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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Alpha-1 Antitrypsin Deficiency (AATD): Understanding the Patient Journey and Burdens

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Received: October 31, 2025; **Published:** November 19, 2025

Abstract

Alpha-1 antitrypsin deficiency (AATD) is a hereditary condition that produces two distinct clinical problems depending on genotype and the organ affected. In the lungs, low-circulating alpha-1 antitrypsin (AAT) produces unchecked enzyme activity that destroys elastic lung tissue and sustains inflammation, leading to chronic obstructive pulmonary disease (COPD), emphysema and bronchiectasis [1]. In the liver, misfolded AAT accumulates inside liver cells and can cause neonatal hepatitis, cirrhosis in children and adults, and hepatocellular carcinoma [2].

Genetic variants determine risk. People with two severely deficient copies, such as the PiZZ genotype or null variants, have the lowest blood levels of AAT and the highest risk of both liver and lung disease. Heterozygous states, such as PiMZ, are carrier or intermediate states with variable risk that is strongly influenced by smoking, metabolic liver disease and other exposures [1].

Clinical presentation is often non-specific and overlaps with common respiratory and hepatic diagnoses. As a result, many patients experience prolonged and fragmented diagnostic pathways. Diagnostic delay typically exceeds five years, and the average age at diagnosis is around 45 years [3].

After diagnosis, management focuses on respiratory risk modification and liver surveillance. For eligible patients with severe deficiency and established emphysema, intravenous augmentation therapy is the only disease-modifying, commercially available option, but it carries practical burdens, and its availability varies by country. Clinical trial participation offers alternative avenues but is constrained by genotype-based eligibility, travel burdens and inconsistent access pathways.

A patient-centred understanding of these pathways can, therefore, guide more equitable testing, care delivery and research design. This article provides a clearer understanding of the AATD patient journey and examines how the regional differences in testing, clinical infrastructure and reimbursement can shape patient outcomes.

Keywords: *Alpha-1 Antitrypsin Deficiency; Alpha-1 Antitrypsin; Chronic Obstructive Pulmonary Disease; Rare Diseases; Genetic Disorders; Pulmonology; Hepatology; Augmentation Therapy; Genotypes; Clinical Trials*

Abbreviations

AAT: Alpha-1 Antitrypsin; AATD: Alpha-1 Antitrypsin Deficiency; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease

Introduction

AAT is a circulating serine protease inhibitor that protects lung parenchyma from proteolytic destruction by neutrophil elastase and other proteases. Pathogenic *SERPINA1* variants create a spectrum of genotypes (See table 1).

Genotype	Description
PiMM	Both copies of the gene are healthy, and AAT levels are normal. People with PiMM are not at increased risk of AATD-related disease.
PiMZ	One normal (M) and one abnormal (Z) gene are present. Blood levels of AAT are lower than average but usually high enough to protect the lungs. Most PiMZ carriers do not develop lung or liver disease unless other risk factors - such as smoking, repeated chest infections or fatty liver - are present.
PiZZ	Both genes are the Z variant, which causes the AAT protein to fold incorrectly and build up in liver cells instead of being released into the bloodstream. As a result, circulating AAT levels are very low. These individuals are at the highest risk for lung damage (emphysema) and liver disease (cirrhosis, liver failure or, rarely, liver cancer).
PiSZ	One S and one Z gene lead to AAT levels that are lower than normal but not as low as in PiZZ. Some people with PiSZ develop lung problems, especially if they smoke, but liver disease is less common.
PiSS	Both genes are the S variant, causing slightly reduced AAT levels. Lung disease can occur, but it is uncommon.
Null variants (PiNull)	Extremely rare mutations that result in no AAT being produced at all. These individuals have a very high risk of lung disease but no accumulation of protein in the liver, so liver disease is less likely.
Other rare deficient alleles	Many uncommon mutations have been described that can behave like the Z or Null alleles, depending on whether they produce a misfolded protein or no protein at all.

