Alpha 1 Antitrypsin Deficiency- What is the take Home Message?

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DISCLOSURES

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OBJECTIVES

- Understanding Alpha one antitrypsin and its role.
- Incidence of AAT deficiency.
- Diagnosis and Clinical symptoms.
- Effective treatment modalities for AATD.
- Genetic Counseling for AATD .

Case Vignette

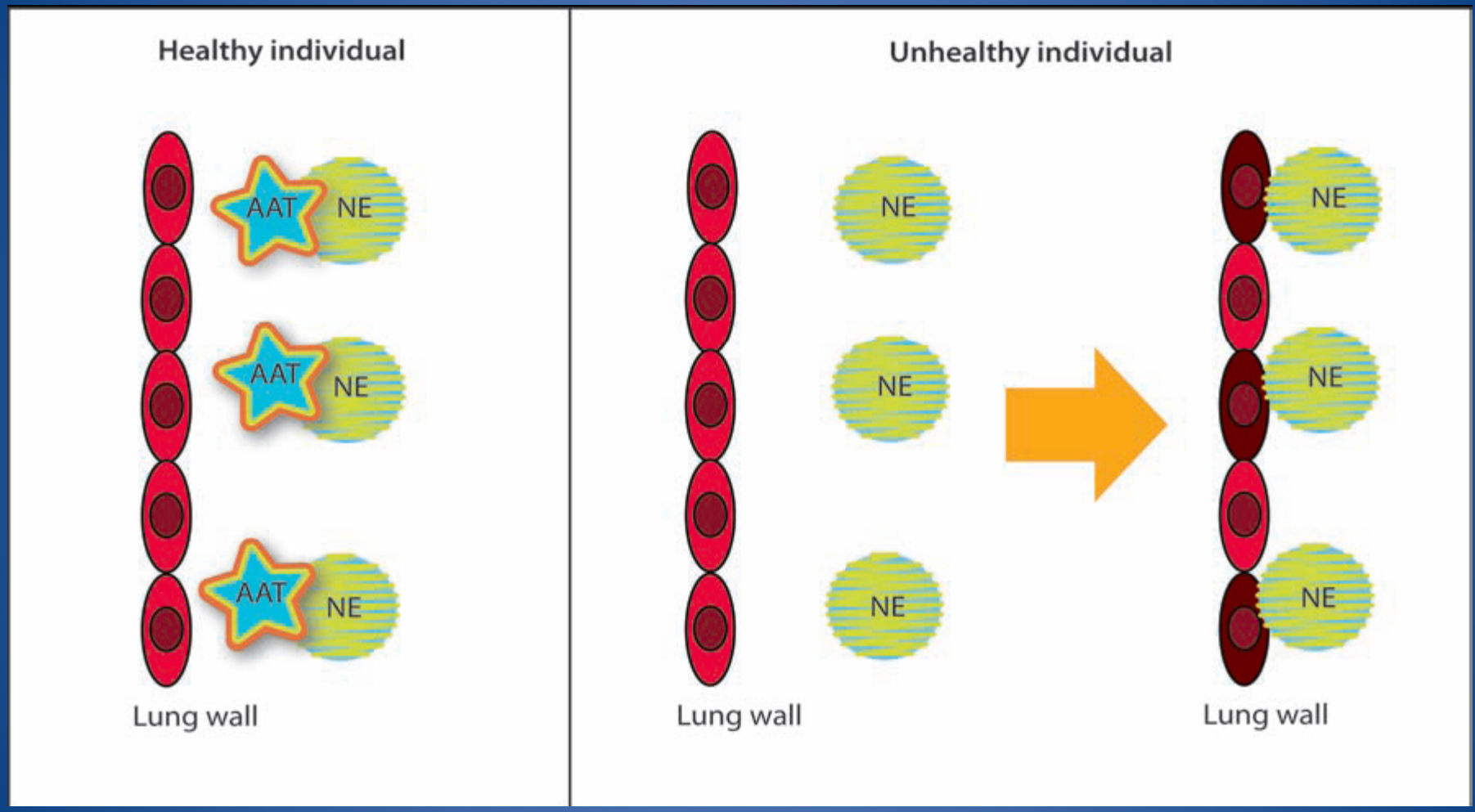
- A 60-year-old white man presents for evaluation of progressive dyspnea.
- He is a former smoker with a 20-pack-year smoking history and a 10-year history of diagnosed chronic obstructive pulmonary disease (COPD).
- There is no family history of COPD.
- Severe airflow obstruction is seen on spirometry, with a forced expiratory volume in 1 second (FEV1) that is 40% of the predicted value.
- Should the patient be evaluated for alpha1-antitrypsin (AAT) deficiency?
- If AAT deficiency is documented, how should his case be managed?

Outline

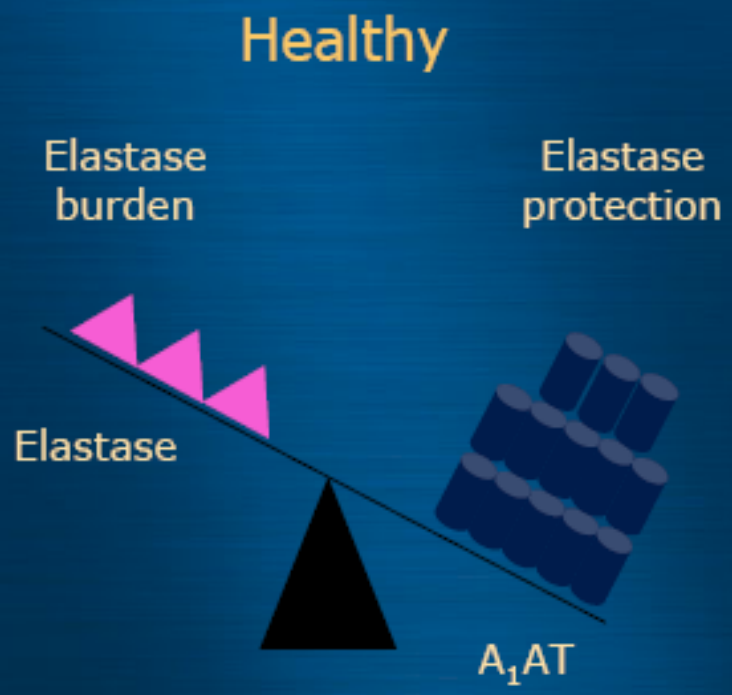
- The Clinical Problem
- Strategies and Evidence
  - Diagnosis
  - Evaluation and Follow-up
  - Treatment
    - Lung Disease
    - Liver Disease
- Areas of Uncertainty
- Guidelines
- Conclusions and Recommendations

What Is Alpha-1 Antitrypsin?

