Alpha-1 Antitrypsin Deficiency

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- Tenured Professor Medicine, Pediatrics, Biomedical Sciences
- Penn State University Distinguished Educator
- Director- ACARE Center of Excellence for Angioedema
- Director- Alpha-1-Antitrypsin Deficiency Center
- Medical Advisory Board for the HAE-A
- Director of AI and Respiratory Clinical Research
- Senior Advisor, Vinmec Allergy Immunology, Hanoi, VN
- Honorary Board of Directors, Lam Dong Medical College

Alpha-1 Antitrypsin Deficiency

Objectives:

- **Recognize** the many ways Alpha-1 Antitrypsin Deficiency (Alpha-1) presents
- **Improve** your understanding of the disease
- **Increase** screening for alpha-1
- **Understand** Management and future research

Question – 1

- Do you currently test patients for Alpha-1 Antitrypsin Deficiency (Alpha-1)?

a. Always
b. Sometimes
c. Rarely
d. Never

Question 2

- What is the reason for not screening?

a. Too expensive

b. To much hassle

c. Do not know what to do with the results

d. To rare to test for

e. Do not need to test since I can clinically recognize an alpha patient

How common is severe AATD?

a. 11,000 people in the USA

b. 110,000 people in the USA

c. 20-25 million people in the USA

d. About the same as the number of HAE patients

How common is severe AATD?

- 1. 11,000 people in the USA
- 2. 110,000 people in the USA $$$$
- 3. 20-25 million people in the USA with MZ
- 4. About the same as the number of HAE patients

- From a 4.4 billion population, 116 million are MS or MZ, and 3.4 million are SS, SZ or ZZ, and affects all racial subgroups. Actually, AATD may be the most common serious hereditary disorder in the world

F de Serres Chest 2002

Caitlin:

- 62-year-old female presents with increasing shortness of breath to the clinic.
- She is a former smoker, having smoked 1 pack per day for 5 years, and quit 5 years ago.
- She has recently had increasing short of breath with activity.
- She is using her inhalers. She states this is the 3rd clinic that she has visited for this problem.

<u>EXAM</u>:

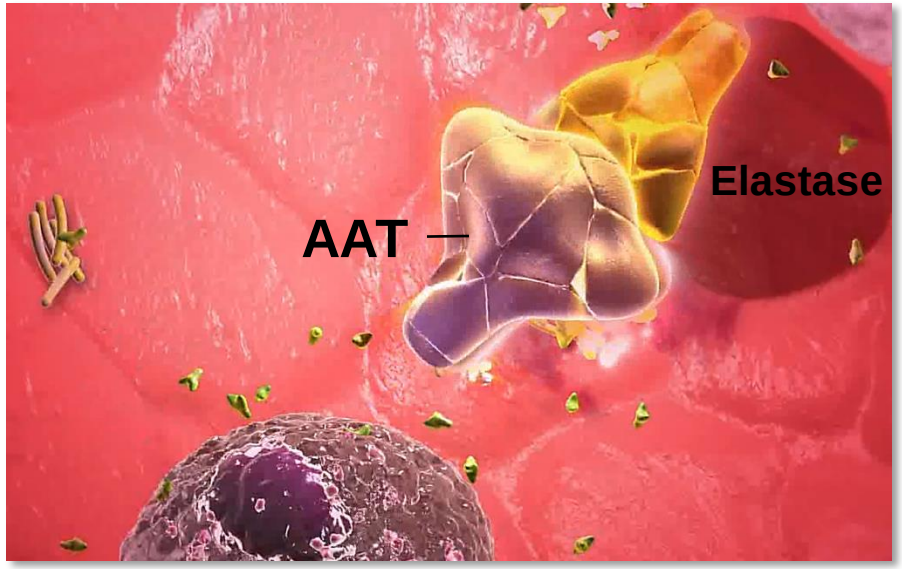
- Prolonged expiratory phase of breathing, with occasional wheezing
- Initial FEV_1 43% of predicted, FEV1/FVC is 60%. FEV1 increase to 55% and ratio to 63% with albuterol
- CBC- 300 eosinophils, IgE is 250 and skin tests are positive for dust mites

Would you screen Caitlin for alpha-1 antitrypsin

1. Yes, for sure
2. It would depend on what her exhaled nitric oxide demonstrates
3. No, because it is obvious she has asthma
4. I would only screen her if she had an abnormal CXR

AAT Neutralizes Elastase

- AAT inhibits various serine proteinases
- Neutrophil elastase has been identified by kinetic studies as the preferential target
  - Inhibition occurs when neutrophil elastase binds to the AAT active site to form stable 1:1 equimolar complexes

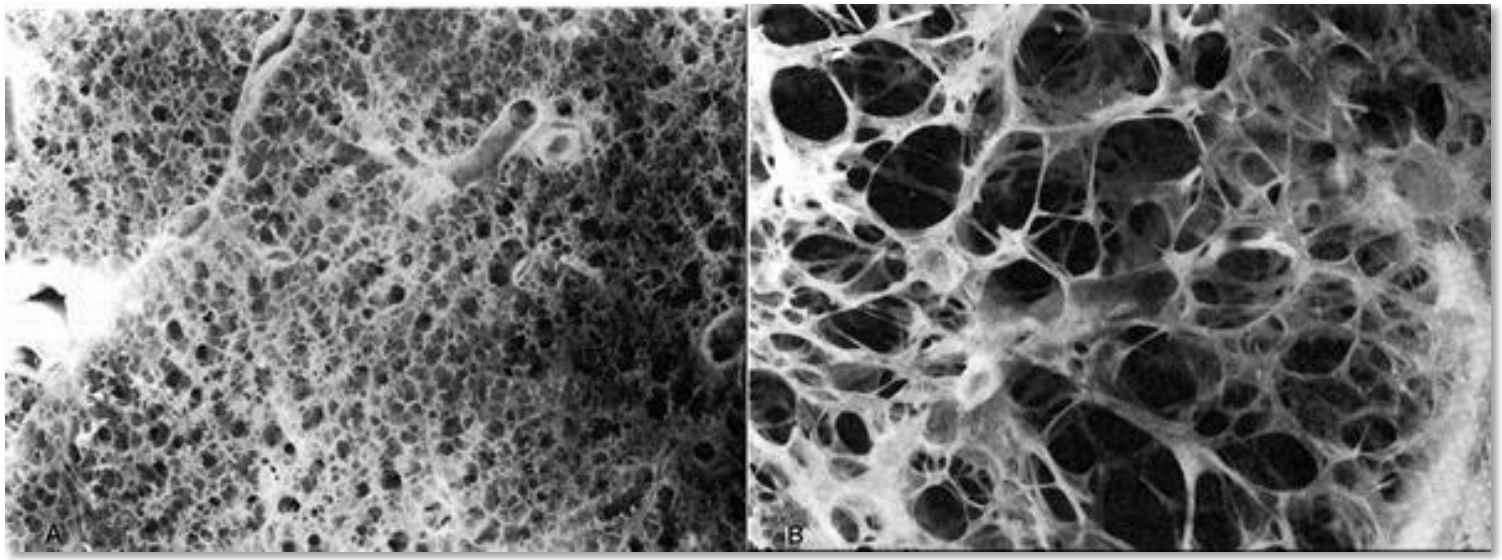


AAT is a protease inhibitor that is released in the lungs in response to elastase, keeping the immune reaction in check

AAT, alpha$_1$-antitrypsin.
American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900.

Excess Neutrophil Elastase Leads to Destruction of Lung Parenchyma[1]

Electron Micrographic Scans of the Lung Parenchyma[2]

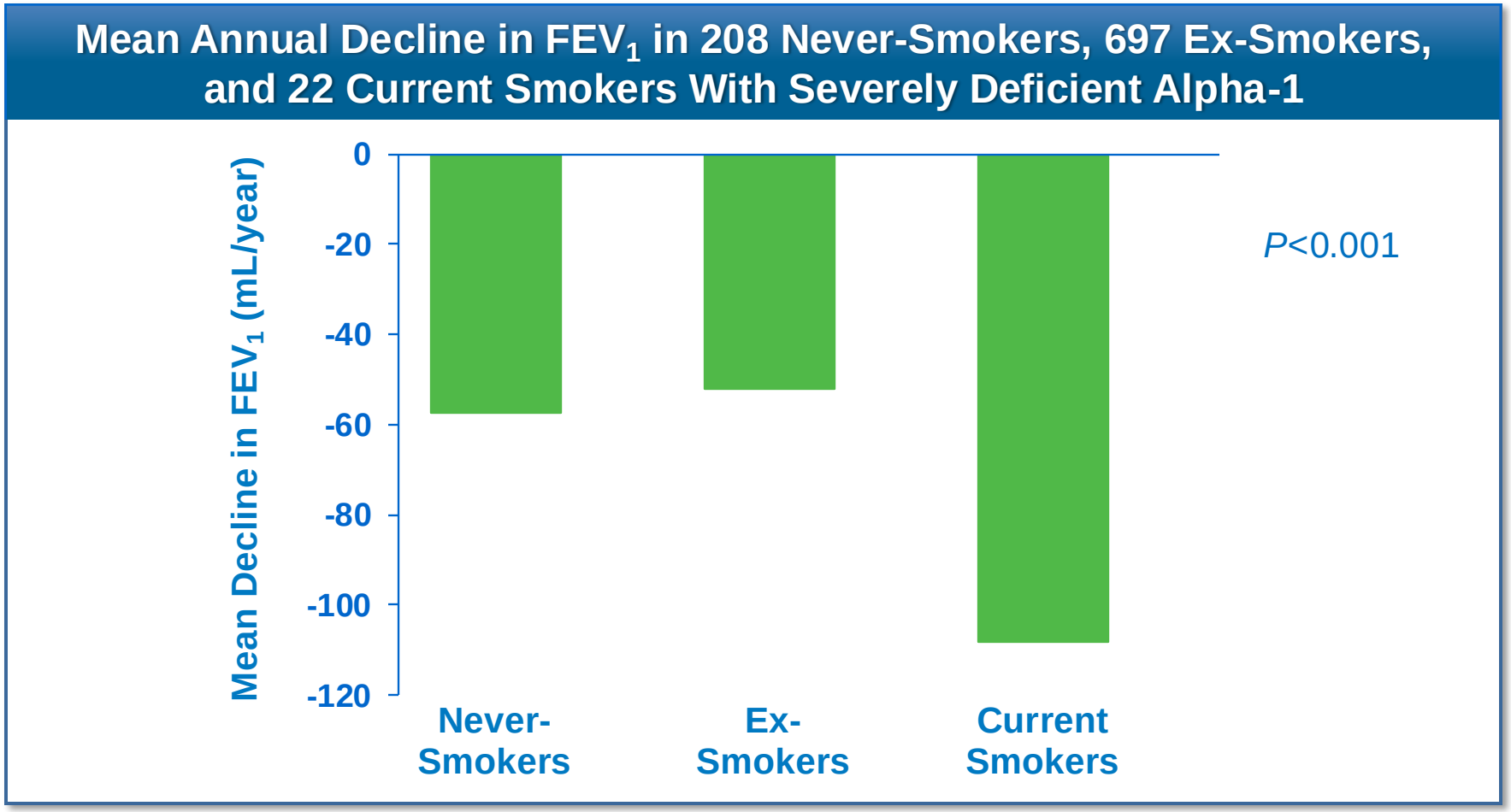


Normal Lung Parenchyma

Severe Emphysematous Lung Parenchyma

1. Köhnlein T, Welte T. *Alpha-1 Antitrypsin Deficiency: Clinical Aspects and Management.* Bremen, Germany: UNI-MED Verlag AG; 2007. 2. Snell GI. Airway bypass stenting for severe emphysema. CTS*Net*. April 16, 2006. www.ctsnet.org/portals/thoracic/newtechnology/article-4.html. Accessed August 7, 2021.

Smoking Accelerates Lung Function Decline in Individuals With Severely Deficient Alpha-1*

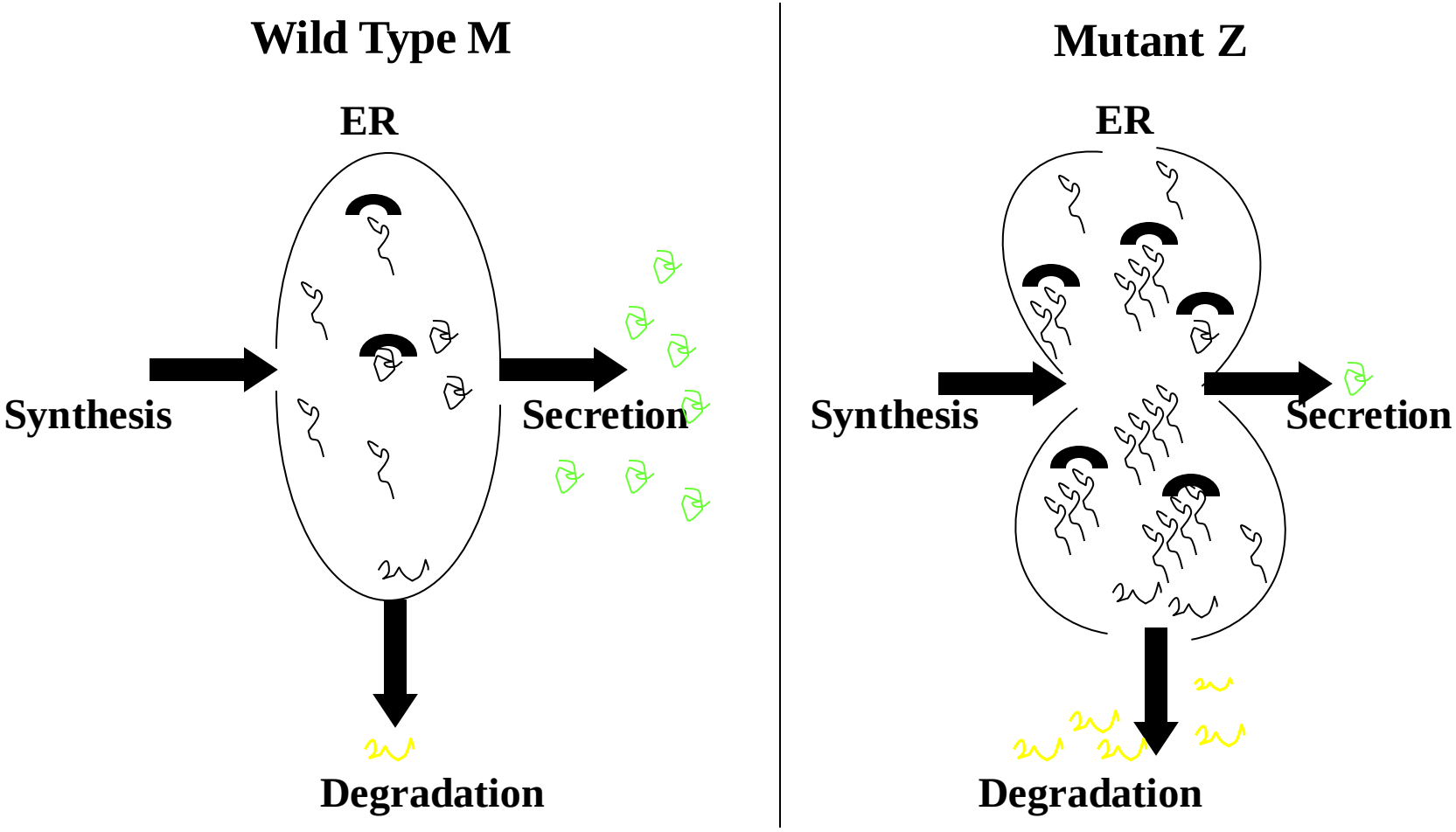


*The authors define severely deficient as serum AAT levels ≤11 μM or a ZZ genotype.

