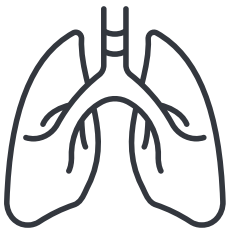


# Guidance for Testing, Diagnosis, and Treatment of Alpha$_1$-Antitrypsin Deficiency (AATD)

## IDENTIFYING AATD IS IMPORTANT TO ALLOW FOR:

**Lifestyle modifications** to reduce the risk of disease progression[1-3]

**Active monitoring** for symptoms of disease[1,2]

Identification of potential individuals with severe AATD through **family testing**[3]

# What is AATD?

Alpha$_1$-antitrypsin deficiency (AATD) is the best documented **genetic cause of chronic obstructive pulmonary disease (COPD)** and can lead to an increased risk of lung disease[2,4]

AATD is caused by a **deficiency in alpha$_1$-antitrypsin (AAT) protein**, which results in the **breakdown of lung tissue and symptoms associated with emphysema**[5-7]

AAT is a **proteinase inhibitor produced in the liver** and **released into the bloodstream**[8,9]

Approximately **11%** of patients with **COPD/emphysema** and **5%** with **asthma** have **severe AATD**[10]

Another 30% with COPD/emphysema and 37% with asthma carry 1 AATD-associated allele that may be the underlying genetic cause of their disease[10]

**>90%**

of patients remain **undiagnosed**, and diagnosis occurs an average of 7 years after onset of symptoms[8,11]

# Testing for AATD

Guidelines for AATD testing have been developed by a number of organizations, including the American Thoracic Society (ATS), European Respiratory Society (ERS), COPD Foundation, and Global Initiative for Chronic Obstructive Lung Disease (GOLD). These organizations **recommend** AATD testing for

- Adults with symptomatic emphysema or COPD[2-4]
- Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators[3]
- Asymptomatic individuals with persistent obstruction on pulmonary function tests and identifiable risk factors (eg, cigarette smoking, occupational exposure)[3]
- Parents, siblings, and children, as well as extended family of individuals identified with an abnormal gene for AATD, along with providing genetic counseling[2,3]
- Individuals with unexplained chronic liver disease[2,3]
- Adults with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis[2,3]

A diagnosis of AATD is made based on a combination of **quantitative** and **qualitative** methods that encompass clinical, biochemical, and genetic features[12,13]

| CLINICAL SIGNS AND SYMPTOMS |
|---|
| Look for relevant symptoms, including common respiratory symptoms[3,*] |
| Test pulmonary function, including worsening of function over time[3,14] |
| Identify the degree and location of emphysema by CT scan[14] |

| AAT DEFICIENCY |
|---|
| Quantify total plasma AAT levels[12]<br>**CPT code: 82103** |
| Qualitatively identify the AAT protein phenotype[12]<br>**CPT code: 82104** (isoelectric focusing)<br>**CPT code: 82542** (column chromatography/mass spectrometry) |

| GENOTYPE |
|---|
| Identify the common alleles associated with AATD[12,15]<br>**CPT code: 81332** (S, Z)<br>**CPT code: 81479** (sequencing of the *SERPINA1* gene) |

Determine the presence of **other contributing factors**, including social determinants and lifestyle (eg, smoking)[3,14]

*Common respiratory symptoms include dyspnea, wheezing, cough, excess sputum production, chronic asthma or emphysema, frequent lower respiratory tract infections, and exercise intolerance.[16,17]

