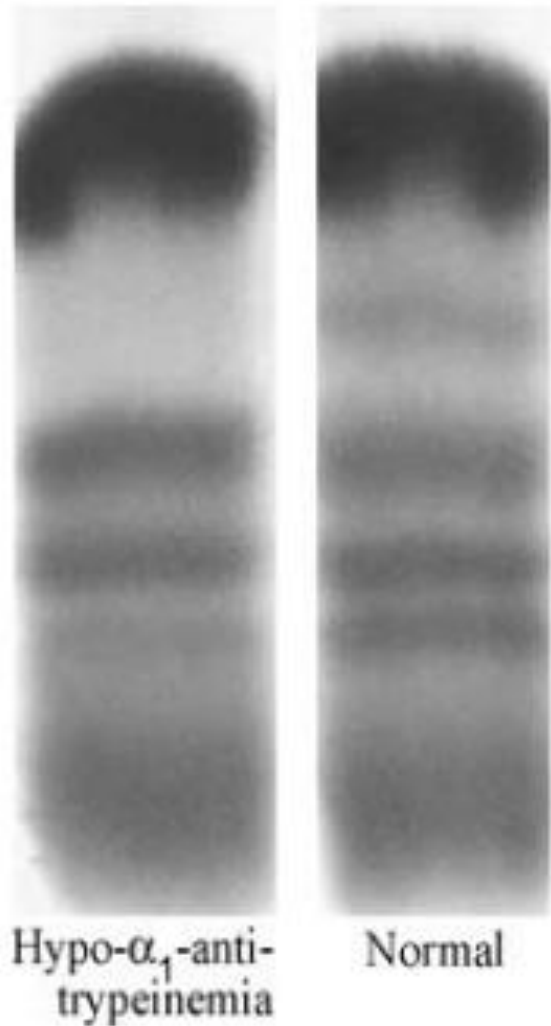


Basics of Alpha-1

Christian Clarenbach, Pulmonologist, University Hospital Zurich, Switzerland



1963 in Malmö
C-B Laurell and Sten Eriksson,
established that AATD is linked to
emphysema

Figure 1. C-B Laurell (1919–2001). Photographed in Malmö in 1972. Left, the original paper electrophoretic strips from 1962 showing the almost complete absence of the alpha-1 band from the plasma of a respiratory disease patient.

Historic milestones of alpha-1 antitrypsin deficiency (AATD)

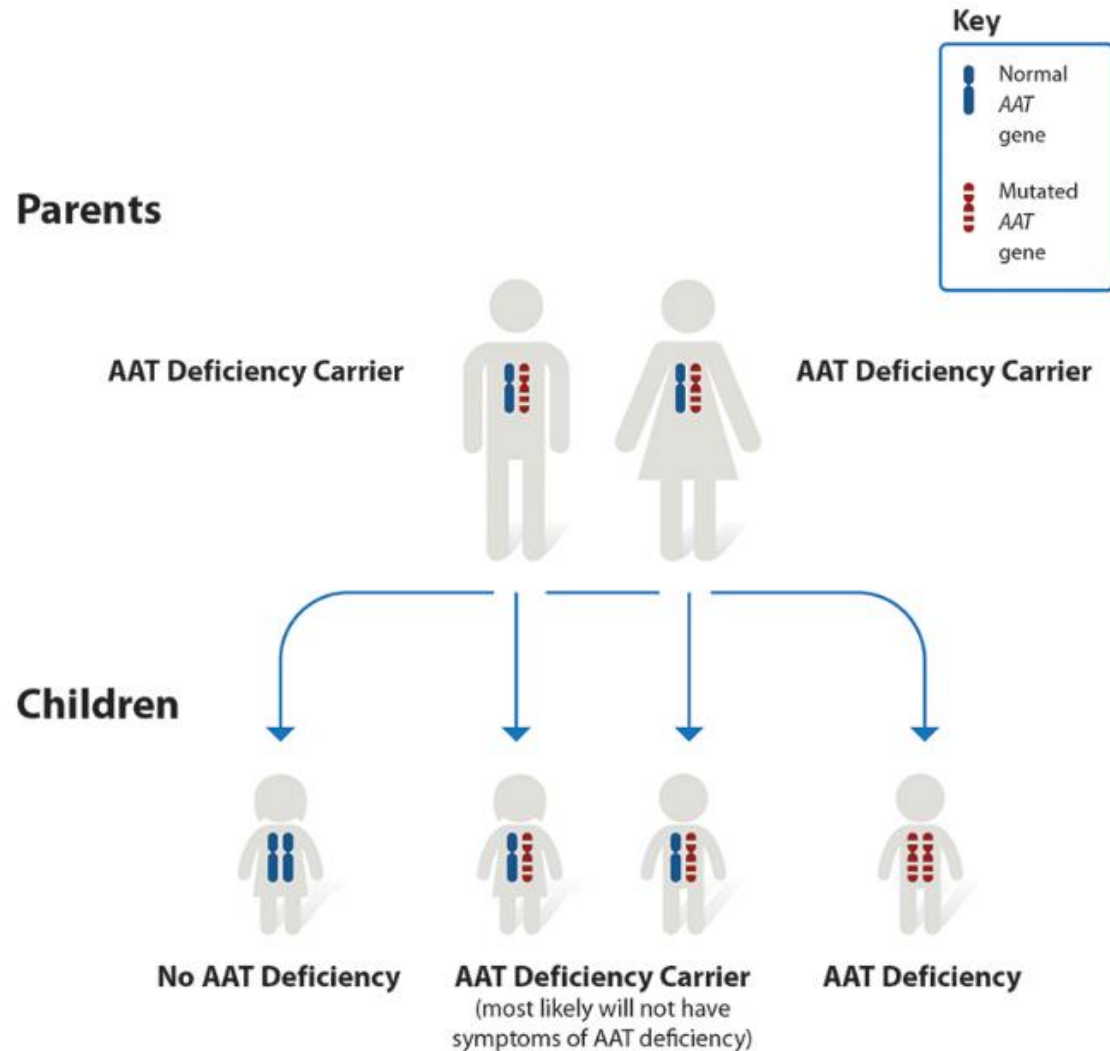
- **1963:** First description by Laurell and Eriksson
- **1969:** The association between liver disease and AATD was described in the USA
- **1978:** Emphysema starts early in AATD smokers
- **1990:** AAT in deficient patients forms polymers in the liver
- **1999:** Initiation of AIR registry
- **2020:** Initiation of EARCO registry

How is AATD diagnosed?

- **Blood level test:** The level of AATD can be checked in a blood test. If the level is lower than normal, it is likely that you have AAT deficiency.
- **Phenotype test:** This test checks for the presence of abnormal forms of the AAT protein in the blood
- **Genetic test:** This test looks for specific genetic changes in your DNA that are linked to an AAT deficiency (blood or buccal swab).