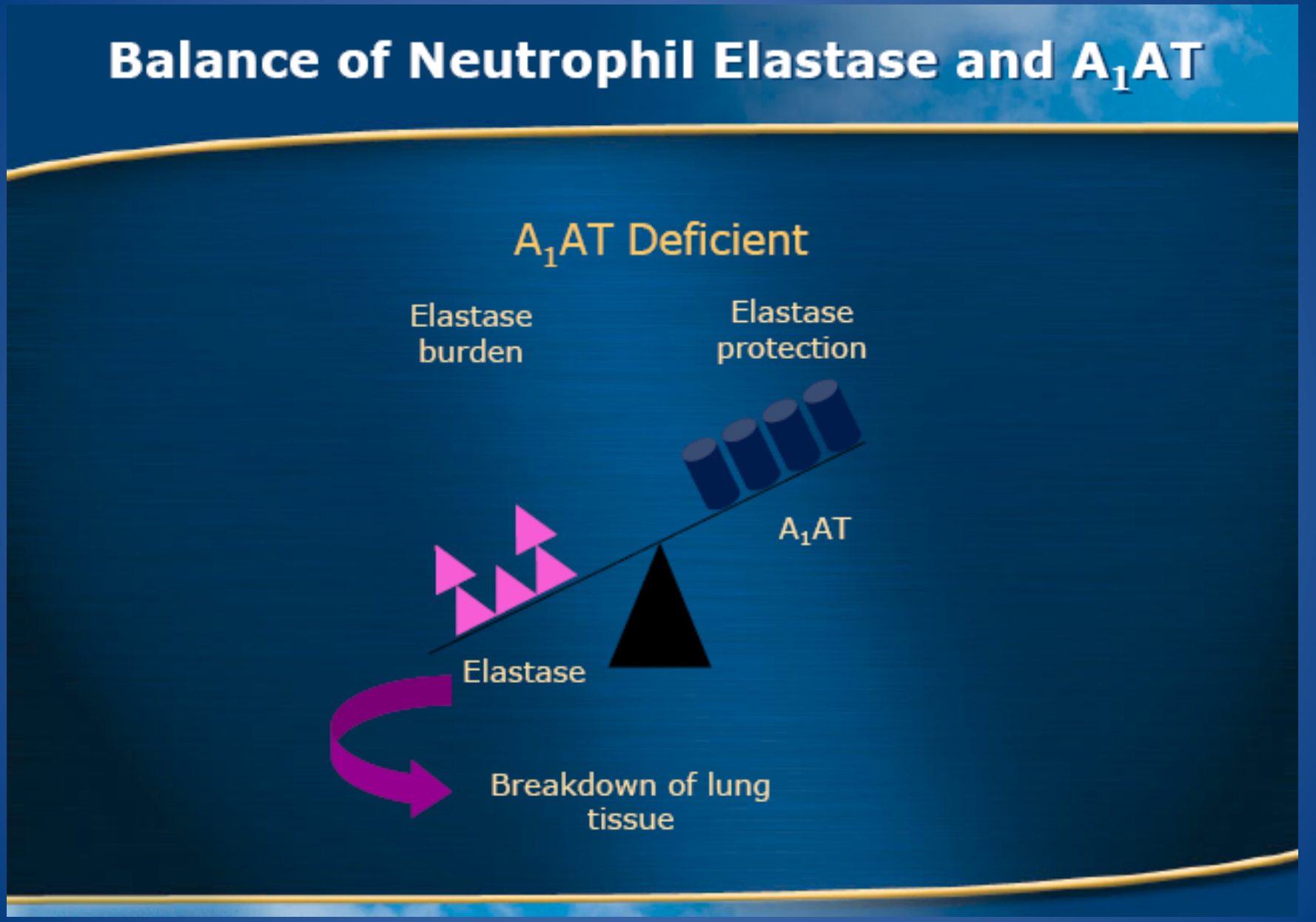
- A normal protein that circulates in the blood
- Majority of the protein is synthesized by the liver, although some is made by lung epithelial cells and macrophages
- The main function of the protein is to protect the normal tissues of the body from being damaged by proteolytic enzymes, such as neutrophil elastase (released by white blood cells)


Healthy individual
AAT
NE
AAT
NE
AAT
NE
Lung wall
Unhealthy individual
NE
NE
NE
Lung wall
NE
NE
NE
Lung wall

Balance of Neutrophil Elastase and A_1AT

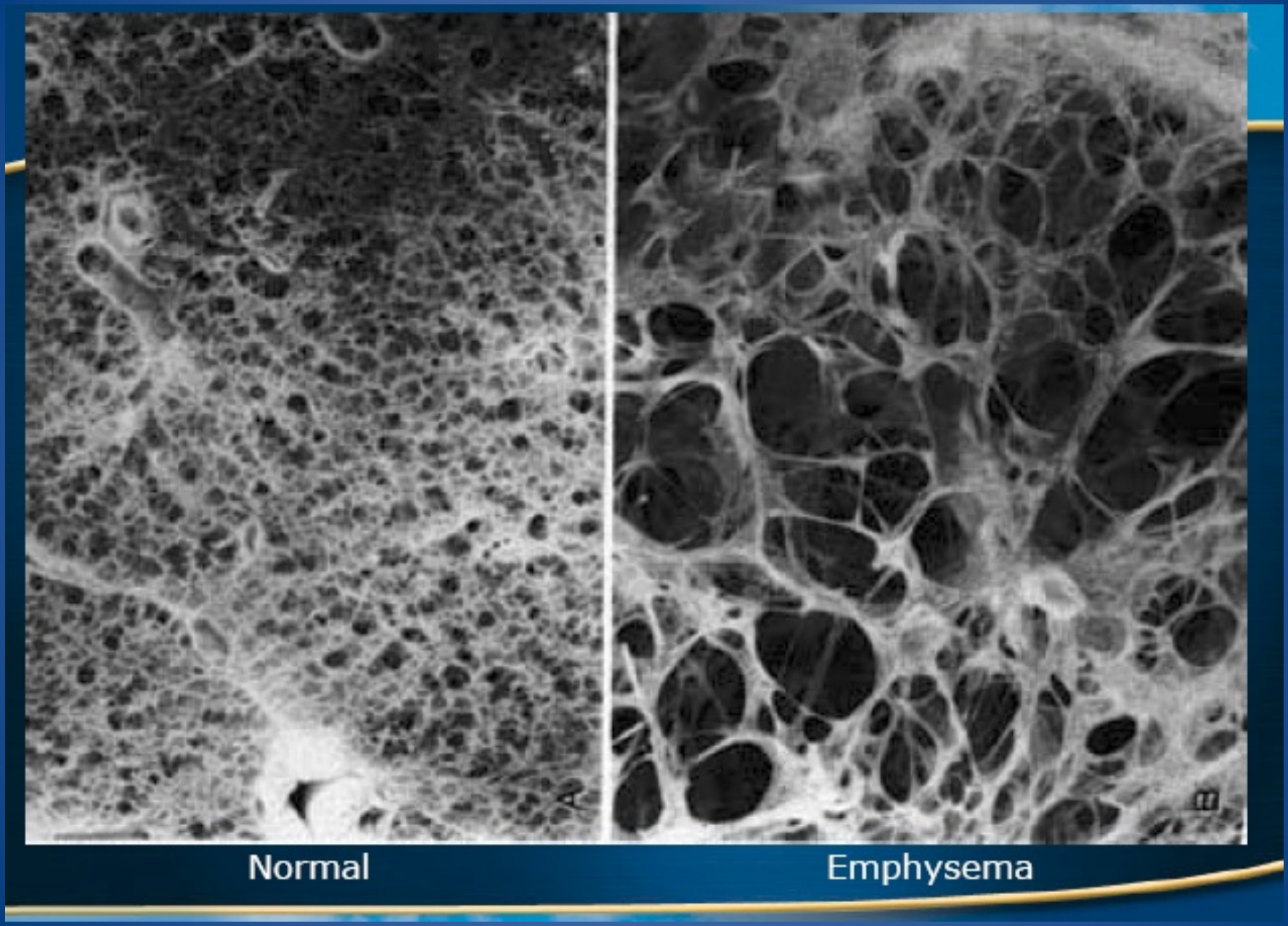


Balance of Neutrophil Elastase and A_1AT



In individuals who develop lung disease due to Alpha-1, the normal balance between AAT and neutrophil elastase does not exist.

Therefore, the damaging effects of neutrophil elastase are unchecked, which can lead to emphysema.


Normal
Emphysema

INCIDENCE

- AAT deficiency is relatively common in populations of European ancestry, with an estimated prevalence of 1 case per 3000 to 5000 persons in the United States.