Table 1: *AATD genotypes [1].*

AATD is a rare genetic disorder with two distinct clinical presentations depending on the genotype and the most affected organ.

In the liver, the disease is caused by pathologic polymerisation of the AAT protein, resulting in intra-hepatocyte accumulation of AAT molecules (called a 'toxic gain of function'). This buildup results in certain liver disorders, such as neonatal hepatitis, cirrhosis (both in children and adults) and hepatocellular carcinoma. Approximately 10 to 15 per cent of newborns with these genotypes develop some form of hepatic disease, and approximately 10 to 15 per cent of affected adults develop hepatic disease [2].

In the lungs, the disease results from a 'toxic loss of function' - specifically, the destruction of elastin by elastase and other proteases due to insufficient levels of AAT. This activity fuels persistent inflammation, causing COPD, emphysema and bronchiectasis [1].

The severity of AATD depends on which versions of the SERPINA1 gene a person carries. People with two abnormal copies (such as PiZZ or PiNull) have the most severe form of the disease, while those with only one abnormal copy (PiMZ or PiMS) are carriers with variable - often low - clinical risk that can be influenced by lifestyle and environmental factors like smoking or alcohol use.

AATD has been identified in all racial groups, but it is most prevalent in people with Northern European (1 in 1,600) and Spanish or Portuguese descent [4]. The Z gene is more frequently found in individuals with Northern or Western European descent, and the mutation for the Z variant is suspected to have arisen in southern Scandinavia [5]. It has been observed that confined or isolated populations with less genetic diversity, such as those located in alpine valleys or on islands, seem to have a higher prevalence of the Z-gene and S-gene AATD phenotypes.

Clinical presentations are often non-specific and overlap with common respiratory and hepatic disorders; this contributes to frequently prolonged diagnostic pathways, which in turn affect prognosis, quality of life and access to disease-specific interventions. Equally, variations in healthcare infrastructure, physician awareness and testing protocols across regions can mean some individuals wait years and see multiple specialists before learning the true cause of their breathlessness, liver dysfunction or premature emphysema. Diagnostic delay typically exceeds five years, resulting in an average age at diagnosis of about 45 years [3].

Once diagnosed, patients and families face complex decisions about treatment access, disease progression and management and, ultimately, clinical trial participation - juggling logistical burdens, potential benefits and limited treatment options, such as augmentation therapy.

The patient's journey from initial symptoms to diagnosis

Although every patient story is unique, two archetypal diagnostic pathways recur in the literature and in patient reports.

Scenario 1: First manifestation in the family

Many adults with AATD first present with respiratory complaints that are indistinguishable from common airway diseases. Primary-care clinicians commonly attribute exertional breathlessness, wheeze or recurrent chest infections to asthma or smoking-related COPD; patients are often prescribed inhaled therapies and receive follow-up in primary care, sometimes for years, before AATD is considered. This can lead to 'doctor-shopping' as patients seek second opinions for unexplained or worsening symptoms, or as they are referred serially between primary care, emergency departments and speciality clinics.

When speaking with Patient A (a UK-based female in her mid-50s with AATD), she explained how her childhood history of asthma and repeated chest infections led to early label-based management. Following a case of pneumonia in her early 40s, she struggled to recover exercise tolerance; clinicians repeatedly reassured her that this was asthma-related and managed infections in primary care. It was only after 18 months of persistent symptomatic decline that a primary-care nurse suggested AATD testing.

International guidelines, such as those provided by the Global Initiative for Chronic Obstructive Lung Disease ('GOLD'), recommend testing all adults with COPD or incompletely reversible asthma, unexplained emphysema or persistent liver disease of unknown cause, and siblings of diagnosed individuals [6]. However, the route described by this patient - where primary-care advocacy rather than routine testing triggers diagnosis - is familiar in many settings and illustrates how testing gaps at first contact create prolonged uncertainty and prevent timely specialist referral [7,8].