AAT, alpha$_1$-antitrypsin; FEV$_1$, forced expiratory volume in 1 second.

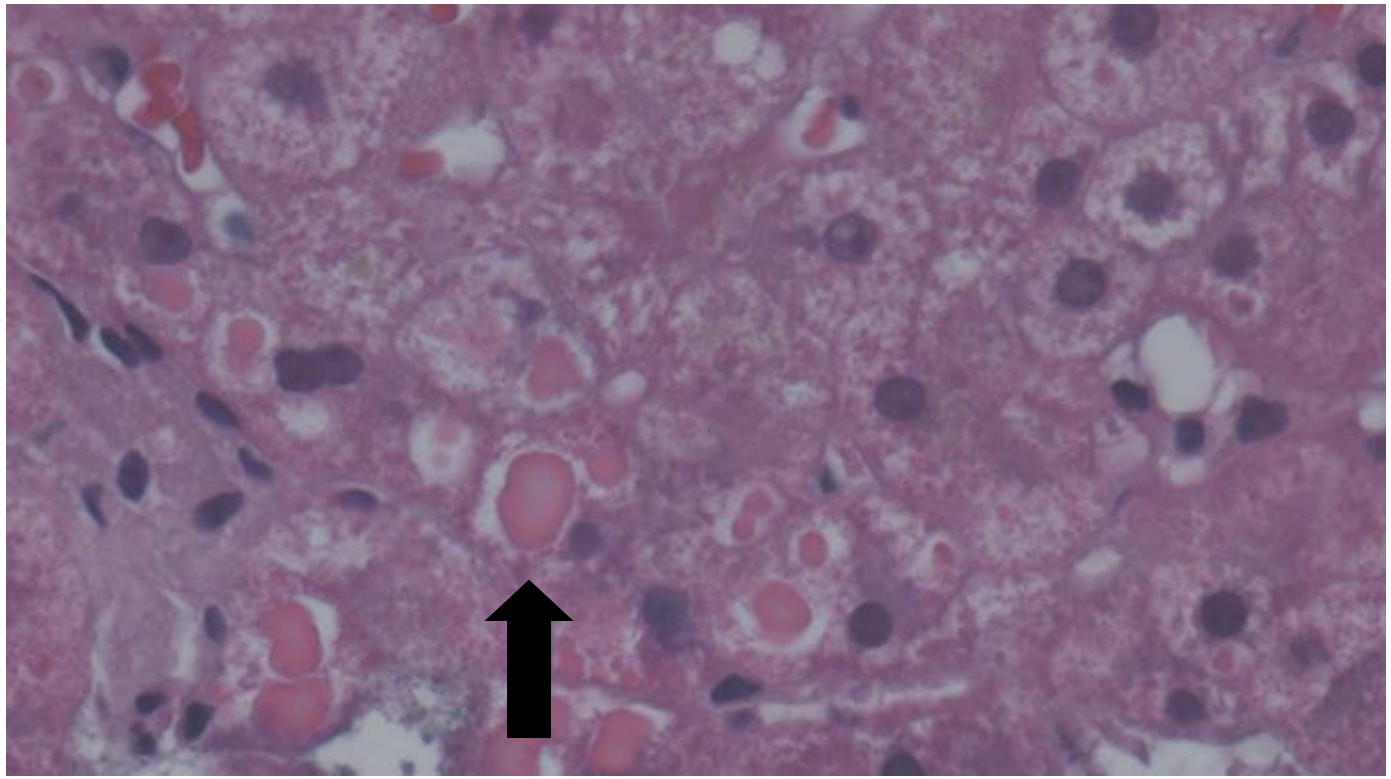
The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med.* 1998;158(1):49-59.

AAT Protein Processing



Proteasomal and autophagic degradative pathways may govern hepatic risk

Human ZZ Liver



PAS + intracellular inclusions are polymerized AAT ‘Z’

How do you identify AATD?

a. History and physical

b. Chest X-ray

c. CT Scan

d. Spirometry

e. I can not with the above tests

Alpha-1: A Major Risk Factor for COPD

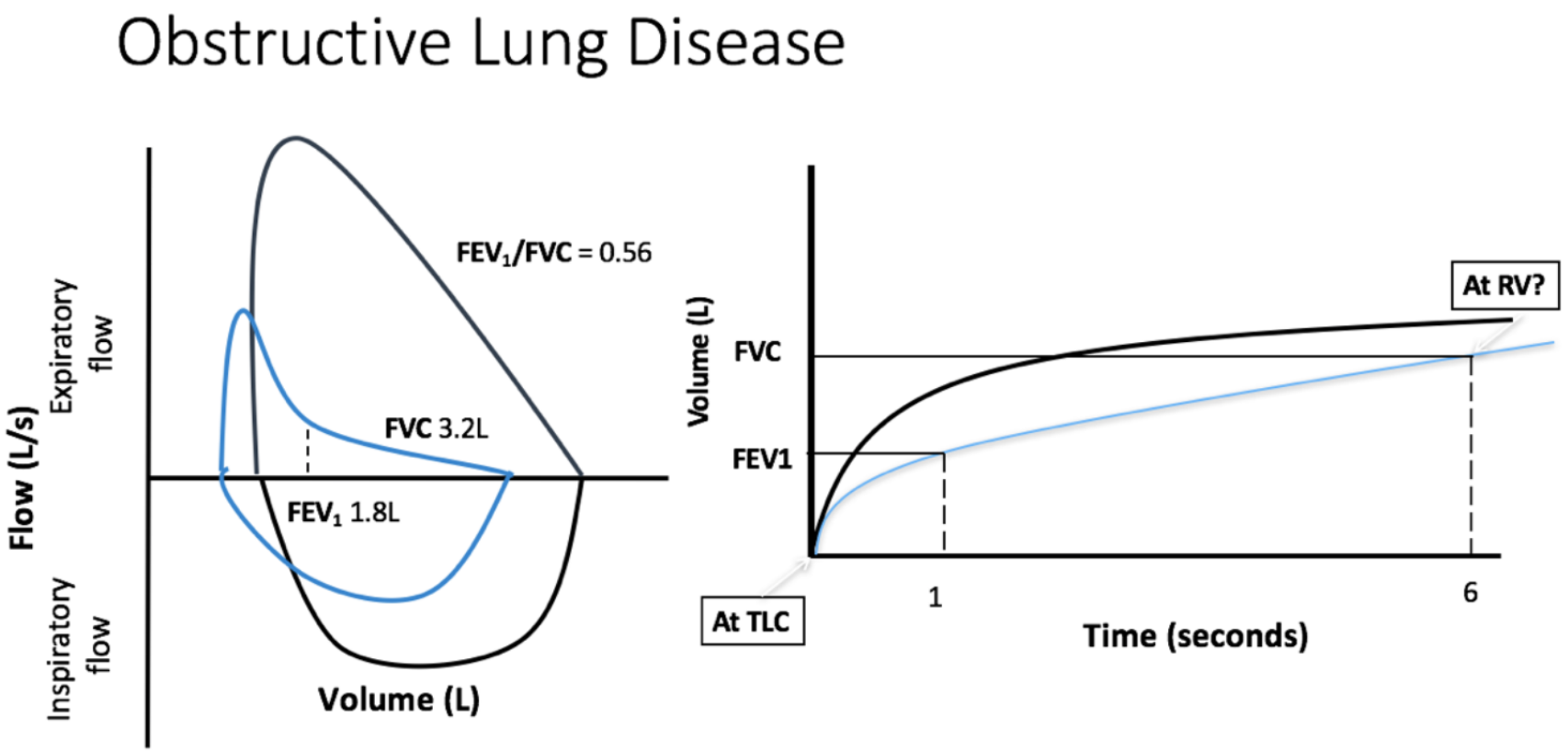
- Approximately 30 million adults in the US have airway obstruction or COPD[1]
  - COPD is now the fourth leading cause of death in the US[3]
  - Alpha-1 may be a contributor in up to 3% of all COPD cases in the US[4]

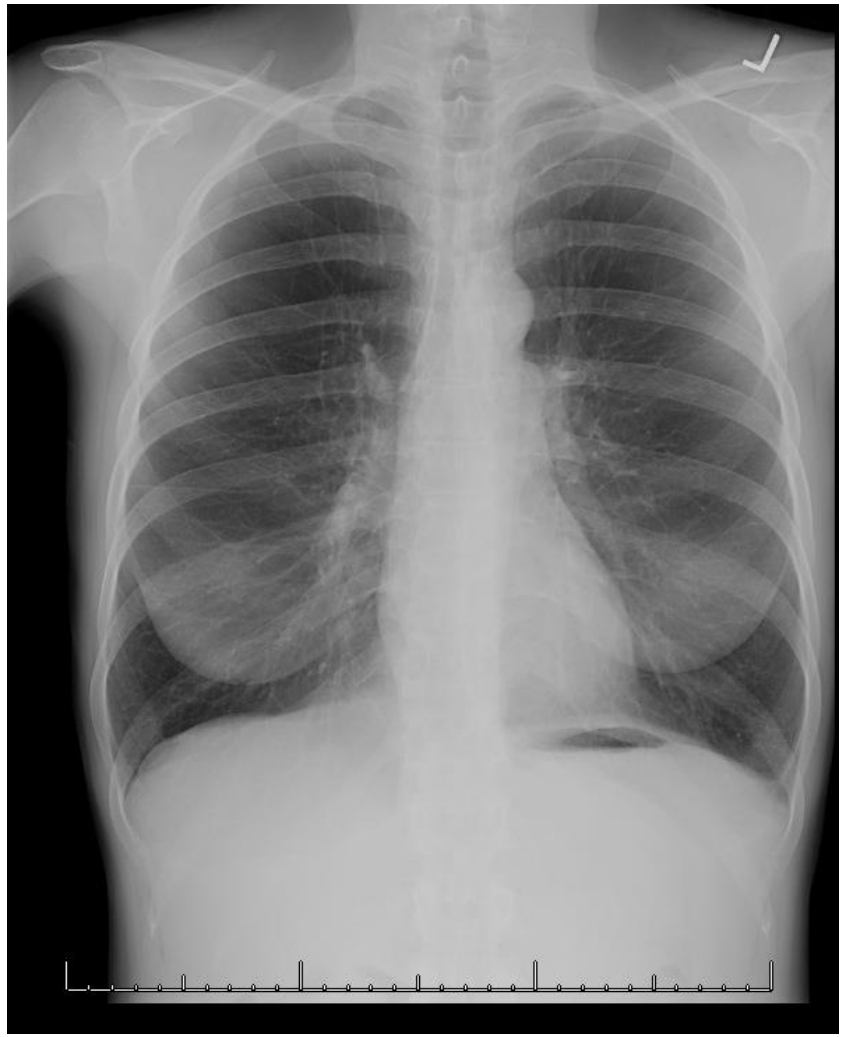
Alpha-1–related lung disease presents with common respiratory symptoms:

- Dyspnea (84%)[5]
- Decreased exercise tolerance[6]
- Wheezing (76%)[5]
- Cough (42%)[5]
- Excess sputum production (50%)[5]
- Frequent lower respiratory tract infections[6]
- History of suspected allergies and/or asthma[7]

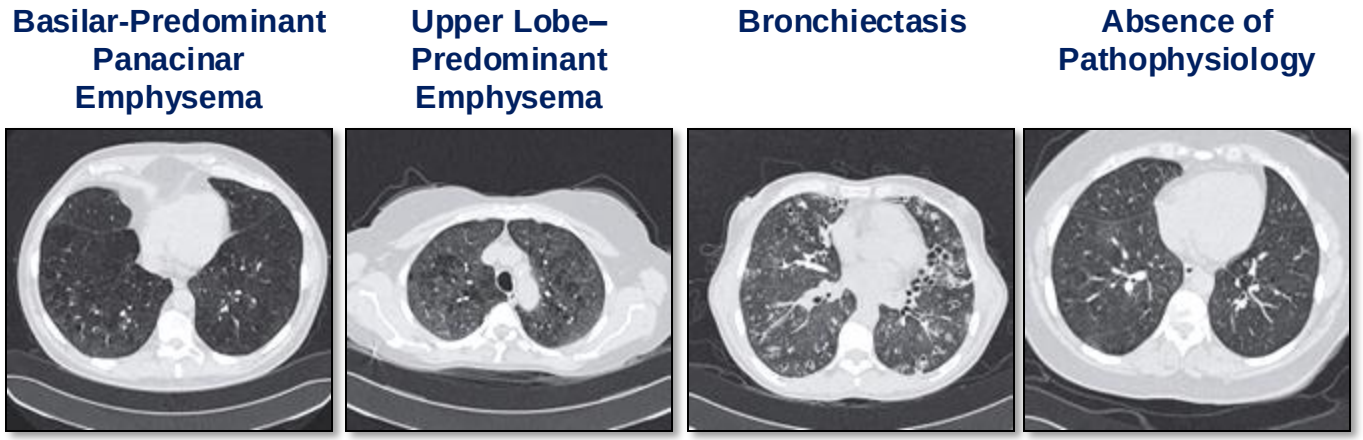
1. COPD Foundation. COPD Across America. February 7, 2020. https://www.copdfoundation.org/What-is-COPD/Understanding-COPD/Statistics.aspx. Accessed August 7, 2021. 2. Campbell EJ, et al. *Chest.* 2000;117(5 suppl 1):303S. 3. Centers for Disease Control and Prevention. Basics about COPD. CDC website. https://www.cdc.gov/copd/basics-about.html. Updated June 9, 2021. Accessed August 7, 2021. 4. Campos MA, et al. *Chest.* 2005;128(3):1179-1186. 5. McElvaney NG, et al. *Chest.* 1997;111(1):394-403. 6. What is alpha-1? Alpha-1 Foundation website. https://www.alpha1.org/what-is-alpha1. Accessed August 7, 2021. 7. Eden E, et al. *Respir Med.* 2006;100(8):1384-1391.