AATD is inherited and caused by mutations in SERPINA1 gene



The alpha-1 gene has over 100 variants

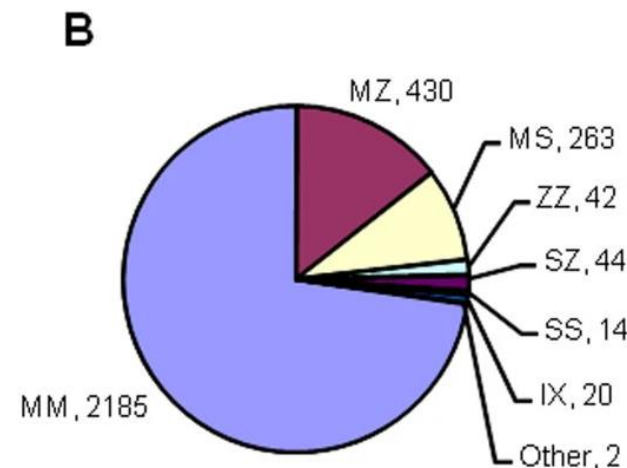
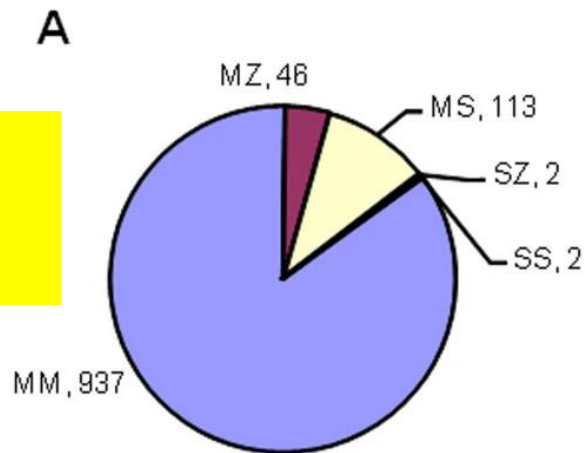
Each child has a

- 25% chance of inheriting two normal genes
- 50% chance of being a carrier,
- 25% chance of inheriting two mutated AAT genes

Prevalence: What is the rate of people being affected?

- Z mutation carried by 4 % (1 out of 25) Northern Europeans
- Prevalence of AATD is estimated to be about 1 in 2500 to 1 in 5000 individuals
- It is not so rare! but frequently AATD is undiagnosed or misdiagnosed as asthma, COPD or liver disease of unknown origin (or caused by alcohol)

1100 individuals at random from the general population



3000 individuals from a target population with an increased likelihood of having AATD

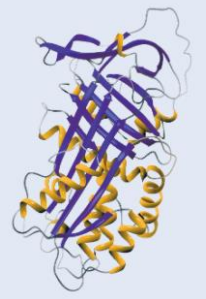
Analysis of AAT mutations in Ireland. (A) 1,100 DNA samples in the Biobank collection were genotyped for the S and Z mutations. (B) 3,000 Irish individuals were screened as part of the national targeted detection programme following ATS/ERS guidelines.

Prevalence

Table 1. Estimated percentages of individuals with α -1 Antitrypsin genotypes SZ, ZZ, and SS among the total population of selected countries.

Country	α 1-Antitrypsin genotype		
	SZ	ZZ	SS
Austria	0.053	0.018	0.041
Belgium	0.181	0.028	0.295
Denmark	0.151	0.073	0.078
Estonia	0.061	0.061	0.016
Finland	0.010	0.004	0.005
France	0.195	0.017	0.578
Germany	0.041	0.010	0.044
Hungary	0.034	0.005	4.762
Italy	0.075	0.027	0.052

What is alpha-1 antitrypsin?

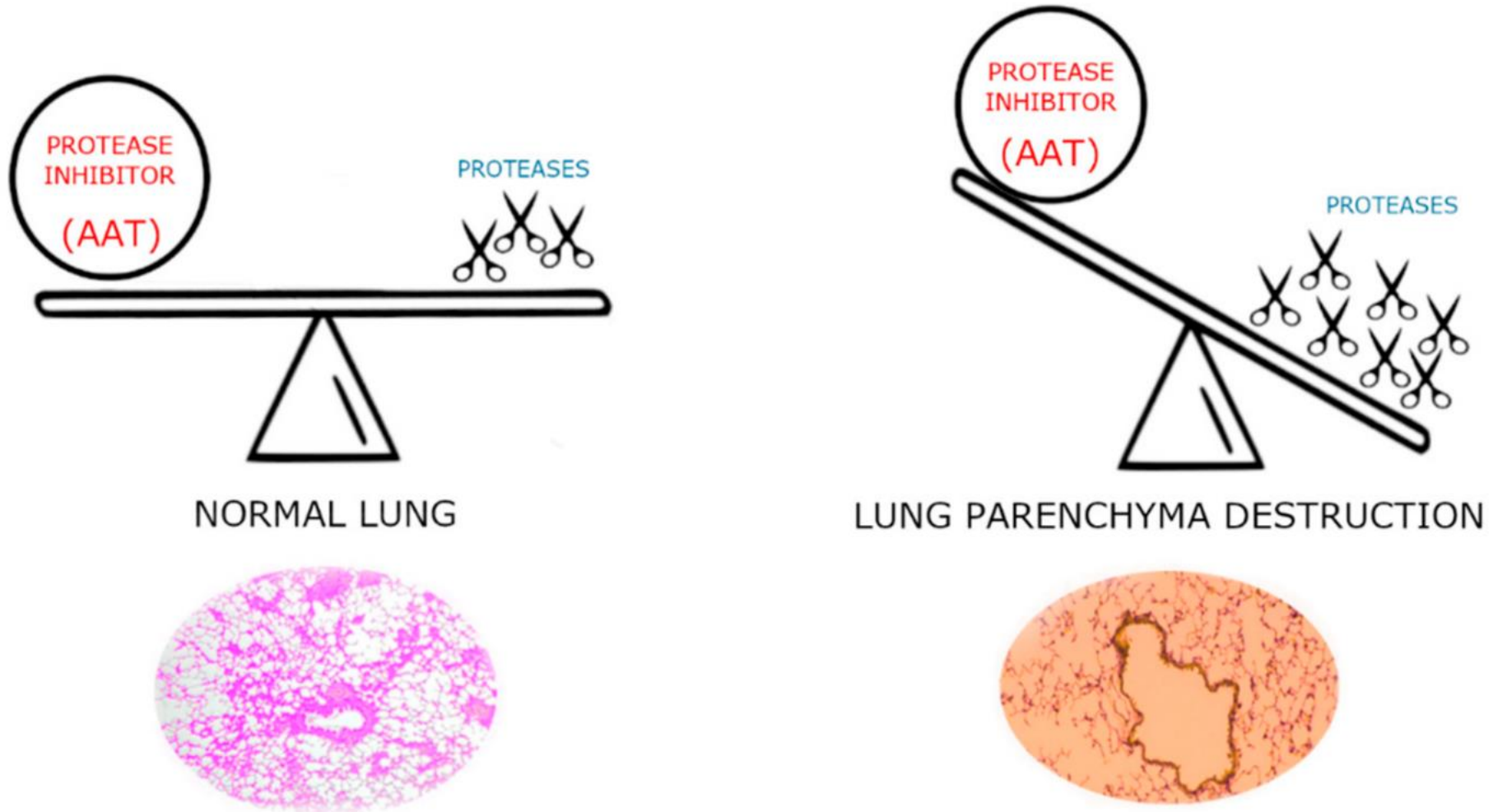


<https://www.alphanet.org>

- Alpha-1 antitrypsin is a protein primarily produced in the liver that protects the lungs and other tissues from damage caused by inflammation.
- M protein = normal
 - MM genotypes do not have Alpha-1 deficiency
- Z protein = most important mutation → mutations lead to a change in the protein structure
 - MZ genotype means you have one copy of the “Z” deficiency variant
 - ZZ genotypes are affected by Alpha-1. ZZ means you have two deficiency variants (alleles). This means you are at risk for lung and liver disease.