Scenario 2: Known familial AATD history

When AATD is already documented in a family, cascade testing of first-degree relatives enables earlier detection and pre-emptive risk modification. Relatives identified as carriers or affected can be offered targeted testing, genetic counselling and earlier baseline surveillance for liver or lung manifestations. This pathway shortens diagnostic latency and may delay or prevent severe disease in some individuals.

However, the lack of uniform cascade testing procedures in many systems may mean missed opportunities for early intervention. Medical records may also be incomplete, and counselling services are not always provided consistently worldwide. Even when familial cases are known, practitioner inertia or structural barriers frequently impede systematic outreach.

For example, after Patient A's diagnosis, she discovered her father, who had already been diagnosed with a different genetic condition, had the PiZZ genotype - something the family was not informed of prior to her own diagnosis. Despite this clear family history (and the patient being one of six children), they were never offered genetic counselling at any stage.

Diagnostic bottlenecks and the burden of delay

Diagnostic delay is well documented. Multiple cohort studies and registry analyses have identified median delays of several years between symptom onset and definitive AATD diagnosis; where measured, longer diagnostic delays are associated with worse lung function, higher symptom burden and lower transplant-free survival [7,9].

Reasons for delay typically include:

- Low clinician awareness or failure to test routinely in COPD/emphysema; testing rates in eligible populations are frequently low [10].
- Symptom overlap with common airway diseases (asthma, smoking-related COPD), leading to misdiagnosis.
- Variable availability of genotype/phenotype testing across countries/regions and care settings.
- Fragmented referral pathways.
- Patient-level factors: adaptation to symptoms, stigma, socioeconomic barriers to specialist access.
- Studies show that for each incremental year of diagnostic delay, there are measurable adverse effects on symptom burden and lung function, underscoring the clinical urgency of earlier detection [7,9].

From diagnosis to treatment: management options for AATD

Post-diagnosis management focuses on two broad goals: disease-modifying care, where indicated, and comprehensive supportive care/surveillance of symptoms. As such, management of AATD usually follows a two-pronged approach:

1. **General respiratory care and risk modification:** Smoking cessation is the single most important intervention to slow lung disease progression in AATD. Standard COPD management (bronchodilators, vaccinations, treatment of infections, pulmonary rehabilitation) is recommended and often yields meaningful symptomatic improvement. Pulmonary rehabilitation, in particular, supports exercise tolerance and self-management [2]. Environmental factors, such as air pollution, also play a role in the evolution of the disease; reducing exposure to these factors should, therefore, also be recommended [11].
2. **Monitoring for liver disease:** Serial liver function tests, imaging and hepatology referral, where indicated, are essential for genotypes that carry hepatic risk (PiZZ and PiSZ).

For many patients, pulmonary rehabilitation improves exercise tolerance, self-management and quality of life; for others with severe deficiency and established emphysema, intravenous augmentation therapy may be recommended [12].

Augmentation therapy - intravenous infusions of plasma-derived alpha-1 proteinase inhibitor - is the only approved disease-modifying therapy specifically indicated to slow emphysema progression in patients with severe deficiency and established emphysema [13].

However, most regulators and payers limit augmentation therapy to adults with severe deficiency and clinical evidence of emphysema; heterozygous carriers (PiMZ) are typically not candidates [13]. Additionally, not all countries reimburse the use of augmentation therapy.

For eligible patients, practical burdens remain - weekly intravenous infusions can impose travel, time off work and caregiver implications if infusions are delivered in hospital infusion centres. Home-infusion models reduce travel and disruption but depend on home-care providers and reimbursement. Policy variation and service availability, therefore, change the lived burden of receiving augmentation therapy even when it is technically accessible in a given country.

How regional differences in available treatments and testing infrastructure shape patient support and outcomes

Awareness amongst clinicians and availability of genotype/phenotype testing vary by country and health system. Although professional society standards recommend targeted testing for adults with COPD, incompletely reversible asthma, unexplained emphysema or unexplained liver disease, uptake of these recommendations is uneven internationally and even within countries [2].

