Detection & Identification
Alpha-1 Antitrypsin Deficiency (AATD)

Epidemiology:
- Hereditary deficiency of serum protein alpha-1 antitrypsin (AAT)
- More than 100,000 severely deficient individuals in U.S.
- Less than 10% currently identified
- Accounts for 1% of all patients with COPD

Who should be tested:
- **All** with diagnosis of COPD, emphysema, bronchiectasis
- Family members of those with abnormal genotype
- Unexplained liver disease in infants, children, or adults
- Family history of COPD or liver disease
- Non-tuberculous mycobacterial infections
- Granulomatosis with polyangiitis (GPA)
- Necrotizing panniculitis

How to test:
- Serum/plasma alpha-1 antitrypsin (AAT) level
  - Won't detect heterozygotes – do not use in isolation, especially for family testing
- Pi-typing/phenotype (isoelectric focusing of AAT protein)
- Genotyping for common mutations
- Best to do level plus another method to confirm and verify
- NextGen Sequencing – needed only for rare and null mutations

Free test kits available from augmentation therapy manufacturers.

Meaning of test results:
- Severely deficient level: 0-57 mg/dL or 0-11 μM
- Normal blood level (depends on lab): ~100-250 mg/dL or ~19-53 μM
- Normal genotype/Pi-type: MM (= Pi MM or Pi M)
  - Including: M1, M2, M3, M4, M5, M6
- Most common severe deficiency: ZZ (= Pi ZZ or Pi Z)
- Other less common severe deficiency mutations: ZNull, NullNull, SZ, FF, FZ, etc.
- Multiple rarer mutations

AAT Heterozygotes:
- As above, some complex heterozygotes (two abnormal genes) are considered severely deficient
- Heterozygotes with one M gene generally have no increased risk of lung disease if no cigarette smoking. Risk of liver disease is very low.
- Blood levels of AAT are intermediate between normal and severely deficient

AATD is a laboratory diagnosis not a clinical diagnosis!

Management
Alpha-1 Antitrypsin Deficiency (AATD)

Avoidance of cigarette Smoke Exposure!!

Diseases associated with AATD:

- Pulmonary emphysema, bronchiectasis
- Cirrhosis, hepatocellular carcinoma
- Necrotizing panniculitis
- Susceptibility to non-tuberculous mycobacterial infection
- Granulomatosis with polyangiitis (GPA)
- Minimum of annual medical follow-up of these conditions

AATD with no organ disease and no symptoms:

- MANY PEOPLE WITH AATD WILL NEVER DEVELOP DISEASE!
- Avoidance of risk factors (for all with AATD):
  - Smoking cessation/prevention, aggressive treatment of lung infections, avoidance of occupational exposures, limit or eliminate alcohol consumption
  - Provide flu, pneumonia, hepatitis immunizations
- Regular monitoring of lung function and liver function

Lung disease due to AATD:

- Usual therapy for COPD and bronchiectasis
- If emphysema present: add intravenous, plasma-derived, alpha-1 antitrypsin protein (60 mg/kg/week) = augmentation therapy
- Monitoring of AAT blood levels during therapy not recommended
- Smoking cessation must precede initiation of augmentation
- Lung transplantation if disease severity indicates

Liver disease due to AATD:

- If no liver disease, 3 drinks/wk might be safe, if liver disease then none
- Liver ultrasound at baseline
- Annual checkup focused on liver health
- Augmentation therapy of no benefit in treating liver disease
- Liver transplantation if disease severity indicates
  - Liver transplantation "cures" AATD since nearly all circulating AAT is made in liver

Necrotizing Panniculitis:

- Weekly augmentation therapy, usually at higher doses than recommended for lung disease, can be highly effective

Hepatocellular carcinoma:

- Early diagnosis can lead to surgical cure

Treatment of heterozygotes (MZ, MS)

- No evidence at present that augmentation therapy is of benefit to heterozygotes
- Avoidance of smoking is key to preventing disease
- Similar recommendations for SS homozygote genotype