!Without enough AAT in blood, you are at risk for disease!

Imbalance between proteases and antiproteases





Avoidable risk factors



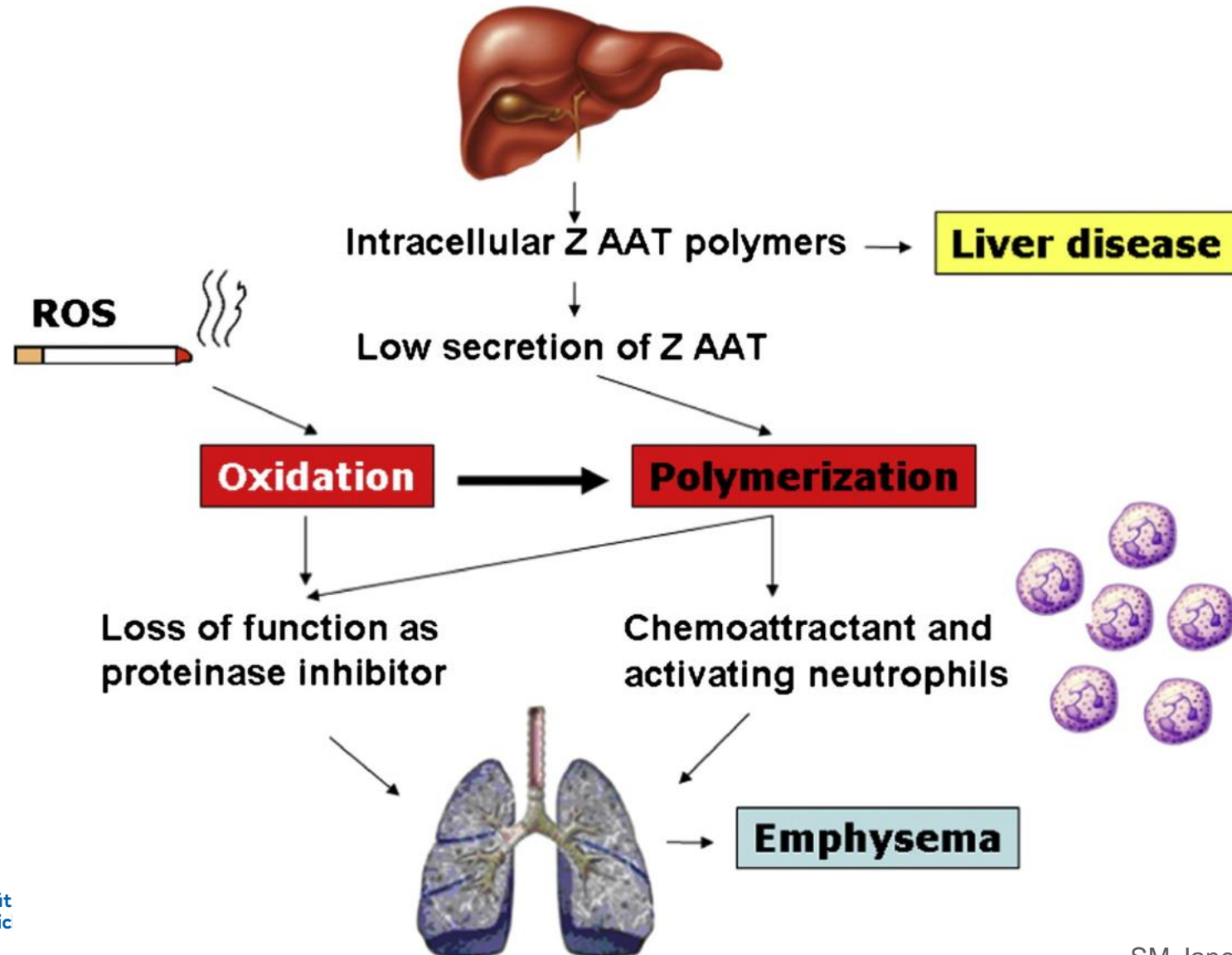
- Z genotype AAT aggregates may get stuck in liver!

Drinking alcoholic beverages and your diet can increase the chances of liver disease

- Smoking causes lung inflammation, white blood cells are attracted to your lungs.
- Neutrophils release a substance “neutrophil elastase” that may damage lung tissue.
- In AATD, you cannot produce enough functional AAT to counteract neutrophil elastase.

If you are smoking and AAT deficient, your lungs are at high risk for disease

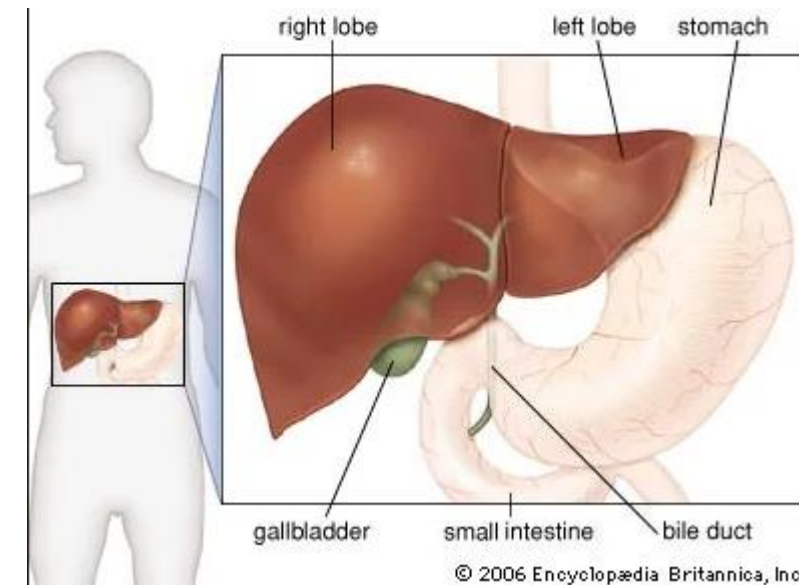
AATD basic principles that lead to disease manifestations



Clinical presentation – liver disease from AATD

What does the liver in healthy state?