Spiromtery


Obstructive Lung Disease
Flow (L/s)
Expiratory flow
Inspiratory flow
FEV1/FVC = 0.56
FVC 3.2L
FEV1 1.8L
Volume (L)
Volume (L)
FVC
FEV1
At RV?
At TLC
1
6
Time (seconds)



Radiographic Presentation of Alpha-1 is Variable



Silverman EK, Sandhaus RA. *N Engl J Med.* 2009;360(26):2749-2757.

Alpha-1 Testing Guidelines


American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency


Clinical Practice Guidelines

The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult

2003, ATS/ERS	2016, Alpha-1 Foundation
• Symptomatic adults with emphysema, COPD, or asthma with airflow obstruction incompletely reversible after bronchodilator treatment • Individuals with unexplained liver disease • Asymptomatic individuals with persistent obstruction on PFTs and identifiable risk factors (e.g., cigarette smoking, occupational exposure) • Adults with bronchiectasis and no evident etiology • Adolescents with persistent airflow obstruction • Asymptomatic individuals with persistent airflow obstruction and no risk factors • Adults with C-ANCA-positive vasculitis	• All individuals with COPD, regardless of age or ethnicity (remember asthma with fixed obstruction is defined as COPD) • All individuals with unexplained chronic liver disease • All individuals with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis • Parents, siblings, and children, as well as extended family, of individuals identified with an abnormal A1AT gene should be provided genetic counseling and offered testing

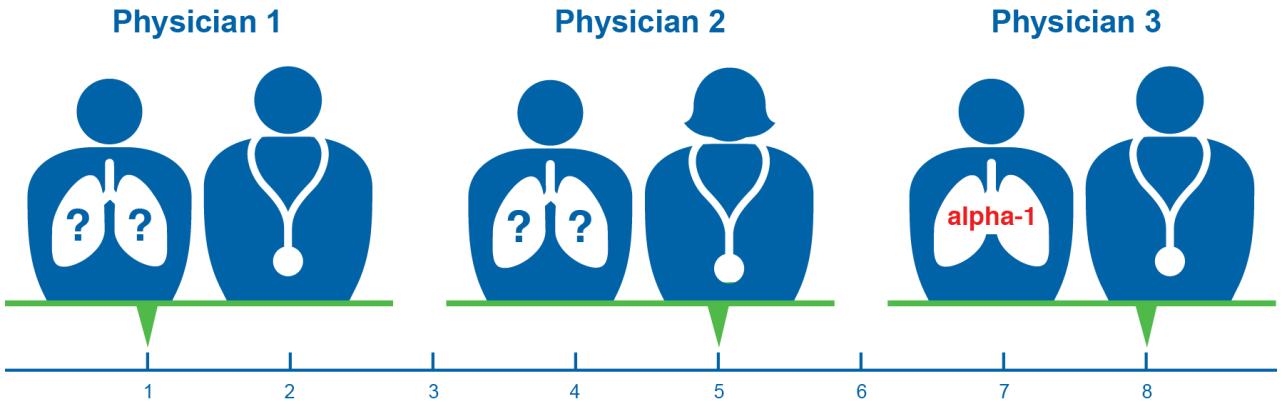
American Thoracic Society, European Respiratory Society. *American Journal of Respiratory and Critical Care Medicine* 2003; 168: 818-900.

Sandhaus RA, Turino G, et al. *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* 2016; 3(3): 668-682.

There Is a Lengthy Delay in Diagnosis

In a survey of 1020 members of AlphaNet,* the average…

- **Number of physicians seen** before correct diagnosis: **2.7 to over 3**
- **Years** between onset of symptoms and diagnosis: **8.3**
- **Age** when identified as AAT deficient: **46**

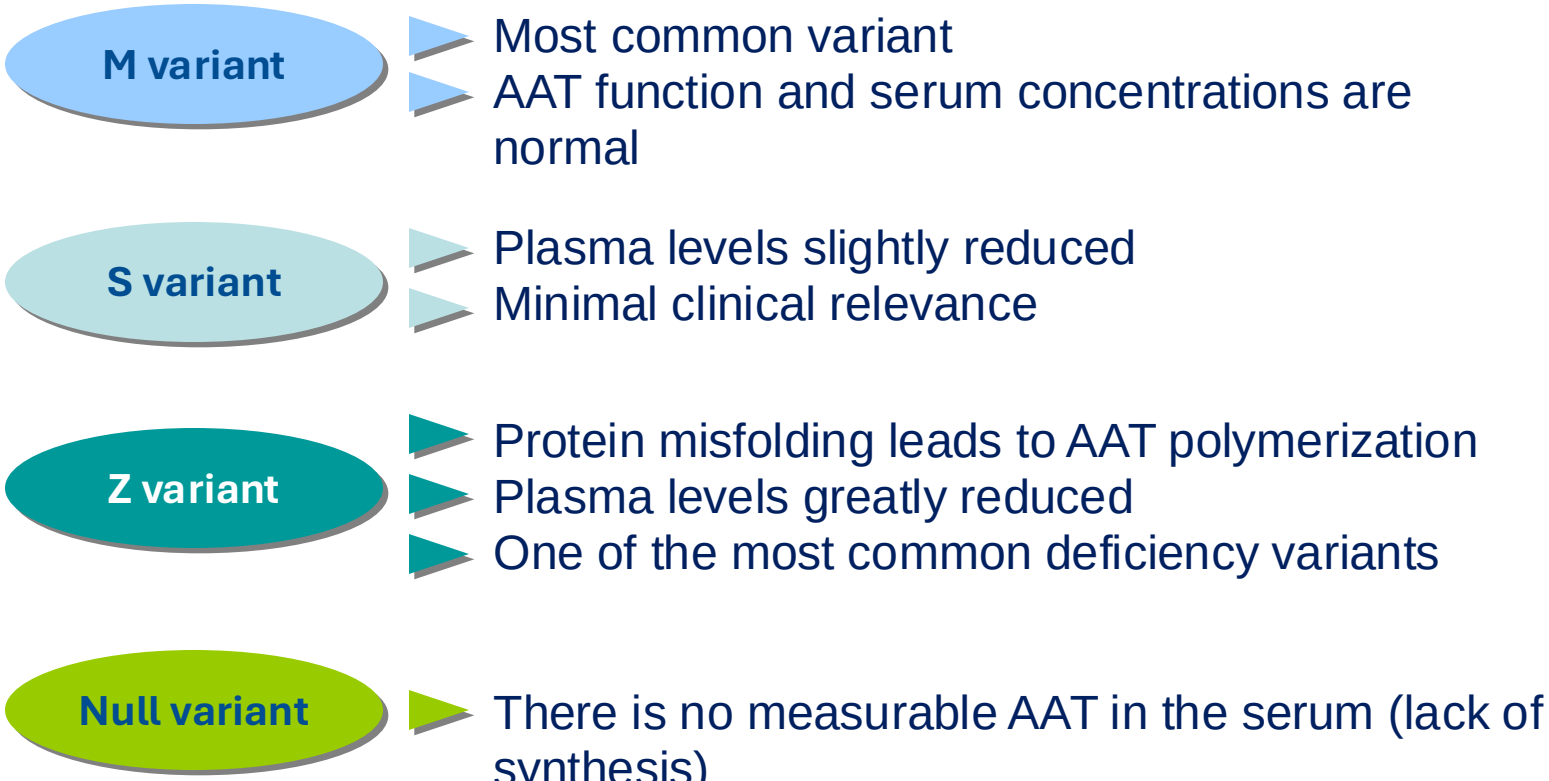


*AlphaNet: Not-for-profit organization providing health management services led by alpha-1 experts and patients.

AAT, alpha$_1$-antitrypsin.

Campos MA, et al. *Chest*. 2005;128(3):1179-1186.

Most Common AAT Variants



AAT, alpha$_1$-antitrypsin.
American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900.

Testing for Alpha-1

Serum

- Screening blood test to measure level of circulating A1AT protein
- A1AT is an acute-phase reactant which increases during infection or inflammation
- Normal serum levels generally range from 100 – 220 mg/dL (normal 20-48 mmol/l)

Phenotyping

- Isoelectric focusing (electrophoresis) gel analysis of A1AT protein
- Identifies different band patterns associated with different alleles
- Determine whether patient is carrier or has disease

Genotyping

- DNA analysis to determine alleles, most often through polymerase chain reaction testing which targets S and Z alleles
- Occasionally set up to detect less common alleles, such as F and I

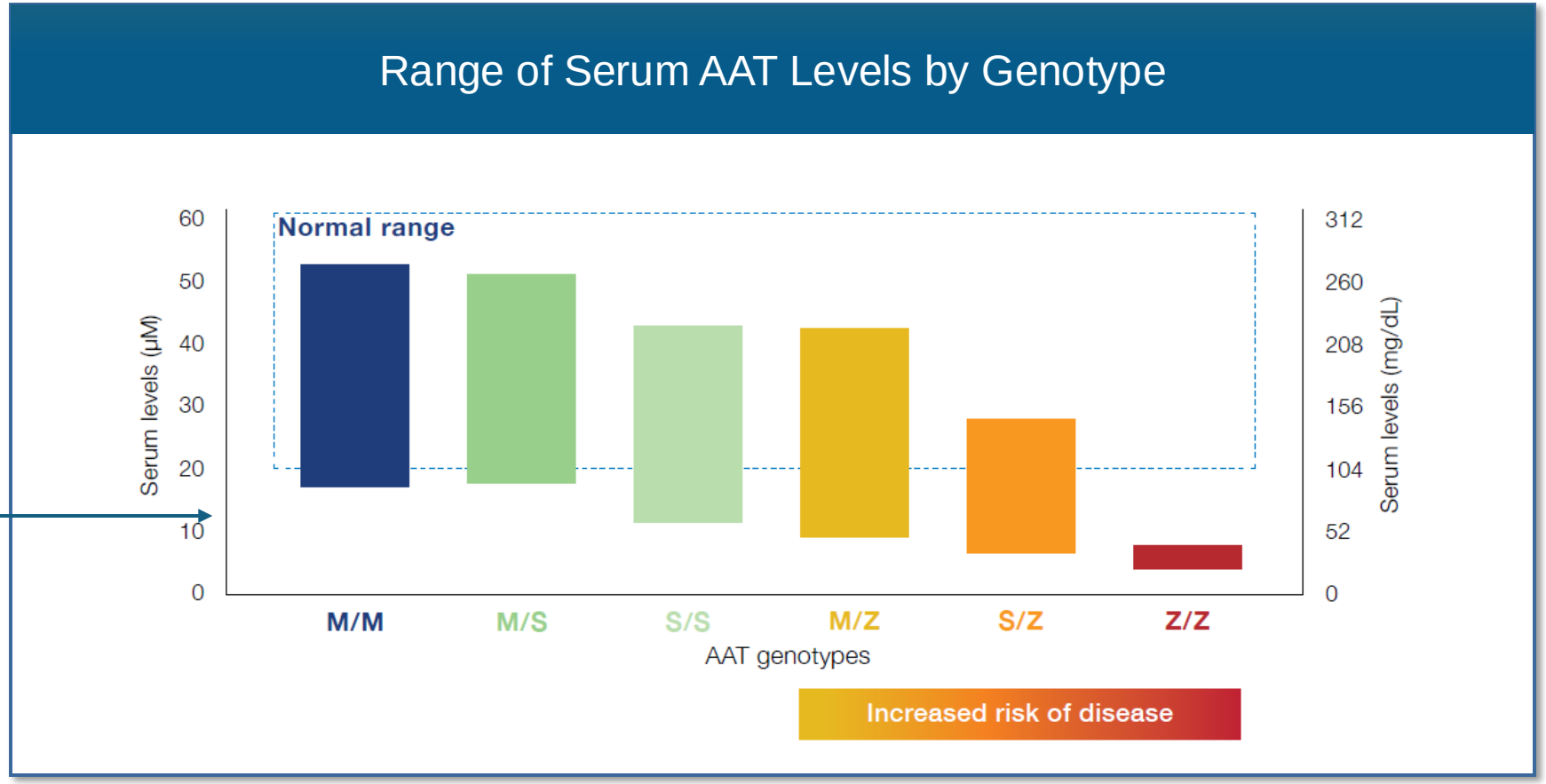
Gene Sequencing

- Should be performed for inconclusive cases to achieve definitive diagnosis
- Detects rare mutations and new/novel mutations

Stoller JK. *Cleveland Clinic Journal of Medicine* 2016; 83(7): 507-514.
Strnad P, McElvaney NG, et al. *New England Journal of Medicine* 2020; 382: 1443-1455.

Screening All COPD Patients Can Help Detect Those at Increased Risk for Lung Disease

11mmol
Or
58 mg/dl



Free, easy, and confidential screening kits are available

AAT, alpha$_1$-antitrypsin.
Data on file, Alpha-1 Genetics Laboratory, Grifols.