Genetics

- One of the most common genetic disorders worldwide
- Mainly affects those of Northern European and Iberian descent
  - Largest core of patients in US, UK, Germany, Spain, and Scandinavia
  - 200,000 infants in Sweden screened yielded a frequency of 1 in 1550 with Pi-Z

"Not a rare disorder, but a rarely diagnosed disorder."

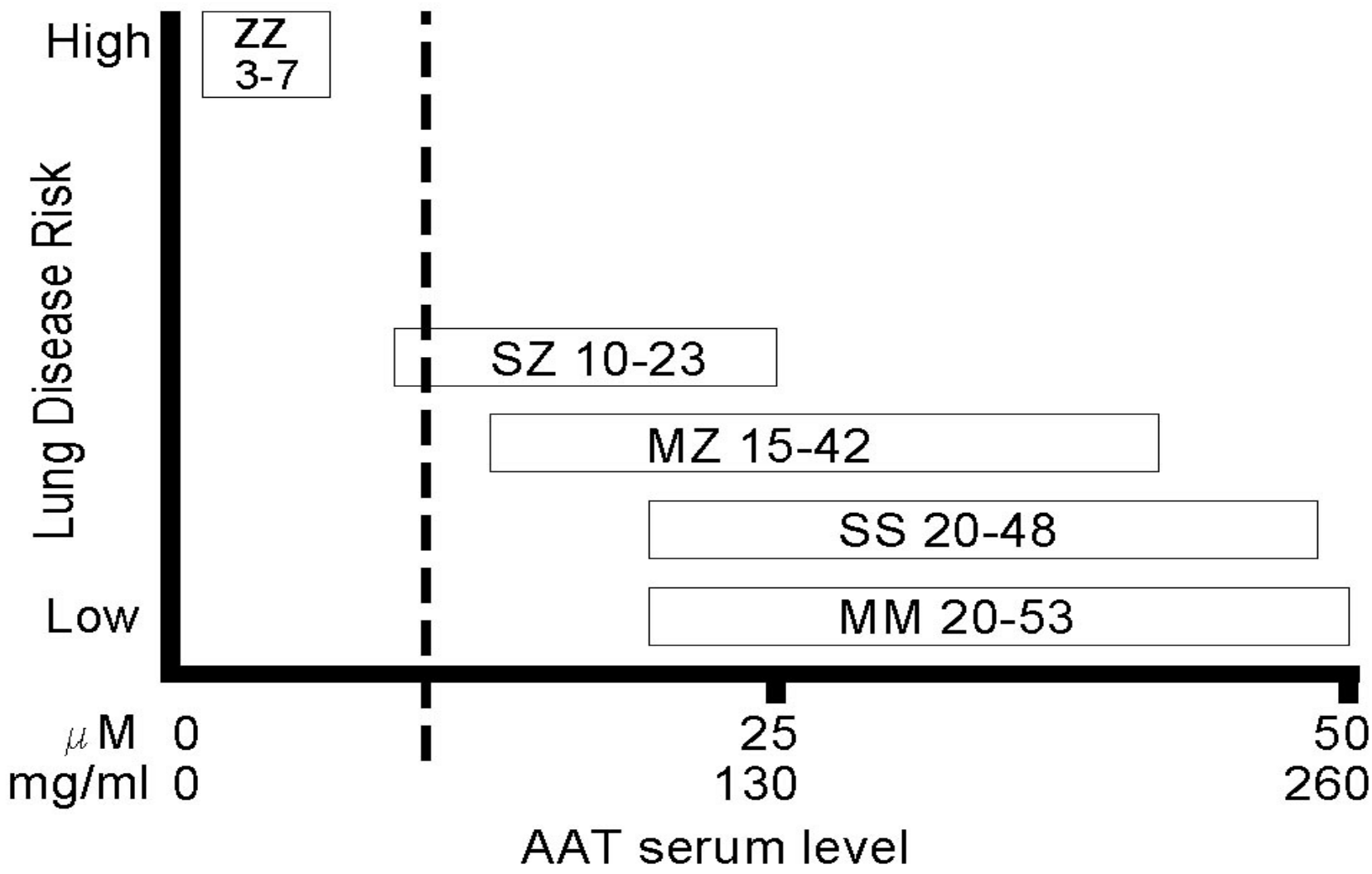
NORMAL

- Most persons inherit two copies of the *PI*M* allele, which is associated with normal AAT levels.

AAT

- Most persons with AAT deficiency inherit two copies of the *PI*Z* allele
- Patients with the Z protein phenotype have approximately 15% of normal AAT levels

- The *PI*S* allele is slightly more common than the *PI*Z* allele in most European populations and is associated with mildly reduced AAT levels.


High
Low
Lung Disease Risk
ZZ
3-7
SZ 10-23
MZ 15-42
SS 20-48
MM 20-53
μM 0
mg/ml 0
25
130
50
260
AAT serum level

Diagnostic Tests for Alpha1-Antitrypsin (AAT) Deficiency and Associated Disease Risks

Table 1. Diagnostic Tests for Alpha$_1$-Antitrypsin (AAT) Deficiency and Associated Disease Risks.*

Inherited Genetic Variants†	Protein Phenotype‡	Serum Protein Level§	Molecular Genotype¶	Risk of COPD	Risk of Liver Disease
ZZ	Z	Very low	ZZ	Very high	High
ZNull	Z	Very low	Z/non-S, non-Z	Very high	Unknown
MZ	MZ	Intermediate	Z/non-S, non-Z	Possibly increased	Possibly increased
MNull	M	Intermediate	Non-S, non-Z/non-S, non-Z	Unknown	None
SZ	SZ	Low	SZ	Increased	Possibly increased
NullNull	None	None	Non-S, non-Z/non-S, non-Z	Very high	None

* COPD denotes chronic obstructive pulmonary disease.

† Conventions for the description of AAT genotypes, protein phenotypes, and alleles are inconsistent. In this article, we have elected to use the convention of describing the genotype with the notation PI XX, in which X designates one of the two inherited *SERPINA1* (also called *PI*) alleles. For protein phenotypes, we have used X or XX, depending on whether one or two types of AAT protein are detected with isoelectric focusing, and we have used *PI*X* to describe a single allele of the *SERPINA1* gene.

‡ Among patients who are receiving AAT augmentation therapy, those with the PI ZZ and PI ZNull genotypes appear to have the MZ protein phenotype, and those with the PI NullNull genotype appear to have the M protein phenotype, since augmentation-therapy products are made up primarily of the M AAT protein.

§ Most hospital and commercial laboratories express their results in milligrams per deciliter in the United States and in grams per liter in Europe. The lower limit of the normal range for patients with the PI MM genotype is dependent on the laboratory but is generally 70 to 104 mg per deciliter (0.7 to 1.04 g per liter). Patients with the Z protein phenotype typically have AAT levels of 10 to 50 mg per deciliter (0.10 to 0.50 g per liter). A growing number of reference laboratories express AAT levels in micromoles per liter, with the lower limit of the normal range defined as 20 μmol per liter. Patients with the Z protein phenotype typically have levels of 2 to 10 μmol per liter. There is overlap between the levels seen in patients with a variety of heterozygous genotypes and in those with PI SS and PI MM genotypes. To convert the values for AAT from milligrams per deciliter to micromoles per liter, divide by 5.2 (based on the molecular weight of AAT of 52 kD).

¶ Molecular genotyping is typically performed with the use of allele-specific probes that detect *PI*S* and *PI*Z* alleles.

The NEW ENGLAND JOURNAL of MEDICINE

It’s a fact

Studies have shown that, once a patient with Alpha-1 develops symptoms, it takes an average of seven years and visits to five different doctors before the diagnosis of Alpha-1 is made.