- Takes up proteins, carbohydrates and fats, stores them for your body to be used.
- Produces a fluid «bile» that is important to digest.
- Cleans blood of toxins, processes medication.
- **Alpha-1 antitrypsine is primarily produced by liver!**

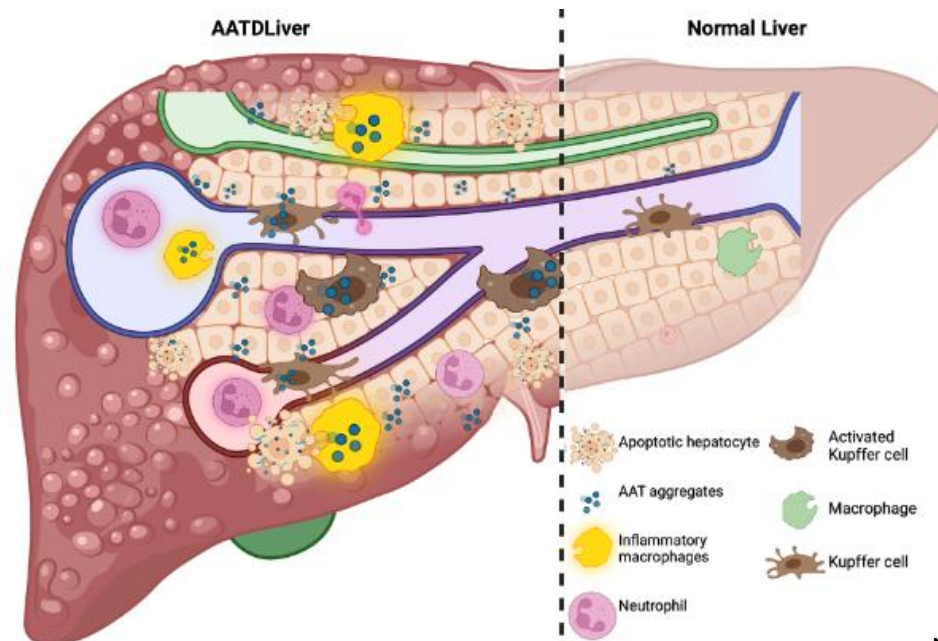


Clinical presentation – liver disease from AATD

What does disturb the liver in AATD?

- Genetic mutation leads to a structurally abnormal «misfolded» Z-AAT.
- Abnormal protein forms aggregates «polymeres» that may get stuck in the liver.
- This may cause liver disease such as fibrosis and cirrhosis (at later stage).

Important risk of being misdiagnosed with alcoholic liver disease



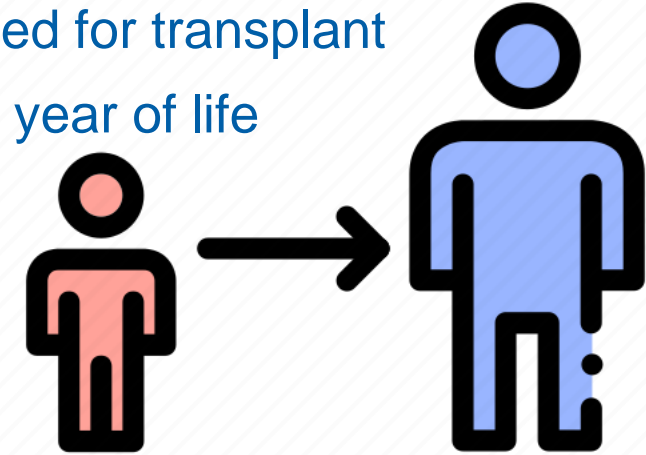
Clinical presentation – liver disease children vs adults

In children

- Highly variable symptoms: asymptomatic vs severe liver failure with need for transplant
- Yellow skin «jaundice» 10 % of infants with ZZ, usually resolves to 2nd year of life
- ~15% of kids with jaundice with progression to fibrosis

In adults

- Typical cirrhosis symptoms: Edema legs and abdomen (ascites), yellow skin
- Cirrhosis may be cause of death in never smokers
- Increased risk for liver carcinoma



Clinical presentation – lung disease COPD

AATD is the major genetic risk factor for:

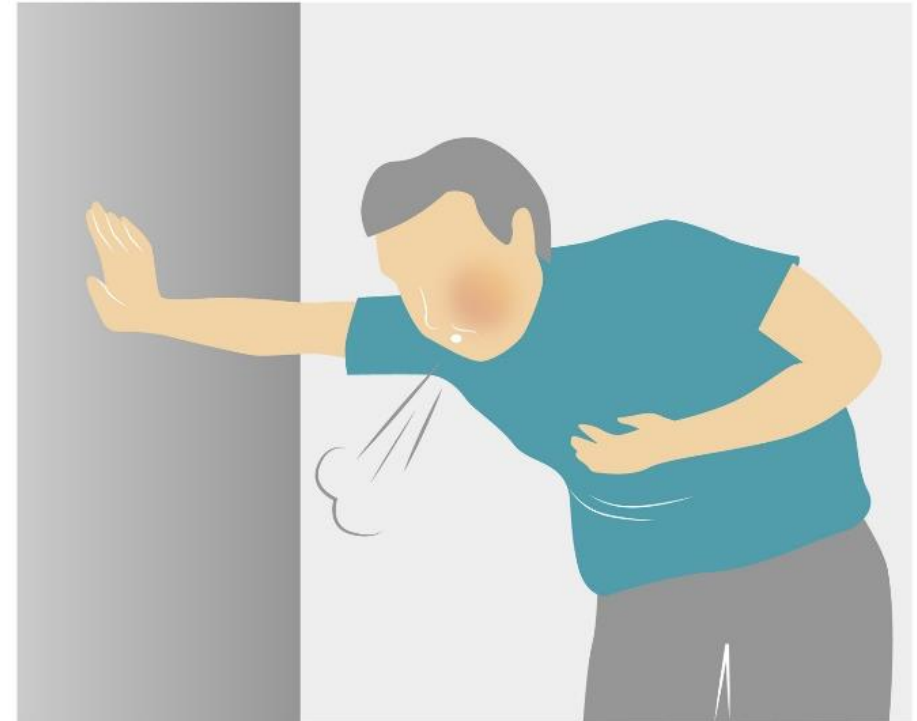
- **C** hronic
- **O** bstructive (hard to exhale)
- **P** ulmonary (lung)
- **D** isease

COPD may include:

- **Emphysema** – damage to the air sacs in the lungs
- **Chronic bronchitis** – long-term inflammation of the airways

Clinical presentation – lung disease COPD - symptoms

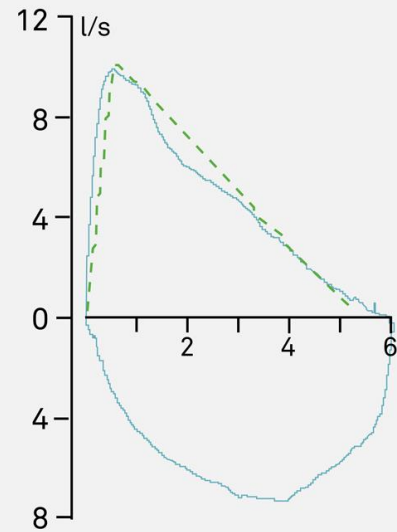
- Shortness of breath, particularly when you're active
- Cough +/- phlegm – some people may dismiss this as just a "smoker's cough"
- Lung attacks – chest infections or “exacerbations”