Management Approaches for Patients With Alpha-1

- Family screening and counseling[1]
- Lifestyle changes[1]
  - Smoking cessation
    - With diagnosis smoking cessation is greater[2]
    - 80% of alpha-1 patients are current smokers or ex-smokers[3]

  - Exercise
  - Avoidance of environmental pollutants
  - Limit alcohol consumption and use of NSAID
- Vaccinations[1]
  - Influenza/Prevnar 20/COVID-19
  - RSV
  - Hepatitis A/B
- Drug therapy for lung disorders[1]
  - Bronchodilators
  - Inhaled steroids
  - Antibiotics
  - Oxygen
- Pulmonary rehabilitation[1]
- Surgical procedures[1]
  - Lung transplantation in end-stage lung disease
  - Valve and volume reduction surgery
  - Liver transplant
- Augmentation therapy[1]

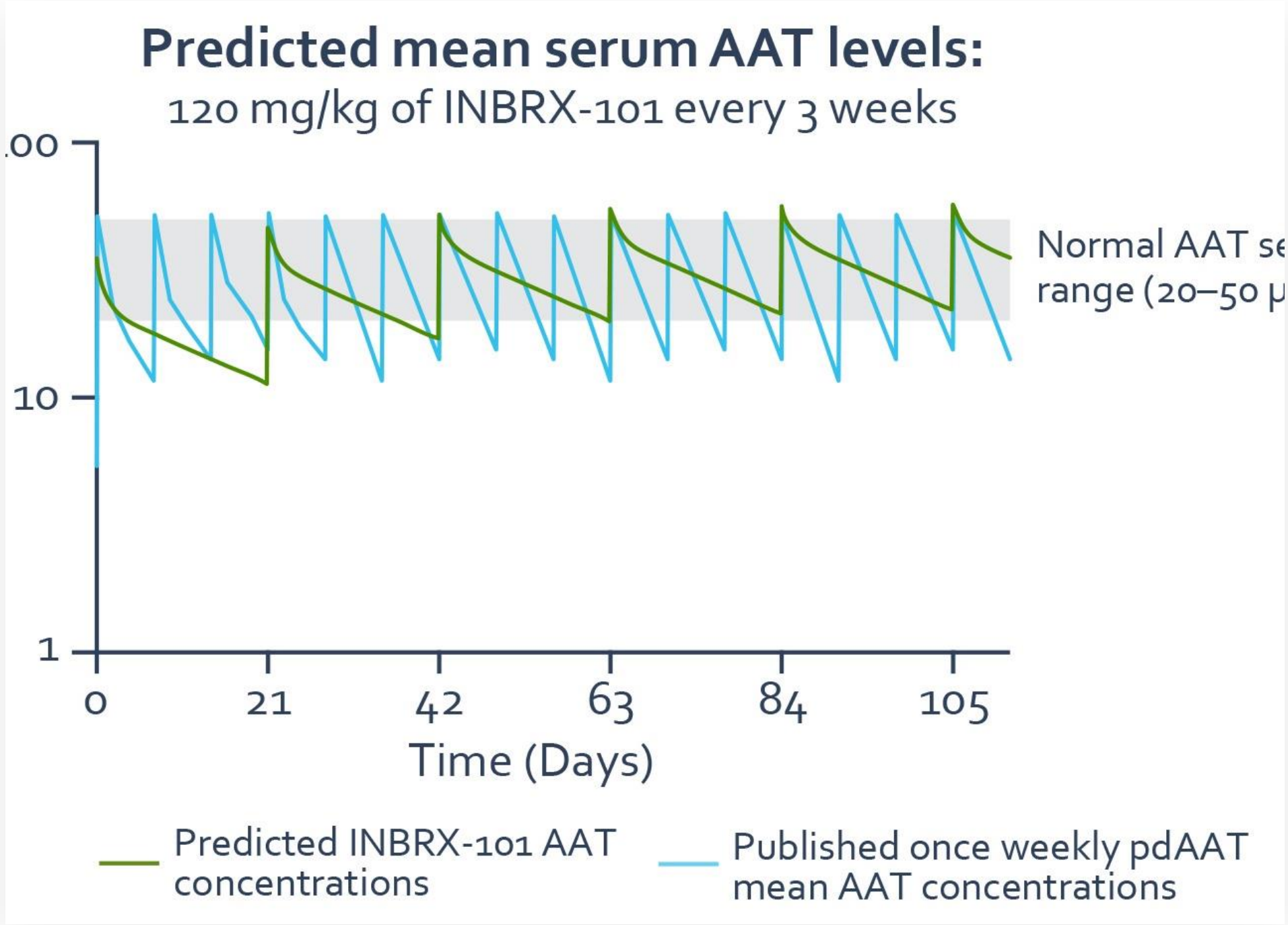
1. American Thoracic Society, European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168(7):818-900. 2. Løkke A, et al. *Thorax*. 2006:61(11):935-939. 3. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med*. 1998;158(1):49-59.

Lung Treatment Options

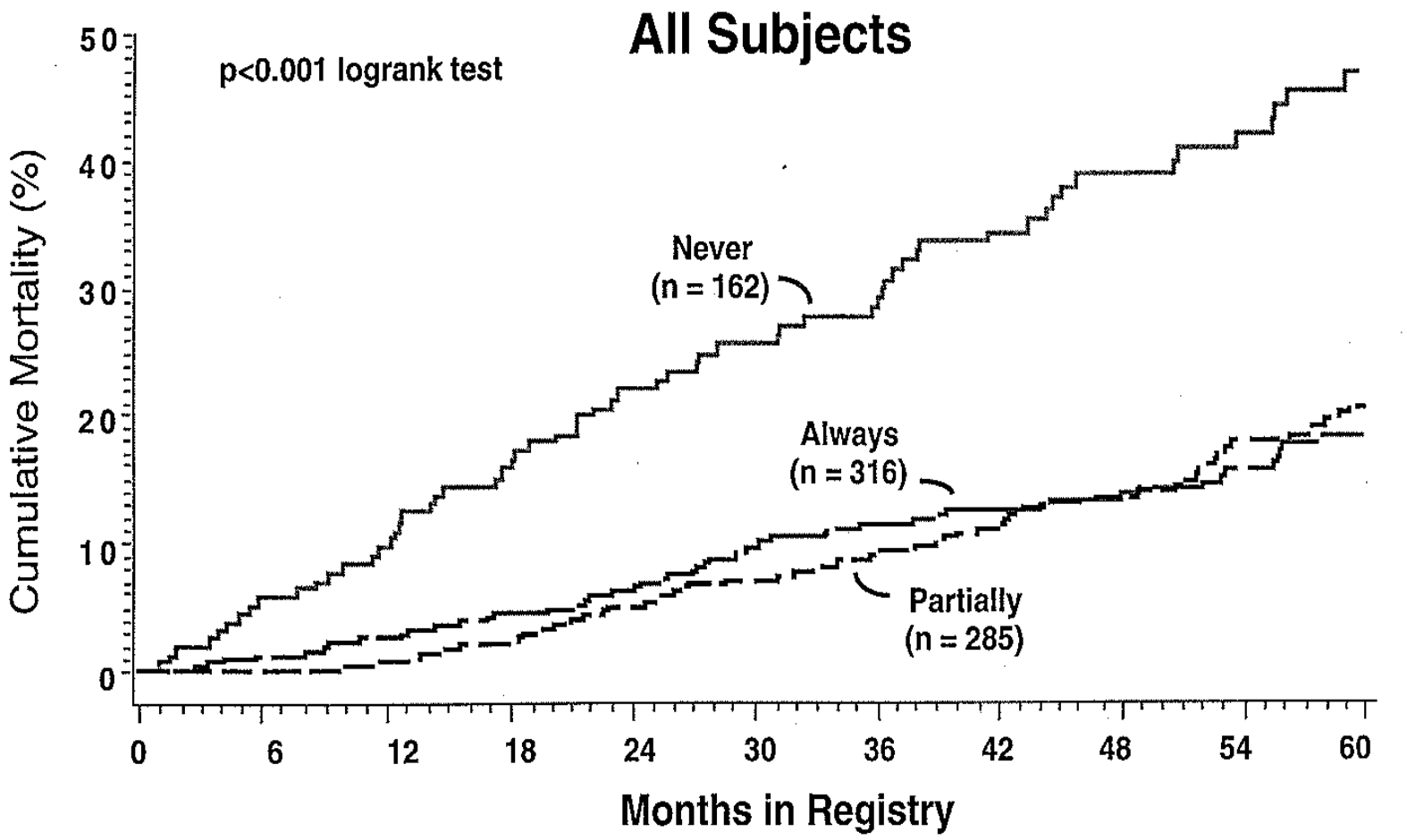
- Standard Therapies in COPD Treatment
  - Smoking cessation
  - Pulmonary Rehab
  - Bronchodilators (rescue/LABA/LAMA)
  - Inhaled steroids
  - Oxygen
  - Lung transplant
  - Exercise and weight restriction
- Management/Evaluation of Liver disease
- Augmentation Therapy
- Vaccines (flu, Pneumococcal, Prevnar, COVID-19, RSV)

Healthy Lung Living

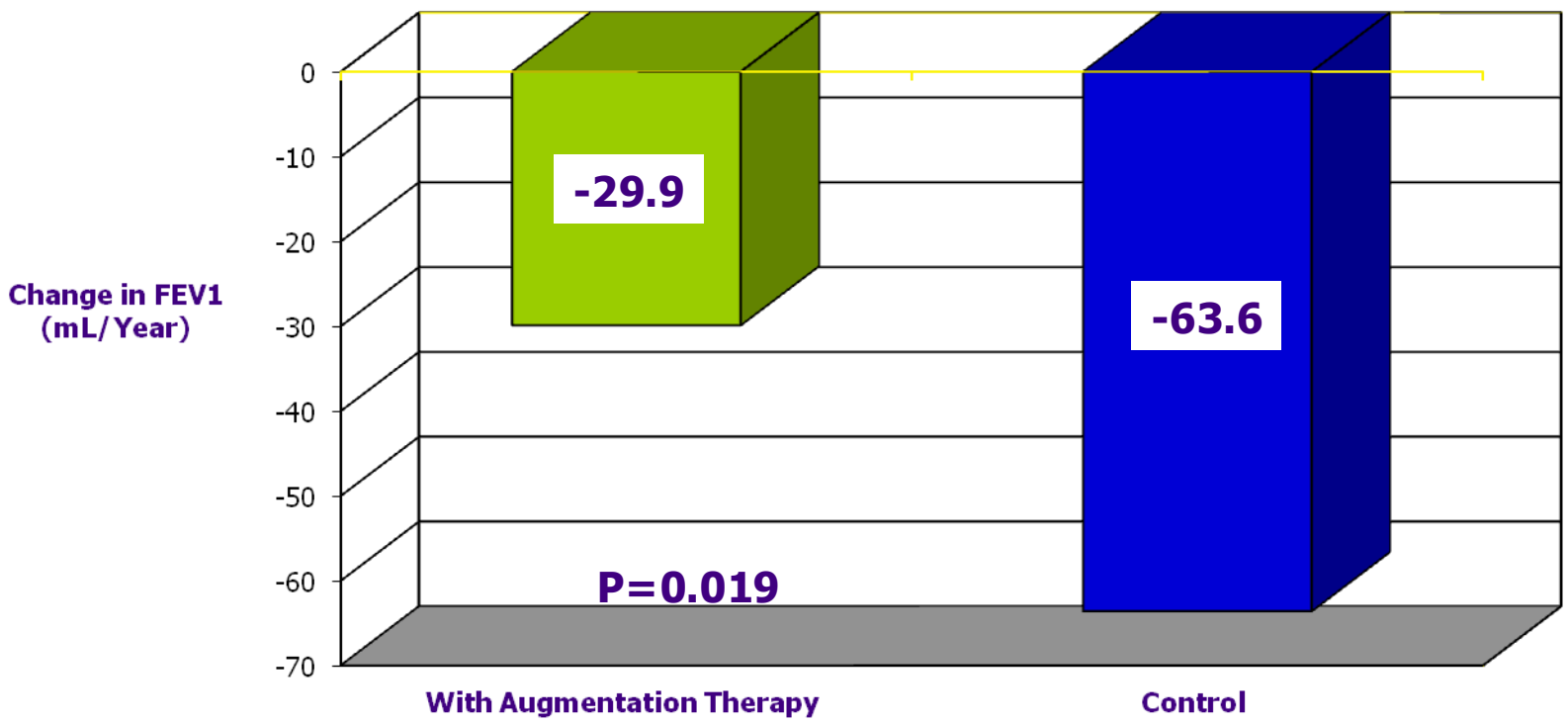
Abdulkarim, Craig, 2022


Predicted mean serum AAT levels:
120 mg/kg of INBRX-101 every 3 weeks
100
10
1
0
21
42
63
84
105
Time (Days)
Normal AAT se
range (20–50 µ
Predicted INBRX-101 AAT concentrations
Published once weekly pdAAT mean AAT concentrations

NHLBI Registry - Mortality



Canadian Registry



Liver Disease Treatment

- There are no specific treatments to prevent alpha-1 liver damage.
- Liver transplantation : trading one disease for another?
- Augmentation therapy has no effect on liver disease.

Expert Opinion on Emerging Drugs

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iemd20

Are clinical trials into emerging drugs for the treatment of alpha-1 antitrypsin deficiency providing promising results?

Joshua De Soyza, Anita Pye & Alice M. Turner

To cite this article: Joshua De Soyza, Anita Pye & Alice M. Turner (2023) Are clinical trials into emerging drugs for the treatment of alpha-1 antitrypsin deficiency providing promising results?, Expert Opinion on Emerging Drugs, 28:4, 227-231, DOI: 10.1080/14728214.2023.2296088

Table 1. Competitive environment: therapies currently in development.

Drug	Pharmacology	Current Phase	Company	National Clinical Trials Number(s)
Kamada-AAT	Inhaled human AAT	III	Kamada	02001688 04204252
Fazirsiran	RNA interference therapy	III	Takeda	05899673 05677971
Alvelestat	Neutrophil Elastase Inhibitor	II/III	Mereo	03636347 03679598
Inbrx-101	Recombinant AAT	II	Inhibrx	05856331
VX-864	AAT corrector	II	Vertex	05643495
Belcesiran	RNA interference therapy	II	Novo Nordisk	04764448
ADVM-043	Gene editing	I/II	Adverum	02168686
OsrhAAT	Recombinant AAT	I	Oryzogen	05315921
PHP-303	Neutrophil Elastase Inhibitor	I	pH Pharma	03627845 03804021
BEAM-302	DNA editing	Pre-clinical	Beam	NA
NTLA-3001	DNA editing	Pre-clinical	Intellia	NA
WVE-006	mRNA editing	Pre-clinical	Wave Life Sciences/GSK	NA

Included pre-clinical drugs are those where clinical trials are approved. AAT: Alpha-1 Antitrypsin.

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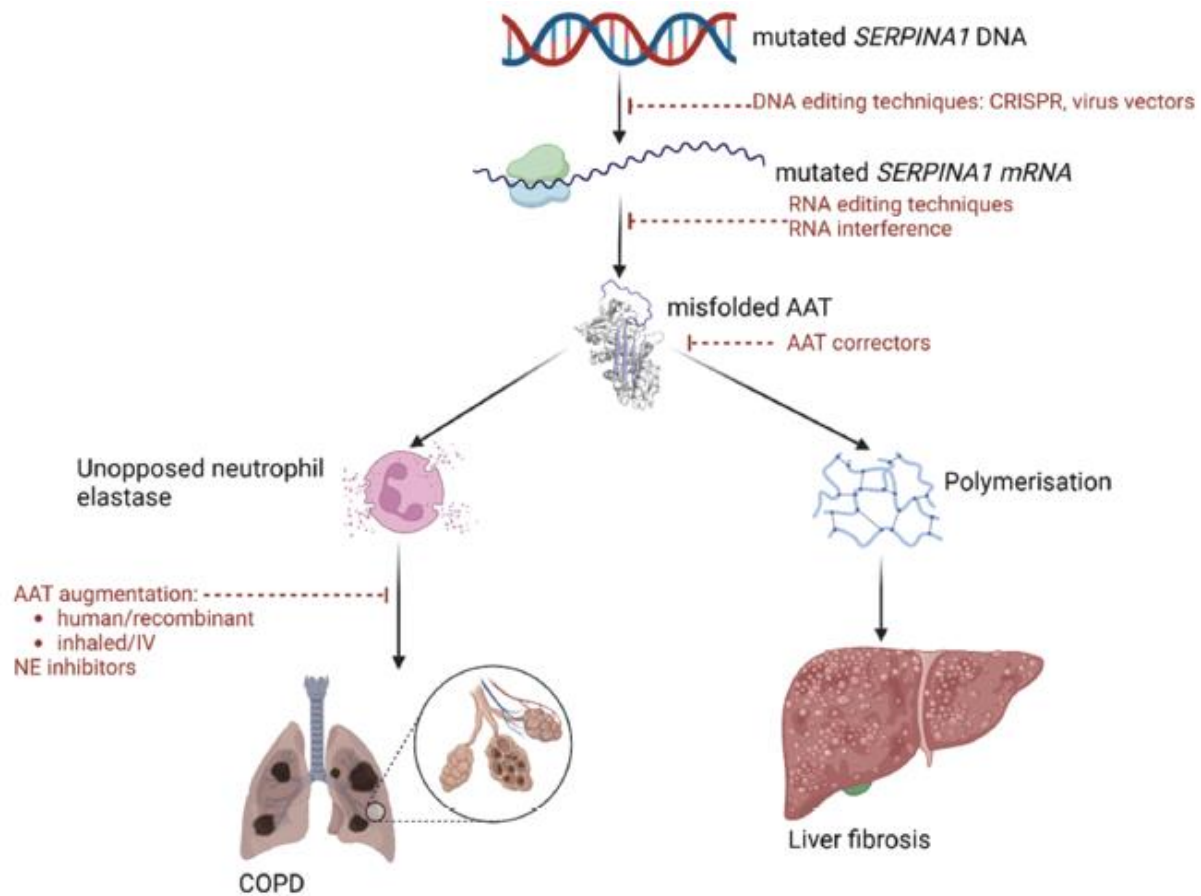


Figure 1. Pathogenesis and therapeutic targets in alpha-1 antitrypsin deficiency.

