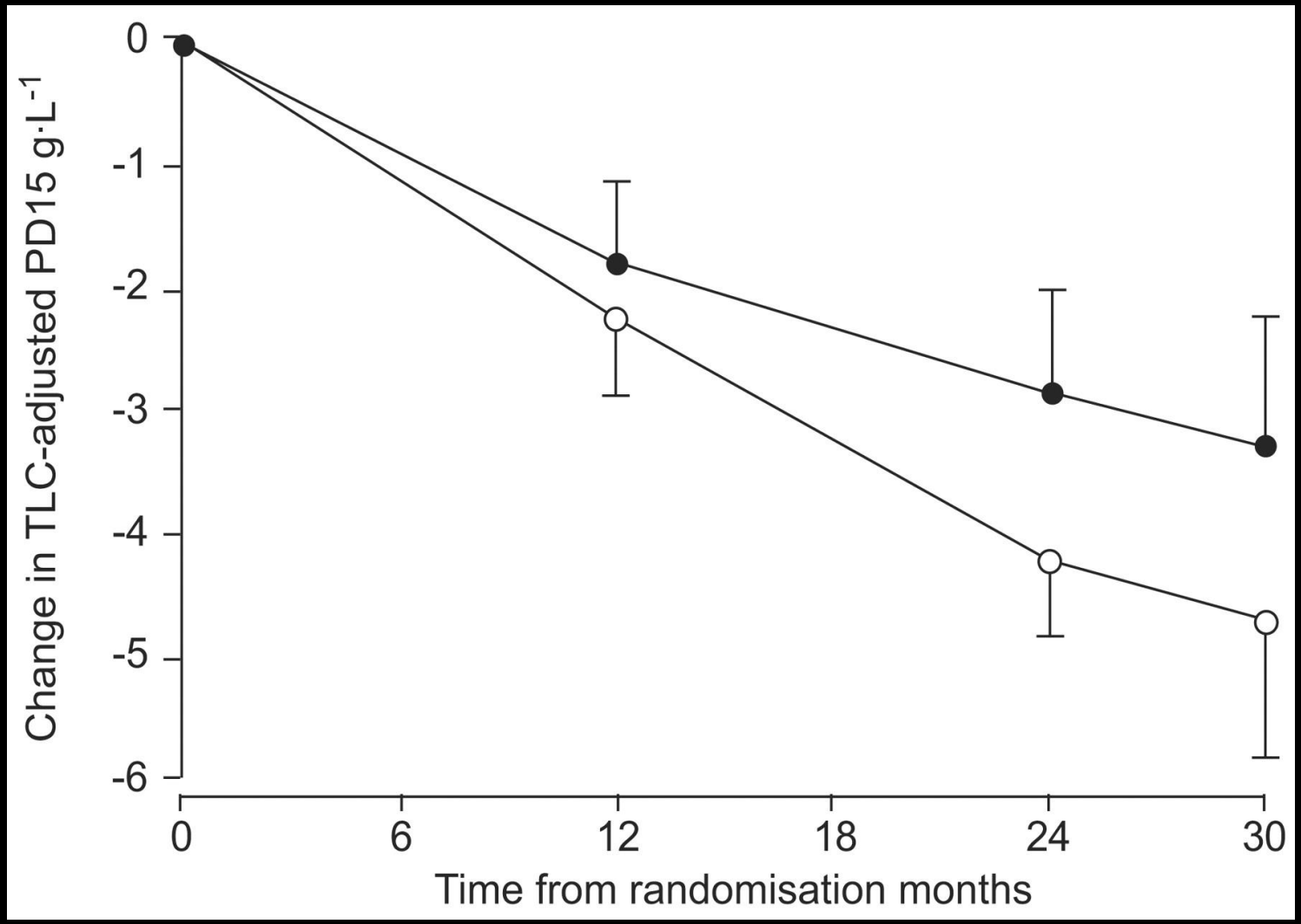
Dirksen A, Dijkman JH, Madsen F, et al. *AJRCCM* 1999; 160: 1468-1472.

Dirksen et al. ERJ 2009

- Randomised, double blind, placebo-controlled, parallel group study
  - Weekly alpha 1 augmentation therapy
  - 77 patients
  - 2.9 g/l vs 4.1 g/l
- No effect on rate of exacerbations but decreased severity of exacerbations

Dirksen A, Piitulainen E, Parr DG, et al. *ERJ* 2009; 33: 1345-1353.

Change from baseline in total lung capacity (TLC)-adjusted 15th percentile lung density (PD15) over the course of the study using Method 1 for densitometric analysis on the modified intent-to-treat population. •: Prolastin®; ○: placebo.



