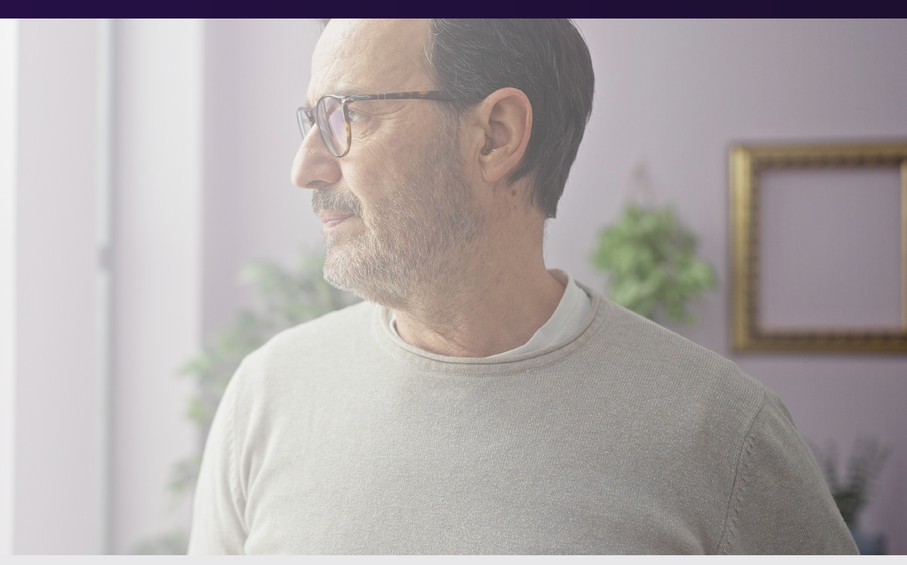
AATD:
An Underdiagnosed Genetic Driver of COPD



AATD is a genetic, heterogeneous disease with the potential to significantly impact pulmonary health

Alpha-1 antitrypsin deficiency (AATD) is an inherited genetic disorder caused by pathogenic variants in the *SERPINA1* gene.[1]
AATD affects approximately 100,000 individuals in the United States.[2]

Disease severity varies widely based on[3]:

- **Genotype** (eg, PiZZ vs PiMZ)
- **Serum AAT levels**
- **Environmental exposures**
- **Age and comorbidities**

Diagnosis is often delayed 5 to 8 years after symptom onset[2]

Patients are susceptible to an incomplete diagnosis for years before obtaining a correct one.

Diagnostic challenges

- **AATD** shares many overlapping symptoms with common pulmonary conditions like COPD and asthma.[4]
- Fewer than **10%** of individuals with severe **AATD** are currently diagnosed.[2]
- Symptoms frequently overlap with typical COPD.[4] Approximately 1–2% of patients with COPD have AATD[4]
- **GOLD** guidelines recommend **AATD** testing in all COPD patients, yet testing remains **inconsistent**.[4]

AATD is a progressive disease that may cause irreversible lung damage

Low AAT levels allow unchecked protease activity, resulting in potential ongoing tissue injury and accelerated lung decline.[3]

- AATD is an underlying driver of COPD and early-onset emphysema[3]
- Smoking, air pollution, and dust exposure are also contributing factors to increased risk of accelerated lung disease[5]

Early-onset emphysema is a hallmark of AATD

Genotype	Typical Plasma AAT Level Range (μM)	AAT Level Classification	Associated Risk of Emphysema
MM	~20 to 53	Normal	No increased risk
MS	~20 to 52	Normal	No increased risk
SS	~20 to 48	Normal to mildly reduced	No increased risk
MZ	~15 to 42	Moderately reduced	Possible mild increase
SZ	~10 to 23	Reduced	Increased risk (~20 to 50%)
ZZ	~2 to 8	Severely reduced	High risk (~80 to 100%)

Data from Mulkareddy, V. Roman J. [ital] Am J Med Sci. 2024;368(1):1-8.