Therapeutic Advances in Chronic Disease

Review

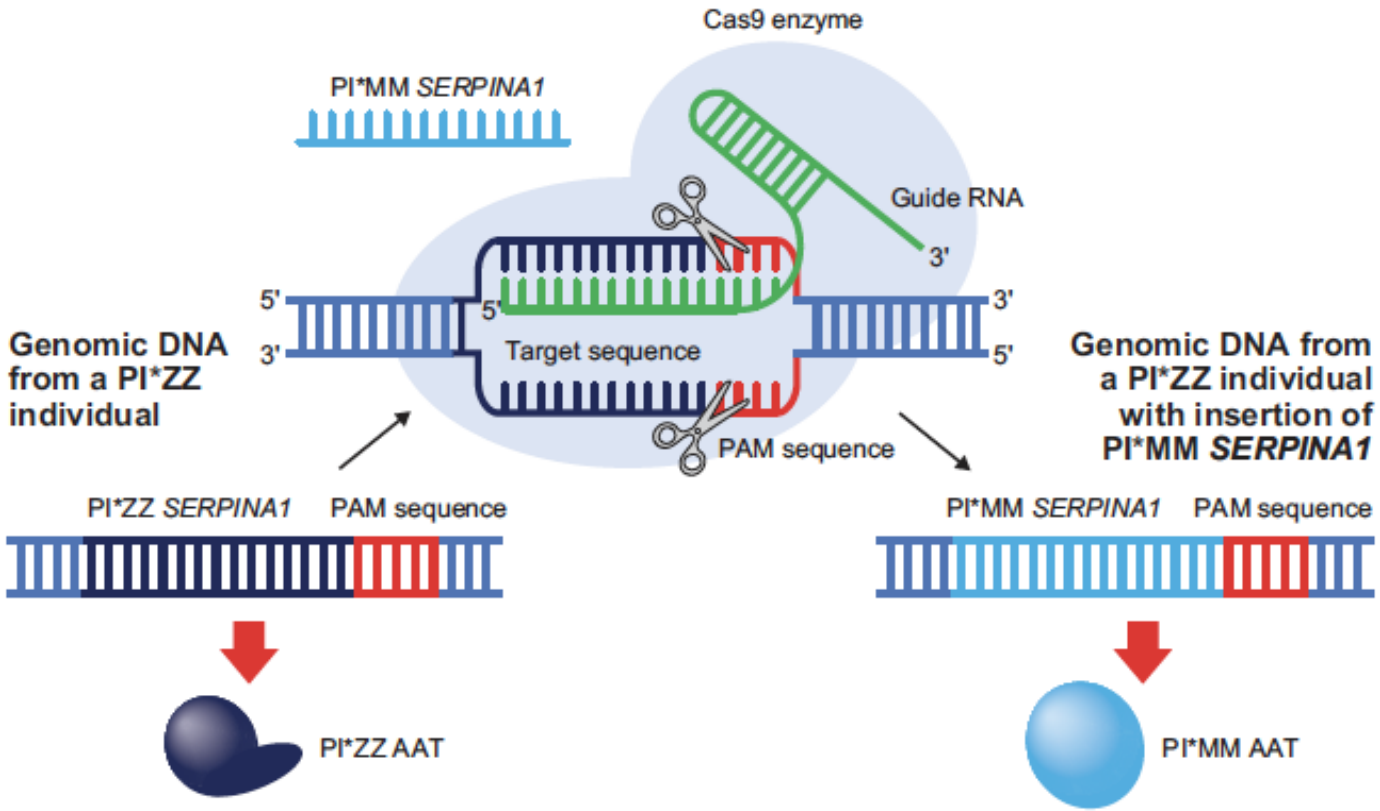
Alpha-1 antitrypsin deficiency research and emerging treatment strategies: what's down the road?

Franck F. Rahaghi

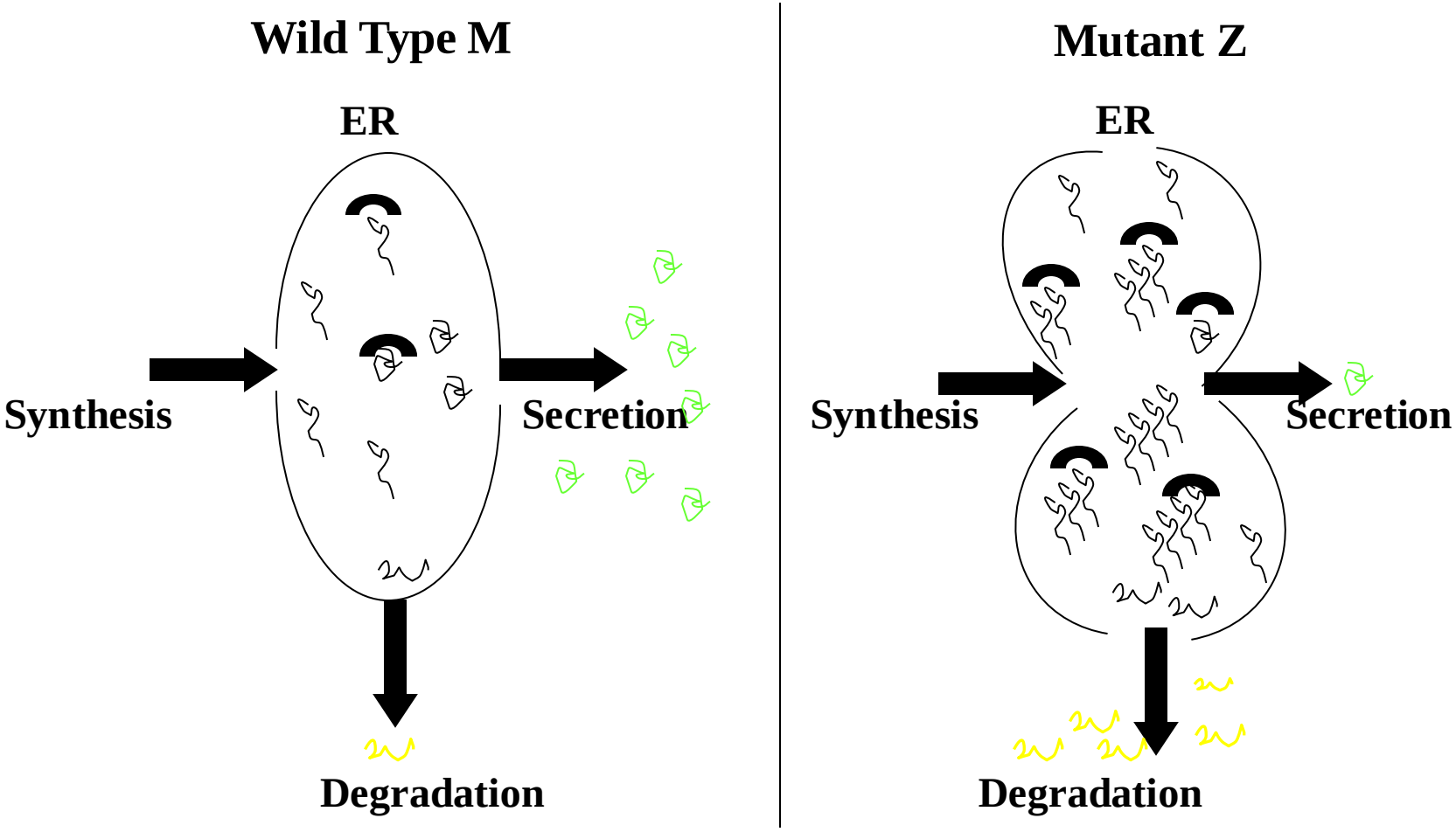
Ther Adv Chronic Dis

2021, Vol. 12: 77–90

DOI: 10.1177/20406223211014025

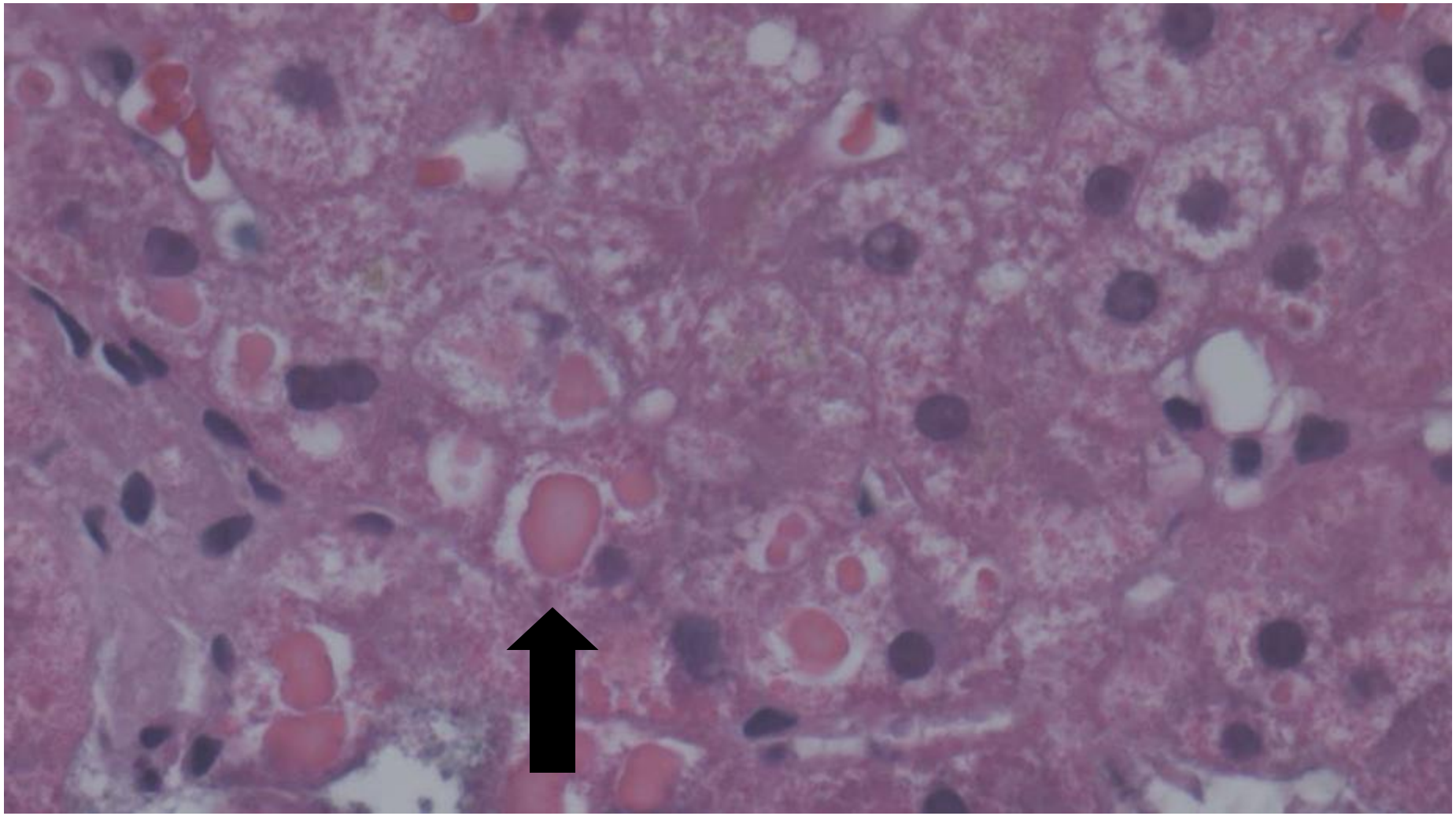


AAT Protein Processing



Proteasomal and autophagic degradative pathways may govern hepatic risk

Human ZZ Liver



PAS + intracellular inclusions are polymerized AAT ‘Z’

TAK-999 (ARO-AAT)

FIRST-IN-CLASS RNAi THAT SILENCES HEPATOCYTE PRODUCTION OF MUTANT ALPHA-1 ANTITRYPSIN

UNMET NEED

- AATLD is a genetic condition with high unmet medical need and no approved therapies that causes progressive liver disease

PROGRAM BACKGROUND

- Co-development partnership with Arrowhead Pharmaceuticals[1]
- Potential 1L treatment to halt, reverse, prevent onset, or slow progression of liver fibrosis
- Most common Z-mutant results in improper protein folding and accumulation in hepatocytes leading to liver injury and fibrosis

MARKET OPPORTUNITY

- PiZZ AATD[2] prevalence: ~100 K in US; ~130 K in EU
- Of these[3,4], ~35% of adults develop clinically significant liver fibrosis and ~10-20% of children develop severe liver fibrosis

NEXT STEPS

- Engage with regulatory agencies to assess best path forward.
- Pivotal trial start 2021 or early 2022.