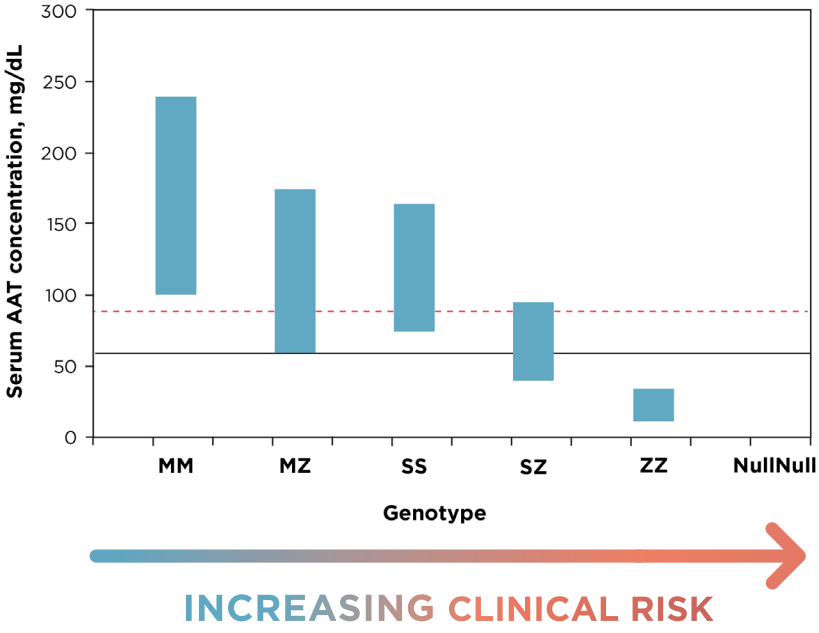
# Interpreting Test Results

There are a few considerations when interpreting AAT serum levels

AAT is an acute-phase reactant and can be elevated by systemic inflammation[12]

Patients with borderline normal plasma levels of AAT may warrant genetic testing because these levels may correspond to phenotypes associated with asymptomatic or misdiagnosed AATD within a patient's family[3]

## Range of AAT Serum Levels According to Genotype[18]




Lower limit of normal: 90 mg/dL (~17 µM)
Protective threshold: ~50 mg/dL (11 µM)

» MS is not shown, but typical values are 110-340 mg/dL (18-52 µM)[19]

Image modified from Brode, et al 2012[18]

**While the majority of AAT-deficient individuals have either the ZZ or SZ genotype, they are not the only patients who may present clinically.[2,18] Individuals with at least one disease-associated allele may develop AATD[18]**

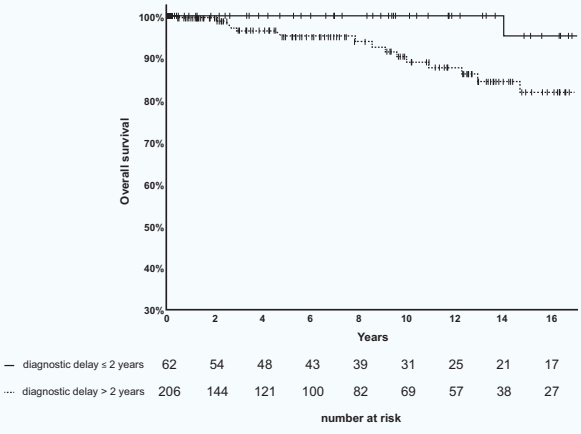
| Genotype* | Status of AAT alleles[3] | Clinical risk |
|---|---|---|
| **MM** | Normal | No increased risk of lung or liver disease due to AATD[3] |
| **MS** | 1 mildly deficient allele | Relatively low risk of lung disease[3,10] |
| **MZ** | 1 severely deficient allele | Low to moderate risk of lung disease (COPD), which is elevated in smokers; risk of liver disease[3,10,20,21] |
| **SS** | 2 mildly deficient alleles | Low to moderate risk of lung disease, relatively low risk of liver disease[3,22] |
| **SZ** | 2 different deficient alleles | Moderate risk of lung disease, which is elevated in smokers; moderate risk of liver disease[23,24] |
| **ZZ** | 2 severely deficient alleles | High risk of COPD, severe emphysema, and/or liver cirrhosis/cancer in nonsmokers[3] |
| **Null Null** | Mutated AAT alleles | High risk of lung disease[3] |

*F and I alleles may also occur.[7,25]

# Timely Diagnosis of AATD

## A delayed diagnosis of AATD is associated with worsening of COPD-related symptoms and pulmonary function and reduction in overall survival[26,27]

**Kaplan–Meier plot of overall survival (OS) by diagnostic delay (n=268)**




» Patients with AATD who have a diagnostic delay of >2 years have lower survival* than patients with a shorter diagnostic delay of ≤2 years (15-year survival rate, 81.7% vs 95.2%; log-rank *P*=0.08)[27,†]

*Survival defined as the time from AATD diagnosis until death.