LUNG SYMPTOMS OF AAT DEFICIENCY

If you have respiratory symptoms, you and your physician may observe:

- Shortness of breath while at rest or with exercise
- Wheezing, persistent cough
- Recurrent lung infections
- Persistent sputum (or phlegm) production
- History of suspected allergies and/or asthma
- Sinus infections

Who Should be Screened ?

- Family history of Alpha-1
- Family history of emphysema, bronchiectasis, liver disease, or panniculitis
- Early onset emphysema (age < 45 years)
- Emphysema in the absence of, or out of proportion to a recognized risk factor, such as smoking, occupational exposure, etc.
- Emphysema with a prominent basilar hyperlucency (worse disease at the bases of the lungs)
- All individuals with a diagnosis of chronic obstructive pulmonary disease (COPD)
- Bronchiectasis
- Chronic asthma in adolescents and adults
- Recurrent pneumonia or bronchitis
- Unexplained liver disease
- Wegener's granulomatosis (C-ANCA positive

Diagnosis

Alpha 1 is a laboratory diagnosis, not a clinical diagnosis.

Can't definitively make the diagnosis based on the patient's medical history or physical examination.

Diagnosis is made by a simple blood test

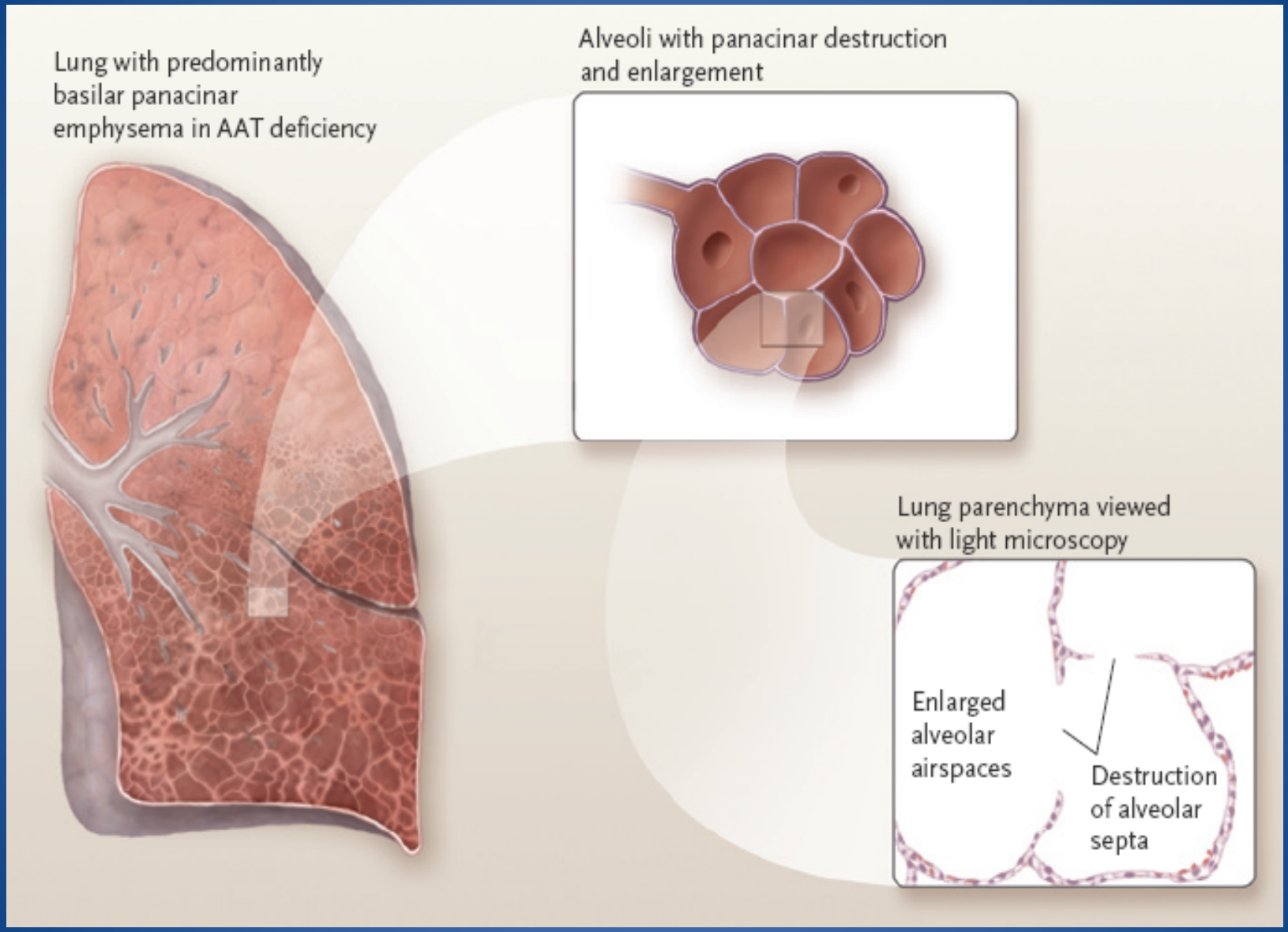
Diagnosis

The most widely available and least expensive specific test for Alpha-1 is the AAT serum level.

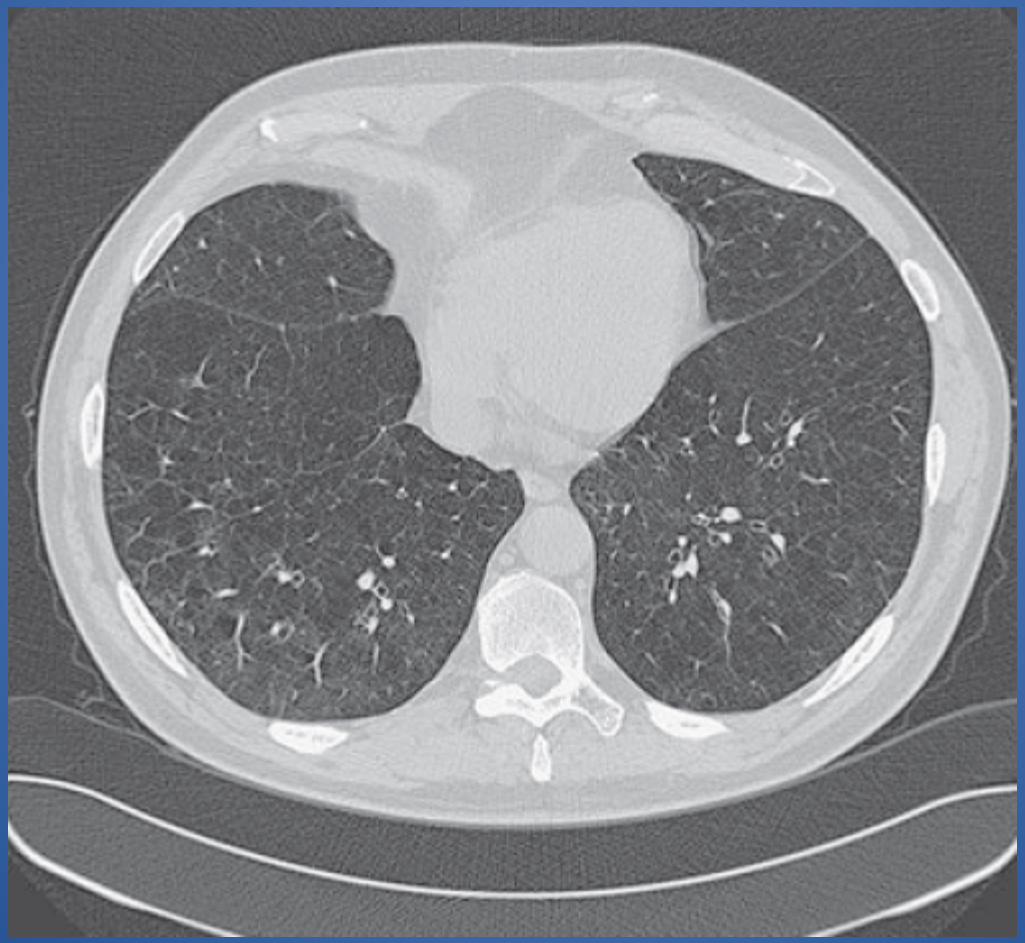
This test, when performed correctly, can easily detect the most common forms of severe deficiency of AAT.