TAK-999 Results in Rapid & Sustained Reduction in Serum Z-AAT

Interim 24-week liver biopsy results in four patients from the Phase 2 AROAAT2002 open-label clinical study demonstrate:

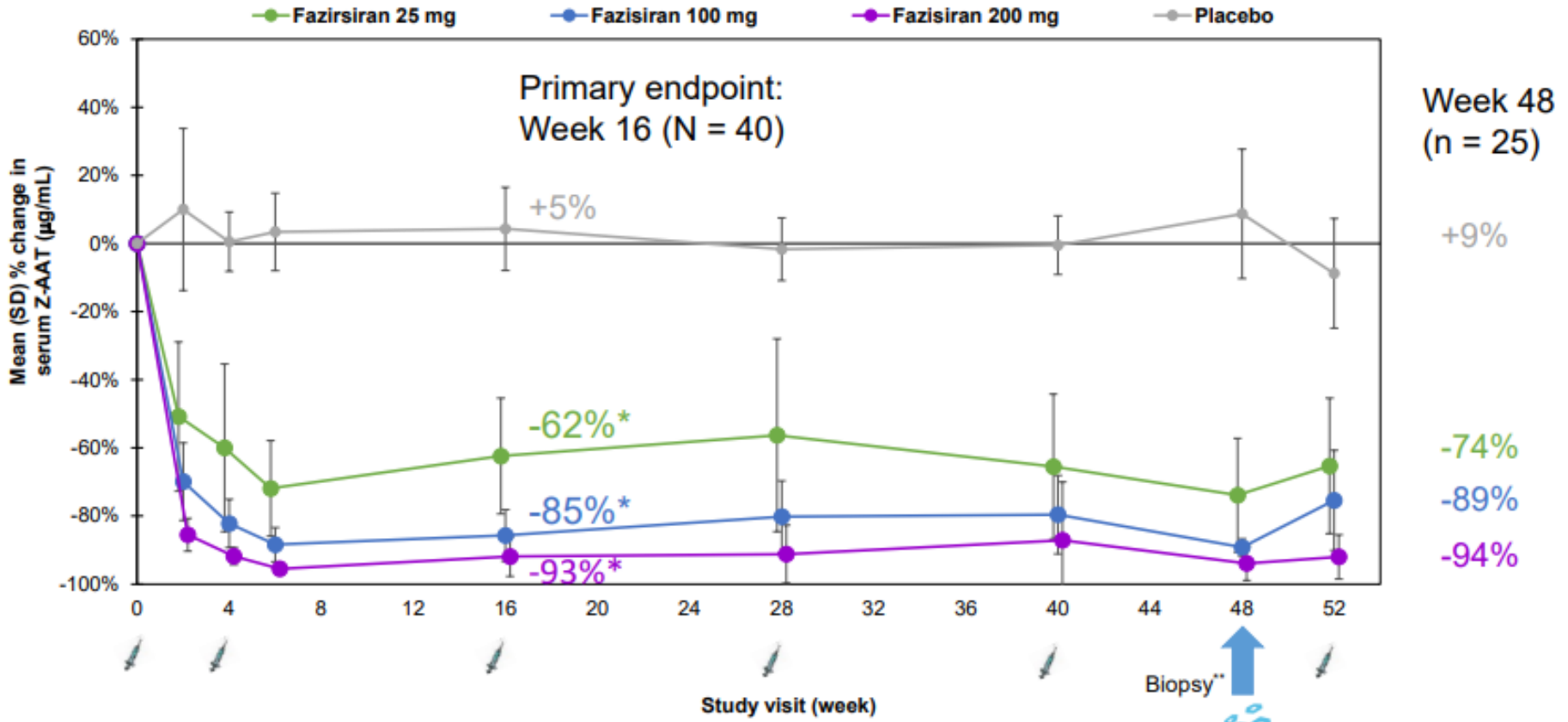
	N = 4	Description
Serum Z-AAT	Decrease in all patients	Up to 93%
Total Intrahepatic Z-AAT	Decrease in all patients	Up to 95%
Intrahepatic Z-AAT Polymer	3 patients have reduction from baseline	Maximum reduction 97%
ALT, GGT	Marker of liver injury reduced in all patients	Maximum reduction of 58%, 66%, respectively
FibroScan	Improvement in all patients	3 patients improved >20%

2020 AASLD late-breaker abstract[5] has been accepted and the poster presentation will be available November 13th.

1. Closing of the transaction is contingent on completion of review under antitrust laws, including the Hart-Scott-Rodino Antitrust Improvements Act of 1976 in the US
2. PiZZ AATD: Severe AATD or alpha-1 antitrypsin deficiency (low or no AAT in the blood) is a hereditary condition most commonly caused by homozygosity for the mutant Z allele of AAT
3. Source: Alpha-1 Foundation; Blanco et al, International Journal of COPD 2017;12:561–569
4. Source: Clark et al, Journal of Hepatology 2018;69(6):1357–1364
5. AASLD late-breaker abstracts will be available to the public electronically on the AASLD website November 1, 2020

Takeda

Fazirsiran reduced serum Z-AAT concentration in a dose-dependent manner (n = 40 to Week 16, n = 25 with fibrosis to Week 52)



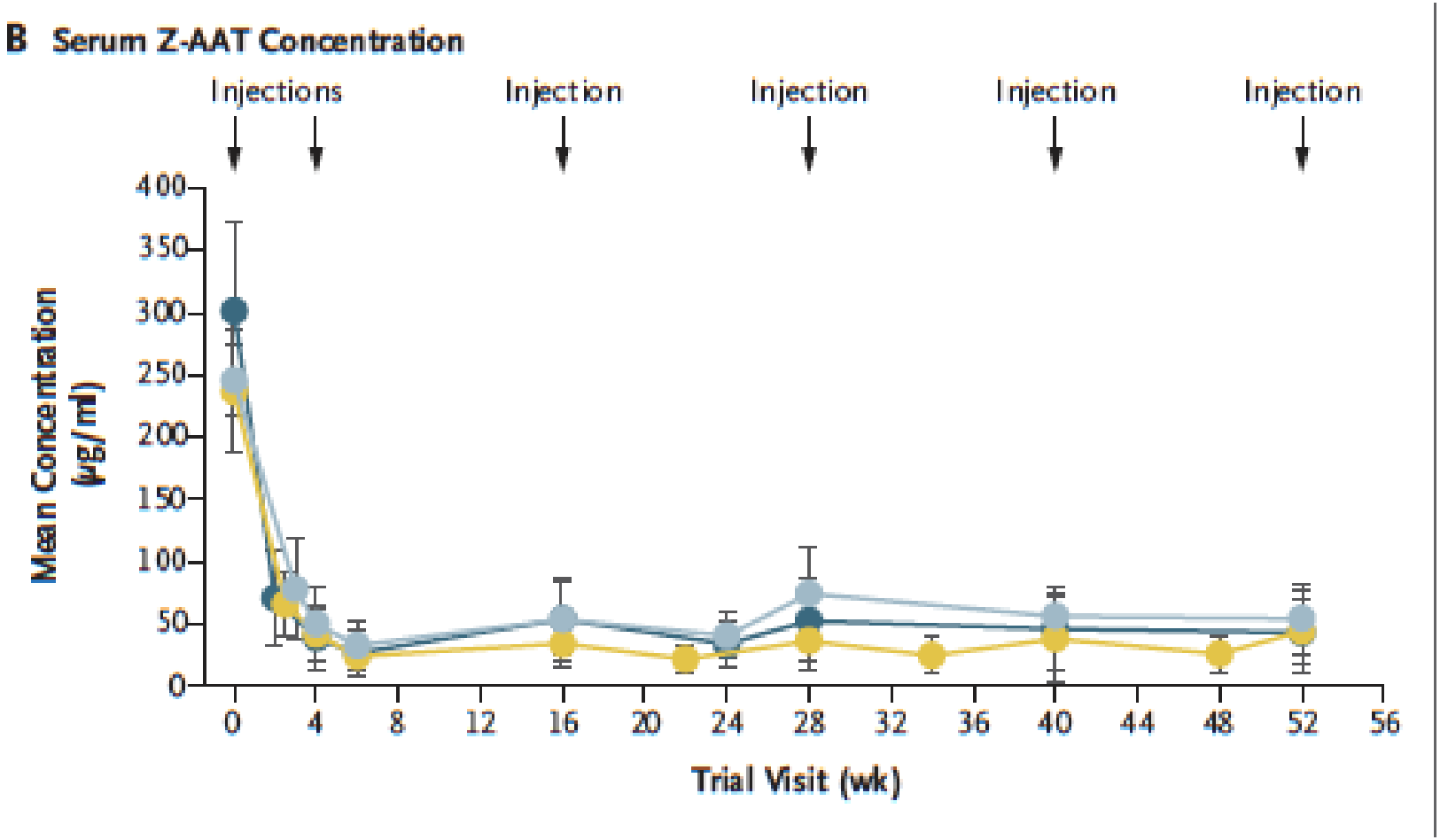
*$p < 0.001$ vs placebo ** Post-dose biopsies were collected at week 48, 72, or 96

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency

Pavel Strnad, M.D., Mattias Mandorfer, M.D., Ph.D., Gourab Choudhury, M.D., William Griffiths, M.D., Christian Trautwein, M.D., Rohit Loomba, M.D., Thomas Schluep, Sc.D., Ting Chang, Ph.D., Min Yi, Ph.D., Bruce D. Given, M.D., James C. Hamilton, M.D., Javier San Martin, M.D., and Jeffery H. Teckman, M.D.



N Engl J Med 2022;387:514-24.
DOI: 10.1056/NEJMoa2205416

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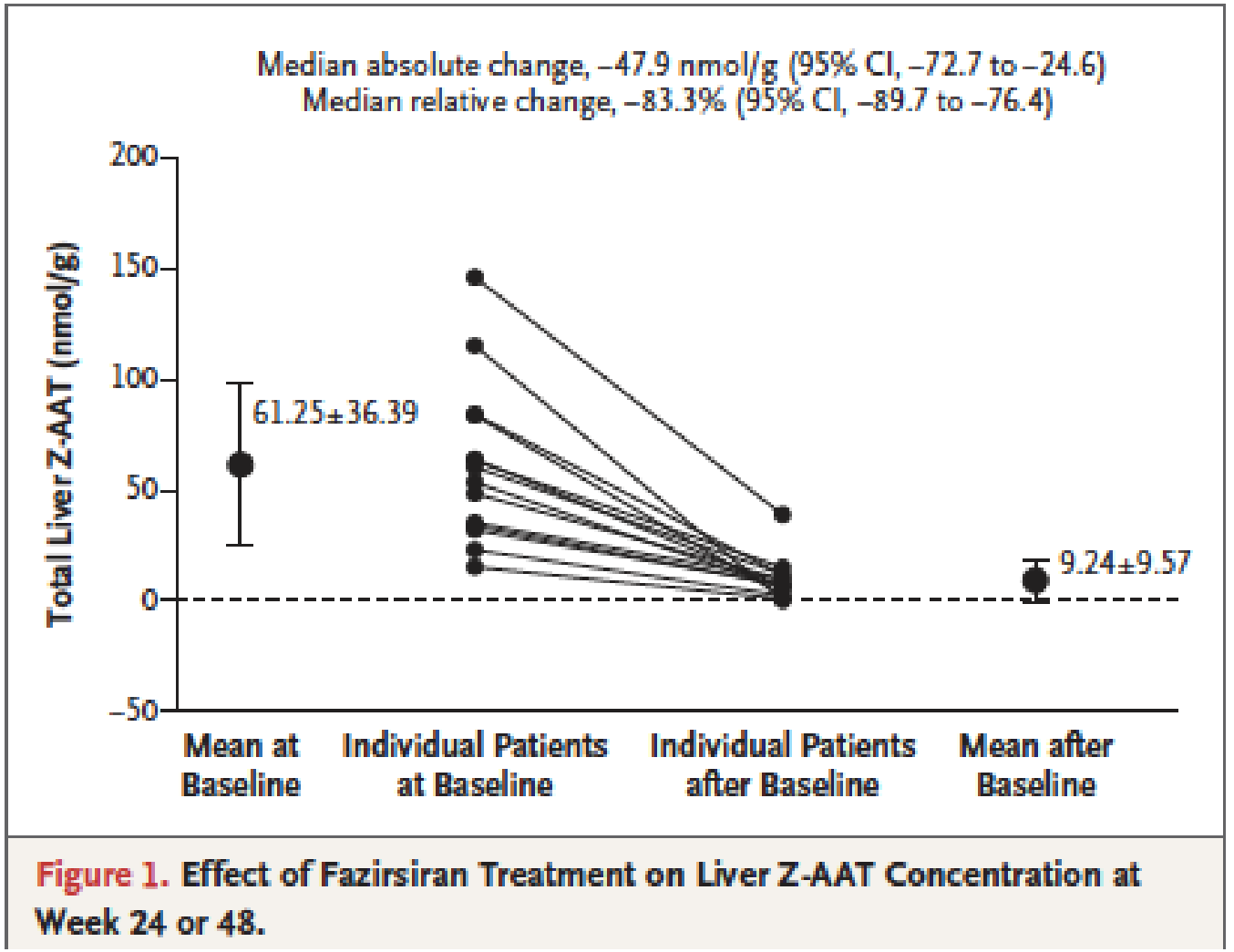


Figure 1. Effect of Fazirsiran Treatment on Liver Z-AAT Concentration at Week 24 or 48.

Summary of safety and adverse events

Subject Incidence, n (%)	Placebo (n = 14)	Fazirsiran 25 mg (n = 9)	Fazirsiran 100 mg (n = 8)	Fazirsiran 200 mg (n = 9)
TEAEs	13 (92.9%)	9 (100%)	8 (100%)	9 (100%)
TEAEs in 4 or more subjects				
COVID-19	2 (14%)	0 (0%)	2 (25%)	6 (67%)
Headache	3 (21%)	4 (44%)	1 (13%)	2 (22%)
Procedural pain	3 (21%)	1 (11%)	0 (0%)	4 (44%)
Arthralgia	3 (21%)	2 (22%)	2 (25%)	0 (0%)
Diarrhea	2 (14%)	2 (22%)	1 (13%)	0 (0%)
Nausea	3 (21%)	1 (11%)	0 (0%)	1 (11%)
Back pain	0 (0%)	1 (11%)	1 (13%)	2 (22%)
Fatigue	2 (14%)	1 (11%)	1 (13%)	0 (0%)
Treatment-related TEAEs	8 (57%)	2 (22%)	4 (50%)	4 (44%)
Serious TEAEs	3 (21%)	0 (0%)	0 (0%)	2 (22%)
TEAEs leading to drug discontinuation, dose interruptions or study withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- No TEAE-related study drug discontinuation, dose interruptions or premature study withdrawals
- Two SAEs in the fazirsiran 200 mg group: both infective exacerbations of bronchiectasis in 2 participants with history of pulmonary disease who were receiving AATD augmentation therapy
- SAEs in placebo group
  - 1 patient with acute pancreatitis, influenza and staphylococcal wound infection
  - 1 patient with decreased pulmonary function test and hypertensive crisis who was on AAT augmentation therapy
  - 1 patient with presyncope