A. Dirksen et al. Eur Respir J 2009;33:1345-1353

Metaanalysis

- **5 studies with a total of 1509 patients**
  - 4 non-randomized trials
  - 1 randomized trial
- **Results**
  - FEV_1 decline was slower by 23% with augmentation therapy
  - Mainly with FEV_1 30%-65% of predicted benefited (those with fastest decline)

CT densitometry may be a more sensitive measurement of emphysema and its progression.

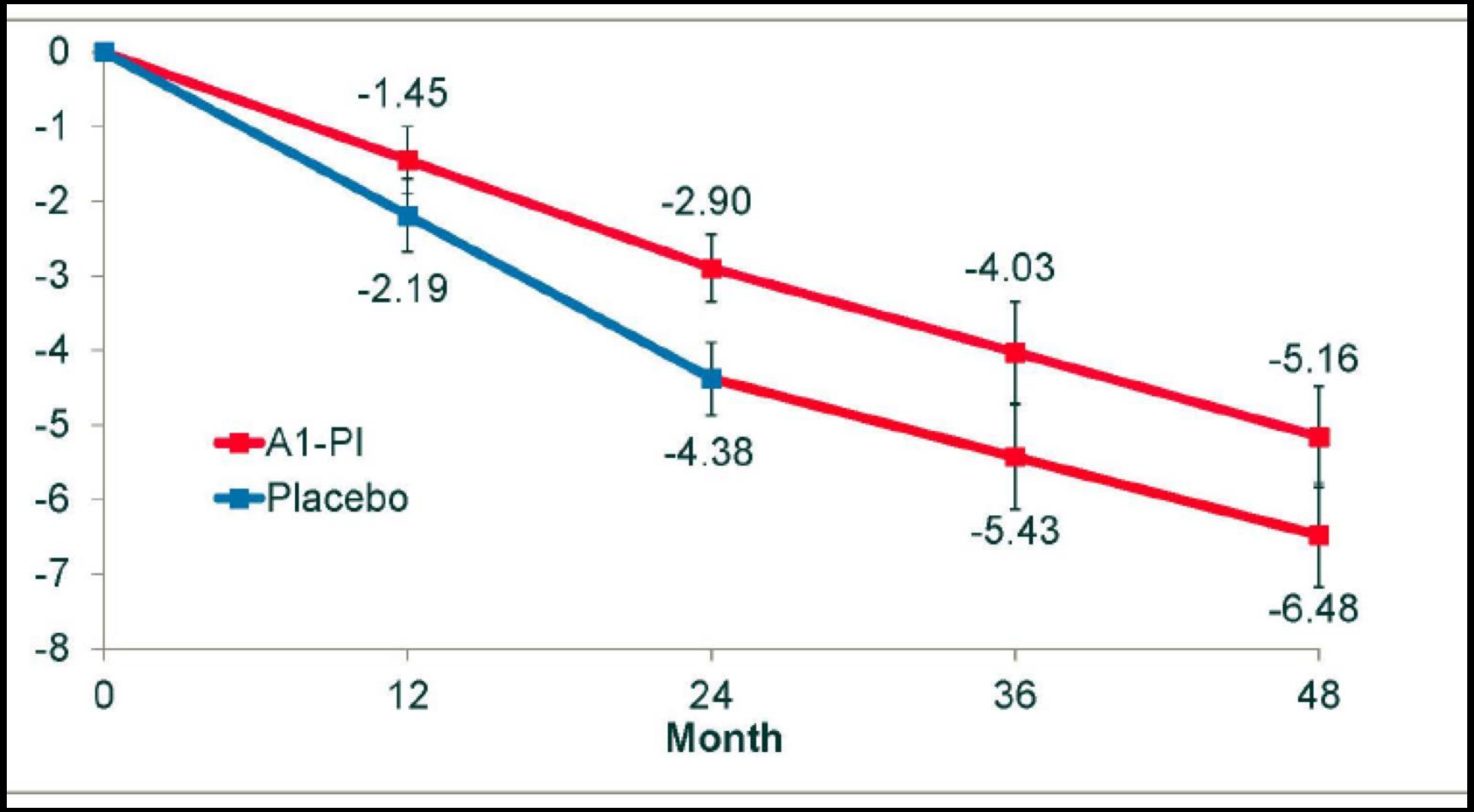
Chapman et al. Eur Resp Society Abstract 2005

The Rapid Trial

- multicentre, double-blind, randomised, parallel-group, placebo-controlled trial– 2 year CT densitometry follow-up
  - Zemaira (60 mg/Kg)
  - Placebo group crossed over to Rx – followed + 2 years.
  - 180 patients
- Prespecified (in 2003) primary end point of combined CT densitometry score at TLC and FRC was not significantly different (p=0.027) between treated and placebo.
- CT densitometry at TLC was significantly different (p=0.007)
- None of the other secondary endpoints were different between groups (FEV1, exacerbations, quality of life)
- Placebo patients crossed over to treatment and followed for an additional 2 years showed slowing of decline in CT densitometry at TLC