Lower levels of the AAT protein correlate with higher risk of emphysema[3]

- Varying degrees of disease severity are observed across different genotypes
- ZZ: Severe genotypes have lower AAT levels
- MM: Associated with normal AAT levels

The economic burden of AATD reflects chronic disease management, frequent exacerbations, and advanced interventions.

5% of AATD patients will eventually need lung transplants[6]

Higher rates of hospitalizations and emergency department visits

- In a 2021 study, the **incidences of AATD-associated PEs** among patients with a severe AATD clinical course were **1.8 to 2.8 times greater** than in patients with a nonsevere AATD clinical course[7]

Escalating costs associated with disease progression

- Together, physician visits and inpatient stays account for **~60% to 70%** of nondrug medical costs in AATD, reflecting recurrent exacerbations, complications, and ongoing disease monitoring[8]

Plasma-derived augmentation therapy is currently the only established treatment available and has been for decades

- Requires lifelong weekly IV infusions
- Produces peaks as well as troughs in serum AAT levels that do not steadily remain above the threshold[9]

A clear unmet need remains

There is an unmet need for a longer-acting therapy that enables less frequent dosing than plasma-derived AAT while helping maintain normal AAT levels and slowing lung function decline.

AATD represents an underdiagnosed disease with significant clinical, humanistic, and economic impact. Improving outcomes for patients with AATD will require advancement in therapeutic approaches alongside earlier and consistent testing/diagnosis and extending to long-term disease management.

AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PE, pulmonary exacerbation.

References: 1. Turner AM, Ficker JH, Vianello A, et al. Advancing the understanding and treatment of lung pathologies associated with alpha 1 antitrypsin deficiency. *Ther Adv Respir Dis*. 2025;19:17534666251318841. **2.** Ashenhurst, JR, Hoang Nhan, et al. Prevalence of alpha-1 antitrypsin deficiency, self-reported behavior change, and health care engagement among direct-to-consumer recipients of a personalized genetic risk report. *Chest*. 2022;161(2):373-381. doi:10.1016/j.chest.2021.09.041 **3.** Mulkareddy V, Roman J. Pulmonary manifestations of alpha 1 antitrypsin deficiency. *Am J Med Sci*, 2024;368(1):1-8. doi:10.1016/j.amjms.2024.04.002. **4.** Smith MD, Couch KA. Improving screening for alpha-1 antitrypsin deficiency in adults with COPD. *Jt Comm J Qual Patient Saf*. 2025;51(10):659-665. doi:10.1016/j.jcjq.2025.07.002 **5.** Torres-Durán, M., Lopez-Campos, J.L., Barrecheguren, M. et al. Alpha-1 antitrypsin deficiency: outstanding questions and future directions. *Orphanet J Rare Dis* 13, 114 (2018). https://doi.org/10.1186/s13023-018-0856-9 **6.** Zamora MR, Ataya A. Lung and liver transplantation in patients with alpha-1 antitrypsin deficiency. *Ther Adv Chronic Dis*. 2021;12 (suppl):20406223211002988 doi:10.1177/20406223211002988 **7.** Herrera EM, Joseph C, Brouwer ES, Gandhi V, Czorniak M. Alpha-1 antitrypsin deficiency-associated clinical manifestations and healthcare resource use in the United States. *COPD.* 2021;18(3):315-324. doi: 10.1080/15412555.2021.1917532 **8.** Sieluk J, Levy J, Sandhaus RA, Silverman H, Holm KE, Mullins CD. Costs of medical care among augmentation therapy users and non-users with alpha-1 antitrypsin deficiency in the United States. *Chronic Obstr Pulm Dis.* 2018;6(1):6-16. doi:10.15326/jcopdf.6.1.2017.0187 **9.** Teschler, H. Long-term experience in the treatment of α1-antitrypsin deficiency: 25 years of augmentation therapy. *European Respiratory Review* 2015;24(135):46-51;doi:10.1183/09059180.10010714

MAT-US-2604160-v1.0-05/2026

sanofi