Where national guidelines and system incentives encourage routine testing of COPD or early emphysema, index diagnosis is often earlier; where testing is discretionary or laboratory access is limited, identification depends on clinician suspicion or patient initiative [8,14]. Clinics with integrated testing protocols and clear referral pathways typically capture more early cases and provide cascade testing to relatives, whereas fragmented systems leave diagnostic responsibility diffused among multiple clinicians.

In jurisdictions with routine reimbursement for augmentation therapy, clinicians are more likely to test proactively and refer to specialist centres. Conversely, in settings where reimbursement is uncertain, testing may be deferred because available interventions are limited locally.

However, availability and reimbursement vary substantially across countries. Some countries or regions reimburse augmentation therapy routinely; others restrict access with narrow eligibility criteria or provide it only through special programmes, clinical trials or private payment.

The result is an inequitable landscape in which two patients with identical genotypes and clinical severity may receive different standards of care solely because of geography. Reliance on private programmes, in particular, increases inequity and makes access contingent on employment or private insurance status, further amplifying geographic and socioeconomic disparities.

How clinical trial participation may impact and interact with treatment and access

Clinical trials are frequently the only route to novel therapies before regulatory approval and can be a path to care where approved options are limited. Yet, they also introduce additional burdens, such as travel and time costs, eligibility constraints and interaction with reimbursed therapies.

Rare-disease trials concentrate participants at specialist sites, producing travel and accommodation demands that are substantial barriers to participation; travel burden is repeatedly cited in surveys as a top obstacle [15,16].

Strict inclusion criteria (such as genotype, prior treatments, spirometry levels and comorbidities) may also exclude many patients who nonetheless seek options. For example, heterogeneity in genotype (PiZZ versus PiMZ versus PiSZ) means only a subset of diagnosed patients are eligible for any given trial, even if expressing signs of the disease. One of the reasons Patient A gave for not participating in clinical trials is that her heterozygous genotype (PiMZ) made her ineligible - a common reality for carriers who simultaneously seek therapeutic options and find few trial pathways available.

Trial participation can also complicate or delay access to reimbursed therapies depending on national policies and sponsor rules; sponsors and regulators increasingly recognise this issue and offer expanded access or compassionate-use programmes for some indications, but these pathways are inconsistent [17]. Additionally, patients are less likely to participate in clinical trials in a country

where reimbursement is available, as they have other options; if no reimbursement is available, they are more likely to participate, as it is their only option.

Accessing augmentation therapy often requires coordination amongst treating physicians, payer or regulatory authorities and patient organisations. Physicians must document genotype and clinical severity to meet payer criteria, and regulators and payers evaluate cost-effectiveness and define eligibility.

Patient advocacy and peer networks also fill multiple roles along the AATD pathway: they provide lay education that helps patients interpret laboratory results and avoid unmoderated, anxiety-provoking internet searching; they offer peer support that mitigates isolation and uncertainty; and they assist with trial-matching, travel logistics and awareness of registries and compassionate-use programmes. These services are particularly valuable where specialist centres are distant, less information or support is available, and health-system navigation is complex.

Variations in any of these components produce access delays. Slow payer review, lack of local infusion infrastructure or absence of clear clinical documentation all impede treatment initiation and can equally delay or prevent enrolment in clinical trials that may require evidence of prior therapy or detailed clinical characterisation. These administrative and logistical barriers not only restrict access to approved treatments but also limit participation in research that could expand future therapeutic options.

Conclusion

AATD presents clinicians, patients and health systems with layered challenges: a dual liver-lung biology, genotype-dependent clinical pathways and major geographic variation in diagnosis and access to treatment. Delays in suspicion and testing, inconsistent cascade screening, and wide variation in reimbursement and infusion infrastructure create avoidable inequities: two patients with the same biological risk can have very different outcomes depending on where they live and whether they can access specialist care or augmentation therapy.