CLASSIC PRESENTATION

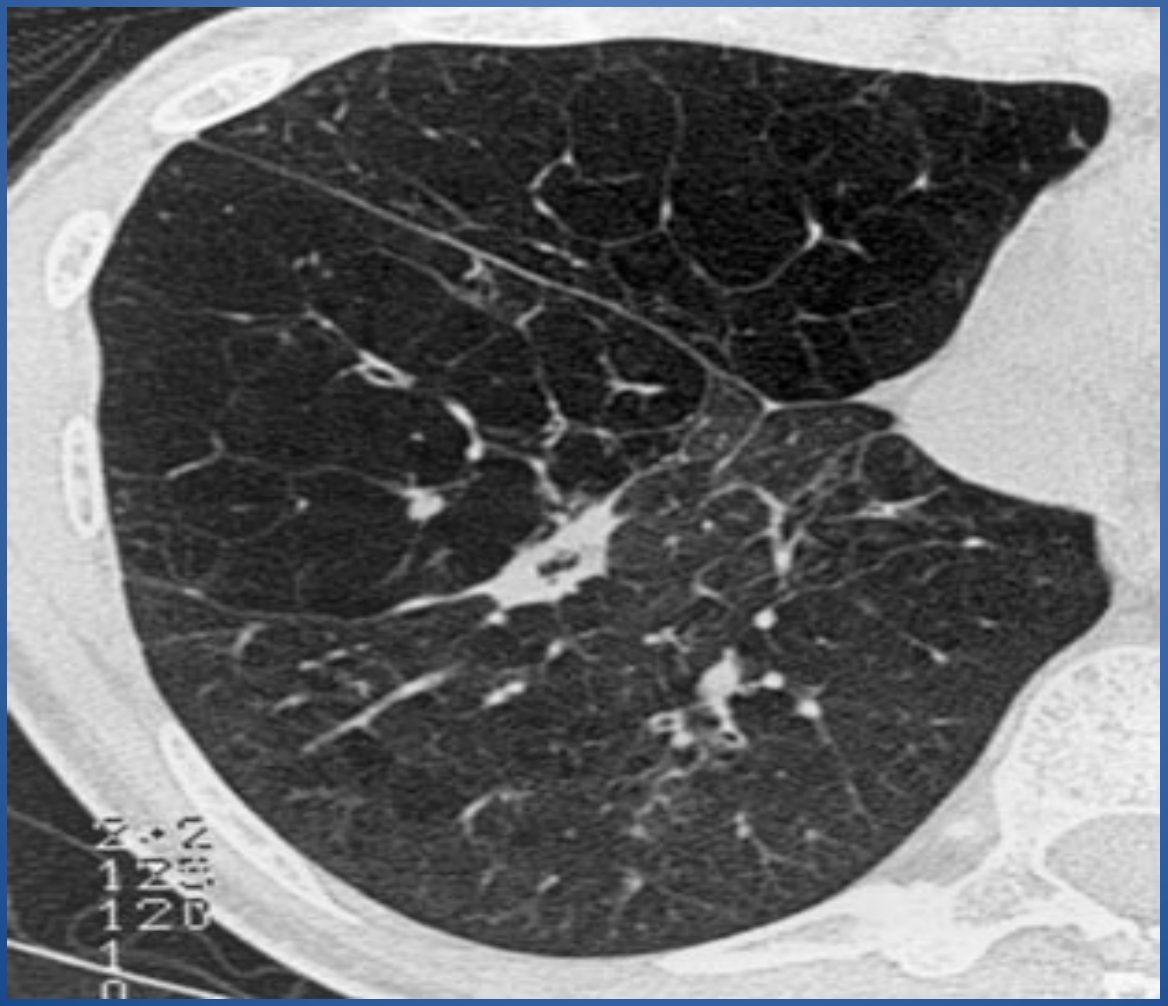
- The classic pulmonary presentation of AAT deficiency is severe, early-onset panacinar emphysema with a basilar predominance in adults


Lung with predominantly basilar panacinar emphysema in AAT deficiency
Alveoli with panacinar destruction and enlargement
Lung parenchyma viewed with light microscopy
Enlarged alveolar airspaces
Destruction of alveolar septa