Balance of Neutrophil Elastase and A1AT: A1AT-Deficient

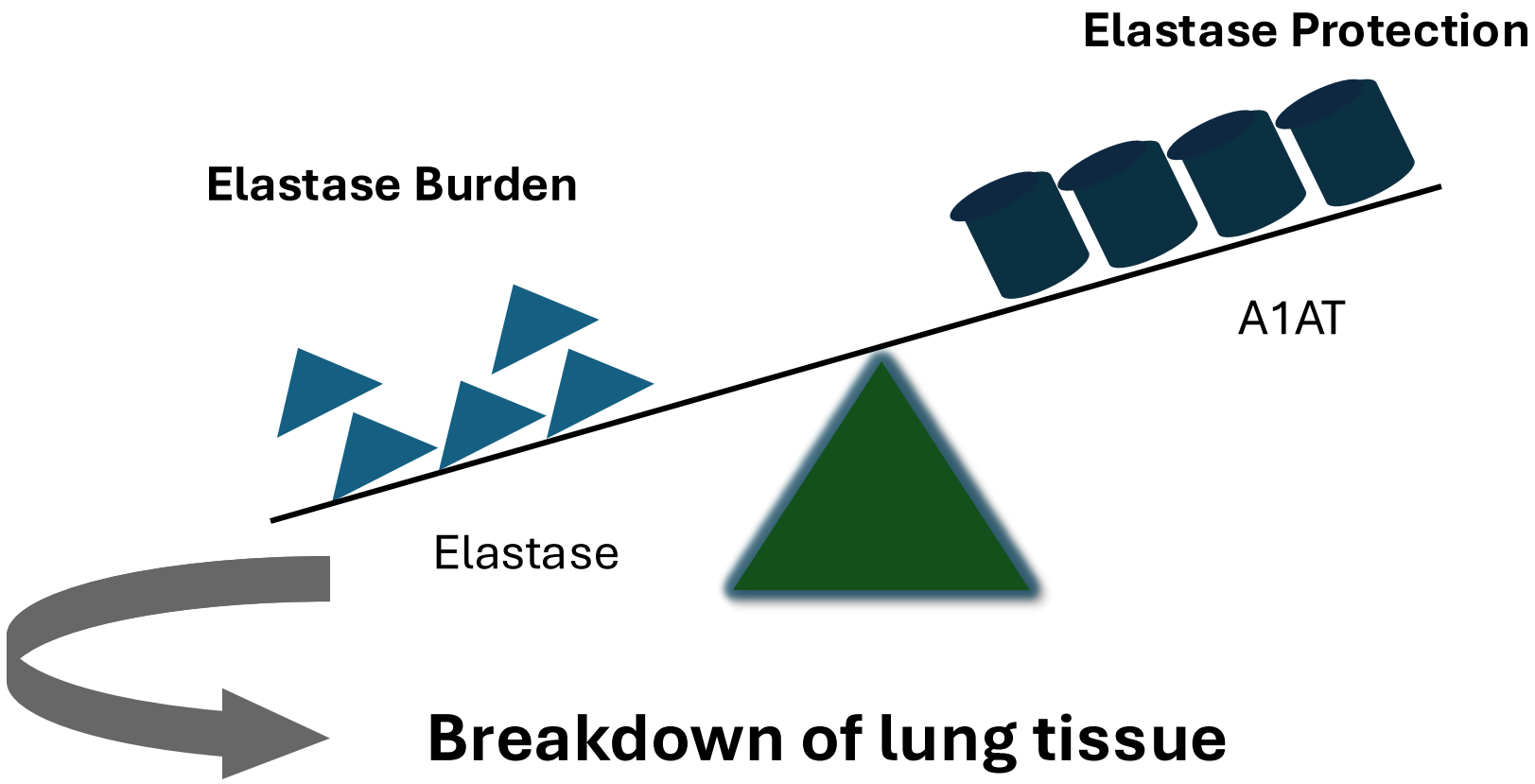
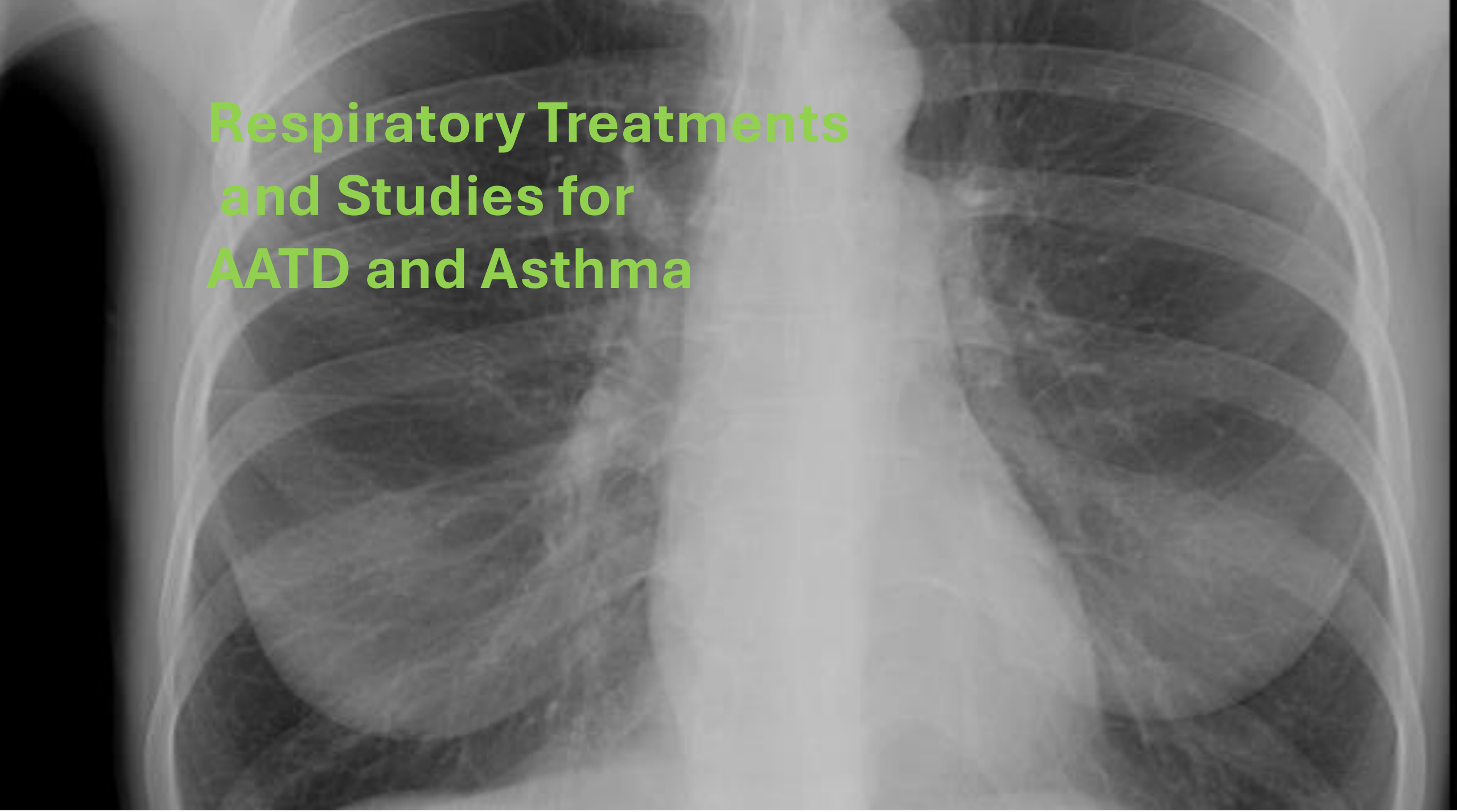
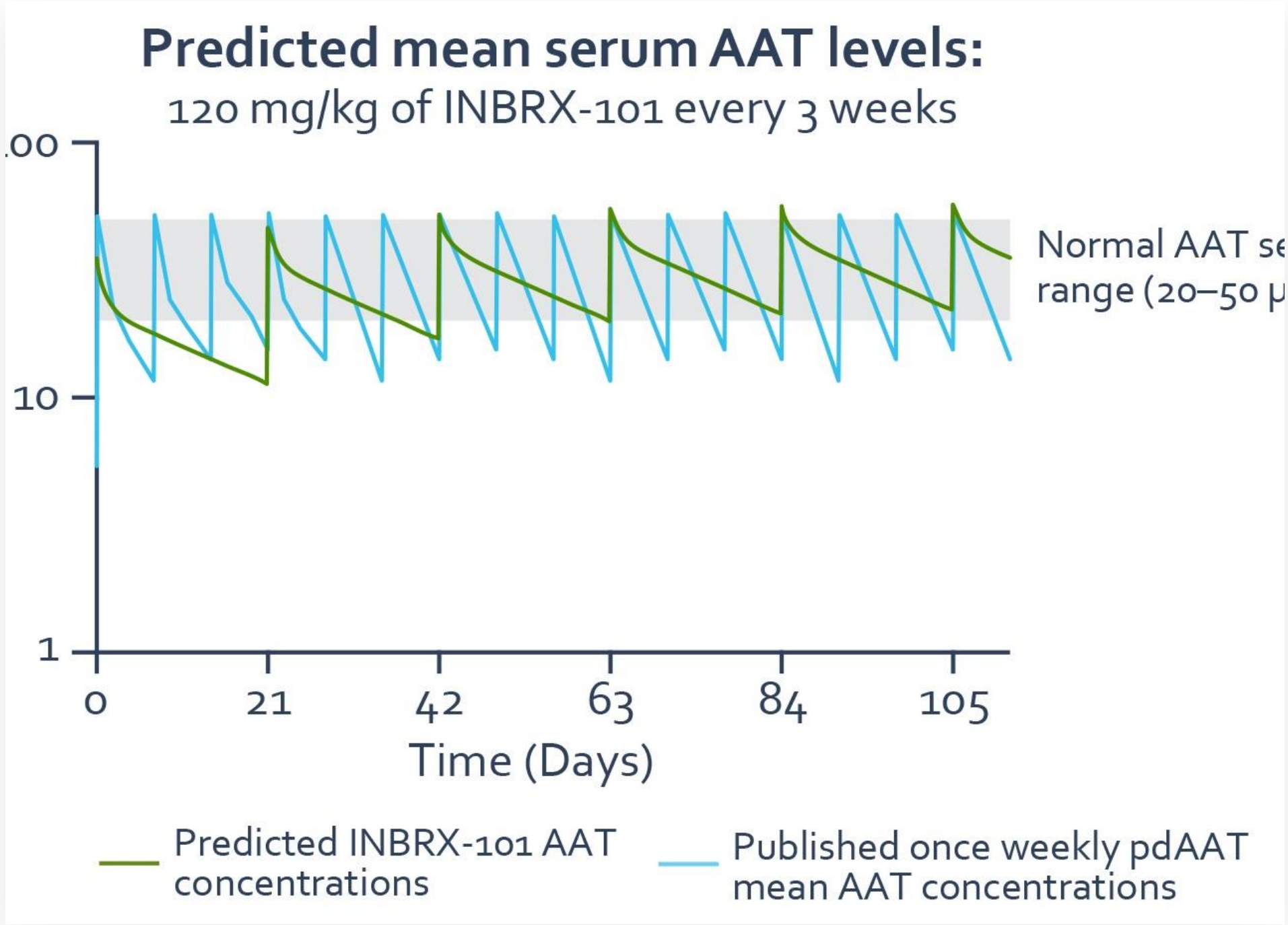


Figure courtesy of Dr. Kyle Hogarth.



Respiratory Treatments and Studies for AATD and Asthma


Predicted mean serum AAT levels:
120 mg/kg of INBRX-101 every 3 weeks
100
10
1
0
21
42
63
84
105
Time (Days)
Normal AAT se
range (20–50 µ
Predicted INBRX-101 AAT concentrations
Published once weekly pdAAT mean AAT concentrations

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Original Research

Recombinant Alpha-1 Antitrypsin–Fc Fusion Protein INBRX-101 in Adults With Alpha-1 Antitrypsin Deficiency: A Phase 1 Study

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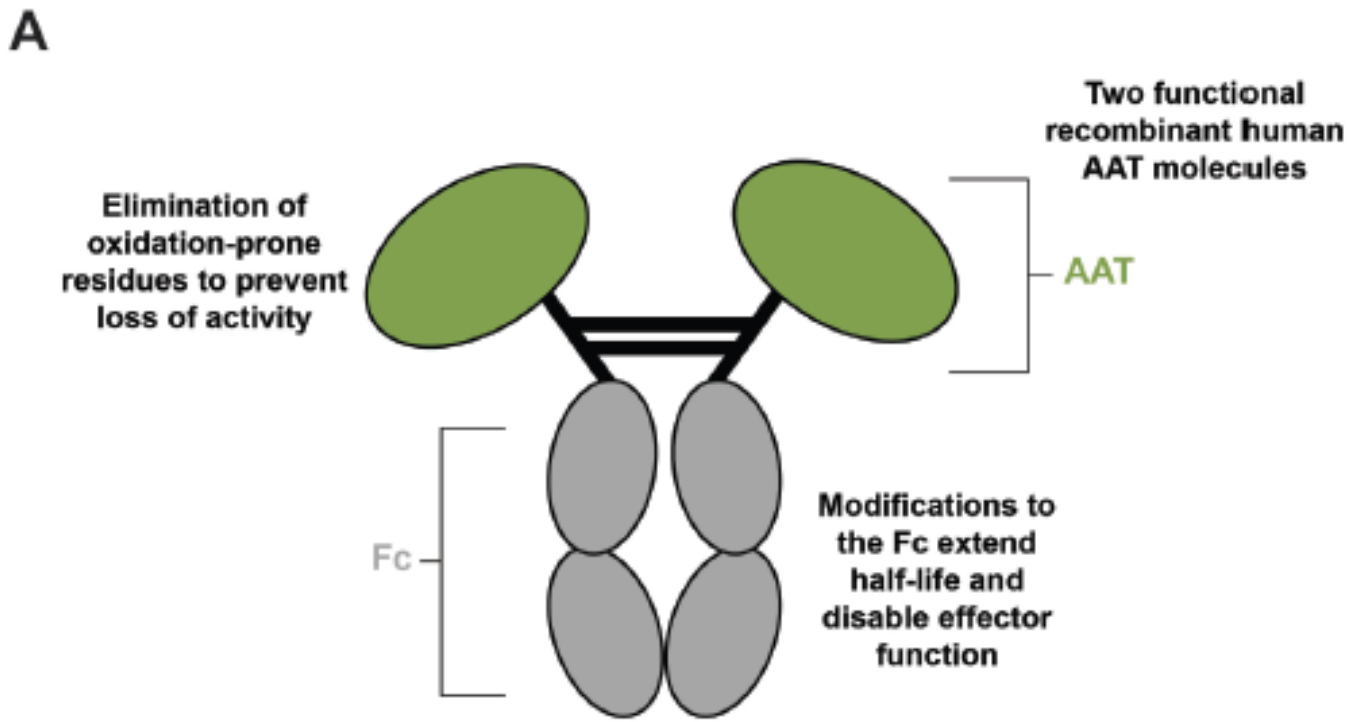