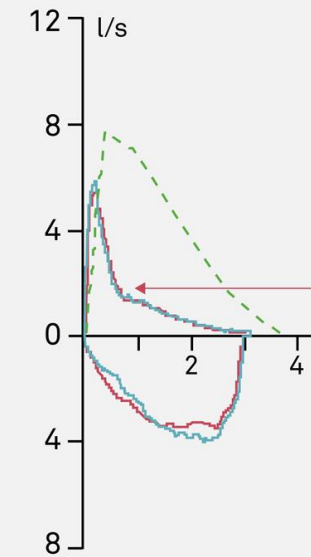
Lung function test



Normale Spirometrie

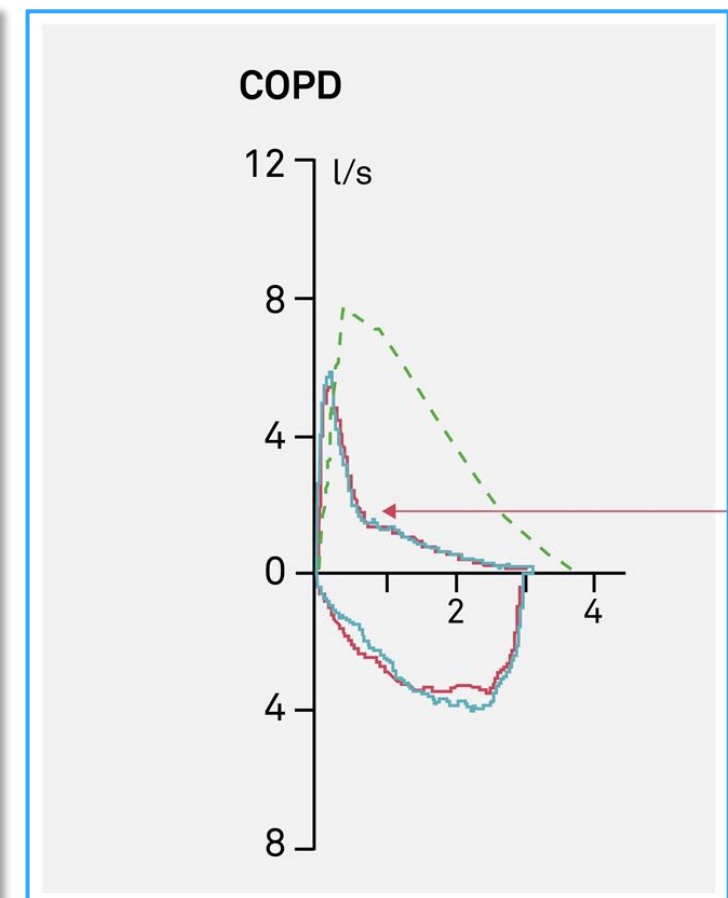
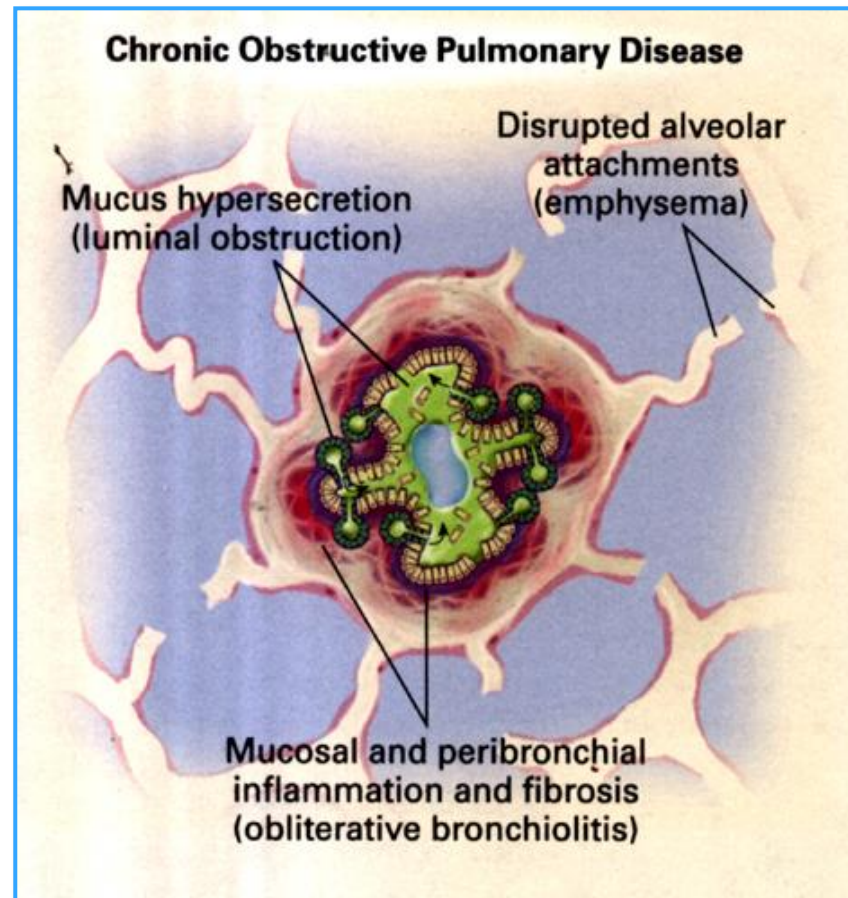
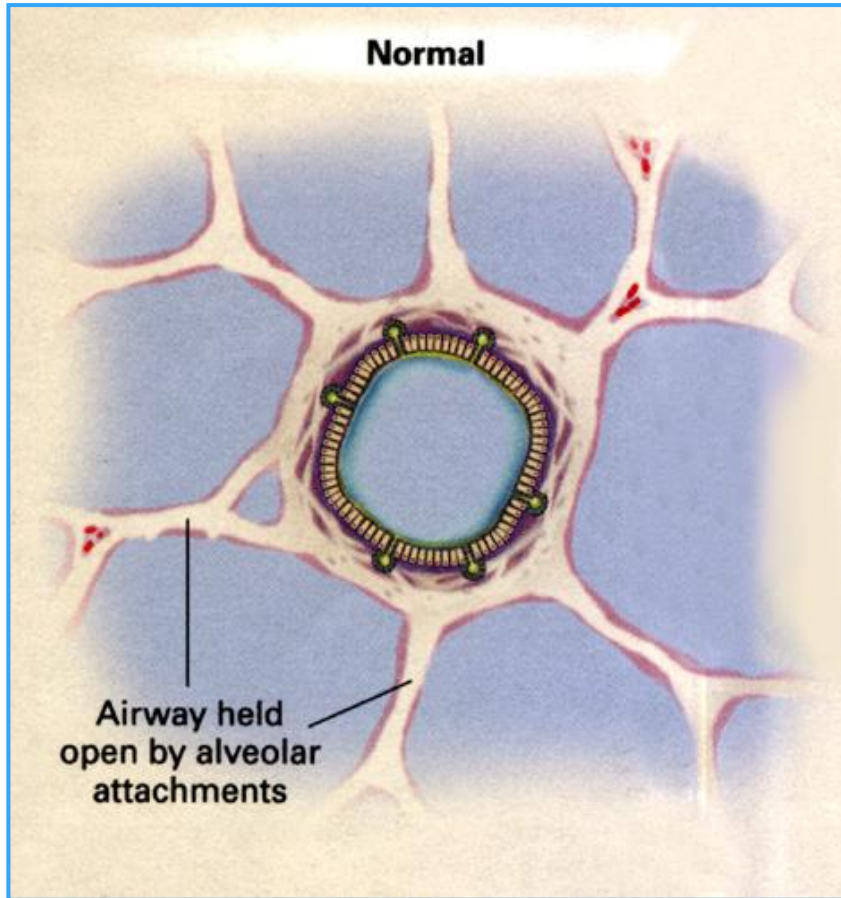