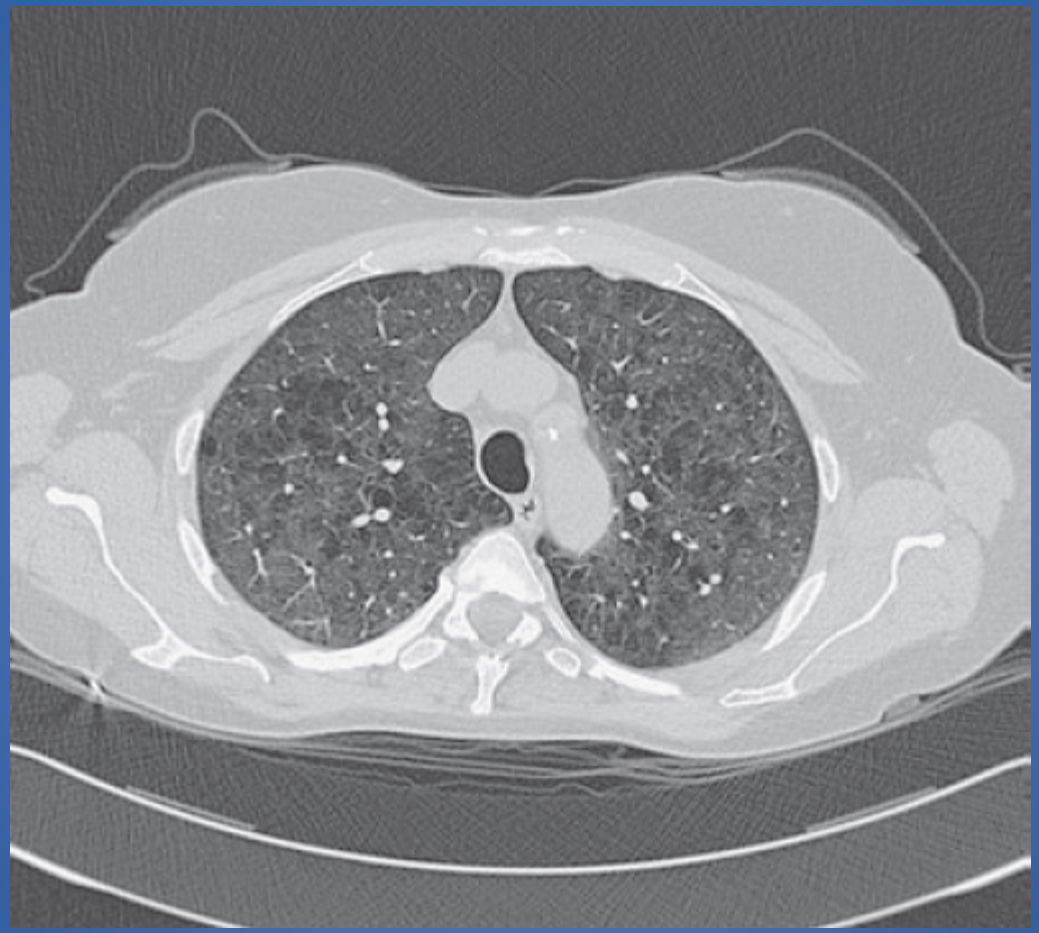
Radiographic Finding in AATD



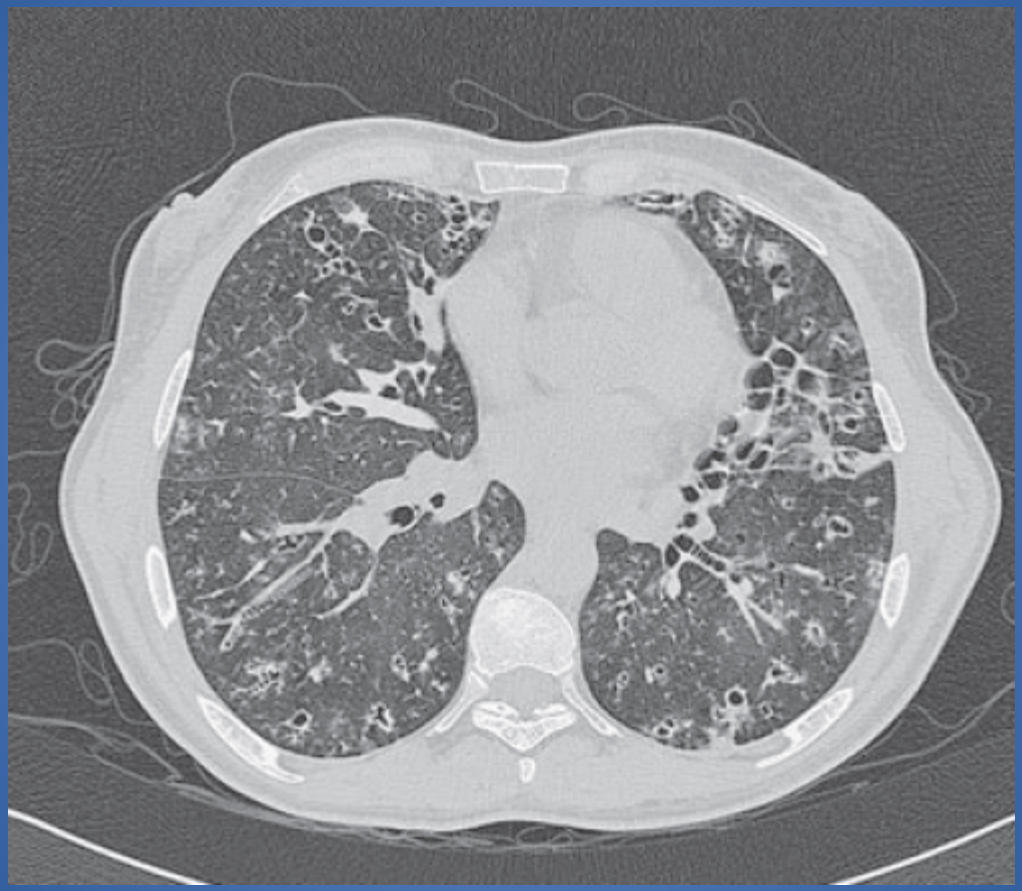
Radiological features in AATD



Upper Lobe Emphysema



Bronchiectasis



Normal Lungs

Missed Clinical Recognition

- Average alpha-1 patient has symptoms for 7.2 years before diagnosis is made
- 44% of alpha-1 patients see at least 3 doctors before a diagnosis is made

Lung Disease

- Alpha-1–related lung disease presents with common respiratory symptoms:
  - Dyspnea (84%)
  - Decreased exercise tolerance
  - Wheezing (76%)
  - Cough (42%)
  - Excess sputum production (46%)
  - Frequent lower respiratory tract infections
  - History of suspected allergies and/or asthma

Cause of Death in Alpha-1 Antitrypsin Deficiency

- Respiratory failure (50%-72%)
- Liver cirrhosis (10%-13%)

Yearly mortality rate:
1.7% to 3.5%

Quitting smoking

No treatment for emphysema has a greater effect on survival than quitting smoking.

Make a concerted effort to inform patients about the serious consequences of smoking on AAT deficiency and provide them with one of the many aids to help them quit.

Normal nonsmoking adults lose approximately 20 to 30 ml of pulmonary function from their FEV-1 each year.

A smoker who is not alpha-1 antitrypsin deficient will lose 45 to 90 ml.

Alpha-1 antitrypsin deficient patients who do not smoke will lose 80 to 100 ml of lung function from their FEV-1 each year and those who smoke lose more than 300 ml.

Preventing respiratory infections

Pneumonia and annual influenza vaccines will help prevent respiratory infections.

The ATS/ERS AAT Deficiency Task Force recommends early antibiotic therapy for all exacerbations with purulent sputum. Aggressively treatment of infections may help decrease the potential for additional lung injury from an influx of neutrophils into the alveolus.

Providing pulmonary rehabilitation

Reducing hypoxemia

Oxygen also increases exercise capacity, improves mental performance, decreases dyspnea with exercise, and improves sleep quality.

AUGMENTATION THERAPY

AREAS OF UNCERTAINTY

- The effectiveness of AAT augmentation therapy in slowing the progression of COPD related to AAT deficiency has not been conclusively shown

- A Registry of Patients With Severe Deficiency of Alpha1 -Antitrypsin

- From the Alpha1-Antitrypsin Deficiency Registry Study Group*
- Survival was enhanced in recipients of augmentation therapy compared with non-recipients . In the subset of patients with FEV1 35 to 49 percent predicted, the rate of FEV1 decline was also slowed in recipients of augmentation therapy.

Longitudinal follow-up of patients with alpha(1)-protease inhibitor deficiency before and during

therapy with IV alpha(1)-protease inhibitor.

- A longitudinal study following 96 patients with severe alpha-1 antitrypsin deficiency analyzed the rate of decline in FEV1 before and after weekly augmentation therapy .
- This study showed that the rate of decline in FEV1 during augmentation therapy was slowest in those patients with mild airflow obstruction.

Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency?

- study compared the rate of FEV1 decline among 97 Danish former smokers with severe alpha-1 antitrypsin deficiency who did not receive augmentation therapy with the rate of decline in 198 severely deficient German former smokers who received weekly infusions (60 mg/kg) over a mean of 3.2 years
- Overall, the rate of decline of FEV1 was lower among the treated patients than among the untreated (-53 mL per year versus -75 mL per year, p=0.02).

Criteria for Augmentation therapy.

- When intravenous augmentation therapy is entertained, proper patient selection is essential. The selection criteria include:
- High-risk phenotype
- Plasma AAT level below 11 µmol/L
- Airflow obstruction by spirometry
- Likely compliance with the protocol
- Age equal to or greater than 18 years
- Nonsmoker or ex-smoke

Efficacy of Augmentation Therapy

- Intravenous augmentation therapy is recommended for individuals with established airflow obstruction with AATD.

