Alpha-1: A Major Risk Factor for COPD

- AATD
  - Genetic Condition that Leads to Increased risk of Lung and Liver disease
  - AAT protein is a major circulating serine proteinase inhibitor
    - Deficiency leads to unopposed neutrophil elastase activity
    - Connective tissue destruction
  - Leads to COPD, Emphysema, Bronchiectasis

Image courtesy of the National Human Genome Research Institute (www.genome.gov).
Low Levels of AAT Leave Lung Tissue Vulnerable

Normal Protection

- Neutrophil elastase burden
- Antineutrophil protection

AAT Deficient

- Neutrophil elastase burden
- Antineutrophil protection

AAT, alpha-1-antitrypsin.
Destruction of Lung Tissue

**Infection Response**

**Low Levels of AAT Leave Lung Tissue Unprotected**

AAT, alpha-1-antitrypsin.
Algorithm for the diagnosis of alpha-1 antitrypsin deficiency

AAT serum or dried blood spot

- AAT blood level *

AAT level low (<100 mg/dL)

- Confirm AAT level
- Perform IEF† or genotype PCR

- No abnormal protein or allele identified and AAT level confirmed <100 mg/dL: Obtain alternate test (IEF or genotype PCR)

- Abnormal protein consistent with AAT level

AAT level normal (≥100 mg/dL) but moderate to high clinical suspicion of deficiency (e.g., allelic variant F or other)

- Confirm AAT level when patient wellΔ
- Specific allele suspected: Obtain genotype PCR
  - If genotype PCR not available for suspected allele: Obtain gene sequencing
  - No specific allele suspected: Obtain gene sequencing

- Abnormal allele identified consistent with AAT level

AAT level normal and low clinical suspicion of AAT deficiency

- Normal
- No further testing

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**AAT**: alpha-1 antitrypsin; **PCR**: polymerase chain reaction (looks for specific AAT alleles); **IEF**: isoelectric focusing (assesses protein migration).

* Alternatively, in patients with a high clinical suspicion of AAT deficiency, such as those with neonatal cholestasis or childhood cirrhosis, a genotype PCR test may be the first step.

† Either IEF or genotype PCR is acceptable for diagnosis of AAT deficiency; no need to confirm with alternative test if result is clear and consistent with AAT level.

Δ AAT is an acute phase reactant, so a low AAT may increase into the normal range during acute illness.
Table 1. Diagnostic Tests for Alpha₁-Antitrypsin (AAT) Deficiency and Associated Disease Risks. *

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

* 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.
Prevalence of Alpha-1 in the US

More Common Than Previously Thought

There Is a Lengthy Delay in Diagnosis

In a survey of 1020 members of AlphaNet,* on average

- **2 to 3 physicians seen** before correct diagnosis
- **8.3 ± 6.9** years between onset of symptoms and diagnosis
- Patients were **45.5 ± 9.5 years of age** when identified as AAT deficient
- **Steady increase in age at diagnosis** (P<0.05) was observed between 1968 and 2003

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

AAT, alpha-1-antitrypsin.
Survival in AAT according to FEV1

# Alpha-1 Antitrypsin Deficiency Testing

## Guidelines

- Test all adults with COPD regardless of age, ethnicity.
- Test all adults with unexplained chronic liver disease.
- All individuals with necrotizing panniculitis, granulomatosis and polyangiitis, unexplained bronchiectasis.
- Test asymptomatic patients with persistent obstruction on pulmonary function tests and with identifiable risk factors (eg, smoking, occupational exposure).
- Test siblings of individuals with alpha-1 whether heterozygote or homozygote. (Genetic Counseling). Parents, children, minor siblings, extended family members. (Genetics Information Non-discrimination Act)

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Serum Level Alone Can Miss as Many as 90% of Those With MZ Genotype

Alpha-1 Antitrypsin Genetics Laboratory in Florida

89.9% of the Pi MZ population who were tested had levels ≥90 mg/dL

28% of the Pi MZ population who were tested had levels ≥140 mg/dL

Data on file, Alpha-1 Antitrypsin Genetics Laboratory.
Management Approaches for Patients With Alpha-1

- Family testing and counseling
- Lifestyle changes
  - Smoking cessation
  - Exercise
  - Avoidance of environmental pollutants
  - Limit alcohol consumption
- Vaccinations
  - Influenza/pneumococcal
  - Hepatitis A/B
- Drug therapy for COPD/Emphysema
  - Bronchodilators
  - Inhaled steroids
  - Antibiotics
  - Oxygen
- Pulmonary rehabilitation
- Surgical procedures
  - Lung transplantation in end-stage lung disease
  - Lung volume reduction surgery is not recommended
- Augmentation therapy

Augmentation Therapy

• Who Should be considered for Treatment
  • Alpha -1 level less than 11 micromol/L (80 mg/dL)
  • 95% are ZZ or SZ
  • FEV1
    • Less than 65% (strong recommendations)
    • Less than 30% (weak recommendations)
    • Greater than 65% discussion of benefits vs cost/lack of evidence (strong recommendations)

• Treatment Not Recommended
  • Continue to Smoke
  • Liver Disease or have undergone transplant
  • MZ genotype who have COPD

The Diagnosis and Management of Alpha-1. Journal of the COPD Foundation;3(3); 2016.
Once You’ve Identified an Alpha-1 Patient, There Is a Specific Treatment

Treatment of Alpha-1

AAT Deficient

- Neutrophil elastase burden
- Antineutrophil imbalance

With Augmentation Therapy

- Neutrophil elastase burden
- Antineutrophil in balance

Reduce the burden of neutrophil products

Augment the lung concentration
Summary

• AATD is Under recognized
• TEST, TEST, TEST
• Genetic Counseling
• Start Intravenous Augmentation Therapy Early
Questions?