Clinical trials can provide additional therapeutic pathways but are limited by genotype- and severity-based eligibility, travel demands and inconsistent expanded-access arrangements. As illustrated by Patient A's experience, carriers are often also excluded from many trials and from augmentation therapy, leaving them to navigate supportive care without a disease-specific option.

Because regional differences in testing practice, clinical infrastructure and reimbursement materially shape when patients are diagnosed and what treatments they can access, aligning diagnostic pathways and clarifying access routes is central to reducing diagnostic delay and downstream burdens.

Engaging with advocacy groups may help a patient navigate the complexities of access to diagnosis and treatment throughout locally available pathways. Addressing the logistical and psychosocial challenges faced at each step of the patient journey - from initial presentation and family cascade testing through treatment choices and trial participation - should also be a priority for clinicians, health services and policy makers.

Bibliography

1. Stoller JK., *et al*. "Alpha-1 Antitrypsin Deficiency". GeneReviews, University of Washington, October 2006 (2023).

2. American Thoracic Society, and European Respiratory Society. "American thoracic society/European respiratory society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency". *American Journal of Respiratory and Critical Care Medicine* 168.7 (2003): 818-900.

3. Greulich T and Vogelmeier CF. "Alpha-1-antitrypsin deficiency: increasing awareness and improving diagnosis". *Therapeutic Advances in Respiratory Disease* 10.1 (2015): 72-84.

4. Anariba DEI. "Alpha1-antitrypsin (AAT) deficiency: background, pathophysiology, etiology of alpha1-antitrypsin deficiency". EMedicine (2022).

5. Hutchison DCS. "α1-antitrypsin deficiency in Europe: Geographical distribution of Pi types S and Z". *Respiratory Medicine* 92.3 (1998): 367-377.

6. Global initiative for chronic obstructive lung disease. "2025 REPORT global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease" (2025).

7. Meischl T., *et al*. "The impact of diagnostic delay on survival in alpha-1-antitrypsin deficiency: results from the Austrian alpha-1 lung registry". *Respiratory Research* 24.1 (2023): 34.

8. Tasch JJ., *et al*. "A novel approach to screening for alpha-1 antitrypsin deficiency: inpatient testing at a teaching institution". *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* 5.2 (2018): 106-110.

9. Stoller JK., *et al*. "Delay in diagnosis of alpha1-antitrypsin deficiency". *Chest* 128.4 (2005): 1989-1994.

10. Riley L., *et al*. "Testing patterns and disparities for alpha-1 antitrypsin deficiency". *The American Journal of Medicine* 136.10 (2023): 1011-1117.

11. Wood AM., *et al*. "Outdoor air pollution is associated with disease severity in 1-antitrypsin deficiency". *European Respiratory Journal* 34.2 (2009): 346-353.

12. Brantly M. "Treatment for alpha-1 antitrypsin deficiency: does augmentation therapy work?" *American Journal of Respiratory and Critical Care Medicine* 208.9 (2023): 948-949.

13. Fraughen DD., *et al*. "Augmentation therapy for severe alpha-1 antitrypsin deficiency improves survival and is decoupled from spirometric decline - a multi-national registry analysis". *American Journal of Respiratory and Critical Care Medicine* 208.9 (2023).

14. Tejwani V., *et al*. "The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: the association between diagnostic delay and worsened clinical status". *Respiratory Care* 64.8 (2019): 915-922.

15. "Addressing the barriers to patient participation in clinical trials". Global Genes (2023).

16. Holm KE., *et al*. "Clinical trial attitudes among individuals with alpha-1 antitrypsin deficiency". *Respiratory Medicine* 229 (2024): 107676.

17. Polak TB., *et al*. "Generating evidence from expanded access use of rare disease medicines: challenges and recommendations". *Frontiers in Pharmacology* 13 (2022).

Volume 14 Issue 11 November 2025