  Evidence that such therapy is beneficial is stronger for patients with moderate airflow obstruction (i.e. FEV1 35-60% predicted)

- The task force recommended such therapy in patients who have undergone lung transplants and then have acute rejection episode or during an episodes of respiratory infection

- Not recommended for patients without emphysema

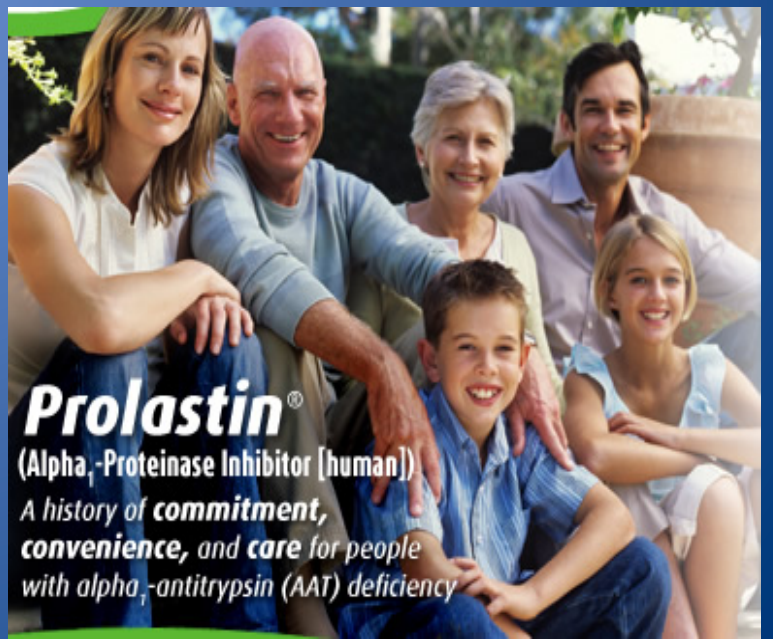
Zemaira®

alpha$_1$-proteinase inhibitor (Human)

Unmatched purity. Uncompromised care.

Aralast

[alpha$_1$-proteinase inhibitor (human)]



Lung transplantation

- COPD often develops at an early age in AAT-deficient patients, they tend to be good candidates for lung transplantation.
- Case series suggest that AAT-deficient patients who have undergone bilateral lung transplantation have improved rates of survival, as compared with those receiving single lung transplants.

American Thoracic Society Documents

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

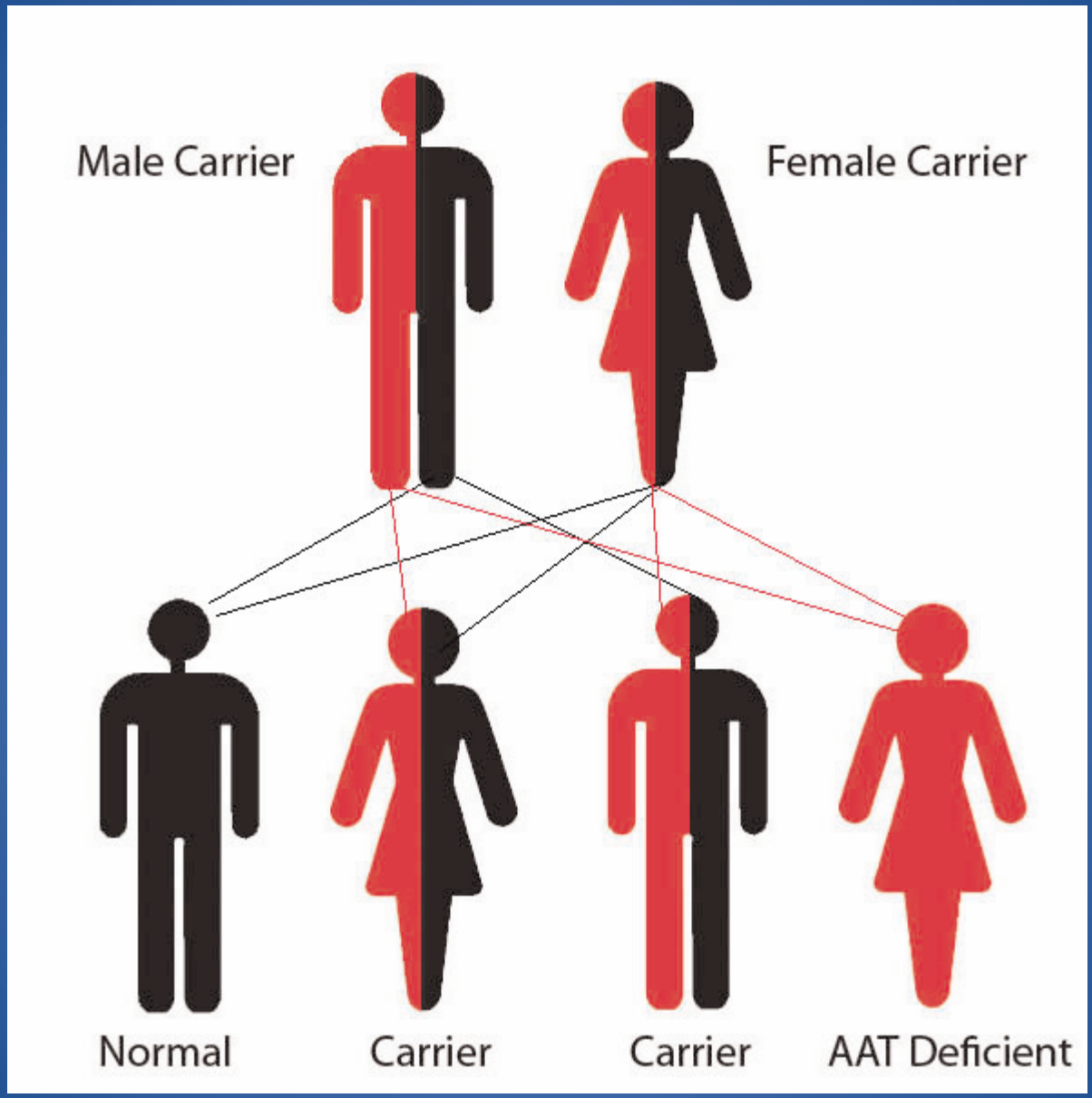
This Joint Statement of the American Thoracic Society and the European Respiratory Society was approved by the ATS Board of Directors, December 2002, and by the ERS Executive Committee, February 2003