COPD



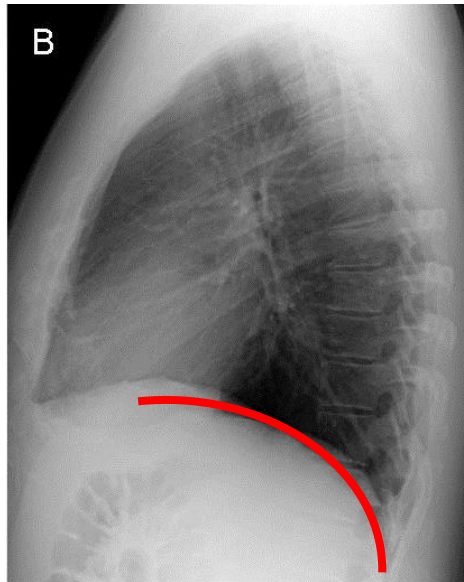
No change of curve after inhalation of bronchodilator

Clinical presentation – COPD – What happens in the airways?

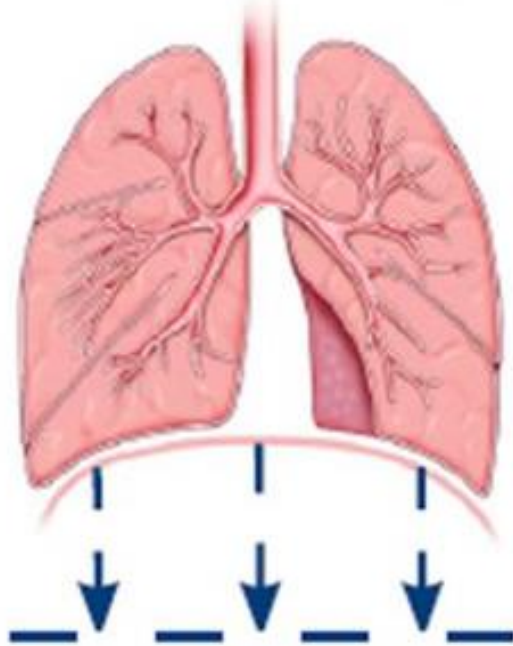


What happens to your lungs?