†Data from a prospective study of 268 patients with AATD from an Austrian Alpha-1 Lung Registry in which the majority of patients (82.1%) were ZZs and the median diagnostic delay was 5.3 years.[27]

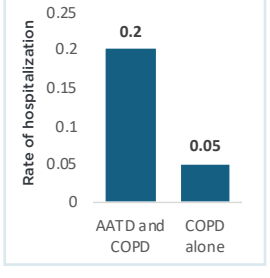
Image from Meischl, et al 2023.[27]

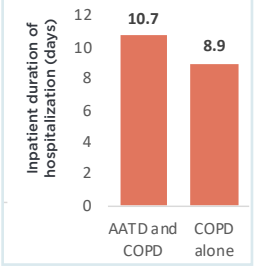
# Patients with AATD often experience moderate-to-severe exacerbation of symptoms and frequent hospitalizations[28,29]

» In a single-center non-interventional study of 922 patients (mean age, 54.5 years) with AATD and COPD on augmentation therapy, **91.5% experienced ≥1 acute exacerbation** over 1 year of follow-up, with each lasting an average of 17 days[29]

– Patients who experienced ≥3 exacerbations per year had significantly worse quality of life compared with those with fewer (<3) exacerbations (*P*<0.01)[29]

Patients with AATD and COPD have **higher utilization of healthcare resources** compared with patients with COPD alone due to severe pulmonary exacerbations[30]




» In a longitudinal cohort study using health insurance data between 2008 and 2013 (n=590; minimum age of 30 years), patients with AATD had **more frequent outpatient consultations and hospitalizations** compared with patients with non-AATD COPD, emphysema, or asthma[28]

# Management of Patients with AATD

**Managing a patient with AATD is multifactorial and includes nonpharmacologic and pharmacologic approaches that encompass 4 main strategies[31]**

## EDUCATION ON AATD AND PREVENTIVE MEASURES

### EARLY SMOKING CESSATION

Smokers have significantly more rapid decline in lung function that can be reduced with smoking cessation[32,33,*]

### MINIMIZED EXPOSURE TO RESPIRATORY IRRITANTS

High occupational exposure to mineral dust may lower $FEV_1$ levels.[†] Counsel patients to avoid or limit occupational inhalational exposure[34]

### MODERATION OF ALCOHOL CONSUMPTION

Patients with an AATD genotype may be at risk for liver disease and should be counseled against drinking alcohol[3,35]

### APPROPRIATE IMMUNIZATIONS

Patients with AATD should be advised to follow national influenza and pneumococcal vaccination protocols as described for managing COPD[31]

### FAMILY TESTING

Prompt diagnosis will allow family members to be tested[2,3]

*Data from two retrospective cohort studies of the annual decline in $FEV_1$ by smoking status in 608 PiZZ individuals from the Swedish national AATD register and the impact of smoking cessation on the annual change in $FEV_1$ in 161 patients from the Danish 1-AT-deficiency study.[32,33]

†Based on a prospective study of 128 patients with AATD and at least 1 Z allele.[34]

## MANAGING SYMPTOMS

Interventions commonly used to manage COPD, such as corticosteroids, antibiotics, and pulmonary rehabilitation, are appropriate for managing chronic and acute exacerbations in patients with AATD[3,4,31]

## MONITORING AND FOLLOW-UP

Patients with AATD, irrespective of whether they are receiving augmentation therapy, should be regularly monitored to evaluate disease progression[2]

| FREQUENCY[2] | PARAMETER[2] |
|---|---|
| **At baseline** | CT scan<br>Complete pulmonary function testing |
| **Annually** | Spirometry<br>Assessment of liver involvement |

See next page for ATS ERS and GOLD guidelines on considerations for augmentation therapy.

# CONSIDERATIONS FOR AUGMENTATION THERAPY

AAT serum levels and pulmonary function of an AAT-deficient patient help determine whether the patient is an appropriate candidate to receive augmentation therapy[3,4]

## ACCORDING TO ATS-ERS STANDARDS[3]

Consider augmentation therapy if

- **AAT serum level <52 mg/dL (level of evidence II-2*):** Consideration for treatment is independent of the phenotype and based on level and presence of obstructive lung disease[3,12]
- **$FEV_1$ (postbronchodilation) 30% to 65% predicted (level of evidence II-2*):** Individuals with normal or nearly normal pulmonary function can be treated if they experience a rapid **decline in lung function (change in $FEV_1$ >120 mL/year)**. Patients with very poor lung function, already treated, should be kept on treatment[3]

*Grade of evidence II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.[3]

## ACCORDING TO THE GOLD 2025 REPORT AND COPD FOUNDATION[2,4]

Considerations for augmentation therapy

- Observational studies suggest a reduction in spirometric progression in treated vs nontreated patients, with the most effective reduction in patients with $FEV_1$ 35% to 49% predicted[4]
- **Never or ex-smokers with an $FEV_1$ of 35% to 60% predicted (Evidence B†):** These individuals are suggested to be the most appropriate for augmentation therapy[4]
- **AATD and $FEV_1$ ≤65% predicted:** Intravenous augmentation therapy is recommended[2]
- Individuals with necrotizing panniculitis: Intravenous augmentation therapy is recommended[2]
- **AATD and $FEV_1$ >65% predicted:** Intravenous augmentation therapy should be considered and discussed with these individuals. This recommendation is based on data from a study powered on CT scan as an outcome[2,4]

†Evidence Category B: Evidence is from randomized clinical trials with important limitations or when there is a limited body of evidence.[4]

ATS=American Thoracic Society; CT=computed tomography; ERS=European Respiratory Society; $FEV_1$=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease.