Balance of Neutrophil Elastase and A1AT: Healthy

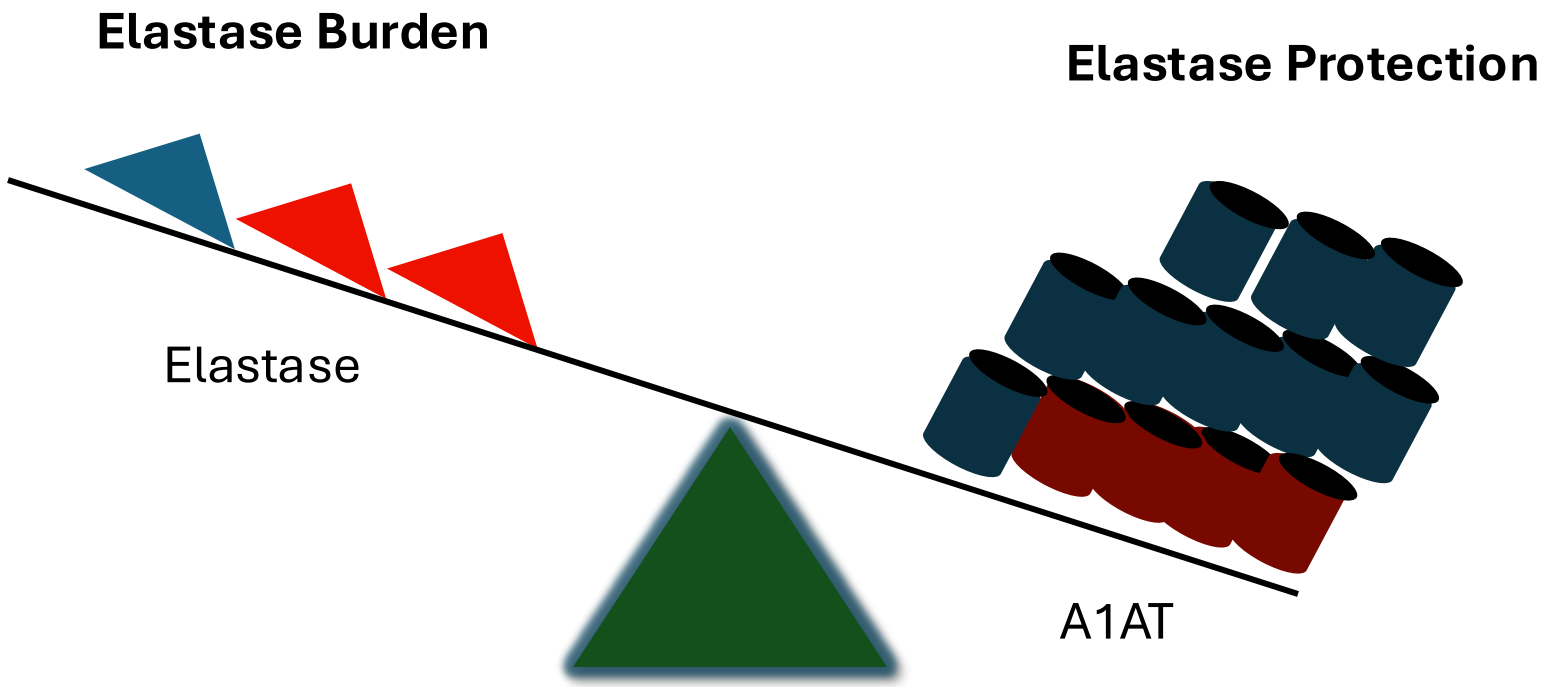

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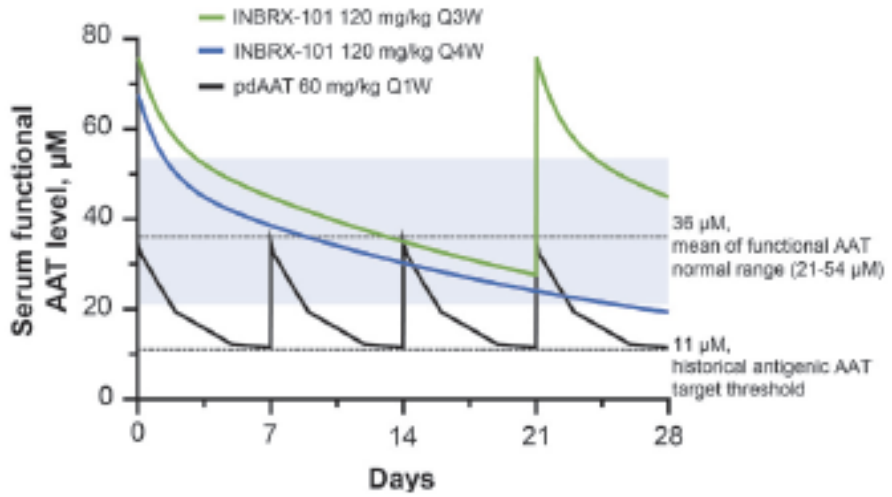
Figure 3. Pharmacokinetics and Pharmacodynamics Modeling to Determine Phase 2 Dosing

PD parameter, mean (SD), µM	Regimen		
	pdAAT 60 mg/kg Q1W	INBRX-101 120 mg/kg Q3W[c]	INBRX-101 120 mg/kg Q4W[c]
$C_{trough,ss}$	13.6 (3.0)[a]	28.0 (7.8)	20.9 (7.8)
$C_{avg,ss}$	17.8[b]	43.0 (7.9)	33.7 (6.6)
$C_{max,ss}$	34.5[b]	65.9 (14.4)	57.2 (14.8)



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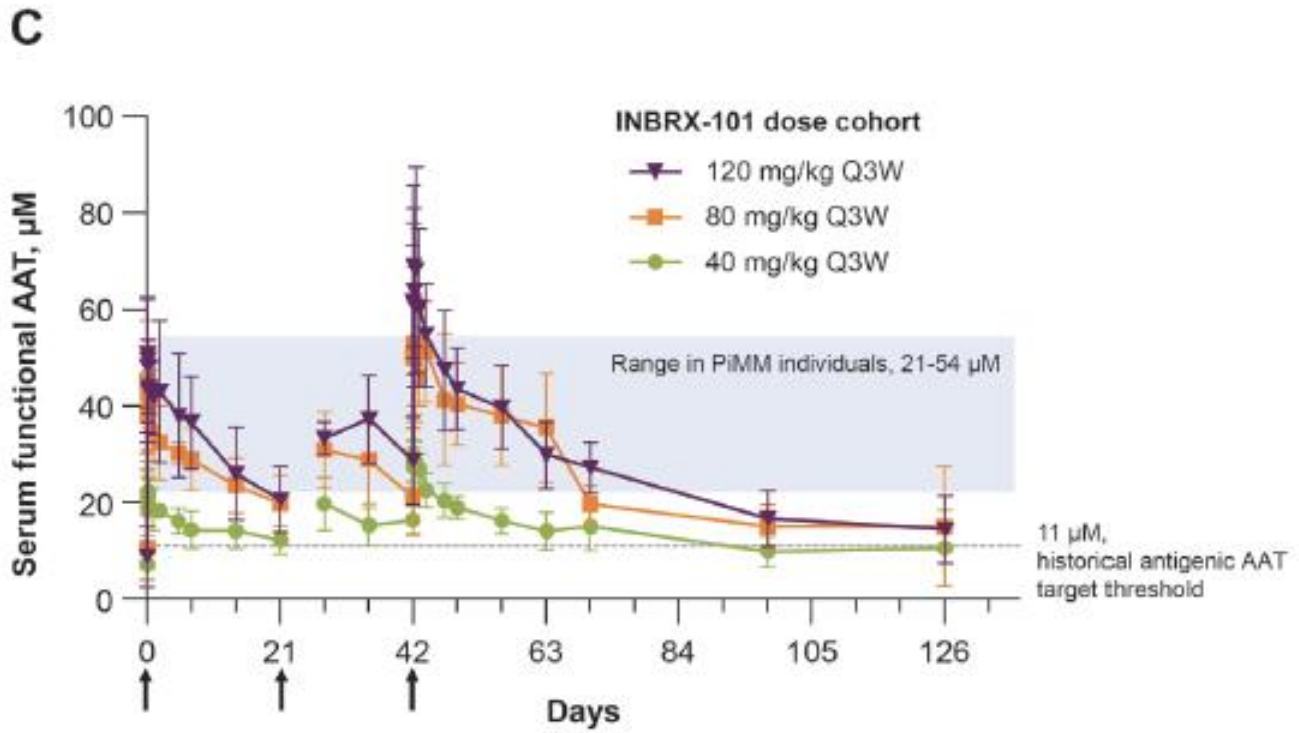

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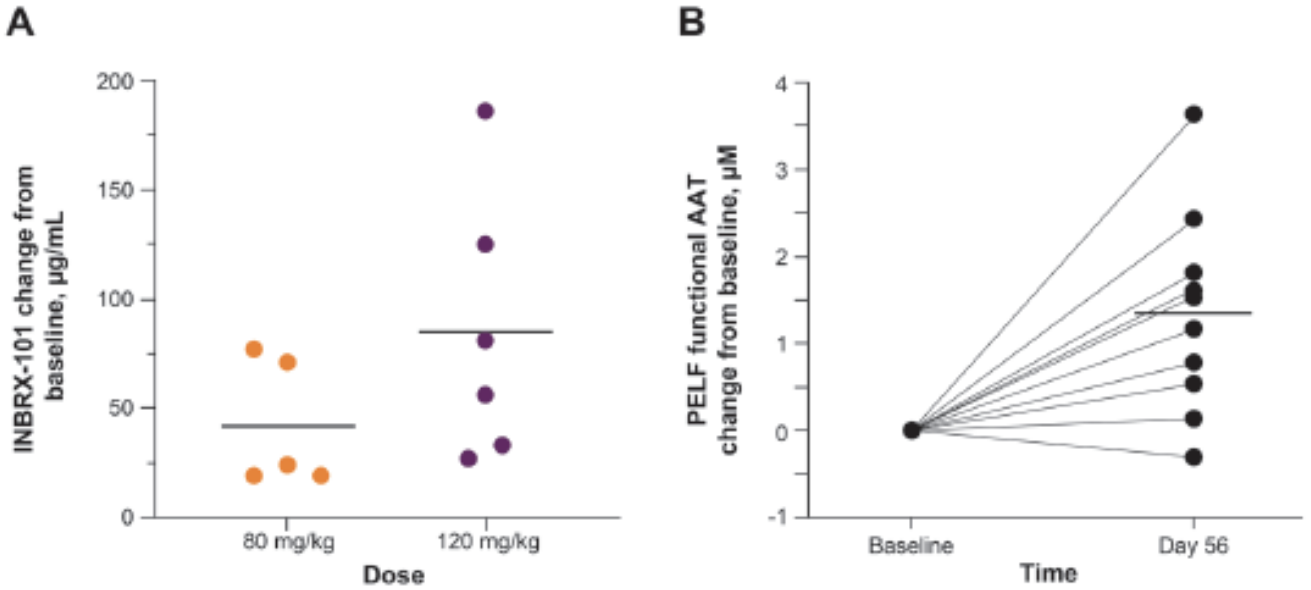
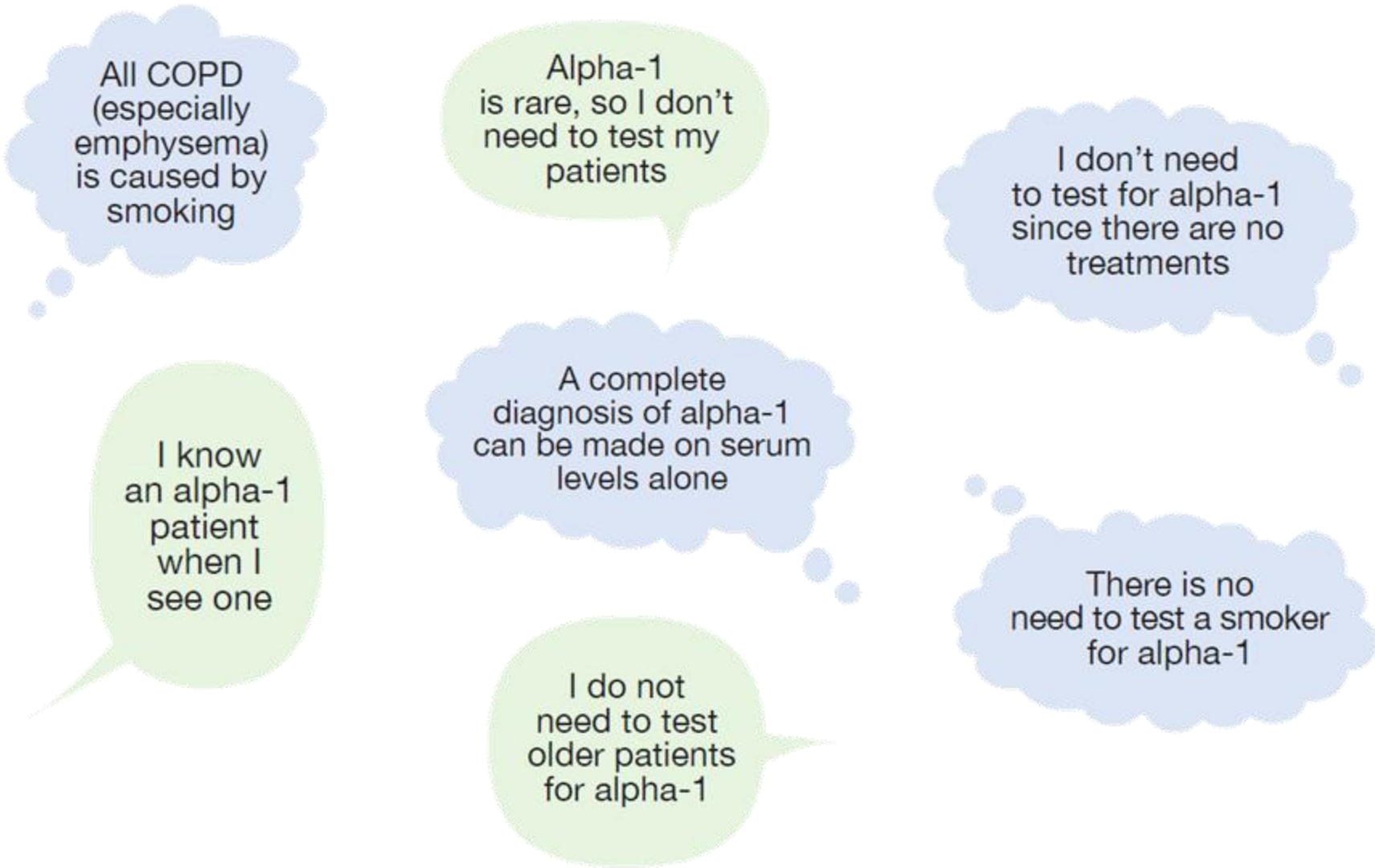
Figure 2. INBRX-101 (A) and Functional Alpha-1 Antitrypsin Levels (B) in Pulmonary Epithelial Lining Fluid



Replace COPD and Alpha-1 Myths…



Thank you from Allergy, Asthma and Immunology Penn State University, Hershey, PA, USA