Normal Xray

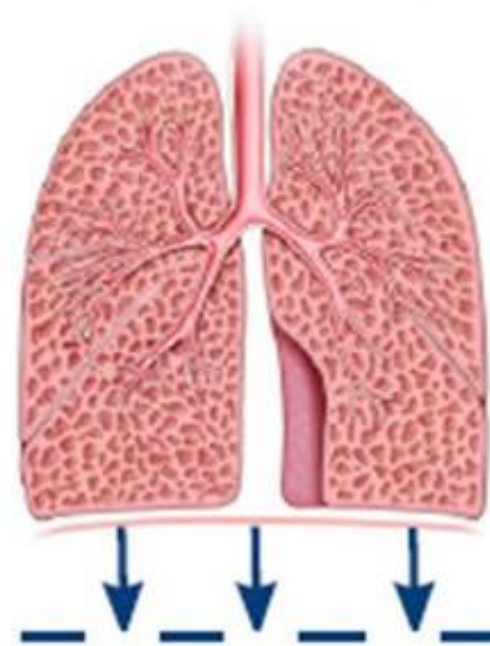


Healthy lung



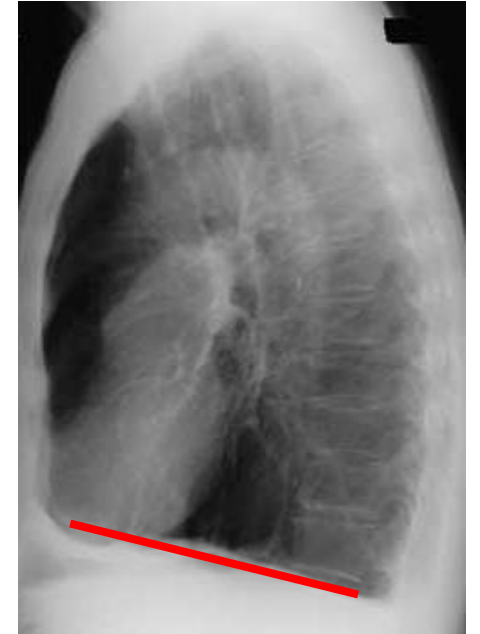
Dynamic movement of your diaphragm

COPD with Emphysema

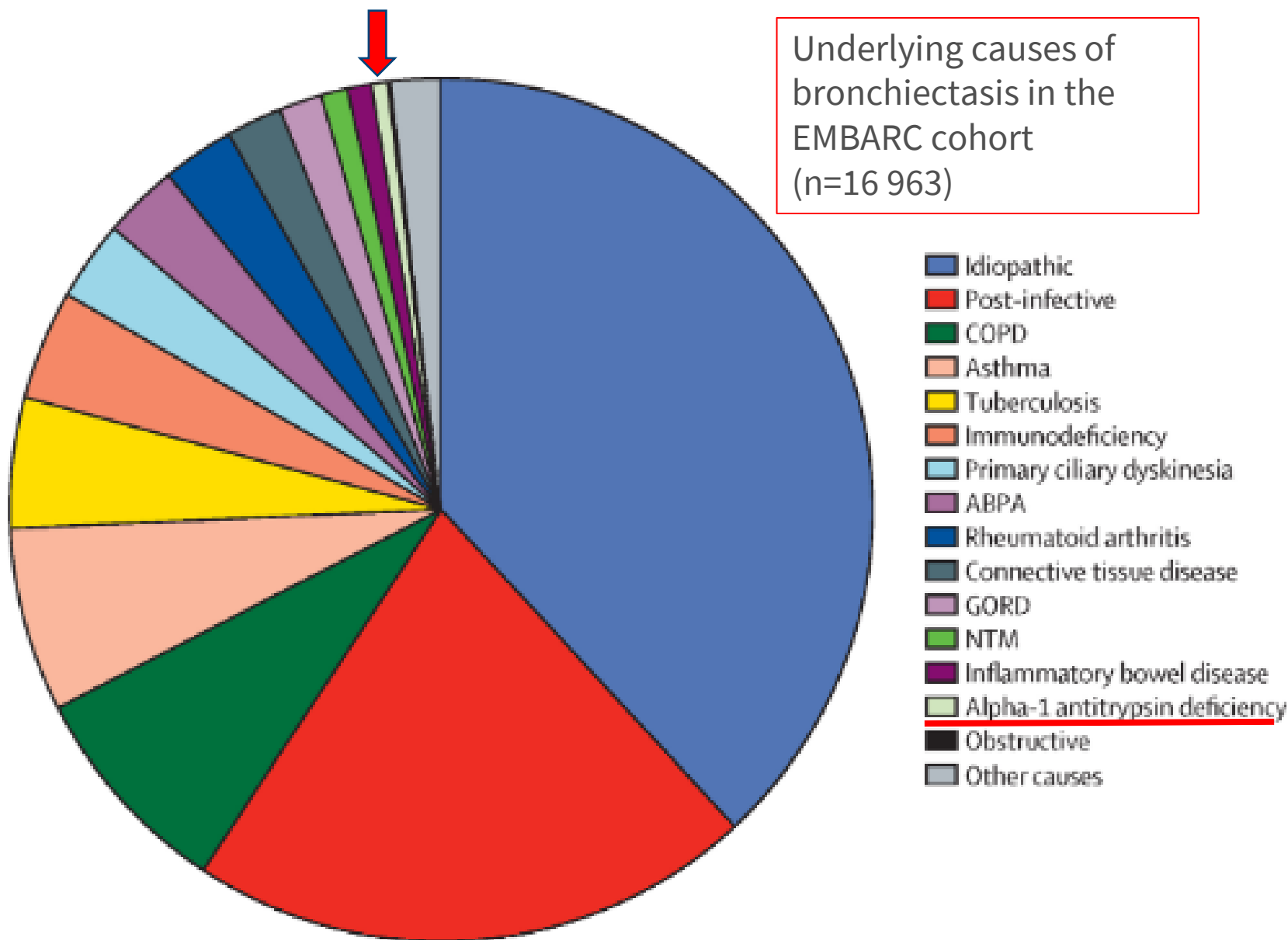


Limited movement of your diaphragm

Xray of emphysema



Clinical presentation – Bronchiectasis



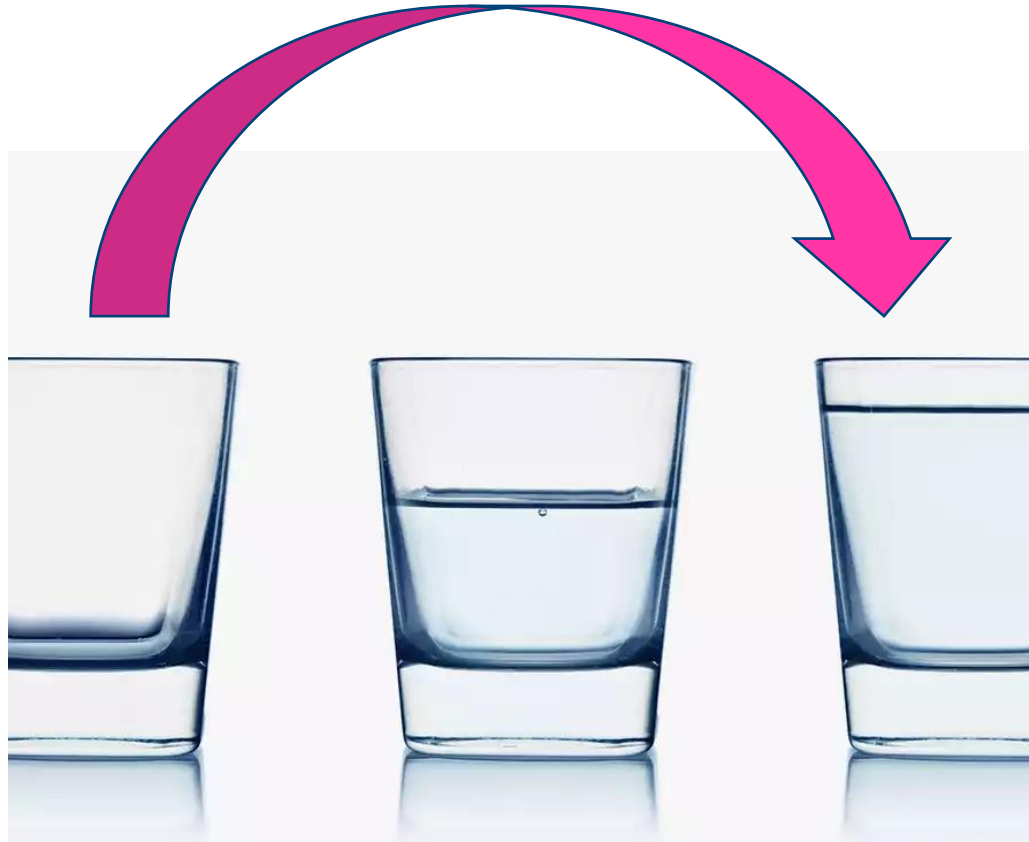
Clinical picture – Panniculitis - An inflammation in the bottom layers of the skin

- Very rare! Approx. 1 out of 1000 AATD patients
- Often young <40Years
- Inflammation of the subcutaneous fat
- AATD-panniculitis frequently improves with intravenous AAT augmentation therapy



- Woman, 33y from Zurich
- Referred for «skin lymphoma»
- **Diagnosis: ZZ AATD Panniculitis**
- **Therapy: Alpha-1 Substitution**