**References: 1.** Craig TJ. *J Allergy Clin Immunol Pract.* 2015;3(4):506-511. **2.** Sandhaus RA, et al. *Chronic Obstr Pulm Dis.* 2016;3(3):668-682. **3.** American Thoracic Society; European Respiratory Society. *Am J Respir Crit Care Med.* 2003;168(7):818-900. **4.** Global Initiative for Chronic Obstructive Lung Disease. 2025 GOLD Report. https://goldcopd.org/2025-gold-report/ Accessed February 28, 2025. **5.** MedlinePlus. Alpha-1 antitrypsin deficiency. https://medlineplus.gov/genetics/condition/alpha-1-antitrypsin-deficiency/#inheritance Accessed June 11, 2025. **6.** Siri D, et al. *Ann Allergy Asthma Immunol.* 2013;111(6):458-464. **7.** Meseeha M, Attia M. Alpha-1 antitrypsin deficiency. In: StatPearls [Internet]. StatPearls Publishing; 2023. **8.** Campos MA, et al. *Chest.* 2005;128(3):1179-1186. **9.** Fregonese L, Stolk J. *Orphanet J Rare Dis.* 2008;3:16. **10.** Veith M, et al. *Int J Chron Obstruct Pulmon Dis.* 2020;15:2827-2836. **11.** Stoller JK, et al. *Chest.* 2005;128(4):1989-1994. **12.** Kueppers F, Sanders C. *Allergy Asthma Proc.* 2017;38(2):108-114. **13.** MedlinePlus. Alpha-1 antitrypsin testing. https://medlineplus.gov/lab-tests/alpha-1-antitrypsin-testing/ Accessed June 11, 2025. **14.** Stoller JK. Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency. Updated September 13, 2022. https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency Accessed February 28, 2025. **15.** Lascano JE, Campos MA. *Postgraduate Med.* 2017;129(8):889-895. **16.** Alpha-1 Foundation. *Lung disease.* https://alpha1.org/lung-disease/ Accessed June 11, 2025. **17.** McElvaney NG, et al. *Chest.* 1997;111(2):394-403. **18.** Brode SK, et al. *CMAJ.* 2012;184(12):1365-1371. **19.** Exeter Clinical Laboratory Internation-al. Alpha-1-Antitrypsin Blood Sciences Test. https://www.exeterlaboratory.com/test/alpha-1- antitrypsin/ Accessed April 21, 2025. **20.** Hakim A, et al. *Hepatol Comm.* 2021;5(8):1348-1361. **21.** Ghosh AJ, et al. *Am J Respir Crit Care Med.* 2022;205(3):313-323. **22.** Martín T, et al. *Respir Res.* 2024;25:260. **23.** McElvaney GN, et al. *Eur Respir J.* 2020;55:1902410. **24.** Franciosi AN, et al. *Am J Respir Crit Care Med.* 2020;202(1):73-82. **25.** Sinden NJ, et al. *BMC Pulm Med.* 2014;14:132. **26.** Tejwani V, et al. *Respir Care.* 2019;64(8):915-922. **27.** Meischl T, et al. *Resp Res.* 2023;24:34. **28.** Greulich T, et al. *Eur Respir J.* 2017;49:1600154. **29.** Campos MA, et al. *Respir Med.* 2009;103(10):1532-1539. **30.** Yang KC, et al. *Eur Resp J.* 2023;62(suppl 67):PA649. **31.** Barjaktarevic I, Campos M. *Ther Adv Chronic Dis.* 2021;12:49-63. **32.** Piitulainen E, Eriksson *S. Eur Respir J.* 1999;13:247-251. **33.** Seersholm N, et al. *Am J Respir Crit Care Med.* 1995;152:1922-1925. **34.** Mayer AS, et al. *Am J Resp Crit Care Med.* 2000;162:553-558. **35.** Santos G, Turner AM. *Faculty Rev.* 2020;9:1.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