Chapman KR, Burdon JGW, Piitulainen E, et al. *The Lancet* 2015; 386: 360-368

The Rapid Trial



CT Lung Density at TLC

Chapman KR, Burdon JGW, Piitulainen E, et al. *The Lancet* 2015; 386: 360-368

Important Points

- No Data on the treatment of the following groups:
  - Active smokers
  - Patients without obstruction
  - Patients without emphysema on HRCT
  - MZ patients or other carriers
- Test for IgA level
- Hepatitis A and B vaccination series may be beneficial

What is the cost of treatment per quality-adjusted-life-year?

1. $ 40,000
2. $100
3. $ 250,000
4. 1,000,000

Gildea TR, Shermock KM, Singer ME, et al. *AJRCCM* 2003; 167: 1387-1392

Follow up

- Annual pulmonary function tests
- Annual liver function tests
- Annual liver ultrasounds
- Updated clinical practice guidelines published July 2016

Brantly ML, Campos M, Cross CE, et al. *Chronic Obst Pulm Disease* 2016; 3: 668-682

Inhaled Alpha-1

- Phase 2/3 multicenter randomized, double-blind, placebo-controlled study in Europe and Canada completed
  - 168 patients
  - Inhalation of 80 mg bid of human AAT (nebulized) vs placeboa for 50 weeks
  - Primary endpoint: Time to first moderate to severe exacerbation
  - Secondary endpoints: frequency of moderate exacerbations, PFTs, and safety

Stolk J, Tov N, Chapman KR, et al. Eur Respir J 2019; Aug 29 ahead of print

Inhaled Alpha-1

- **Results:**
  - Time to first moderate or severe exacerbation was at median 112 days (IQR 40, 211) for AAT and 140 days (IQR 72, 142) for placebo, p=0·0952.
  - The mean yearly rate of all exacerbations in the AAT and placebo groups was 3.12 and 2.67 (p=0.31), respectively.
  - More patients receiving AAT reported treatment-related TEAEs (Treatment Emergent Adverse Events) compared to placebo (57·5% *versus* 46·9%, respectively) and they were more likely to withdraw from the study.
  - We conclude that in AATD patients with severe COPD and frequent exacerbations AAT inhalation for 50 weeks showed no effect on time to first exacerbation but may have changed the pattern of the episodes.

Stolk J, Tov N, Chapman KR, et al. Eur Respir J 2019; Aug 29 ahead of print

Alpha-1 Liver Disease

- 2 on going studies looking at the progression of liver disease in alpha-1 antitrypsin deficiency
- In Pi*ZZ individuals, risk of any liver disease or dysfunction in childhood is 15-50%
- Significant but possibly silent liver disease in older adults likely over 50%
- 30% of alpha 1 liver cirrhosis patients have hepatomas at autopsy
- Hepatomas can develop in the absence of cirrhosis
- Annual LFTs and liver ultrasound

Fairbanks K et al. American Journal of Gastroenterology 2008

Current Research

- **Alpha-1 Registry**
  - www.alphaoneregistry.org
  - To study the natural history of PiZZ, SZ, MZ alpha 1 antitrypsin deficiency
- Alpha-1 Antitrypsin Deficiency Adult Liver Study.
  - To study the natural history of Alpha 1 liver disease
- Carbamazepine for treatment of alpha 1 liver disease
  - To study the efficacy of carbamazepine in decreasing liver fibrosis
- Alpha-1 Coded Testing Study (ACT)
- Endoscopic Lung Volume Reduction in Patients With Advanced Emphysema Due to alpha1 Antitrypsin Deficiency
- Lung Volume Reduction Coils for Emphysema in Alpha-1 Antitrypsin Deficiency (LuReCAA)

Phase 1 Study to Assess the Safety, PK and PD of INBRX-101 in Adults With Alpha-1 Antitrypsin Deficiency (rhAAT-Fc)

- Recombinant human alpha-1 antitrypsin fusion protein
- Assessing safety profile and serum and BAL levels

Biomarkers

- GGT
- Desmosine and isodesmosine (elastin degradation products)
- Fibrinogen

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Treatment of Liver Disease

- **Viral, non-viral genes**
- **Micro-RNAs**
- **DNA methylation**

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Conclusions

- Alpha 1 antitrypsin deficiency is much more prevalent than previously thought
- It can present in multiple different clinical scenarios
- Smoking cessation is the most important treatment modality
- Intravenous augmentation therapy is effective
- Future research is promising

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