Therapy



**Substitution therapy
by human plasma
derived Alpha-1
Antitrypsine**

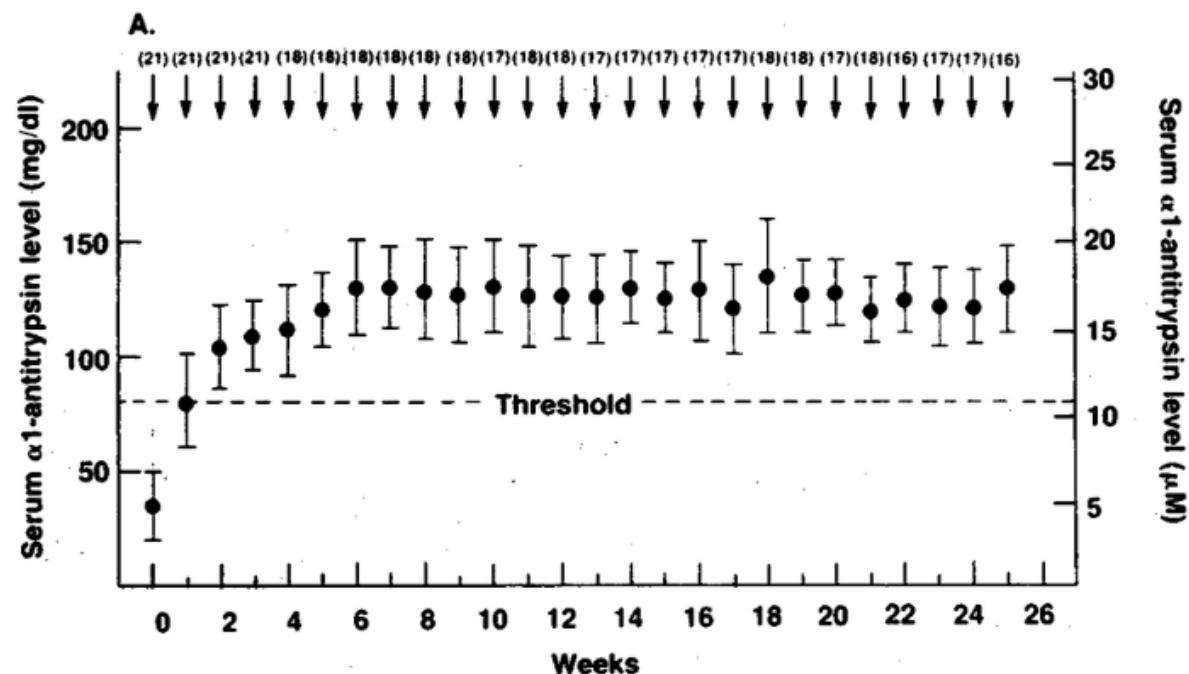
Disadvantages:

- Weekly infusions
- No treatment of the genetic mutation

Replacement Therapy for Alpha₁-Antitrypsin Deficiency Associated with Emphysema

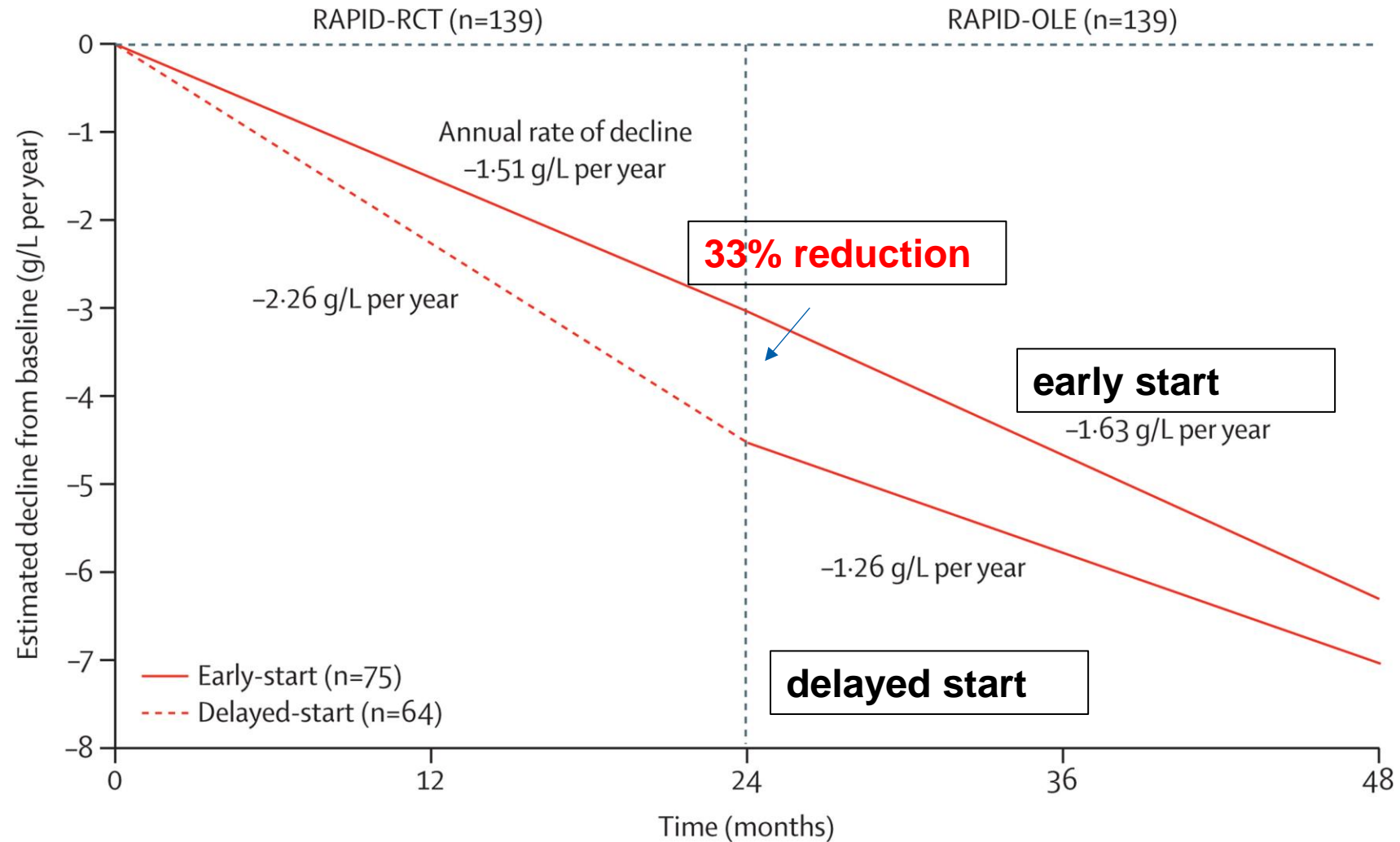
Mark D. Wewers, M. Anthony Casolaro, Stephanie E. Sellers, Sonia C. Swayze, Kathleen M. McPhaul, Janet T. Wittes, and Ronald G. Crystal

1. Once-weekly IV-AAT, at a dose of 60mg/kg, increased AAT levels in blood and ELF above a putative protective threshold
2. Approval by the Food and Drug Administration (FDA) in **1987**



21 patients

Lung Density Decline- study over 2 years- effect of treatment?



Significantly lower rate of lung density decline in patients treated with augmentation therapy

Who should be tested for alpha-1-deficiency?

- Emphysema, COPD
- Asthma (with no fully reversible airflow obstruction)
- Bronchiectasis of unknown origin
- Liver disease of unknown origin
- Necrotizing Panniculitis and some subforms of vasculitis
- Siblings and kids from homozygous alpha-1 individuals (family creening)

Why don't we detect all patients?

- Lack of knowledge
- Recommendations to test or do family screening are not applied
- God bless... not all AAT deficient individuals develop disease!

**You are the ambassadors of AATD.
Raising awareness is also your task!**



Thank You

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