Liver Disease

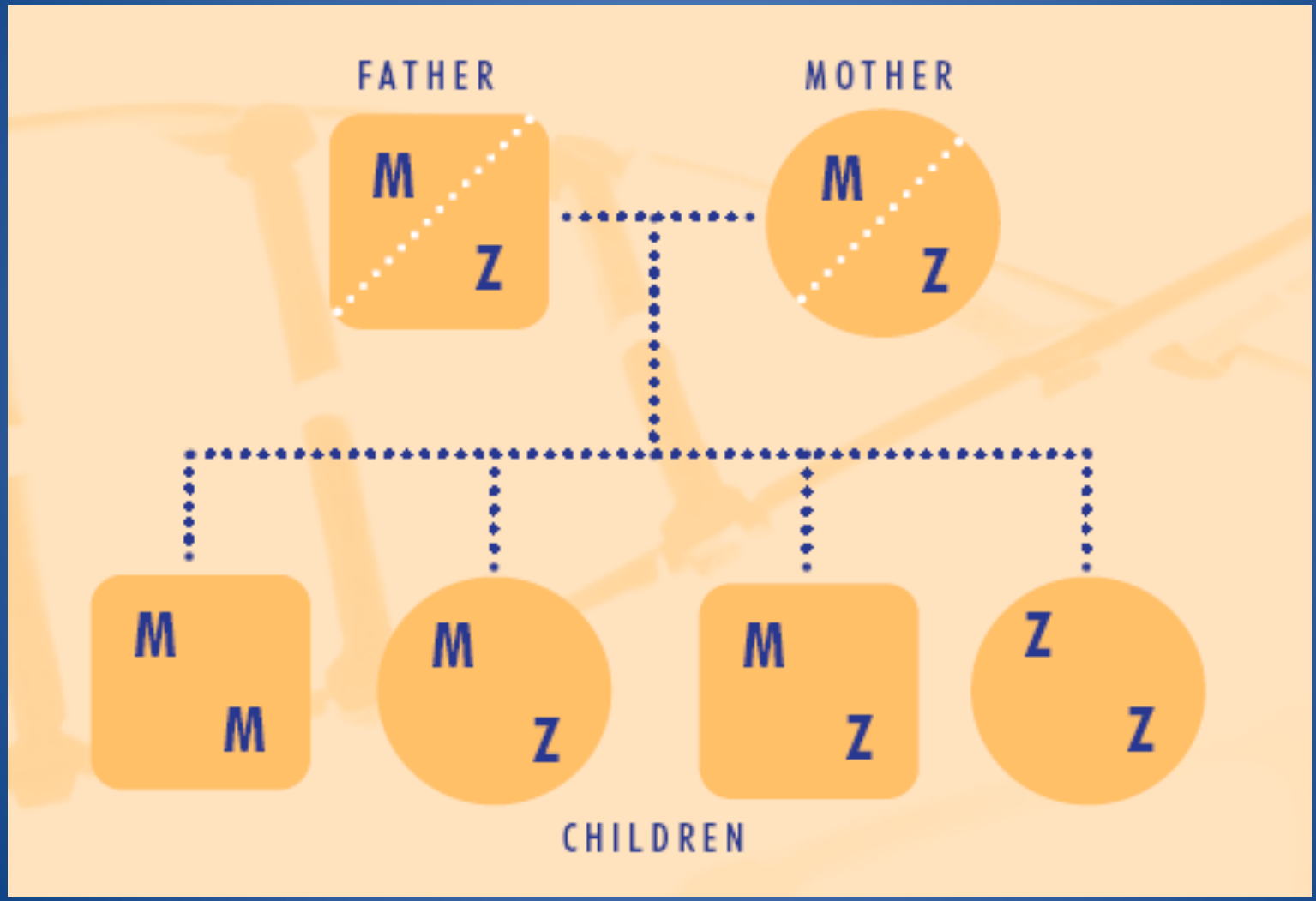
Only 2.5% of newborns diagnosed with PI*ZZ die because of acute liver failure.

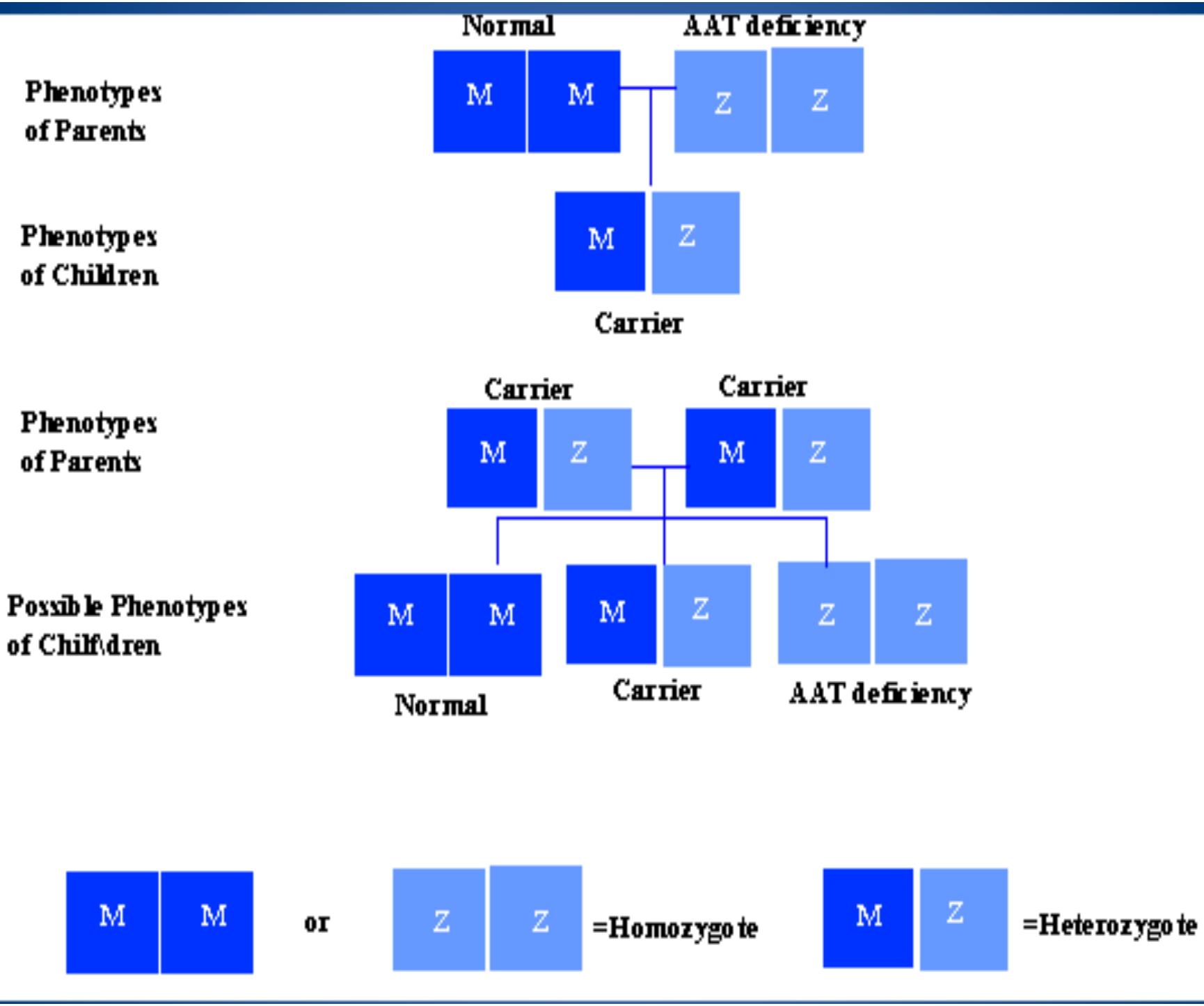
Patients over 50 years of age can also develop hepatocellular carcinoma and liver cirrhosis

Genetic Counseling


Male Carrier
Female Carrier
Normal
Carrier
Carrier
AAT Deficient

GENETICS OF ALPHA-1




Normal
AAT deficiency
Phenotypes of Parents
M
M
Z
Z
Phenotypes of Children
M
Z
Carrier
Carrier
Carrier
Phenotypes of Parents
M
Z
M
Z
Possible Phenotypes of Chilf\dren
M
M
M
Z
Z
Z
Normal
Carrier
AAT deficiency
M
M
or
Z
Z
=Homozygote
M
Z
=Heterozygote

Conclusions and Recommendations

- AAT deficiency is often unrecognized and may lead to COPD and severe liver disease.
- AAT deficiency can be readily diagnosed by measurement of the serum or plasma protein level, which should be confirmed by assessing the genotype or protein phenotype when AAT levels are below the normal range.
- According to professional guidelines, AAT testing is warranted in the patient in the vignette, given his diagnosis of COPD.
- In patients with AAT deficiency, close monitoring for the development or progression of lung disease or liver disease (among those with at-risk genotypes) is required.

Conclusions and Recommendations

- In addition to usual therapies for COPD in patients with AAT deficiency, AAT augmentation therapy should be considered (if available), although compelling evidence of benefit is lacking from randomized trials.

- Additional information about AAT deficiency is available from the Alpha-1 Foundation (www.alphaone.org).

Questions